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Proceedings of the 43rd Annual Scientific Meeting

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Proceedings of the 43rd Annual Scientific Meeting,
The Committee on Problems of Drug Dependence, Inc.

Editor: Louis S. Harris, Ph.D.

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Problems of Drug Dependence, 1981

Proceedings of the 41st Annual Scientific Meeting
The Committee on Problems of Drug Dependence, Inc.

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Foreword

For more than a half century, the Committee on Problems of Drug Dependence has played a distinguished part in research on drugs that affect the central nervous system. It has served as a catalyst and bonding agent for the work of academic researchers, governmental and international organizations, and the pharmaceutical industry while also conducting its own programs to evaluate the efficacy and dependence liability of new compounds. The broad range of CPDD interests is reflected in the diversity of its membership: chemists and biochemists, pharmacologists, physicians, psychologists, sociologists, and others share in its endeavors.

The 43rd Annual Scientific Meeting of the Committee on Problems of Drug Dependence was held in San Francisco on July 12-15, 1981. Characteristically, a broad and stimulating program of information and ideas was presented. Probably no other single meeting covers current research in drug abuse so comprehensively. For the third year, the National Institute on Drug Abuse is pleased to present the CPDD proceedings in its, Research Monograph series.

William Pollin, M.D.
Director
National Institute on Drug Abuse

Abraham Wikler, M.D.

In Memoriam: Abraham Wikler, M.D.

Abraham Wikler died on March 7, 1981, in Lexington, Kentucky where he had lived and worked for more than forty years. He was 70 years old. His wife, Ada, as always, was at his side.

Abe Wikler's scientific work has had a direct and profound influence on our current understanding of drug dependence and on the lives and careers of many of us in this room. My own entry into the field of psychiatry and psychopharmacology was directly attributable to the reading of Abe's 1957 review article and monograph, The Relation of Psychiatry to Pharmacology.

Abe's career in psychiatry began with a residency training at the Hospital at Lexington. Following this he was asked by Clifton Himmelsbach, in 1942, to set up an experimental neuropsychiatry laboratory in the Research Department. Calling on the neurophysiological techniques that he had acquired from Fulton at Yale, Lloyd at the Rockefeller Institute, and the familiarity with Pavlovian thought that he acquired while studying with Wasserman at Northwestern, Abe began to focus on the nature of physical dependence, drug seeking behavior, and the basis of relapse. In the process, he was able to demonstrate that physical dependence was not merely a "psychic" phenomenon and that there were physiological changes at all levels of the CNS accompanying it. Further, by using nalorphine, he demonstrated that such changes could develop early in the course of drug use. In fact, Abe, Harris Isbell and Nathan Eddy were the first to demonstrate nalorphine-precipitated withdrawal in opiate dependent humans.

Abe recognized that these changes could not explain relapse many months after withdrawal of drugs. Abe's clinical acumen led him to postulate that the recurrence of abstinence phenomena when addicts talked about drugs or returned to environments associated with drug taking was due to conditioning, in which the stimuli associated with withdrawal symptoms and with positive drug effects came to elicit these effects as conditioned responses long after the drug had been withdrawn. He also postulated that the withdrawal phenomena which

develop early in the course of use provide a regularly recurring motive that permits the addict to work, or "hustle," for an immediate reward - the alleviation of withdrawal distress. Thus, "hustling" to obtain drugs, with its repeated immediate reinforcement, strengthened the drug taking behavior even as it served to alleviate the addict's boredom and even the hustling could become a conditioned response. Then, in a long series of experiments involving rats, Abe was able to demonstrate that a conditioning process which develops during opiate use increases the likelihood of opiate self-administration for months after withdrawal.

This view of addiction as a process involving learning and conditioning, which Abe was one of the first to champion, has now been accepted as a fundamental aspect of our understanding of drug dependencies and relapse and led, in Abe's lifetime, to a number of distinct approaches to both opiate and alcohol dependence based on these ideas.

For these and other contributions, Abe Wikler was given the Nathan B. Eddy Memorial Award in 1976 for excellence in Drug Abuse Research. The Abe Wikler I have just described is world famous and belongs to all of science.

Abe Wikler, the man - friend, colleague, teacher and collaborator - was known to a small circle. Those of us who came to the scientific meetings of the Committee on Problems of Drug Dependence were part of that more privileged circle, for Abe rarely missed these meetings. Each of us who knew Abe would probably have our own unique way of describing this complex man, but all would agree that Abe was a man of vast breadth of scientific and general interests. They ranged from the philosophy of science to pharmacology and included experimental psychology, electroencephalography, neurology, neurophysiology and all of general psychiatry. All this was in addition to a thorough knowledge of drug dependence in all of its manifestations.

To those of us whose first relationship with Abe was student to teacher, Abe was both stimulating and overwhelming.

While Abe had a lively sense of humor and enjoyed a good story, he found nothing humorous in sloppy thinking. Woe to the colleague, no matter how deep the friendship, who got the facts wrong, changed definitions in the middle of an argument, or simply used terms that were not defined operationally. For Abe usually knew the facts, had conscientiously mastered the literature, thought precisely, and defined all terms operationally.

Although he had an encyclopaedic knowledge of drug abuse, Abe seldom became involved in public debates about drug abuse. He did not often participate in high level policy making. He had little patience for the circumlocutions or self-serving behaviors that are the daily bread of politicians and administrators. As Ada put it - Abe didn't like flim-flam. He restricted his influence to his fellow scientists and physicians. These were manifestation of his immutable honesty and deep compassion. He believed that there was a natural order and

was committed to understanding it.

Abe had extraordinary powers of concentration. His preoccupations were from time to time taken as absent-mindedness. His absent-mindedness together with his humorous but sardonic characterizations created a rich store of Wikleriana.

He was a wonderful colleague and friend who was unfailingly kind and considerate. He took time to write detailed critiques of papers, letters of recommendation, and to drop delightfully descriptive hand-written notes from his sabbaticals. He was also a dedicated teacher who took great pride in his pupils and disciples.

Abe retired from the Public Health Service in 1963 to become Professor of Psychiatry and Pharmacology at the University of Kentucky. He continued to work a seven day week. Fifteen years later, he became Professor Emeritus. The second retirement finally changed his work habits - he no longer came into the office on Sunday.

Abe's last book Opioid Dependence, was published in 1980, just a few months- before he died. The preface was typically Wiklerian. It pointed out the tautological and untestable-nature of the pleasure-pain principle and other "unconscious intervening variables." It described drug dependence and the complex conditioning processes- that cause relapse as a "disease, sui generis." The term sui generis, meaning not like any other - unique - was *one* of Abe's favorites. Abe Wikler was many things - researcher, teacher, colleague, friend, father, husband. But above all, Abe Wikler was a scholar - sui generis.

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Introduction of Nathan B. Eddy Memorial Award Recipient

Louis S. Harris

It is a great pleasure and honor for me to introduce the recipient of this year's Nathan B. Eddy Memorial Award.

Everette Lee May was born on August 1, 1914, in a small town in Virginia. He received his baccalaureate degree from Bridgewater College and his Doctorate in Chemistry from the University of Virginia. After two years as a Research Chemist at National Oil Products, he joined the staff at the NIH in 1941, where he remained until he retired from the Public Health Service Officer's Corps in 1976 to join us as Professor of Pharmacology at the Medical College of Virginia, where he is continuing his distinguished career.

In his early years at the NIH, Dr. May made important contributions to our efforts to control malaria. His synthetic program with Erich Mosettig led to many new chemotherapeutic agents. In the early 1950s, Dr. May began his long collaboration with Nathan B. Eddy in the search for a non-addicting analgesic, a search which has continued to this day. It was during this period he first synthesized LAAM, and created the new benzomorphan series which has proved so fruitful.

Dr. May has contributed to the field of drug abuse, not only as a scientist, but through his service on numerous national and international committees and commissions. He served as Editor of the Journal of Medicinal Chemistry at a crucial period of its development. He is most proud of the host of young chemists who came to his laboratory for training and who are now having fine careers on their own.

Dr. May has been the recipient of many awards, the most noteworthy being:

1. The Hillebrand Award in Chemistry in 1968

2. The HEW Distinguished Scientist Award in 1974

3. The APA Research Award in Medicinal Chemistry in 1976

4. The ACS Smissman Award in Medicinal Chemistry in 1978

His career is summed up by the following citation:

> "Everette Lee May - humble, gentle man, brilliant, yet unassuming chemist, tirelessly searching for the non-dependence-producing analgesic. The Committee on Problems of Drug Dependence honors one of its most dedicated members."

The Committee on Problems of Drug Dependence—Past, Present, and Future
The Nathan B. Eddy Memorial Lecture

E. L. May

I am thrilled and highly honored to be the eighth recipient of The Nathan B. Eddy Memorial Award. It is especially gratifying to be joining such stalwarts as Seevers, Isbell, Wikler, Martin, Kosterlitz, Way and Goldstein. At the same time I stand here in deep humility, fully aware of the inestimable help and contributions of others, far too many to name in full. So, may I simply express heartfelt thanks to a few - those who nominated me; the Awards Committee who selected me; my former colleagues at the National Institutes of Health, especially Arthur Jacobson, Joe Ager and Kenner Rice; Louis Harris, William Dewey, Mario Aceto, Bob Balster, Billy Martin and their colleagues at The Medical College of Virginia; and finally my family, all of whom have always been supportive and understanding.

Concerning the man we honor today, a few anecdotes may be of interest. I knew him for nearly 40 years and was indeed privileged to be closely associated with him professionally and socially from 1941 until his death in 1973. He was a sensitive and proficient teacher, a wise counselor and a warm friend.

Dr. Seevers, in his address in 1974, spoke of Dr. Eddy's dedication, vitality and intellectual vigor, qualities maintained even after a severe illness (bacterial endocarditis) at age 64 left him with a nagging cardiac ,arrhythmia. Indeed, just four months before his death, on landing at Dulles Airport following a 10-day World Health Organization meeting in Geneva, he proceeded directly to Warrenton, Virginia to help "wrap up" The First International Conference on Narcotic Antagonists..

His horrendously bad eyesight was common knowledge and Dr. Isbell, in his 1975 lecture mused that it was surprising that he (Dr. Eddy) could see well enough to play expert bridge. I can tell you authoritatively that he not only knew his own hand well but also

the essential content of his partner's and opponents' holdings after a round or two of bidding. And, as his partner, it could at times be uncomfortable, even embarrassing. It was reliably recounted to me that on the Saturday before he died peacefully in his sleep the following Tuesday night, he and his partner twice bid and made a "grand slam" at the Cosmos Club in Washington, D.C., his favorite "hangout."

In pondering a topic and contents for my lecture, I was truly puzzled. If I talked about chemistry, only a few of you would be interested. And, needless to say, I cannot speak intelligently on pharmacology, biochemistry, psychology, medicine, socioloav and other disciplines represented in the audience. Thus, Ihave taken the easy way out of my dilemma and will try to tell YOU about the Committee on Problems of Drua Dependence - its genesis, a little of what it has been doing, and its possible future role. Perhaps in these reminiscences some of my own research and participation can be mentioned.

The Committee on Problems of Drug Dependence as we now know it was spawned as the Committee on Drug Addiction early in 1929 by The National Research Council (NRC), National Academy of Sciences (NAS). Its first meeting was January 12, 1929. This committee, unchanged except for the addition of two members, served until 1939. In May of 1929, the committee decided to develop a chemical-pharmacological-clinical research plan.

About this time, Lyndon Small, with Ph.D. training from Harvard, a brilliant alkaloid chemist and Assistant Professor of Research Chemistry at the University of Virginia, had just returned from two years of postdoctoral study with Dr. Heinrich Wieland of Munich, Germany. He accepted the directorship of the chemical effort (called the Drug Addiction Laboratory), and space was supplied by the Cobb Chemical Laboratory at the University of Virginia. Funds, at first not to exceed $50,000.00 per year, were from a 10-year Rockefeller grant to be administered by the NAS. Dr. Small and a few graduate students were to be concerned with chemical modification of the main ohenanthrene alkaloids occurring in opium-morphine. codeine and thebaine. A program involving <u>total</u> <u>synthesis</u> of partial or simulated structures of morphine was to be directed by Dr. Erich Mosettig, recruited by Dr. Small from Vienna.

Nearly a year later (June, 1930) when the need for pharmacological examination became pressing, a physician turned pharmacologist, Nathan Eddy, who had been teaching physiology and pharmacology at The University of Alberta, Edmonton, was appointed to head such a pharmacology program at The University of Michigan. It is not quite clear from Dr. Eddy's account just why Michigan was chosen as the site for his investigations, but it was probably because during part of the preceding two

years he had worked in the laboratory of Dr. Robert Gesell at The University of Michigan. In any event, Dr. Eddy came to Ann Arbor, June 1, 1930 and was given the title of Research Professor of Pharmacology with the rank of Associate Professor. Dr. Eddy, in addition to initiating base-line studies for morphine and codeine, served in a liaison role by visits to the University of Virginia and other centers of activity in the Committee's interest,including human evaluation at the Addiction Research Center (ARC) in Lexington, Kentucky. I had the good fortune to become a minuscule part of this program about 1935 when I enrolled in the Graduate School of Chemistry at Virginia and was accepted into Dr. Small's Laboratory with Dr. Mosettig as my research advisor.

From 1929-1939, at least 200 new compounds were prepared and evaluated. And although this effort was not productive of practical results, a fair amount of good basic chemistry evolved along with solid pharmacology and structure-activity

In addition to many journal publications, Supplement No. 138 to The Public Health Reports entitled "Studies on Drug Addiction", appeared in 1930 - authors: Small, Eddy, Mosettig and Himmelsbach.

The last full meeting of the Committee on Drug Addiction was held January 28, 1939, but it was agreed that (as a Division of Medical Sciences Committee of the NRC) it would continue in an advisory capacity. In June of the same year, Drs. Eddy and Small were recipients of the first Scientific Award of the American Pharmaceutical Manufacturers Association, presented by the Honorable Harry J. Anslinger, Commissioner of the Bureau of Narcotics, progenitor of the Drug Enforcement Administration (DEA). Dr. Eddy, in his acceptance remarks, noted that the award was an important recognition of the coordinated research sponsored by the Committee.

It was in June of 1938 that plans for transfer of the Virginia program to the National Institute (later to become Institutes) of Health (to continue the research of the Committee on Drug Addiction in continuing close association with the PHS Hospital at Lexington) began to take shape. This was mainly through the interest and efforts of PHS Surgeon General Thomas Parran, and Dr. Ross Harrison, Chairman of the NRC. So, at the close of business at Virginia about mid-1939, Small, Eddy and Mosettig moved to Washington, D.C. to resume their studies under governmental auspices with, as stated before, the Committee on Drug Addiction, serving in an advisory capacity.

With the outbreak of World War II and deep involvement of the United States late in 1941, malaria became a defense problem, so that efforts during the next five years were almost entirely devoted to this (malaria) project. Nevertheless, Dr. Eddy, with collaborators Sumwalt and Krueger, was able to complete (1941)

another PHS supplement on the "Pharmacology of the Opium Alkaloids." In addition, with Dr. Small and representatives from the pharmaceutical industry, the Bureau of Narcotics, the Public Health Services and the NAS Narcotics Advisory Committee, Dr. Eddy made arrangements for the manufacture, distribution and further clinical testing of metopon, a morphine relative which had been synthesized by Small and associates at Virginia.

In the meantime, some exciting reports were emanating from Germany relating the discovery of new, totally synthetic analgesics, pethidine and methadone and congeners. Methadone received especial attention because of its close pharmacologic similarity to morphine and because of a feared opium shortage. Consequently, the NRC-NAS at that time formed a (new) "Committee on Drug Addiction and Narcotics" (about 1947), "to deal with present and future problems relating to synthetic narcotics and drug addiction." The membership of the Committee included Dr. Isaac Starr of the University of Pennsylvania Medical School as Chairman; Dr. Eddy as Secretary, Mr. Anslinger and Drs. Raymond Bieter, Dale Cameron, Walter Palmer, Maurice Seevers and Lyndon Small as members. The first meeting of this committee was held October 2, 1947, at the NAS Building, Washington, D.C., and was attended by liaison representatives from the office of the Surgeon General of the Army, the Bureau of Medicine of the Navy, the Naval Medical Research Institute, the Food and Drug Administration (FDA), the American Medical Association (AMA) and the American Drug Manufacturers Association. This liaison relationship continued for many years.

With cessation of the malaria project, Dr. Eddy began a "mass" testing program for analgesics, refined the Wolfe-MacDonald, hot-plate method of testing for antinociception, and, I believe, began rather informally the coordination part of the then NAS-sponsored drug dependence program that has persisted to this day. Dr. Mosettig and I resumed our research in this area with operations on the methadone and isomethadone molecules and at length prepared all of the possible a and ß-methadols and isomethadols and their O-acetyl derivatives, some 24 compounds in all. These were tested subcutaneously and orally in the hot-plate method and for acute toxicity. One has become popular as LAAM, levoalphaacetylmethadol, as many of you know.

About 1952, we began our research at The National Institutes of Health (NIH) on the phenylmorphans and benzomorphans, which ultimately led to phenazocine, metazocine and indirectly to SKF 10,047, pentazocine and cyclazocine. The demonstration of vast differences in biological behavior of optical pairs and their corresponding racemates in these two basic series principally by Julian Villarreal of the University of Michigan, has proved interesting and is still being explored.

Time will not permit me to give the genesis of the research fund, the grants program, and the establishment of Dr. Seevers' depend-

ence studies in monkeys at Michigan about 1950. This is all well detailed in Dr. Eddy's book which he finished just before he died in 1973, "The National Research Council Involvement in the Opiate Problem, 1928-1971." Suffice it to say that the (world-wide) pharmaceutical industry has supplied until fairly recently most of the (fluid) funds for the committee with, however, substantial supplemental help by various government agencies, particularly The National Institute on Drug Abuse (NIDA). Eventually, Dr. Seevers' facility included a Beagle-dog colony for assessing barbiturate dependence. The program has grown steadily and there has been good coordination of effort among the NIH, The University of Michigan, The Addiction Research Center, The Veterans Administration and other various grantees, all under the NRC, NAS umbrella. Dr. Eddy retired from NIH in August, 1960 but continued as coordinator of the evaluation program. He also succeeded Dr. Isaac Starr as Chairman of the Committee in 1961 and was in turn, succeeded by Dr. Dale Cameron in 1962 at which time Dr. Eddy again became Executive Secretary. About the same time, I became a member of the Committee and succeeded Dr. Eddy as coordinator at NIH in 1965. Dr. Cameron, then Superintendent of St. Elizabeths Hospital in Washington, D.C., served as Chairman until 1967 and was succeeded by Dr. Henry Brill of New York State who served for three years. On July 1, 1965, the name of the Committee was officially changed to Committee on Problems of Drug Dependence (CPDD) to indicate an awareness of and interest in the increasing abuse of other types of drugs. According to Dr. Eddy's account the initial suggestion for such a change came from a paper written by Harris Isbell in which he used such terms as morphinism, cocainism, pharmacopsychosis, etc.

Dr. Eddy resigned as Executive Secretary in 1967, continued as a member until 1970 and became Chairman for a second term 1970-1971. He remained as a consultant until his death in 1973. Dr. Frank Fraser who, as many of you know, performed expertly at ARC for many years, was Chairman from 1971-1972 and was followed by Dr. Leo Hollister, our present Executive Secretary.

It was about this time that an evaluation program complementary to that at the University of Michigan was considered. Because of a gradually increasing influx of new compounds and the greater sophistication and time required to study the compounds being submitted, particularly the agonist-antagonists, Michigan facilities had become overloaded. Consequently, Drs. Harris and Aceto; at The Medical College of Virginia, established such a complementary program which has been in full operation since 1974. The coordination of effort and agreement of results in cases of deliberate overlap have been remarkable and gratifying. In retrospect, it was a timely move for another reason, coinciding with the slowdown and ultimate cessation of human testing for abuse potential at the ARC.

The Committee had the services of a salaried (by NRC-NAS) Executive Secretary, Mr. Duke Trexler, from 1969-1975 when NAS decided to relinquish sponsorship. Although such an action should not have been unexpected (as the average life of NAS committees is about three years), there was at least temporary distress and confusion within the Committee. Nevertheless, due principally to the tireless efforts of Chairman Hollister, interim Executive Secretary Theresa Harwood, committee members and no doubt the still pervasive spirit of Nathan Eddy, the Committee became independent and incorporated with backing by a consortium of nine prestigious scientific societies. Each society furnishes from its membership one person to serve on The Board of Directors. Otherwise, the Committee functions almost as before and has actually broadened its scope of operations to include in vitro binding and self-administration studies as well as a rodent-Infusion test for physical dependence liability.

In his award address in 1976, Dr. William Martin recited some of the accomplishments of the committee - studies and interpretations that helped pave the way for maintenance therapy and, for the development of new and improved antitussive and pain-relieving agents with reduced abuse liability. I should like to add a few to his here-abbreviated and paraphrased list: its considerable role in the classification of controlled substances, including pethidine and methadone which were uncontrolled until tested at Lexington; the stimulation and the promotion of basic research on drugs that affect the central nervous system (CNS), the discovery and characterization of the mixed agonists-antagonists, for example; and the sponsoring of clinical efficacy studies in which not only potentially useful compounds were fairly evaluated but new and improved protocols were developed. And when speaking of clinical trials, one can't help being reminded of Ray Houde who, with his colleagues Stanley Wallenstein and Ada Rogers, has performed admirably for the committee in his quiet and unassuming manner for at least 30 years. Other names that come to mind in the clinical area are Beecher, Keats, Lasagna, DeKornfeld, Lee, Belleville, Forrest and Brown; the last four associated with Veterans Administration grants from the Committee. I should say, too, that the "big five" at Lexington, Himmelsbach, Isbell, Fraser, Wikler and Martin, have had worthy successors in Don Jasinski and Chuck Gorodetzky, as have the "big three" at Michigan, Seevers, Deneau and Villarreal, in Hank Swain, Jim Woods and Tad Smith. Lou Harris, Mario Aceto, Bill Dewey and Bob Balster are competently handling operations at the Medical College of Virginia associated with CPPD activities; while Lou has served effectively as program chairman for 7-8 years, a considerable and, at times, delicate task. And finally, Arthur Jacobson as the biologic coordinator at NIH, sees to it that submitted compounds reach their proper destination, and then disseminates the test results as rapidly and tactfully as possible.

As implied before, the Committee served capably,I think, in an advisory capacity to the FDA, the DEA and The World Health Organization for many years. And while this function has been diminished during the last several years, because these bodies now have their own "standing" advisory groups, CPDD - generated data and opinions are still sought in difficult decisions. The CPDD is fortunate to have superb liason representation from FDA, DEA and NIDA in Ed Tocus, Howard McLain and Heinz Sorer, respectively.

The CPDD published an article, "Testing for Dependence Liability in Animals and Man." in 1966 which was revised in 1971 and will undergo a second revision soon. It co-authored, with the AMA, several position papers on such important subjects as "Methadone Maintenance," "The use of Opiates in Clinical Practice," and others.

So, here we are today and the burning question is'whither The Committee tomorrow?" Can it continue to be effective in assessing, for efficacy and abuse potential, agents that act on the central nervous system? Can it continue to stimulate research toward Dr. Eddy's goal of discovering the near-ideal pain-relieving agent? Can it help restore through advice and research the lost facility of testing for abuse potential in man? Can it continue, through its annual meetings, to serve as a proper forum for new research and ideas on CNS type drugs? And finally, can it continue to serve as a buffer between the pharmaceutical industry and government - in effect be the honest broker in developing new and improved medicines? We believe it can do all this and more.

Often, when I think of Dr. Eddy's scientific zeal and the dedication of the committee he "sparked" for so many years, I am reminded of a line from one of the poems of the great Alfred Lord Tennyson: "To strive, to seek, to find and not to yield."

AUTHOR

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Precursors of Addiction

David N. Nurco, D.S.W.

INTRODUCTION

Our topic, "Precursors of Addiction," is one about which much has been written, sometimes by-authors who did not even regard it as their major theme. Actually, the term 'precursors" is used cautiously in this context. The term "causes" would be obviously too presumptuous for a scientist to employ, although a number of popular scientific writers seem to suggest that they have identified the root causes, such as poverty and the insensitivity of society to the needy. Certainly, such sociodemographic factors play a role in the phenomenon, but we should never lose sight of the fact that the vast majority of persons in rather dire socioeconomic circumstances do not pursue careers in addiction. It is clear that certain other factors, still unknown or rather speculative at this time, must also be present before the phenomenon of addiction can manifest itself. Moreover, it is by no means certain that any given factor-, either known or unknown, is absolutely essential to the addictive process. Rather, it may be that different factors operate in different people, so that no universal requirements or sine qua nons for addiction exist.

Although available methodology does not permit as much rigor as we would like, we are prepared to lay a foundation in the search for the causes of addiction. Therefore, at this time we will settle for a softer term, "precursors." Note that a precursor merely suggests the presence of an association between an earlier and a later event, and that even this association might not be invariable in every case. In this sense, our use of the word "precursors" connotes an association perhaps even more tentative than that implied by the word "predictors."

Theoretical Background

Actually, comparatively little is known about the precursors of addiction in the sense of factors capable of distinguishing between subsequent addicts and nonaddicts in populations at high risk. Still, there is quite a sizable literature on closely related

topics, and we shall attempt to review this literature briefly here under the appropriate topical headings.

Social and Demographic Formulations. Much of the sociological literature has emphasized the relationship of "known narcotic addiction" to social conditions that may, in part, lead to deprivations of various sorts (Chein et al. 1964; Shaw 1942). Several such conditions are associated with the "urban crisis," including poor housing; crowding; low socioeconomic status and lack of social mobility; family disorganization, typically manifested in broken families and low levels of cohesion; and minority group membership. The latter point has clearly been demonstrated by the disproportionate representation of Negroes, Puerto Ricans, and immigrants in the addict population (Chein et al. 1964). According to several writers, it is for the above reasons that we find concentration of drug addicts in urban centers.

Unfortunately, the current literature leaves unanswered many important and relevant questions related to, or flowing from, the above relationships. For example, granted that addicts are concentrated in the deprived and disorganized strata of the populations of large cities, the question remains as to whether or not they originated in these same strata. Were they born and reared there, is there a "drift" so that addicts, or persons in a pre-addict stage who subsequently became addicts, moved into these levels from elsewhere? Kleinman (1978), in a searching attempt to predict onset of addiction, has reported that social class has a marked effect on (young) age of addiction among inner-city (ghetto) natives, but virtually no effect among migrants to the city. Thus, it appear that a form of acculturation is a necessary precondition for the effects of social class to operate.

Even where social class precursors appear strong, why is it that some children born into lower strata become addicts while others do not? Was there something different in the socialization process among those who subsequently became addicts as compared to those who did not? And did this "something different" manifest itself in differential patterns of overt behavior which can be identified by the usual techniques of social-research?

It may be that differences in the impact of the socialization process are a function of the perceptions of the individuals involved, Thus, individuals can be subject to similar life experiences, and yet each may define these experiences differently. For example, an addict and a nonaddict may both have been brought up under similar socio-economic circumstances, yet it is entirely possible that each will have defined these circumstances differently.

Chein et al. investigated this question, but their findings were inconsistent, i.e., they found that while black users of drugs were more deprived in a material sense than were nonusers, this relationship did not hold for whites and Puerto Ricans in their study. (Controls were selected from the same types of neighborhoods as users of drugs.) However, it is possible that the important variable may be the perception of socio-economic status

rather than its reality. The crucial point may be whether addicts, prior to entering on a "career" of addiction, defined themselves as deprived rather than whether they were, in fact, deprived. Also, the perceived deprivation may extend to matters other than socio-economic status, including various aspects of family functioning such as maternal &privation and chronic absence of father; health; physique; ability to "fight" or perform other activities socially valued by peers and others in the reference groups; sexual adequacy; etc.

Interpersonal Relationship Theories. Let us next consider a set of variables usually termed interpersonal (as distinguished from intrapersonal) and some theories relevant to drug abuse that might be classified according to this rubric.

In (Dollard et al. 1939), he and his associates postulated a relationship between frustration and aggression, on the one hand, and criminality, on the other. They wrote:

> All factors which have been found to be causally related to criminality derive this connection because of implying, directly or indirectly, on the part of the offending individual either higher-than-average frustration or lower-than-average anticipation of punishment.

More recently, Berkowitz (1965) has suggested that a person does not have to be frustrated to engage in aggressive acts. One might also add that frustration may lead to reactions other than agression. Haner and Brown (1955), for example, reported a study in which children frustrated in the playing of a game responded by increased goal-directed activity. With respect to theories of drug abuse etiology, it may be that frustrating experiences are responded to more frequently in a more aggressive-destructive or passive-withdrawing way by certain deviant groups than by "normal" individuals.

The second part of Dollard et al's, statement is frequently supported by observations and other research data obtained from drug addicts. Information concerning, early memories reflects, in many instances, the experience of "getting away with" infractions (Laskowitz 1965). There is also said to exist, for a large segment of the known, young, narcotic-using population, a background of unstable, pampering attitudes on the part of the mother, possibly linked to a compensatory need to make allowance for the son not having a stable, significant role in the home. Moreover, researchers have noted the reports of parents of addicts that as preaddicts they did not participate in performing household chores (Chein et al. 1964).

It may be that narcotic use has appeal both for those individuals whose life style includes avoidance of frontal displays of anger toward the frustrating object as well as for those who are unable to tolerate feelings of anger and tend to explode with little provocation. The first group would seem to be one described as "retreatist" by Merton (1957), since such persons behave as though they have relinquished institutionally-prescribed ways for pursuing

goals as well as the goals themselves. This is the group which Cloward (1959) described as turning to drugs as a "coping" defense, and such persons appear to be the ones most likely to report feelings of enhanced competence when they are "high."

In an effort to study adolescents' preferred response to frustrations, Gold (1960) used the Rosenzweig Picture Frustration Test (a projective technique composed of 25 cartoon-like pictures, each depicting two persons involved in a mildly frustrating situation) and compared the verbal responses of adolescent addicts with those of delinquent and nondelinquent controls. His results, which corroborated an earlier study by Diamond, suggested that addicts typically tend to avoid blame and try to gloss over frustrating situations.

Intrapersonal Psychological Traits. While the group of theories lmmediately preceding may be viewed primarily as interpersonal, in the sense that an interaction between the individual and significant others is assumed as the principle underlying their operation as well as their genesis, a second class of theories may be viewed as primarily intrapersonal or trait theories, in the sense that the individual is viewed as the "carrier" of certain psychological traits or predispositions that may operate or exist independently of the presence or actions of others. This is not to deny the role of social interaction in either the genesis or expression of such traits; it is merely a question of emphasis in that the focus of interest is on the individual as an individual, rather than as an element in a larger functioning system.

There can be no doubt that the vast majority of theories having relevance to the etiology of drug abuse are primarily intrapersonal, or psychological trait theories. (Essentially synonymous terms preferred by some theorists are personalogical or characterological theories.) Such theories vary greatly in level of complexity, scope, and sophistication. A very few may be regarded as general theoretical systems, such as those of Freud (1920), Murray (1938), Cattell (1957), and Eysenck (1967); however, the overwhelming majority have reference to a single dimension, trait, or characteristic that is purported to have considerable salience for some domain of human behavior.

It is perhaps most convenient to begin by considering a sizable body of literature concerning the personality characteristics of drug abusers. Although helpful in many ways, these studies are largely irrelevant from the point of view of drug abuse etiology. We refer, of course, to the many studies of the personality characteristics of adult and jwenile drug abusers as revealed by a variety of questionnaires and other devices. This literature has recently been reviewed in detail by Haertzen (1978). The reason for the substantial irrelevancy of this research to issues of etiology is the fact that, with few-exceptions, subjects have been studied and groups compared after the fact, i.e., after the syndrome of drug abuse has, by definition, been firmly established.

Consequently, as Fox (1978) has pointed out in another context, it is impossible to know for a certainty whether trait differences observed between drug-abusing and nondrug-abusing groups are causes, effects, or concomitants of the behaviors in question. Fortunately, a few studies of a prospective (Robins and Wish 1977) and retrospective (Robins et al. 1970) nature provide evidence consistent with the view that certain personality characteristics antedate the appearance of the behavior subsequently defined as deviant; therefore, there would seem to be considerable circumstantial evidence that the distinguishing personality characteristics of at least some drug abusers existed prior to the abuse of drugs per se.

Perhaps the most widely used instrument in the drug abuse field to measure personality traits has been the Minnesota Multiphasic Personality inventory (MMPI) (Hathaway and McKinley 1967). Moreover, a number of additional inventories may be viewed as "spin-offs" of the MMPI, such as the California Psychological Inventory (CPI)(Gough 1957) and the Addiction Research Center Inventory (ARCI) (Haertzen and Hill 1963). To a lesser extent, several studies have employed the Sixteen Personality Factor Questionnaire (16PF) (Cattell and Eber 1961) and the Eysenck Personality Inventory (EPI) (Eysenck and Eysenck 1964). With respect to the MMPI, the typical addictive personality pattern that emerges is usually interpreted as one of psychopathic or antisocial personality, as indicated by primary peaks on the Pd (Psychopathic Deviate-Scale 4) and Ma (Hypomania-Scale 9) scales. Secondary peaks on scales Sc (Schizophrenia-Scale 8) and D (Depression-Scale 2) are sometimes noted as well, but elevations on the latter are frequently a function of current circumstances, e.g., economic conditions , incarceration, treatment status, etc. On the other hand, scales 4 and 9 are thought to tap more enduring, characterological traits, and for this reason they are frequently regarded as revealing the essence of any trait commonalities among addicts in general. Interestingly enough, this description appears applicable to alcohol addicts as well, although the relationships may not be quite so pronounced (Hill et al. 1962). With respect to the CPI, addicts are said to score low on measures of responsibility and socialization (Haertzen 1978). On the 16PF, there is evidence that addicts as a group significantly exceed the standardization norms on Scale C (emotionally unstable), Scale L (suspecting and jealous), Scale M (eccentric and unconcerned), and Scale O (insecure and anxious) . These characterizations are both internally-consistent and in keeping with clinical formulations and observations made over the years by numerous workers in the drug abuse field (Nurco 1979). It must be emphasized once again, however, that nearly all such research has been conducted with already confinned drug abusers, and hence it is of dubious value as a basis for prognostic indicators of later outcome, i.e., as the basis for assembling "risk factors" in the prospective study sense.

Single Principle Theories. We next consider a variety of "limited" Theories or hypothetical mechanisms thought to be characteristics of at least some narcotic users and possibly causative of their addictive conditions. Each of these theoretical constructs is unidimentional, i.e., involves a single explanatory principle, and can therefore hardly be viewed as a comprehensive theory of behavior

even in the addictive realm. Nonetheless, it seems possible that one or more of these constructs may possess some validity as both an explanation for addictive behavior and as a specification of a necessary pre-condition for such behavior to occur.

i. The Immediate Gratification Hypothesis. It has become commonplace to observe that an important factor in deviant behavior appears to be the very great difficulty certain persons experience in deferring gratification. This factor seems to be of particular importance in the life styles of addicts. Sullivan (1953) suggests a conceptual basis for the emergence of this trait: "Delays in satisfaction constitute dangers to early infantile survival and as such are sources of augmented tension to which we refer as fear." Addicts appear to behave as if the tensions of unfulfilled wants create an unbearable situation. Waiting becomes unbearable because future gratification cannot be guaranteed. Moreover, addicts and other deviant groups appear to have an inability to trust persons in authority, e.g., they do not appear confident that others will operate in their best interests. Mischel (1961) has suggested that preference for delayed rather than immediate reward may be associated with significant differences in maturity, social responsibility, long-term goal direction, autonomy, and father's presence during the formative years.

ii. The Disturbance in Sexual Identification and Functioning Hypothesis. Following Chein et al. (1964), it has been hypothesized that addicts, even prior to their entering upon a "career" of addiction, are-likely to experience problems in the establishment of personal identity, and that these problems will manifest themselves in an inability to establish an adequate sexual identification. This inadequate sexual identification is said to be evident in a confusion as to gender and an ineptness in carrying out sex-related roles.

With regard to the latter, addicts are said to display poor performance in major life roles, e.g., occupational, educational, and familial. Moreover, male addicts may not share concepts of the self which are associated with male self-images in American culture, e.g., power, strength, competence, effective and appropriate assertiveness, and responsibility as provider, father, and head of household. Even in the preaddict phase, males may show signs of being passive and dependent, Also, they show disturbances in mutual interpersonal relationships related to reciprocity, i.e., giving and taking. They may also tend to feel that they are being manipulated, but that they rarely manipulate others.

Addicts may be likely, early in their lives, to show real confusion as to gender. This may be particularly evident during adolescence, but it may also appear at an earlier stage of development. The symptoms of this confusion may be evident in a concern over the adequacy of their sexual performance and a profession of disinterest in sexuality, or at least an indication that it is unimportant in their system of values.

Chein et al. (1964) offer case materials to support these hypotheses. However, most of their material pertains to addicts after they become addicts: It would therefore be important to elucidate symptoms of disturbance, as characterized by differences in sexual behavior, both before and after addiction.

iii. The Risk-Curiosity Hypothesis. Curiosity is typically regarded as a natural and healthy attribute in nearly every culture. However, the potential addict is said to be driven by insecurity and inadequacy of a sexual nature, such as described by Chein et al. (1964) and others, in that sexual identification with a member of the same sex for the addict is incomplete. Thus, the addict may be more likely to take chances (risks) when it is inappropriate to do so. Our own research in this area suggests that addicts, when talking about their preaddiction behavior, often emphasize the chances they have taken and the fights they have engaged in, all of which gives-the impression that they are trying to prove themselves. Thus it may be that the preaddict is more likely than his peers to take the risk involved in opiate experimentation, perhaps the biggest risk of all.

iv. The Boredom-Relief Hypothesis. This explanatory principle invokes the concept of boredom. Many individuals experience extreme boredom, which can lead to both depression and an inability to function. One mechanism for fighting off such boredom is the frantic pursuit of almost any activity. Applied to narcotic addiction, such a mechanism provides. a "double reinforcement" rationale: In seeking narcotics, the addict runs about filling up his day with "taking care of business" and thus alleviates boredom with these activities. After the individual has taken the narcotic, the drug experience itself removes the boredom and the cycle is further strengthened and repeated.

The foregoing proposed explanatory principles are, quite obviously, seriously limited insofar as their being comprehensive theories of human behavior is concerned. Nonetheless, they may, in a limited capacity, serve as indicators or "markers" for a more general, integrated theory of behavior that has yet to emerge. In this context, it might be well to point out that the disturbed sexual identification hypothesis, and to some extent the withdrawal-retreatism hypothesis before it, are descendants of a quasi-psychoanalytic tradition that seeks causality in certain theories of psychopathology (Freud 1920). To a lesser extent, this is also true of the frustration-aggression hypothesis of Dollard et al. (1939). On the other hand, the immediate gratification, risk: curiosity, and boredom-relief hypotheses may all be subsumed under a more general personality trait conception which emphasizes a deficiency of impulse control. Such a conception has been common among European theorists since before the time of Jung (1924), although his notion of introversion-extraversion is perhaps the best known variant.

Economic and Political Formulations. Although the operation of economic and sociopolitical factors are implicit in the social and demographic formulations previously discussed, no discussion of

these matters would be complete without reference to the radical, sociopolitical analysis of the addiction street-crime syndrome provided by Karmen (1974). Kannen characterizes both the heroin addict and the victim of his criminal activities as the joint victims provided by the illicit drug industry complex. Karmen's paper can be read with profit even by those who do not subscribe to his political views, primarily for the insights it provides into the complex symbiotic relationships among the various legal and illegal components present in any society.

Genetic Predispositions. Even the most casual reader of scientific journals concerned with the understanding and treatment of deviant behavior could hardly fail to be impressed by the increasing number of articles in which genetic explanations and formulations of the behavior in question are advanced. In addition to the exemplary work of Rosenthal (1971 and 1970), Rosenthal and Kety (1968), and Kety (1959) with respect to the major psychoses, Guze and his colleagues (1973) with respect to hysteria, and Eysenck (1967) and Miner (1973) with respect to. neurosis, there is also the prominent work of Gottesman (1962, 1963) and Gottesman and Shields (1971), among many others. Loehlin and Nichols (1976) have also explored the heritability of various traits within what might be considered the normal range, as had Gottesman (1963) earlier. Almost needless to say, substantial genetic contributions to the traits, syndromes, or behaviors in question have almost invariably been found.

With regard to the area of drug and alcohol abuse, somewhat less work along these lines has thus far been accomplished, although the work of Goodwin et al. (1973) with alcoholics is a notable exception. Moreover, Dole (1978) has stated his belief that a specific biochemical abnormality will eventually be discovered among addicts. It is interesting to note in this connection that (partial) genetic explanations of addictive behavior flow naturally from intrapersonal trait theorizing, especially since various traits have been shown to have substantial genetic loadings (Crowe 1972; Cancro 1971). Perhaps this demonstration has been most striking with respect to extraversion (Gottesman 1963), the very trait most frequently implicated in addictive behavior and the one most closely tied to a physiological basis in Lester's (1974) formulation.

It is well known that narcotic addiction is a far rarer phenomenon in most white subcultures than in black ones. In addition, there is evidence that white narcotic addicts were involved in more deviant behavior than were blacks prior to the onset of-addiction. Therefore, as we investigate the theories presented in this paper, we expect to find that those theories relating to psychopathology are more appropriately applied to whites, while those relating to sociological factors are more appropriately applied to blacks,

REFERENCES

Berkowitz, L. The concept of aggressive drive: some additional considerations, In R. Berkowitz (Ed.), Advances in Experimental Social Psychology (Vol. II) . New York: Academic Press, 1965.

Cancro, R. Intelligence: Genetic and Environmental Influences. New York: Grune & Stratton, 1971.

Cattell, R.B. Personality and Motivation Structure and Measurement. New York: World Book Company, 1957.

Cattell, R.B, and Eber, H. The 16 Personality Factor Questionnaire (3rd Edition). Champaign, I11.: Institute for Personality and Ability Testing, 1961.

Chein, I., Gerard, D.L., Lee, R.S., and Rosenfeld, E. The Road to H: Narcotics, Delinquency, and Social Policy. New York: Basic Books, 1964.

Cloward, R. Illegitimate means, anomie, and deviant behavior. American Sociological Review, 1959, 24, 174-176.

Crowe, R.R. The adopted offspring of women criminal offenders. Archives of General Psychiatry, 1972, 27, 600-603.

Dole, R. A clinician's view of addiction. In J. Fishman (Ed.) The Bases of Addiction: Report of the Dahlem Workshop on the Bases of Addiction. Berlin: Abakon Verlagsgesellschaft (in Komm.), 1978.

Dollard, J., Doob, L., Miller, N., Mowrer, O.H., and Sears, R.R. Frustration and Aggression. New Haven, Conn.: Yale University Press, 1939.

Eysenck, H.J. The Biological Basis of Personality. Springfield, Ill.: Charles C. Thomas, 1967.

Eysenck, H.J., and Eysenck, S.B.G. Manual of the Eysenck Personality Inventory, London: University of London Press, 1964.

Fox, B.H. Premorbid psychological factors as related to cancer incidence. Journal of Behavioral Medicine, 1978, 1, 45-133.

Freud, S. A General Introduction to Psycho-Analysis. New York: Liver-wright, 1920.

Gold, L. Reaction of Three Differential Groups of Adolescents to Frustration. Unpublished Ph.D. dissertation, New York University, 1960.

Goodwin, D.W., Schulsinger, F., Hermansen, L., Guze, S.B., and Winokur, G. Alcohol problems in adoptees raised apart from alcoholic biological parents. Archives of General Psychiatry, 1973, 28, 238-243.

Gottesman, 1.1. Differential inheritance of the psychoneuroses. Eugenics Quarterly, 1962, 9, 223-227.

Gottesman, I. I. Heritability of personality: A demonstration. Psychological Monographs, 1963, 77 (9).

Gottesman, I., and Shields, J. Schizophrenia and Genetics. New York: Academic Press, 1971.

Gough, H.G. California Psychological Inventory Manual. Palo Alto, California: Consulting Psychologists Press, 1957.

Guze, S.B. Hereditary transmission of psychiatric illness. American Journal of Psychiatry, 1973, 130, 1377-1378.

Haertzen, C.A. Historical view of characteristics of addicts. In W.R. Martin and H. Isbell (Eds.), Drug Addiction and the U. S. Public Health Servide. Proceeding of Symposium Commemorating the Fortieth Anniversary of the Addiction Research Center at Lexington, Ky. Rockville, Md.: DHEW Pub. (ADM) 1978, 77-434.

Haertzen, C.A. and Hill, H.E. Assessing subjective effects of drugs : an index of carelessness and confusion for use with the Addiction Research Center Inventory (ARCI). Journal of Clinical Psychology, 1963, 19, 407-412.

Haner, C.F. and Brown, P.A. Clarification of the instigation to action concept in the frustration-aggression hypothesis. Journal of Abnormal and Social Psychology, 1955, 51, 204-206.

Hathaway, S.R., and McKinley, J.C. The MMPI Manual. New York: The Psychological Corporation, 1951; revised 1967.

Hill, H.E., Haertzen, C.A., and Davis, H. An MMPI factor analytical study of alcoholics, narcotic addicts, and criminals. Quarterly Journal of Studies on Alcohol, 1962, 23, 411-431.

Jessor, R., and Jessor, S.L. Problem Behavior and Psychosocial Development : A Longitudinal Study of Youth. New York: Academic Press, 1977.

Jung, C.J. Psychological Types. London: Routledge & Kegan Paul, 1924.

Kandel, D.B. Longitudinal studies of drug use: An overview. In D. B. Kandel (Ed.), Longitudinal Research on Drug Use: Empirical Findings and Methodological Issues. Washington, D.C.: Hemisphere (Halstead-Wiley) , 1978.

Karmen, A. The drug abuse--crime syndrome: A radical critique. In C. Winick (Ed.), Sociological Aspects of Drug Dependence. Cleveland: CRC Press, 1974.

Kety, S.S. Biochemical theories of schizophrenia. Science, 1959, 129, 1528-1532.

Kleinman, P.H. Onset of addiction: A first attempt at prediction. International Journal of the Addictions, 1978, 13, 1217-1235.

Laskowitz, D. Psychological characteristics of the adolescent addict. In E. Aarms (Ed.), Drug Addiction in Youth. Oxford: Pergamon Press, 1965.

Lester, D. A Physiological Basis for Personality Traits. Springfield, Ill.: Charles C. Thomas, 1974.

Loehlin, J.C., and Nichols, R.C. Heredity, Environment, and Personality. Austin, Texas: University of Texas Press, 1976.

Merton, R.K. Social Theory and Social Structure. New York: Free Press, 1957.

Miner, G.D. The evidence for genetic components in the neuroses. Archives of General Psychiatry, 1973, 29, 111-118.

Mischel, W. Father absence and delay of gratification: A cross-cultural comparison. Journal of Abnormal and Social psychology, 1961, 63, 116-124.

Murray, H.A. Explorations in Personality: A Clinical and Experimental study of fifty Men of College Age. New York: Oxford University Press, 1938.

Nurco, D.N. Etiological aspects of drug abuse. In R. L. DuPont, A. Goldstein, and J. O'Donnell (Eds.), Handbook on Drug Abuse. Washington, D.C.: U. S. Government Printing Office, 1979.

Nurco, D.N., Cisin, I.H., and Balter, M.B. Addict careers: I. A New typology. International Journal of the Addictions, 1981, 16 (6).

Nurco, D.N., Cisin, I.H., and Balter, M.B. Addict careers: II. The first ten years. International Journal of the Addictions, 1981, 16 (7).

Nurco, D.N., Cisin, I.H., and Balter, M.B. Addict careers: III. Trends across time. International Journal of the Addictions, 1981, 16 (8).

Robins, L.N., Darvish, H.S., and Murphy, G.E. The long-term outcome for adolescent drug users: A follow-up study of 76 users and 146 non-users. In J. Zubin and A. Freedman (Eds.), Psychopathology of Adolescence. New York: Grune & Stratton, 1970, 26.

Robins, L.N., and Wish, E. Childhood deviance as a developmental process: A study of 223 urban black men from birth to 18. In M. F. McMillan (Ed.), Child Therapy: Treatment and Research. New York: Bnmner-Mazel, 1977.

Rosenthal, D. Genetic Theory and Abnormal Behavior. New York: McGraw-Hill, 1970.

Rosenthal, D. Genetics of Psychopathology. New York: McGraw-Hill, 1971.

Rosenthal, D., and Kety, S.S. The Transmission of Schizophrenia. London: Pergamon Press, 1968.

Shaw, C., and McKay, H. Juvenile Delinquency and Urban Areas. Chicago: University of Chicago Press, 1942.

Sullivan, H.S. The Interpersonal Theory of Psychiatry. New York: Norton, 1953.

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Developmental Epidemiological Studies of Substance Use in Woodlawn: Implications for Prevention Research Strategy

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DEVELOPMENTAL EPIDEMIOLOGICAL STUDIES OF SUBSTANCE USE IN WOODKLAWN IMPLICATIONS FOR PREVENTION RESEARCH STRATEGY

by S.G. Kellam, C.H. Brown, and J. Flemming

Effective prevention program directed at substance use require that specific antecedents in the life course be identified and their functions in the paths leading to use or nonuse determined. Aimed at reducing these risk factors, specific interventions can then be tested experimentally.

Scientists have looked askance at the possibilities of preventing substance abuse in the specific sense jUst described, believing that our knowledge is far too insufficient to warrant such an undertaking. It may be time, however, to examine the status of our information regarding the early and evolving paths leading to substance use and other important outcomes.

We examine in this paper the data from other laboratories regarding antecedents of teenage substance use, as well as data from the Woodlawn studies. The Woodlewn data l re longitudinal and prospective and concern antecedents in first grade of teenage substance use 10 years later when the study population was 16 or 17 years old. These data were gathered in l black, urban, poor community on the South Side of Chicago. We will focus our discussion section on a research strategy leading to validated programs for the prevention of substance use.

A life-span developmental orientation provides an important framework for longitudinal research About such remote origins. Baltes, Reese, and Lipsitt (1980) describe three perspective which comprise this orientation. The first is that of individuals' socialization and development. The second is concerned with cohort effects and refers to evolving societal patterns of behavior and values as these influence the behavior of individuals. The third perspective concerns those idiosyncratic events which influence an individual's behavior without necessarily affecting the broad population of which the individual is a member.

Longitudinal research about substance use involves each of these perspectives. Some studies involve combinations of the three; others focus mainly upon one or another perspective. The early and evolving psychological and biological characteristics of the individual will be important in longitudinal research on use. The social structural context in which the person develops and is socialized over time must also be part of our purview.

An important perspective, one that has been central in the Woodlawn project from its beginning, is that of the Social adaptation of individuals. By this term we mean the adequacy of role performance of the individual in a particular social field at a particular stage of life. Social adaptation refers to the interaction between the natural raters who define the social tasks in particular social fields and the individual's responses to these social task demands. It is here that many of the currently known antecedents can be found, as the reader wi1l see.

We summarize our work and that of others on the antecedents of teenage use of alcohol, marijuana, and cigarettes. Our own data were gathered prospectively in Woodlawn on total populations

of first-grade children in this poor, black, Chicago ghetto community in consecutive cohorts in the 1960s. We will focus on the 1966-67 first-grade children regarding their psychological well-being and social adaptational status in first grade. These children and their families were followed up 10 years later when they were age 16 or 17. These data are community epidemiological in that they were gathered on total populations within a particular urban neighborhood and include a set of outcomes as well as hypothetically important causes and mediators. Since the data are prospective, the risk of distortions from after-the-fact reporting is eliminated.

The Woodlawn Study Population

Between 1964 and 1969 we made assessments of the mental health of all the first-graders in Woodlawn at several points in each school year. Further assessments were made on samples of these children in third grade. We also conducted interviews in spring of 1965 and spring of 1967 with the mothers (or mother surrogates) of the children who were in first grade in those two years. These assessments were coupled with service and evaluation programs (Kellam, Branch, Agrawal, 6 Ensminger, 1975) and were supported by a community board composed of leaders from the community's larger citizen organizations in all of these service and research ventures (Kellam & Branch, 1971; Kellam, Branch, Agrawal, & Crabill, 1972).

For 'the long-term follow-up study, the target population has been the entire first-grade population of 1966-67, the 1,242 students who remained in the Woodlawn first-grade classrooms that school year, together with their families.

In 1975-76, we located and reinterviewed 939 (75%) of the mothers or mother surrogates of the 1,242 families from the 1966-67 study. The mothers' refusal rate was 5.9%. An additional 18.5% of mothers were not reinterviewed because we could not find them, because the families had moved from Chicago, or because their children from the study population were deceased. After the mother was interviewed and had given permission, the teenager was approached for reassessment. Of the 939 teenaged children of the reinterviewed mothers, 75% (n=705) participated in the reassessments. The study population for this paper consists of the 705 teenagers whom we reassessed (Agrawal, Kellam, Klein, and Turner, 1978).

In order to assess possible bias resulting from sample. attrition, we compared the mothers whom we reinterviewed with those we did not, using the early information. we had on both. We found little or no difference in the social adaptational status or psychological well-being (the variables of interest here) between children reinterviewed and those not reinterviewed. (See Kellam, Ensminger, and Simon, 1980.)

A Two-Dimensional View of Mental Health

In the Woodlawn studies, we have distinguished between two broad classes of outcomes: social adaptational status (or role performance) and psychological status. While the two may be empirically related (and in the Woodlawn research we found this to be the case), they are nevertheless conceptually quite

distinct, and their correlates and consequences are by no means identical. Many more first-grade children were thought by their teachers to be maladapting than were symptomatic in the view of observing clinicians. The short- and long-term courses of social adaptational status and psychological well-being were strikingly different. Other investigators (Loney, 1980; Robins, 1966; Watt, 1978) have reported similar findings.

Social Adaptational Status

In considering social role performance we have developed the Life Course-Social Field Concept (Kellam et al., 1975) based on the theoretical writings of Havighurst (1952), Erikson (1959, 1963), and Neugarten (1968). Every individual in society passes through stages of life, some of which are more clearly defined than others (Neugarten, 1979). Each stage involves that individual in specific social fields in which there are persons who define social tasks and judge the adequacy of the individual's performance in that field. Such persons, whom we have termed "natural raters," are similar to Lippitt's "socialization agents" (1968). The parents at home, the teacher in the classroom, and the foreman at work are examples of such natural raters in specific social fields. The process involved is highly interactional, and we have named it social adaptation.

The natural raters rate the adequacy of each individual's performance, sometimes formally as teachers do with grades and sometimes informally as parents judge how well their child is behaving. Social adaptational status (SA)--the adequacy of performance as rated by the natural rater in a specific social field--is a societal judgment of the individual's performance. This approach is an elaboration of Parsons's (1964) concept of role performance as the adequacy with which an individual meets the expectations of social roles. We conceive of this interactional process as the basic interface between the individual and society.

Psychological Well-Being

In contradistinction to SAS, there is the question of how the individual is feeling inside: his or her psychological well-being (PWB). By PWB we mean the thought processes, affective status, self-esteem, and other aspects of the psychological status of the individual. These two components--SAS and PWB--represent the two major dimensions of mental health. One represents mental health from the viewpoint of society; the other represents mental health from the viewpoint of the individual.

Past findings have suggested that first-grade SAS has very important long-term predictive and possibly developmental significance for adolescents (Kellam et al., 1975; Kellam, Brown, & Fleming, in press-a; Kellam, Ensminger, Branch, Brown, & Fleming, in press-b; Kellam, Ensminger, & Simon, 1980; Kellam et al., in press-c). These findings are consistent with those reported by Robins (1966) in her studies of the long-term importance of early acting-out behavior to adult pathology and criminality. Watt (1978) has reported that aggressiveness in young males appears to be an early antecedent of adult

schizophrenia. Similarly, Loney (1980) has shown evidence that early aggressiveness is the component of the hyperactivity syndrome which is most prognostic of later outcome. It should be clear from the earlier discussion that aggressiveness as defined by fighting and breaking rules would fall within the social meladaptational area rather than psychological.

Other Longitudinal Studies of Drug Use

The present review is focused on studies which have employed longitudinal research designs, but does not include the Woodlawn studies, since these will be treated specifically in a later section.

Psychological Predictors

Psychological distress has been found important by a number of researchers (Smith and Fogg, 1978) ; Paton, Kessler, and Kandel, 1977; Kaplan, 1975). The perceived use by others is an important psychological-predictor (Jessor and Jessor, 1978; Robins, Davis, and Wish, 1977; Kandel et al., 1978). In a series of related findings Kandel et al. (1978), Sadava (1973), and Smith and Fogg (1978) have all established that favorable attitudes toward substance use are predictive of the initiation of use. Attachment to or alienation from this society's social values and institutions generally show a consistent relationship to substance use (Jessor and Jessor, 1978; Sodava, 1973; Smith and Fogg, 1978; Kandel et al., 1978).

Social Adaptational Predictors

The second major grouping of predictive variables is social adaptational status. A number of investigators have reported that poor high school performance is a common antecedent of substance use (Jessor and Jessor, 1978; Kandel et al., 1978; and Smith and Fogg 1978). In contrast, a study by Mellinger, Somers, Bazell, and Manheimer (1978) indicated that marijuana use by college students was associated with higher grade point averages. Finally, Johnston (1973) reported that although the high school students who used marijuana and hallucinogens tended to have lower grade point averages, they had higher general intelligence.

Smith and Fogg (1978) have found that self-report and peer ratings of obedience were predictive of future marijuana use and were among the best predictors in a discriminant analysis of nonusers, early users, and late users. Looking at a very different form of social behavior, these investigators also report that peer ratings of tenderness show a negative relation to the initiation of marijuana use.

We find consistency across studies in regard to anti-social or aggressive behavior which is possibly one of the strongest predictors of substance use (Johnston, 1973; Johnston, O'Malley, & Eveland, 1978; Kandel et al., 1978). Robins (1978) summarizes her and her colleagues' consistent findings from three independent investigations of the relation between childhood and adolescent antisocial behavior and adult outcomes (Robins, 1966; Robins & Murphy, 1967; Robins et al., 1977). Across all study populations there was a reliable association between early

fighting, truancy, arrests, and drinking and adult alcoholism and later drug abuse. Antisocial behavior was a better predictor of adult outcomes than any family variable.

Sample Populations and Community Epidemiology

The prospective longitudinal study of so-called normal populations is a major methodological advance over the early studies which examined only clinical populations of addicts, either at a single point in time or through retrospective reports (e.g., Ball & Chambers, 1970; Stephens & Cottrell, 1972; Vaillant, 1966). As Kandel (1980) has pointed out, clinical populations of addicted individuals found in hospitals or even outpatient clinics represent very special subgroups of the population of drug users.

Although these newer studies of general population samples have facilitated our understanding of substance use, they too have limitations. One is that almost all these studies have investigated students in junior or senior high school or in college. Those who have dropped out of school are systematically excluded. As the results of the Woodlawn study will demonstrate, important antecedents to future substance use can be found most effectively in total rather than school populations. In addition, important predictors predate the adolescent developmental period and may only be found by using long-term prospective data. An important problem in past research has been the scarcity of such longitudinal studies of well-defined ethnic and social class groups.

In community-specific epidemiological studies such as the Woodlawn project , we can hold the broad characteristics of the community constant, while we focus on the effects of variation in families, in classrooms and schools, and in the other local social contexts. Rates of use and relationships to important determinants may vary from one kind of community to the next. Replication in similar and different kinds of communities must be part of research strategy.

Description of Measures

First-Grade Social Adaptational Status (SAS)

Our primary instrument to measure SAS was the Teacher's Observation of Classroom Adaptation (TOCA). The instrument contains rating scales measuring the different social tasks the teacher expects the child to perform. During a standardized interview, each teacher -rated her students on each social task. Teachers made TOCA ratings early in the 1966-67 school year, at midyear, at year end, and again in third grade. Reliability and validity data for these scales are reported in Kellam et al. (1975). The instrument as used in this paper measured three maladaptive patterns of responding, each with three categorical levels (not at all, mild, and moderate or severe). The three patterns are: shyness (e.g., not speaking up, having few friends, sitting alone); aggressiveness (e.g., breaking rules, fighting, lying); and learning problems, where the score consisted of the most severe rating given by the teacher in either cognitive achievement (does the child learn up to ability

as the teacher perceives it), maturation (acting with sufficient independence to accomplish first-grade tasks), or concentration (paying attention for a sufficient span of time to allow for teaching and learning). This approach to learning problems is similar to Kohn and Rosman's (1972) concept of task orientation and to a learning problems category developed by Lambert and Nicoll (1977).

In addition to the teacher ratings of shyness, aggressiveness, and learning problems, we will also summarize how drug use in the teenage years was related to the first-grade children's performance on the Metropolitan Readiness-For-School Test and the Kuhlmann-Anderson IQ test both administered in first grade by the Chicago Board of Education. We consider these somewhat arbitrarily as SAS measures, since they actually measure children's performance, not their intrinsic ability.

First-Grade Psychological Well-Being

Data on psychological well-being were collected from structured clinical observations, from the mothers, and from the children in third grade. We will discuss only the mother's reports in this chapter. The Mother Symptom Inventory (MSI) was completed by the mothers in a home interview in 1966-67 about their first grade child. The instrument is a 38-item inventory adapted from previous investigations of the epidemiology of symptoms among children (Kellam et al., 1975). The mothers were asked to rate their children on each symptom on a 4-point scale from "not at all" to "very much." These 38 items as used here are combined into a single construct.

Collection of Teenage Substance Use Data

The information on teenage drug use that we use in this paper comes from responses to items in the What's Happening?, a questionnaire administered to the teenagers who participated in the follow-up sessions. The questions concerned the frequency of use of 12 categories of substance use. For the analyses in this paper, we use responses to the question "how often have you ever used?" Drugs are reduced to 5 categories: (1) beer or wine, (2) hard liquor, (3) cigarettes, (4) marijuana or hashish, and (5) other drugs. Drugs in the "other" category were used much less frequently and include psychedelics, uppers, downers, tranquilizers, cocaine, inhalants, heroin, and codeine.

For all categories except cigarettes, rate of use was broken into three categories: (1) never used; (2) used 1 to 19 times; (3) used 20 times or more. Cigarette use was broken into the following three categories: (1) never used; (2) used 1 or 2 times or occasionally; (3) used regularly.

The questionnaires were administered by two black college students to adolescents in groups of five to eight. The college students rotated partners and the leadership role. The assessment questions were presented visually on slides and orally on audiotape to control for reading ability differences and to standardize the pace and the general administration of the questions (Petersen & Kellam, 1977). The group process in which the data were gathered focused on the trust issue, allowing the adolescents to express their fears and questions. During the

administration, the assessors stopped the slides and tape whenever a teenager had questions about either the purpose or the meaning of the items. Confidentiality of responses was emphasized.

The pattern of drug use in the Woodlawn teenagers was heavily centered on beer or wine, hard liquor, marijuana, and cigarettes (Kellam et al., 1980). Males used significantly more beer or wine, hard liquor, and marijuana than did females. There were no significant sex differences in the rates of cigarette use and the use of illicit drugs other than marijuana.

Overall, both males and females reported frequent substance use. More than one-third of the males and about one-sixth of the females reported using marijuana and beer or wine 20 times or more. Fewer used hard liquor frequently, but 47% of males and 38% of females had used it at least once. Rates of use of illicit drugs other than marijuana were low. Only 1% of these 16 or 17 year old teenagers had tried heroin. About 8% reported using cocaine at least 1 time, while 12% reported using unprescribed codeine. We will not include these drugs in the analyses described in this chapter because of the small numbers and the nature of the analyses we wish to describe.

Prediction of Substance Use

Shyness, Aggressiveness, and Learning Problems

The three teacher-rated variables of shyness, aggressiveness, and learning problems were examined as three distinct traits with three levels of "not at all," "mild," and "moderate or severe." Four-variable log-linear analyses, involving first-grade shyness, aggressiveness, learning problems, and a single teenage substance variable, were done separately for males and females (Goodman, 1971, 1973). Similar analyses of these three first-grade measures and teenage symptoms were also done to identify and contrast important antecedent traits of substance use and symptoms; these will be reported elsewhere (Kellam et al., 1980).

The results clearly demonstrated that first-grade learning problems did not predict teenage substance use. Once learning problems was confirmed as not predicting substance use, it was omitted from the drug analyses. First grade learning problems in males (and to a lesser extent females) strongly predicted teenage psychiatric symptoms, however. Table 1 contains the distribution for males' drug use by aggressiveness and shyness. Substance use by teenage males was positively predicted by first-grade teacher ratings of aggressiveness 10 years later. Comparing aggressive versus not-aggressive categories for each category of substance use in Table 1, we see that aggressive males used these substances more frequently and were less likely to be nonusers than were non-aggressives. In contrast teenage marijuana and cigarette use (with similar trends for beer or wine and hard liquor) were inversely related to first-grade teacher ratings of shyness. However, the combination of shyness and aggressiveness (as shown in the last column of Table 1) generally produced enhanced use.

In strong contrast to the results for males, first-grade ratings of shyness and aggressiveness were not related to drug use among female teenagers. To emphasize further the sex contrast, first-grade ratings of psychiatric symptoms were unrelated to male substance use ten years later but did predict teenage cigarette use among females. In an earlier paper we reported that of the high symptomatic females, 17% were frequent users of cigarettes compared to 32% of those females who were rated as nonsymptomatic by their mothers in first grade (Kellam et al., 1980).

The complete log-linear statistics in the form of likelihood ratio chi-square tests for teenage drug use are available in the full length manuscript. We have drawn threeinferences from the log-linear analyses of shyness, aggressiveness, learning problems, and substance use.

(1) Aggressiveness in males in first grade leads to 1-1/2 times more use by teen agers of beer or wine, hard liquor, marijuana, and cigarettes compared to not-aggressive males.

(2) Shyness without aggression in first grade leads to an inhibition of both cigarette and marijuana use by teenagers. Trends in this direction are evident for hard liquor and beer *or* wine.

(3) While shyness without aggression appears to decrease use, shyness in the presence of aggression seems to enhance use. In fact the moderate/severe shy in combination with the moderate/ severe aggressive males in first grade show the highest substance use in three of the four substance categories ten years later. This effect is most clear for cigarettes and marijuana.

First-Grade Readiness and IQ Test Scores

The rates of drug use as a function of female first-grade performance on the Metropolitan Readiness Test are presented in Table 2. The same relationships hold for males. These data confirm that for *beer or* wine, hard liquor, and marijuana, the level of heavy use by teenagers was positively predicted by test performance in first grade. Similarly, students performing less well on the test were more likely to have never used these drugs. Also predictive of the heavy use of beer or wine was higher first-grade IQ as measured by the Kuhlmann-Anderson instrument. It should be noted that both of these first-grade test measures were predictive for both males and females, in contrast to the shyness and aggressiveness results. These results are statistically independent of those in the shy/aggressive analyses. These therefore represent two different paths leading to later use or non-use.

Table 1

First-Grade Shyness and Aggressiveness and Teenage Substance Use by Males

Teenage substance use[b]	Not Shy		Shy[a]	
	Not Aggressive (n=160)	Aggressive (n=32)	Not Agressive (n=20)	Aggressive[a] (n=22)
Cigarettes				
Never Used	29.2%	9.4%	35.0%	9.1%
Regular use	30.4	40.6	5.0	59.1
Marijuana				
Never Used	26.2	12.9	65.0	31.8
Heavy Use	35.6	35.5	10.0	45.4
Hard Liquor				
Never Used	58.4	40.6	75.0	31.8
Heavy Use	10.6	18.8	0.0	18.2
Beer or Wine				
Never Used	13.8	6.2	25.0	9.1.
Heavy Use	28.8	37.5	20.0	50.0

[a]Includes only moderate and severe levels. Mild levels are included in the log linear analyses. See full manuscript available from first author;

[b]Percentages for level of use within each substance category do not add to 100% because the category "moderate use" is not included.

Table 2

First-Grade Readiness Test Scores[a]
and Teenage Substance Use by Females

Teenage substance use[b]	First-Grade Readiness			
	Immature (n=53)	Low Normal (n=115)	Average (n=114)	Average (n=41)
Cigarettes				
Never Used	29%	18%	22%	27%
Regular Use	21	30	25	26
Marijuana				
Never Used	64	57	40	39
Heavy Use	11	15	18	24
Hard Liquor				
Never Used	75	67	54	49
Heavy Use	2	4	5	10
Beer or Wine				
Never Used	40	30	20	22
Heavy Use	8	14	25	27

[a]Metropolitan Readiness Test

[b]percentages for level of use, within each substance category do not add to 100%, because the category "moderate use" is not included.

Discussion

Research by an impressive number of laboratories has pointed to social maladaptive and psychological behaviors as important predictors of substance use. The Woodlawn studies point to the salience of social maladaptive ratings as early as the latter part of first grade. Aggressiveness and shyness have shown particularly striking relationships to substance use in this population. Many of the other studies have shown that ratings of aggressive behavior have predictive relations with substance use, while others point to psychological predictors which appear to be closely related to aggressive and antisocial behavior.

Major sex differences in patterns and antecedents of use remain unexplained and must have dramatic importance in understanding the origins and evolving paths leading to substance use or nonuse.

Learning problems in Woodlawn first-graders were almost invariably a concomitant of aggressivenees. However, the fact that learning problems frequently occurred without aggressiveness allowed us to differentiate the predictive power of aggressiveness in contrast to that of learning problems. Learning problems alone in first grade did not predict drug use but rather teenage psychological distress in Woodlawn; aggressiveness appears to be the real antecedent of later drug use in males.

Shyness in first grade--the tendency to sit alone, not to speak up in class, not to be with other children--appears to function as an inhibitor of teenage male drug use. It seems to inhibit strongly the regular use of cigarettes and considerably decreases the likelihood of ever using marijuana. The combination of moderate to severe shyness and moderate to severe aggressiveness tended to enhance the aggressive effect in males.

The most striking aspect in observing these results was that these predictors spanned 10 years, from first grade to age 16 or 17. These factors must be studied in other communities similar and dissimilar to Woodlawn before we can be clear as to their generalizability or the specific conditions in which they hold true. In the meantime we are left to conjecture as to their meaning. Based on Woodlawn data, shyness alone inhibits drug use, but with aggression tends to enhance it, thus suggesting that these two "traits" are not opposite ends of the same scale, but are two different phenomena., They are social q aladaptive responses to social demands to interact with others and to obey rules. These social maladaptive patterns may derive from biological predispositions, and/or socilization processes in the family and in the school prior to or during first grade.

A strong beginning has been made by a number of research groups in clarifying the remote and evolving courses leading to substance use among adolescents. We are now in a position to develop an overall research strategy directed at specific programs of prevention of substance use among teenagers. Such a statement deliberately focuses upon the need for research strategies, while recognizing the need to continue the rinds of nonspecific, often educational preventive programs now in place.

A research strategy directed at the ultimate goal of prevention programming will require collaborative design and highly coordinated analyses. This is not the first time that

such integration across investigative groups has been required. Collaborative studies involving several research laboratories have often been successful. The multi-hospital studies of the phenothiazine treatment of schizophrenia in the early sixties are but one example (NIMH, 1964).

Our recommendation for a collaborative preventive research strategy includes the following stages:

1. Collaborative examination of existing longitudinal data bases and planning of analyses where each laboratory would attempt to replicate specifically chosen findings from other laboratories.
2. The collaborative design of new studies with specification of the population samples from whom the data is to be collected. Such planning should include the possibility of extending existing longitudinal data bases to include additional cohort follow-up. Such extension would inform us if predictors of the initiation of use are also predictive of the level of use and abuse later in the life course.
3. Collaborative design at the appropriate stage should include. experimental interventions directed at specific antecedents found to be strong predictors of substance use among teenagers. The purpose of these experimental interventions will be to understand the function of the specific predictors in the causal paths leading to substance abuse.
4. Broad-based evaluation studies of highly specified preventive intervention programs in specific populations is the final stage of preventive intervention research.
5. Following the preventive intervention evaluation studies, we will be in a position to recommend national policy and help to design the implementation of prevention interventions aimed at specific antecedents.

Most of this research must be epidemiological, and much of it will have to be directed at specific community populations. Some research could be done using experimental animal analogs. Aggressive behavior in first-graders can be studied using animal analogs as well as children. Animals can be socialized to be shy and aggressive, and they can also be bred to be shy and aggressive. Such animal studies-allow the examination of the difficulty or ease with which drug-seeking behavior can be initiated and maintained. Experiments like these can help us understand whether the shyness and aggressiveness observed to predict substance use is more likely to derive from socialization, genetic background, or both. Experimental intervention with animals can proceed side by side with experimental intervention with humans, thus augmenting our understanding and saving time and resources in our prevention research strategies.

Substance use is one of a group of adolescent outcomes of great interest to the public and scientist alike. The research strategy described above will be most useful if delinquency, school achievement, psychological well-being, sexuality and other relevant teenage outcomes are studied along with substance abuse. Such studies can help specify which antecedents are generally predictive of a variety of teenage outcomes, and which antecedents are specific to substance use alone (Kohn, 1976).

Susceptibility to Substance Abuse Among American Indians: Variation Across Sociocultural Settings

Philip A. May

According to the 1980 Census there are 1,418,195 American Indians in the U.S., which represents 0.6 percent of the total U.S. population. The Indian population is currently growing rapidly and as a result is very young (median age=19.4; U.S.=29). Most Indians have been characterized as being quite poor, and median education on most reservations is also quite low. Recent trends indicate that an increasingly large number of Indians now reside in and depend on urban area, which is producing many changes in both individual Indians and in many tribal groups.

Many Americans think of Indians as one, homogeneous group, but the opposite is true. Cultural variation was and still is extreme from one tribe and cultural group to the next. Not only is the culture of a group like the Seminole of Florida greatly different from the Sioux of South Dakota, but the personalities and behaviors produced by each of these cultures are also quite different. In addition there is also a variation of behavior within most tribes. This variation of behavior is a vital consideration for anyone studying a particular behavior among Indians. Drug use and related phenomena are certainly no exceptions.

Difficulty of Indian Research

Undertaking research among Indians on reservations, and even in urban areas, is very difficult. Patterns of secrecy, aloofness and a distrust of researchers have been developed by Indians over the years. Access to social gatherings, schools, individuals and data is therefore very difficult for researchers, particularly non-Indians. Suicide and alcohol research among Indians reflect this difficulty.The earliest studies on suicide and alcohol use among Indians were subject to a number of problems. In general, they were overly simplistic and did little more than reinforce the old stereotype of the "drunken Indian" and create a new one of "suicidal Indian" (May 1977; Shore 1975). Neither of these concepts was truly accurate, and recent research has shown wide variation in both behaviors. Indeed, certain tribes and sub-groups among tribes have problems with

these behaviors but most individual Indians and some large tribes have no major problem with either (May and Dizmang 1974).

The following discussion of drug abuse among Indians is subject to the same pitfalls. The study of most types of drug usage among Indians has just begun, and any conclusions and generalizations should be approached with caution. Just as the complexity and variation of Indian self-destruction and alcohol behavior were obscured for many years, the same may hold true in substance-abuse research. The information in this paper, therefore, should be approached with caution.

ALCOHOL

In spite of the considerable attention paid to Indian drinking, insights into prevalence, incidence, variation of patterns, and susceptibility to alcohol intoxication and dependence were slow in developing. Prevalence and incidence are explored here and a few very selective works on Indian drinking are used to illustrate topics vital to the understanding of susceptibility to all types of substance abuse.

Biological Considerations

For many years it was believed that Indians may have deficient ability to metabolize or process alcohol, By 1976 good Research in this area began to emerge. Bennion and Li (1976) reported on a study in which controls were instituted on the important variables of body weight and drinking experience prior to the study. Their results showed no difference in alcohol metabolism between Indians and whites. More recent studies have consistently shown that individual Indiana have an equal or oven greater ability to metabolize ethanol (see Schaefer 1981) than people of other ethnic groups. Some questions still remain about high acetaldehyde levels of Indians and several brain-bared enzymes but there is no proof today of any metabolic deficit among Indians.

Extent of Drinking - Adults

The prevelance and incidence of Indian alcohol use are popularly believed to be high, but this is not validated by research. In the four detailed studios on adult prevalence, the range from one reservation to the next is striking. In the U.S. as a whole 67 to 68 per cent of all adults drink at least once a year or more (Akers 1977). Similar statistics for Indians indicate that 30 percent of the Navajo of the Southwest (some Navajo communities are as high as 42 percent), 69 percent of the Standing Rock Sioux (SD) , 80 percent of the Ute of Igacio (CC) and 84 percent of the Ojibwa of the Brokenhead Reserve in Canada drink (Levy and Kunitz, 1974; Whittacker 1962; Jessor et al. 1968; Longclaws et al. 1980). Therefore, two of the groups surveyed are higher than the U.S. average, one is about the same and one is considerably lower. All of the above tribes are ones with reputations as ‘hard drinking” groups, and the low incidence of reported use in some of them surprises many.

Surveys on a number of other Indian groups, particularly those with less notorious drinking reputations, would probably yield an incidence similar to or lower than the rest of the nation.

Extent of Drinking - Youth

The extent of drinking reported by Indian youth is different from that of adults. Recent national surveys have shown that between 53 and 73 percent of all youth in grades 7-12 drink to some extent (Abelson et al. 1977; N.I.A.A.A. 1981). Surveys of Indian youth show a slightly higher experience with alcohol: 56 to 89 percent with three of four studies above the 71 percent most often reported for U.S. youth. As with other youth in the U.S., factors such as peer pressure, recreation, experimentation, anxiety and depression have been documented as motivations for teenage Indian drinking (Forslund 1978; Cocker-ham 1977; Western Behavioral Studies 1979). Nevertheless, the incidence is higher among the youth of most Indian groups. Variation from one group to the next is present, however.

Frequency of use, heavy use, and abuse are difficult to compare. N.I.A.A.A. (1981) cites statistics that indicate that 11 percent of all U.S. youth use alcohol heavily. Self-report data from various tribes report that 17 to 46 percent are heavy users. There is some problem however, with the comparability of alcohol abuse criteria used in these studies due to quantity and frequency of differences in Indian drinking styles.

Drinking Styles

The variety of drinking styles practiced by Indians has been well researched and described in only a few studies. Various drinking styles are practiced by Indians: abstinence, moderate drinking, flamboyant extended binges, etc. Unfortunately, dozens of articles have focused only on binge drinking, for it is perceived as the unique "Indian" style and is the most easily observed and exotic (May 1977).

In one article Ferguson (1968) describes two major types of drinkers among the Navajo that are also present in a number of tribes. The recreational drinker is typically a younger Navajo male who will drink with a group of friends (mostly male), on various weekends, at special and social events (i.e., dances), for it serves an important social cohesion and recreational function. The drinking in these groups is generally forced, done in large amounts, consumed quickly and for an extended period of time (i.e., all night). Intoxication as a positive trait is often encouraged. Recreational drinking is most common for ages 15-35. Recreational drinking is sporadic, and long periods of abstinence (i.e., a week to several months) occur between each instance. The other type of drinker, the anxiety drinker, however, is much different and the behavior considered less acceptable by most tribes. Anxiety drinkers drink alone, constantly, and are physically and psychologically addicted to alcohol. They fit the pattern of the "wino," have suffered downward social mobility and tend to concentrate in border towns off the

reservation, central cities! or areas where supply is most accessible. In most Indian communities these people are labeled with an ethnic term similar to "alcoholic" and are stigmatized and/or ostracized. Anxiety drinkers are few in most Indian groups, and recreational drinkers predominate. Standard alcoholism indices work fairly well in accurately classifying anxiety drinkers, but are not useful in evaluating the alcohol abuse of recreational drinkers.

As in the rest of the U.S., fewer Indian women drink than Indian men. In some tribes in the southwestern U.S. (Navajo and pueblo) it is rare and quite unacceptable for any woman to drink, particularly after some experimentation. In other tribes such as the Plains and Basin tribes, more women drink and drinking is somewhat more acceptable. Nevertheless, Indian women overall are less likely than Indian men to be drinkers.

A final note on style concerns acculturation. Indians who are acculturated are particularly likely to follow the modal pattern of drinking that is popular in the segment of modem society with which they identify. Indian professionals and bureaucrats generally drink as other professionals do. Indian laborers will drink as their fellow laborers, etc.

Alcohol-Related Problems

Alcohol-related problems are prevalent among Indians and have received a great deal of attention. Alcohol-related mortality, for example, is consistently higher among most tribes than in the general U.S. population. For all U.S. Indians, the age-adjusted rate of motor-vehicle-accident death is 4.4 times more common; cirrhosis of the liver mortality is 4.4 times more frequent; and death from other accidents is 3 times the national average (U.S. Public Health Service 1978). Some tribes such as the Navajo have had low rates of cirrhosis in the past, but recent statistics indicate an increase (May and Broudy 1980). Deaths from exposure and drowning have also been frequently linked to alcohol, while alcohol-related injury and illness have also been documented as problems among many groups of Indians.

Alcohol-related arrests have also been a problem for Indians. Off-reservation arrests have been extremely high for intoxication, driving while intoxicated, and other alcohol-related crimes. Alcohol-specific arrests on most reservations have been high, but not significantly higher than in most U.S. communities (May 1976).

Alcohol Summary

From the above facts Indians have been shown to have no biological susceptibility to intoxication, not an unusually large percentage of adult drinkers, a slightly higher percentage of youthful drinkers, a variety of drinking styles and problems with alcohol-related mortality and arrest. Most of the problems can be related to the recreational drinking style. Drinking rapidly in a forced, group situation produces high blood-alcohol levels and intoxication in a

person who may not drink regularly. High blood-alcohol levels are related to most of the health and arrest problems mentioned above. Acutely high blood-alcohol levels coupled with other environmental and legal factors produce high rates of alcohol-related arrest, death and illness. Ihus,the binge pattern of drinking can be related to most of the alcohol-related problems mentioned above. The major exception is cirrhosis of the liver. Chronic, steady, escape drinking , as practiced by the anxiety drinker, is related to cirrhosis.

Therefore, the style of drinking among some Indian drinkers results in alcohol-relate problems; It should again be pointed out that these statistics are produced by a minority of Indians and that many Indians abstain. Also, many Indians who do drink, do so without major problems.

MARIJUANA

Turning now to other drugs, the use of marijuana by Indians will be examined. As with much of the marijuana research in the U.S., most of the data have been collected from students. National surveys have shown that approximately 10 to 48 percent of all U.S. youth in grades 7-12 have ever used marijuana. Approximately 4 to 16 percent of youth are current and/or recent users (Akers 1977). Four studies on Indian youth in the same grades indicate a range from 22 to 62 percent. Three of the four surveys found over 40 percent users among Indian students. The highest percentage of users, 62 percent, was found among southwestern tribes who are close to the major supply routes from Mexico; the lowest percent, 22 percent, was found in central Canada. Indian students are also reported being current users as often or more often than other youth (17-41 percent). Therefore, use of marijuana appears to be higher among Indians in grades 7-12 (Western Behavioral Studies 1979; Oetting et al. 1980; Cockerham 1977; Longclaws et al. 1980).

Among post-high-school youth, there is also a difference between narijuana reporting in U.S. averages and Indian reports. National college polls have consistently shown 50-55 percent of students use marijuana,with 35-40 percent reporting regular or frequent use (Akers 1977). The two surveys done on Indians of this age group were ione in post-high-school, technical schools which may not be directly comparable. Between 70-78 percent of Indians in these schools were found to have used marijuana, while 50 to 63 percent were regular users (Goldstein et al. 1979; Briggs 1980). Therefore, at the post-high-school level Indian youth report a higher use of marijuana.

Only one survey reports any marijuana data for Indian adults. In Canada, Longclaws et al. (1980) found that 36 percent of the Brokenhead Ojibwa Indians have ever used marijuana and 7 percent used it more than once a week. This is slightly higher than national adult statistics, but comparable to California data. In summary, Indian youths generally report more use of marijuana at all ages. Some variability is evident, based on tribal and/or geographical differences , but much more information is needed.

INHALANTS

The use of inhalants (i.e., glue, gas, solvents, spray paints) has been reported as being quite popular among Indian youth. Samples of U.S. youth from 12-19 years find that 9 and 11 percent have used inhalants, but less than 1 percent do so regularly (Abelson et al. 1977). Of the two studies reporting on Indian youth of the same ages, between 17 and 22 percent have used inhalants (Oetting et al. 1980; Western Behavioral Studies 1979). In a national Indian survey 16 percent reported recent use. In general, almost twice as many Indian youth have used inhalants (Oetting and Goldstein 1979). One study in an Indian boarding school in Oklahoma reported that 13 percent of the students in grades 6-8 were judged to be heavy users (Schottstaedt and Bjork 1977) but boarding schools are frequently populated by high risk or problem youth. Among Indian post-high-school students, studies have indicated 20 and 31 percent of the students have used inhalants. Recent 'use among these students was reported by only 1 and 4 percent of the students (Goldstein et al. 1979; Briggs 1980). Therefore, actual use of inhalants is highest in the early and middle teens and then declines in later years.

Inhalant abuse has received a lot of popular attention on many Indian reservations, for it seems to be an abusive behavior which is notably too popular among Indians. In addition, it is recognized that some physiological damage results from inhalation of particular solvents. An optimistic note is the low recent use reported by the post-high-school Indians. Most Indian youth may only experiment with inhalants at an early age and never use them extensively.

OTHER DRUGS

In the most extensive and complete survey-of all types of drug use among U.S. Indian youth, Oetting, Goldstein, et al. found little difference in use of most drugs by Indians and others in the U.S. As stated above, the use of alcohol, marijuana, and inhalants was found to be greater among Indians, but in most other categories, drug use was equal. One exception was barbituate use. Indians in grades 7-12 were much less likely to use barbituates than other U.S. youth (Oetting and Goldstein 1979). Several other studies provided similar results. Indian youth and Indians adults of many tribes are, therefore, less likely or no more likely to use drugs such as barbituates, amphetamines, cocaine, and opiates.

Several issues deserve mention here. The use of hallucinogens (particularly peyote), is reported to be slightly higher among Indian youth than other youth -in the U.S. Adult Indian use of peyote and, therefore, hallucinogens is probably higher than other U.S. adults. In most cases, however, use by Indians could not be considered abuse. Most adult use of peyote is strictly controlled by the Native American Church (NAC) and is only taken in rigidly controlled highly organized, religious ceremonies. In such situations side effects are minimal, group functioning and group solidarity are enhanced and usage and behavior are strictly controlled (Bergman 1971). Usage of peyote under these conditions could be considered

sacramental and therapeutic. The use of peyote by Indian youth, however, is sometimes outside these church practices and in these instances problematic.

Variation in use of barbituates, amphetamines, cocaine, opiates and various prescription drugs seems to exist from one Indian group to the next. For example, as a means of suicide and suicide attempts, drugs are seldom used by Indians in the Southwest, but overdose is more common among some tribes elsewhere (May and Dizmang 1974). Use of a variety of prescription and street drugs seems to be slightly higher among some Plains Indian tribes (Cockerham 1977). Culture, isolation, and other variables may affect prescription and other drug use.

A SUSCEPTIBILITY SCHEME

With the above material reviewed, a susceptibility scheme is now proposed, 'Ibis scheme is based on the previous literature review, the author's experience, and other literature on alcohol, drugs, crime, suicide, and motor-vehicle accidents among Indians (particularly Levy and Kunitz 1974; Ferguson 1976; Jenson et al. 1977). It is tentative and awaits further direct testing.

The Traditional Cultural Factor

Particular Indian tribes and cultural groups have been found to be higher risk for many types of deviance because their traditional tribal customs tolerate or encourage individualistic, flamboyant behaviors (Levy and Kunitz 1974). Tribes which are characterized by loose, small group or band-level organization have been found to produce more individualistic behavior which can be considered deviant. Examples of these are nomadic tribes traditionally based on a hunting, gathering, and/or raiding complex such as those found in the Plains and Great Basin regions. On the other hand, tribes which are organized in larger groups, have a more rigid and fixed social structure, are much more prone to enforce conformity and less likely to produce deviance. These tribes were and are more sedentary, agriculture or fishery based and organized around strict social systems and rules of governance. This type is exemplified by tribes east of the Mississippi, the Pueblo and northwest coast Indians. In this manner, traditional social organization has been found to be important in producing or impeding various kinds of deviance. Drug use should also follow this pattern.

The Modern Factor

One other theme has also been consistently proposed as influential in producing deviant behavior. Social disorganization, cultural and social change, and cultural conflict which result in interpersonal stress have been frequently cited as causing crime, suicide, and alcohol problems among Indians. This theme states that the acculturation dilemma that many tribes and their members face will raise deviance rates. Therefore, tribes who are firmly entrenched in their traditional ways are less likely to produce high levels of deviant

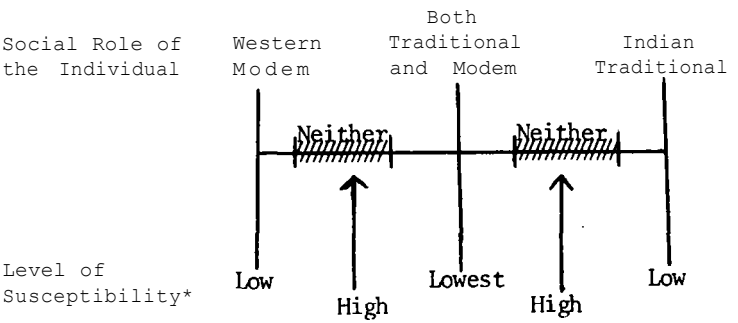
behavior. On the other hand, tribes which are undergoing rapid change and whose way of life is being assaulted will produce higher levels of deviance. Drug use might be highly influenced by this dynamic.

Combining Modem and Traditional

Combining these two schemes, evaluation and explanation of patterns of drug abuse might be possible. Tribes with loose social organization would be expected to have the highest rates of drug abuse while those with high levels of organization would have the lowest rates, particularly under conditions of relative isolation from modernization and acculturation stress. However, tribes undergoing forced and rapid change will also experience higher rates of drug abuse than similar tribes in relative isolation from these pressures. Therefore, the order of risk for drug abuse would be expected to be: highest risk--loosely integrated tribes undergoing rapid change; lowest risk--tightly integrated tribes undergoing little change in life style, economy and exposed to few outside influences.

This scheme must be translated from the tribal to the individual level. Families and individuals make adjustments, decisions, and base their lives on the definitions and options afforded them in their social and cultural context. This is vividly reflected in drinking and drug behavior. Individuals growing up and living in particular tribal cultures will be more or less likely to use drugs based on both traditional Indian culture and change factors. The susceptibility of a particular person can be judged based on the adaptation which the person and also his/her family have made. Their adjustment to particular Indian traditional values and also modem, mainstream values will be reflective on their likelihood to use drugs. Figure 1 illustrates at least four types of adaptation which contemporary Indian individuals can make.

FIGURE 1
COMMMON SOCIAL INTEGRATION ADAPTATIONS OF CONTEMPORARY AMERICAN INDIANS AND SUSCEPTIBILITY TO DRUG ABUSE



*The higher the susceptibility, the greater the use of drugs and extent of drug abuse.

If an individual and his family of orientation are well integrated socially and perceptually with both Indian and modem society, they are the lowest risk for drug abuse. These people would have a steady meaningful job and also relate to traditional Indian values and practices. Thus, these people have a dual source of identity. Closely related to this in terms of susceptibility, are people who are well integrated to traditional Indian society. If they derive satisfaction, positive self-identity and meaning from traditional Indian culture, they are less likely to be drug abusers. The same might be said for Indians who are highly integrated into modem, non-Indian culture except that their identity and self-esteem come from a different source (i.e. , a profession, sports, etc.) Therefore, those with a strong integration or attachment to either modem or Indian society are also low risk, but not as low as those with both. Finally the high-risk people or most susceptible to drug abuse are those who are not integrated into either traditional or modem society via their family of orientation or their own achievements.

This model of susceptibility is not new, but is a logical extension of some previous works. Results which support this have appeared in the alcohol and deviance literature and are now emerging in recent drug surveys (Western Behavioral Studies 1979). One exception between the proposed scheme and previous research, though, is that no previous study has found individuals with "modem only" integration to be good risks. The same may also prove to be true with drug abuse, but reservations, the location of virtually all alcohol studies, are poor places to locate well adjusted Indians with only modem integration. One should look for these types in urban areas, particularly among 2nd and 3rd generation, city-dwelling Indians.

CONCLUSIONS

From the previous material, some patterns of drug use among Indians can be described. Slightly higher levels of use of some drugs among Indian youth are indicators of stress during adolescence when social integration from the family of orientation has weakened, the peer group is powerful, and adult adaptations and roles have not yet been crystalized. Because this period is complicated for Indians bya dual set of options and prejudice, a higher percentage of Indian youth may use particular substances as a temporary escape. Many Indian, adolescent. peer groups define alcohol, inhalants and marijuana as acceptable. But for most young Indians the usage of drugs other. than alcohol is an experimental, transitory behavior. Individuals who are well integrated into and identify with both modem and traditional Indian customs are the least susceptible to drug abuse. Those who are not well established in any socially integrated role of either white or Indian society are the most likely to abuse drugs and to continue their use. This scheme awaits testing and, if validated, translation into applied solutions.

REFERENCES

Abelson, H.I. Fishbume, P.M. and Cisin, I. National Survey on Drug Abuse: 1977. Princeton, NJ: Response Analysis, 1977.

Akers, R. Deviant Behavior, 2nd edition. Belmont, CA: Wadsworth Publishing Co., 1977.

Bergman, R.L. Navajo Peyote Use: Its Apparent Safety. Am. J. Psychiatry 128(6), 695-698, 1971.

Bennion, L. and Li, T.K. Alcohol metabolism in American Indians and whites. N, Engl, J. Med, 294, 9-13, 1976.

Briggs, C. Indian alcohol and drug use among juveniles. Unpublished manuscript, University of New Mexico, 1980.

Cockerham, W.C. Patterns of alcohol and multiple drug use among rural white and American Indian adolescents. Int. J. Addict, 12(2-3), 271-285, 1977.

Ferguson, F.N. Navajo drinking: some tentative hypotheses. Human Org. 27, 159-167, 1968.

Ferguson, F.N. Stake theory as an explanatory device in Navajo alcohol treatment response. Human Org. 35(1), 65-77, 1976.

Forslund, M.A. Functions of drinking for native American and white youth. J. Youth Adol, 7(3), 327-332, 1978.

Goldstein, G.S., et al., Drug use among native American young adults. Int. J. Addict. 14 (6) , 855-860, 1979.

Heidenrich, C.A. Alcohol and drug use among Indian-Americans: A Review of issues and sources. J. of Drug Issues, 6(3), 256-272, 1976.

Jensen, G., Stauss, J. and Harris, V. Crime, delinquency and the American Indian. Hum. Org, 36(3), 252-257, 1977.

Jessor, R., et al., Society, Personality and Deviant Behavior: A Study of Tri-Ethnic Community. NY: Holt, Rinehart & Winston, 1968.

Levy, J.E. and Kunitz, S.J. Indian Drinking. NY: Wiley Interscience, 1974.

Longclaws,L., et al., Alcohol and drug use among the Brokenhead Ojibwa. J. Stud. Alcohol, 41(1), 21-36, 1980.

May, P.A..and Dizmang, L.H. Suicide and the American Indian. Psychiatr. Annals, 4(9), 22-28, 1974.

May, P.A. Alcohol Legalization and Native Americans. Ph.D. Dissertation, University of Montana, 1976.

May, P.A. Explanations of Native American drinking. Plains Anthro. 22 (77),223-232, 1977.

May, P.A. and Broudy, D.W. Health problems of the Navajo and Suggested Interventions, 2nd edition. Window Rock, AZ: Navajo Health Authority, 1980.

National Institute on Alcohol Abuse and Alcoholism. Alcohol and Health: 4th Edition. Washington, D.C.: U.S. Government Printing Office, 1981.

Oetting, E.R. and Goldstein, G.S. Drug use among Native American, adolescents, in Beschner and Friedman (eds.), Youth Drug Abuse, Lexington, MA: Lexington Books, Inc., 1979.

Oetting., E.R., et al., Drug use among adolescents of five southwestern Native American tribes. Int. J. of Addict, 15(3), 439-445, 1980.

Schaefer, J.M. Firewater myths revisited. J Stud Alcohol, supplement no. 9, 99-117, 1981.

Schottstaedt, M. and Bjork, J. Inhalant abuse in an Indian boarding school. Am. J. Psychiatry, 134(11), 1290-1293, 1977.

Shore, J.H. American Indian suicide-fact and fantasy. Psychiatry, 38, 86-91, 1975.

U.S. Public Health Service. Indian Health Trends and Services, Washington, D.C., U.S. Government Printing Office, 1978.

Western Behavioral Studies. Drug Abuse among Indian Children. Ft. Collins, CO: Colorado State University, 1979.

Whittacker, J.O. Alcohol and the Standing Rock Sioux tribe. Quart J. Stud. Alcohol, 23, 468-479, 1972.

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Progress Report of the NIDA Addiction Research Center

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An administrative decision terminating the participation of federal prisoners in research ended the Addiction Research Center clinical research program using volunteer prisoner addicts. In July 1979, the program was relocated to Baltimore City Hospitals where it operates on a speciality ward in a general hospital conducting research in volunteer addicts from the Baltimore area. The first subject was admitted in February 1980; however, the program did not become fully operational until July 1980. This progress report covers the one-year period of July 1980 to July 1981.

The experience to date indicates that non-therapeutic and therapeutic research can be conducted in volunteer addicts in such a manner that ethical concerns as well as counseling and aftercare needs can be met. Several studies of interest to the committee have been completed and will be summarized in this report.

STUDY I - EVALUATION OF ORALLY GIVEN BUPRENORPHINE
STUDY II - EVALUATION OF SUBLINGUALLY GIVEN BUPRENORPHINE

Previously, we reported to the Committee that buprenorphine acts as a partial agonist of morphine with a long duration of action (Jasinski et al., 1976, Jasinski, Pevnick and Griffith, 1978). The drug produces morphine-like effects with a low toxicity and little or no physical dependence. We further proposed that buprenorphine could be utilized as a short term detoxification/maintenance agent for narcotic addiction. The original studies were done with subcutaneously injected buprenorphine. This report covers two recent studies done to evaluate the oral and sublingual routes as modes of administration of buprenorphine.

When given subcutaneously the effects of buprenorphine plateau at acute doses of 1 to 2 mg. It is assumed that for a partial agonist, the initial part of the plateau represents the response to a dose that produces maximum receptor occupation and maximum agonist effects. This in turn would represent a basis for a

daily dose for maintenance. For the oral route, the dose producing maximum agonist effects was estimated to be 20 mg of buprenorphine and for the sublingual route, 2 mg.

Two studies were done comparing the effects of orally and Sublingually given buprenorphine to Subcutaneously given buprenorphine and placebo. The studies were similar, with each involving 10 non-dependent subjects. Each study was conducted as a "double blind", "double dummy" placebo-controlled study. Drug effects were measured with our standard procedures for acute morphine-like effects (Jasinski, 1977). In the first study, each subject was given buprenorphine orally in doses of 20mg and 40 mg, subcutaneously in doses of 1 and 2 mg and placebo administered according to a latin square design at 3-day intervals. In the second study, each subject was given buprenorphine sublingually in doses of 2 and 4 mg, buprenorphine subcutaneously in doses of 1 and 2 mg, and placebo.

The onset, time of peak effect, and duration are similar for orally and subcutaneously given buprenorphine. The subjective and physiologic effects of orally and subcutaneously given buprenorphine were similar, with no dose response. Drug responses were significantly greater than placebo responses. Sublingually given buprenorphine has a slower onset of subjective and objective effects than subcutaneously given; these responses were greater than those to placebo. The duration of effects is similar by both routes with no dose response for either the subcutaneously or Sublingually given buprenorphine.

These studies indicate that maximum agonist effects are produced with a 20 mg oral dose or a 2 mg sublingual dose of buprenorphine and that both doses would be suitable as daily maintenance doses in treating narcotic addiction.

STUDY III - EVALUATION OF CLONIDINE IN MORPHINE WITHDRAWAL

Clonidine has been reported useful in treating the narcotic withdrawal syndromes with its mode of action related to its ability to decrease hyperactivity in the locus ceruleus (Gold et al., 1980, Washton, Resnick, 1980).

The present studies were designed to test the efficacy of clonidine under experimental conditions with known levels of morphine dependence, with negative control (placebo) and positive controls (partial doses of morphine). In addition, it was hoped that some' information could be obtained on the mode of action of clonidine since its hypothesized mode of action in treating withdrawal (suppression of autonomic activity) is inconsistent with previous observations that autonomic changes of withdrawal occurred during withdrawal of nalorphine and cyclazocine without drug-seeking behavior or subjective discomfort (Martin et al., 1965).

Ten subjects dependent upon maintenance methadone or illicit heroin were stabilized on 60 mg morphine sulphate per day administered in 15 mg doses at 6:00 a.m., 10:00 a.m., 4:00 p.m. and 10:00 p.m. After staoilization, five 24-hour substitution tests were conducted at weekly intervals using our standard procedures (Jasinski, 1977). The procedure for the substitution tests is that subjects receive their last maintenance dose of morphine at 4:00 p.m. At 10:00 p.m. (hour 6), 6:00 a.m. (hour 14) and 10:00 a.m. (hour 18), subjects are given an oral medication and a subcutaneous injection, such that each medication is administered three (3) times under "double dummy" conditions to mask the route of administration. The five tests involved the substitution of placebo (orally and subcutaneous), morphine 3 mg and 6 mg subcutaneously and clonidine 0.2 mg and clonidine 0.4 mg orally. Each of these doses was given three times within a substitution test.

The results of these crossover studies indicated that clonidine suppressed autonomic signs of withdrawal to a far greater extent than morphine; in contrast, clonidine was markedly less effective than morphine in suppressing the subjective discomfort of withdrawal, producing only slight alleviation of the withdrawal illness late in the substitution period. Clonidine, but not morphine, produced marked sedation and orthostatic hypotension throughout the 11 hours of observation. It is concluded that clonidine partially alleviates the subjective discomfort of withdrawal, markedly depresses the autonomic hyperactivity and produces sedation; however, the alleviation of subjective discomfort is probably unrelated to the autonomic depression or the sedation.

STUDY IV - EVALUATIM OF DIAZEPAM FOR PENTOBARBITAL-LIKE EFFECTS

Previously we had reported that addicts discriminated pentobarbital from morphine, d-amphetamine and placebo. However, pentobarbital, morphine and d-amphetamine all produce similar feelings of well-being and elation. Quantitative measures of the subjective and behavioral effects of pentobarbital were developed and it was shown that crossover studies could be done to assay sedatives for.pentobarbital-like effects. Since pentobarbital represented a prototype for highly abused sedative hypnotics, such assays could seem to be a means for assessing sedative hypnotics for abuse potential. Using these procedures it was shown that secobarbital, phenobarbital and methaqualone produced pentobarbital-like effects including euphoria (Jasinski et al., 1977).

The current studies were done to determine if diazepam produces pentobarbital-like effects and euphoria. Subjects were 12 volunteer alcoholic and sedative abusers who were not physically dependent at the time of study. Studies were done as double blind crossover studies utilizing the procedure for sedative

hypnotics. Each subject was given by the oral route diazepam 10, 20, and 40 mg; pentobarbital 120 and 240 mg; and placebo. Drugs were administered at 3-day intervals according to a latin square design.

Diazepam produced typical pentobarbital-like effects including euphoria. The onset, peak and duration of effects were similar for both drugs. Relative potencies, meeting the statistical criteria for validity, were similar across subjective and behavioral measures, indicating that diazepam is 10 times more potent than pentobarbital.

STUDY V - EVALUATION OF CHLORDIAZEPOXIDE FOR PENTOBARBITAL-LIKE EFFECTS

A study, similar in design and procedures to the diazepam study, was initiated in six subjects where chlordiazepoxide 50, 100 and 200 mg, pentobarbital 120 and 240 mg and placebo were administered. Chlordiazepoxide produced dose-related pentobarbital-like effects and euphoria, but the responses to the 200 mg dose were less than the 240 mg dose of pentobarbital. Valid assays were not obtained. The study will be extended with larger doses of chlordiazepoxide.

On the basis of these two studies, it is concluded that the current procedures and methods can be utilized to assay the relative abuse potential of benzodiazepines.

STUDY VI - EVALUATION OF ZOMEPIRAC FOR MORPHINE-LIKE SUBJECTIVE EFFECTS AND EUPHORIA

Zomepirac is a non-steroidal anti-inflammatory drug that when given orally is 1/6 to 1/10 as potent as subcutaneously given morphine in relieving pathologic pain (Wallenstein et al., 1980; Forrest, 1980). Its mode of action is more closely related to aspirin than morphine. The drug is felt to have little or no abuse potential. Some analgesic studies, however, have indicated that euphoria may occur as a side effect. This observation led us to consider that zomepirac may be a psychoactive drug with some abuse potential.

A single dose, crossover study was conducted with zomepirac using our standard crossover procedures for assaying the abuse potential of narcotic analgesics (Jasinski, 1977) to learn if zomepirac produces euphoria in non-tolerant, non-dependent narcotic addicts. Each of six subjects was given zomepirac 400 and 800 mg orally, morphine 15 and 30 mg subcutaneously and placebo. Drugs were administered twice weekly under "double blind", "double dummy" conditions.

Morphine produced typical subjective and behavioral effects including euphoria and miosis. The 400 mg dose of zomepirac was

indistinguishable from placebo on all measures. The responses to 800 mg of zomepirac were not significantly different from placebo; however, one subject reported a drug effect because of "stomach pain" and another reported slight relaxation and "liking". There were no significant changes in the incidence of positive stool guaiac following zomepirac administration nor were there any significant Changes in blood pressure, pulse rate, respiratory rate or rectal temperature.

It is concluded that to doses of 800 mg orally, zomepirac is not a euphoriant in narcotic addicts.

STUDY VII - STUDIES OF TOBACCO DEPENDENCE

A series of studies of the acute effects of nicotine delivered by tobacco smoking and intravenously administered nicotine have been done in cigarette smokers with and witnout a history of drug abuse. These studies were done to: (1) investigate the mechanism underlying compulsive tobacco use including delineating the role of nicotine, (2) determine if the addictive process with tobacco is similar to that for morphine, (3) adapt the clinical pharmacological methods used for other substances of abuse to studies of tobacco and nicotine, (4) to introduce and validate behavioral pharmacologic methods into clinical studies and (5) to conduct conjoint human and animal behavioral pharmacologic studies in order to validate animal models (this is done in conjunction with Dr. Stephen Goldberg of our laboratory).

The first studies involved measuring the subjective and physiologic responses to graded doses of nicotine delivered'by tobacco smoke and intravenously after 8 hours of deprivation of cigarettes in 8 subjects.

One set of studies involved the intravenous administration of placebo and nicotine base in doses of 0.75, 1.5 and 3.0 mg at 1-hour intervals to each subject. Each subject received these four doses on four separate occasions according to 4 X 4 latin squares. Thus, there were 32 responses for each dose (8 subjects, 4 replications). Following each dose, physiologic, behavioral and subjective responses were measured continuously for 30 minutes.

Nicotine produced a predominantly euphoric response related to dose. The effects began within 15 seconds of injection and were gone within 3 minutes. Subjects identified the effects as cocaine-like. The two lower doses increased heart rate while the largest (3 mg) lowered heart rate. Subjects accurately discriminated among the doses of nicotine.

Another set of studies involved the same 8 subjects using the same procedures except that nicotine doses were delivered by controlled puffing on cigarettes at 30-second intervals with

smoking down to a 23 mm butt length. The four dose levels were puffing on an unlit cigarette, and controlled smoking of cigarettes delivering 0.4, 1.4 and 2.9 mg of nicotine, again administered at 1-hour intervals on 4 occasions for 32 responses per dose (8 subjects, 4 replications). Subjects accurately discriminated among the cigarettes as to strength, again with onset of positive subjective effects within 15 seconds after termination of smoking.

To characterize the subjective effects of nicotine in terms of other drugs of abuse, 10 cigarette smokers with histories of substance abuse were given placebo intravenously on one day and nicotine intravenously in doses of 0.75, 1.5 and 3 mg on another day. The doses of nicotine were given in ascending order at 1-hour intervals. Following completion of the nicotine injections (Day 1) and the placebo injection (Day 2) subjects completed the Addiction Research Center Inventory and were asked to simulate their responses to the intravenous nicotine and to placebo (Haertzen, 1974). The profile of responses was compared to 10 criterion groups based on 4000 responses for various drug-induced subjective states and diagnostic categories (previous studies have shown that addicts can accurately simulate drug-induced subjective states). These studies indicated that nicotine produces a euphoria and a subjective state that most closely resemble those of morphine and, secondarily, cocaine.

The second major group of studies were behavioral pharmacologic studies of intravenously given nicotine using a self-administration paradigm. Subjects were allowed to self-administer through a catheter in 3-hour sessions on a FR10 schedule with 1-minute time outs and 1 dose per session. Five subjects have completed the studies of self-administration of placebo and nicotine in doses of 0.75, 1.5 and 3.0 mg. In these studies, nicotine served as a positive reinforcer with a pattern of responding similar to that observed in animal studies.

It is concluded from these studies that valid methods have been developed for studying the dependence process underlying compulsive tobacco use and further that nicotine is a euphoriant and a positive reinforcer in man.

The first years' experience in the Baltimore clinical research program indicates that the methods and procedures developed in prisoner volunteers are adaptable, that ethical and treatment concerns can be met in such a way as to allow non-therapeutic and therapeutic research in volunteer addicts and alcoholics, and that sufficient numbers of subjects will volunteer for studies.

REFERENCES

Forrest, W.H. Oral Zomepirac and Intramuscular Morphine in Postoperative Pain. J Clin Pharmacol 20:259-261, 1980.

Gold M.S., Pottash A.C., Sweeney D.R., Kleber H.D. Opiate Withdrawal Using Clonidine a Safe, Effective, and Rapid Nonopiate Treatment. JAMA 243(4):343-346, 1980.

Haertzen, C.A. An overview of the Addiction Research Center Inventory Scales (ARCI): an appendix and manual of scales. DHEW Publication No. (ADM) 74-92, Rockville, Maryland: NIDA 1974.

Jasinski, D.R. Assessment of the abuse potentiality of morphine-like drugs, In: Martin, W.R. Drug Addiction. I. Morphine, sedative-hypnotic and alcohol dependence. Handbook of Experimental Pharmacology. Vol. 45. Springer-Verlag, Berlin and Heidelberg, 1977. pp. 197-258.

Jasinski, D.R., Griffith, J.D., Pevnick, J., Gorodetzky, C., Cone, E. and Kay, D. (1977). Progress report from the Clinical Pharmacology Section of the NIDA Addiction Research Center. Presented at 39th Meeting, Committee on Problems of Drug Dependence, National Research Council, Cambridge, Mass.

Jasinski, D.R., Pevnick, J.S. and Griffith, J.D.: Human pharmacology and abuse potential of the analgesic buprenorphine: A potential agent for treating narcotic addiction. Arch Gen Psychiatry 35:501-516, 1978.

Jasinski, D.R., Pevnick, J.S., Griffith, J.D., Gorodetzky, C.W. and Cone, E.J. (1976). Progress report on studies from the Clinical Pharmacology Section of the Addiction Research Center. Presented at 38th Meeting, Committee on Problems of Drug Dependence, National Research Council, Richmond, Va.

Martin, W.R., Fraser, H.F., Gorodetzky, C.W., and Rosenberg, D.E. Studies of the dependence-producing potential of the narcotic antagonist 2-cyclopropylmethyl-2'-hydroxy-5,9-dimethyl-6,7-benzomorphan (cyclazocine, Win-120-740; ARC II-C-3). J Pharmacol Exp Ther, 150:426-436, 1965.

Wallenstein, S.L., Rogers, A., Kaiko, R.F., Heidrich, G., Houde, R.W. Relative Analgesic Potency of Oral Zomepirac and Intramuscular Morphine in Cancer Patients with Postoperative Pain. J Clin Pharmacol 20:250-259, 1980.

Washton A.M., and Resnick R.B. Clonidine Versus Methadone for Opiate Detoxification. Lancet, 1297, 1980.

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Progress Report from the NIDA Addiction Research Center (Pre-clinical Laboratory), Lexington, KY

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In January 1981, the ARC underwent a reorganization, in which the Center was split into two major units, the Clinical Laboratory in Baltimore and the Preclinical Laboratory in Lexington. In this progress report from Lexington, I will briefly review three ongoing studies from several different labs in the unit.

AN OPIUM RATER: A DRUG METABOLIC CASE STUDY

The subject of this study was a 52-yr-old male from Iran admitted to the hospital at Washington University (St, Louis, Mo.) for treatment of cancer of the esophagus. When it was discovered that the patient had been a, chronic opium eater for many years (and had brought his drug supply with him), Dr. Croughan was consulted on the best method for opioid withdrawal, Dr. Croughan contacted us to assist in determining the amount of intake of dependence-producing opiates and the probable level of physical dependence, When a literature search revealed very little drug metabolic data in opium eaters, it was decided to undertake a limited study in this patient.

Clinical Drug History and Samples

The patient had been ingesting for many years approximately 1 g. per day of smoked opium residue (locally called sukhteh), in three divided daily doses. Two sets of samples were obtained for analysis. The first was samples of the opium residue itself. We -received what was described as a typical l-day intake., consisting of three hand-rolled spherical portions of black gummy material. The second sample set was seven consecutive 24-hr. urine collections.

Methods

Morphine, codeine, normorphine, and norcodeine were the compounds of primary quantitative interest from the perspective of opiate physical dependence. An attempt was also made to identify thebaine,

oripavine, papaverine, and noscapine. Analytic methods used were thin-layer chromatography (TLC), gas chromatography (GC), and gas chromatography/mass fragmentography (GC/MF).

TLC, developed with ethyl acetate:methanol:ammonium hydroxide and sprayed with iodoplatinate, was performed on a methanol triturate of the opium residue samples and on urinary extracts with 15 percent isopropanol in dichloroethane at pH 9-10. Urine was extracted both with and without prior hydrolysis by glusalase or acid. For GC and GC/MF,urine was extracted at pH 9.5 with methylene chloride: isopropanol (7:3) after addition of α'-isocodeine as internal standard. The dried residue of the organic phase was silylated with Tri-Sil Z. GC was performed on a 2 mm. x 36 cm. glass column packed with 3 percent OV-210 on 100/120 mesh Gas Chrom Q; temperature of the column was programmed at 10°/min. between 170 and 260° C. MF was performed on a Finnigan Model 4021 GC/MS instrument using the chemical ionization mode with methane serving as both the carrier and reagent gas. The two most prominent ions of the CI spectrum of each compound were selected for monitoring and were generally the (M + 29), (M + 1) , or (M - 15) ions.

Results and Discussion

Qualitative results of the analysis of the smoked opium residue samples indicated the presence of major amounts of morphine and codeine, minor amounts of nor-morphine and norcodeine, and trace amounts of noscapine. There were also TLC spots consistent with trace amounts of oripavine and papaverine. On quantitative analysis, the three opium portions supplied were very close in weight, ranging only from about 286 to 310 mg., with a total daily intake of a little over 900 mg. Morphine content averaged 11.7 percent or 105 mg./day and codeine 5.3 percent or 47 mg./day, giving an estimated daily morphine plus codeine intake of about 153 mg. This composition of the smoked opium residue shows both similarities and differences from the reported composition of raw opium. The nearly 12 percent composition as morphine is consistent with the 10 percent reported in opium; however, the codeine content of over 5 percent is tenfold higher than usually reported for raw opium. Noscapine in raw opium is usually quoted at 6 percent; a trace amount was found in these samples. Papaverine and thebaine, reported as constituting 1 and 0.2 percent of raw opium, respectively, were not found in these residue samples. On the other hand, minor amounts of normorphine and norcodeine were found in these samples and are not reported as constituents of raw opium.

Roth qualitative and quantitative analyses were also performed on the urine samples. Using GC/MF, those compounds identified in the urine were: morphine, codeine, normorphine, norcodeine, and a trace of noscapine. Those standards which could be detected by the method but were not found in the urine extracts were thebaine, papaverine, and oripavine. Urine samples were quantitatively analyzed for morphine, codeine, nor-morphine, and norcodeine, both in the free form and after acid hydrolysis. Conjugated morphine was the major urinary excretion component with total morphine

excretion, making up about 11 to 14.5 percent of the estimated total daily morphine plus codeine intake, with an average daily excretion of about 13 percent. Total codeine accounted for 2.5 to 3.5 percent of the total morphine plus codeine, with a daily average of 3.25 percent; normorphine, about 1 to 1.5 percent, with a daily average of 1.4 percent; and norcodeine, about 0.25 to 0.5 percent, with a daily average of 0.3 percent. Day-to-day variability was greatest for morphine, but not excessive for any of the monitored compounds. Morphine excretion averaged about 4.5 percent in the free form and 95.5 percent as conjugated; codeine and nor-morphine were excreted about 11 percent as free; and norcodeine about 28 percent as free. The proportion of these compounds originating directly from ingested compounds vs. metabolites of ingested opiates is not known. Comparing the composition of the ingested opium residue to the excretion pattern, it seems likely that at least some of the nor compounds represent metabolites of ingested morphine and codeine, and some of the ingested morphine may be a metabolite of codeine. A total of little less than 18 percent of the morphine plus codeine intake could be accounted for in the urinary excretion of these four compounds. Much of the remainder was probably excreted in the feces, and some may have been converted to other metabolites.

In answer to Dr. Croughan's inquiry concerning potential level of physical dependence, using potency estimates of approximately 6:1 for oral vs. parenteral morphine and 20:1 for oral codeine vs. parenteral morphine, we estimated this patient's habit as approximately equivalent to 20 mg. of parenteral morphine per day, a relatively low level of physical dependence. This estimate was consistent with the subsequent clinical course of the patient, who was withdrawn on 400 mg./day of propoxyphene napsylate over 10 days with minimal discomfort.

SPECIFIC BINDING SITES FOR SKF-10047

This study was undertaken to investigate the binding characteristics of SKF-10047 (N-allylnormetazocine), the prototypic sigma receptor agonist in the three receptor scheme of Martin. Binding studies were carried out in guinea pig brain synaptic membranes, and concomitant pharmacologic studies were done in the rat discriminative stimulus model.

Binding Studies

In the binding studies, synaptic membranes were prepared from homogenates of brain of male Hartley guinea pigs. Incubations of synaptic membrane preparation were carried out at 22° C., first with competing ligand in the absence and presence of 0.1 mM unlabeled SKF for 5 min., followed by addition of 1 mM H^3-SKF and reincubation for 15 min., and then an additional 10 min. on ice. Free ligand was separated from bound by rapid filtration through Whatman GF/C filters presoaked in t-amyl alcohol-saturated water, and radioactivity was evaluated by liquid scintillation spectrometry.

Inhibition of specific H^3-SKF binding (i.e., total minus that in the presence of unlabeled SKF) by several opioids was studied. Binding was saturable and represented about 90 percent of total binding. Inhibition of H^3-SKF binding by a series of opioid derivatives gave similar relative potencies as those previously described for displacing H^3-naloxone and probably represent binding of H^3-SKF to mu receptors, where it is a potent antagonist. However, *l*-etorphine, a potent mu agonist, even at very high concentrations could not completely inhibit the binding of H^3-SKF. These "etorphine inaccessible" sites were preliminarily designated as psi-binding sites. The psi-binding sites were subsequently studied in the presence of 100 mM of *l*-etorphine added to mask the assumed mu receptors. Specific psi-binding was studied with different concentrations of H^3-SKF. Scatchard analysis was consistent with a single class of binding sites with apparent K_d of 322 nM and estimated B_{max} of 792 fmol./mg. protein. Relative potencies of a series of opioid derivatives to inhibit H^3-SKF binding to psi-binding sites showed a rank order totally different from inhibition of binding of H^3-naloxone to assumed mu receptors. SKF itself had an IC50 of 254 nM. Traditional morphine-like drugs (such as morphine and levorphanol) and naltrexone were poor inhibitors of SKF psi-binding. However, *d, l*-cyclazocine, dextrorphan, and phencyclidine (PCP) were potent inhibitors and showed monophasic inhibition curves. Several potent inhibitors showed biphasic inhibition curves, with plateaus at about 30 percent binding. These included *d, l*-pentazocine and haloperidol (the most potent psi-binding inhibitors); ethylketocyclazocine, the prototypic kappa receptor agonist; and propranolol. Psi-binding appeared to show stereoselectivity in reverse of that shown for mu receptors. Several *d*-isomers (such as cyclazocine, SKF, and dextrorphan) were three- to 20-fold more potent than their *l*-isomers: A number of other nonopioids, such as imipramine, chlorpromazine, pimozide, and phenoxybenzamine, showed potent inhibition of psi-binding.

Discriminative Stimulus Studies

In order to evaluate the possible pharmacologic relevance of psi-binding, the discriminative stimulus properties of SKF were evaluated in male Fisher rats trained to discriminate between saline and 3 mg./kg. SKF in a two-choice discrete trial avoidance procedure, in which rats were required to respond on one lever after receiving saline and on a second lever after receiving SKF. Animals were trained and maintained at a 90 percent correct response criterion. There was good concordance between the effectiveness of drugs to inhibit specific SKF psi-binding and their effectiveness in producing SKF-like discriminative stimuli. Those drugs inhibiting psi-binding with good potency in a monophasic fashion (such as cyclazocine, phencyclidine, and dextrorphan) also produced greater than 90 percent SKF-appropriate responding. Those drugs which inhibited psi-binding in a biphasic fashion (such as pentazocine, ethylketocyclazocine, and propranolol) produced significant but less than 90 percent SKF-appropriate responding. Haloperidol, which also exhibited biphasic binding, gave a small degree of

SKF-appropriate responding and was able to partially antagonize the discriminative stimulus properties of the training dose of SKF, Drugs which were poor inhibitors of psi-binding (such as levorphanol and naloxone) did not produce SKF-appropriate responding. Also, naloxone was unable to antagonize the discriminative stimulus properties of either the racemic mixture or pure d-isomer of SKF. Preliminary studies with *d*- and *l*-isomers of SKF were consistent with the binding studies and showed that *d*- was the most potent isomer, was not antagonized by naloxone, and was partially antagonized by haloperidol.

Discussion and Conclusions

There appears to be a class of binding sites in guinea pig brain synaptic membranes for SKF: clearly distinguishable from naloxone binding sites. The characteristics of the binding sites appear to be somewhat different from those which have been ascribed to the sigma receptor. Naloxone has been described as an antagonist at the sigma receptor (although there is some debate and opposing data on this point); naloxone did not antagonize psi-binding of SKF nor the discriminative stimulus properties of SKF. Ethylketocyclazocine is proposed to have little or no effect at the sigma receptor, but did oroduce inhibition of psi-binding and significant SKF-appropriate responding. However, the biphasic nature of some of the inhibition curves and the reactivity of ethylketocyclazocine are also consistent with the hypothesis that psi-binding is a mixture of sigma and kappa binding, a possibility which cannot be definitely ruled out at this time. The Scatchard analysis did show one class of binding sites; however, it is possible that a small difference in the affinity and number between two receptors (i.e., sigma and kappa) might be missed in this analysis. The relative effectiveness of a variety of drugs to inhibit specific SKF psi-binding, including the activity of nonopiates and the activity of haloperidol and chlorpromazine, is consistent with the hypothesis that the psi-binding sites may represent the neuronal substrates mediating psychotomimetic effects of certain opioids and other drugs.

BEHAVIORAL STUDIES OF NICOTINE

The potential role of nicotine in the maintenance of tobacco smoking has been questioned in part because of the difficulty in demonstrating consistent reinforcing effects in controlled laboratory studies. The present studies show that nicotine will maintain self-administration behavior in two species, the beagle dog and the squirrel monkey, using several different schedules of reinforcement.

Dog Studies

In the dog studies, four animals with surgically implanted intravenous catheters were studied under two different reinforcement schedules. In the first study, dogs were given access to response-contingent drug infusions during daily sessions consisting of 15 signalled trials, each lasting a maximum of 10 min. During each trial, the dogs could obtain one drug infusion by making 15

responses (i.e., an FR15 schedule). There was a 4 min. timeout between successive trials. Dogs were initially trained on cocaine, attaining stable responding at an overall rate of 0.8 responses/sec. at a 30 ug./kg. dose. Nicotine was tested at four dose levels, each for 7-10 consecutive daily sessions with randomized treatment order. All doses of nicotine were self-administered above saline levels. There was an inverted U-shaped dose response relationship for both number of infusions and average overall response rate with the highest rates of responding and number of infusions occurring at the 30 ug./kg./infusion dose. The local response rate (i.e., from the third to the last response of each ratio) declined monotonically from 1.8 resp./sec. at 10 ug./kg. to 0.5 resp./sec. at 300 ug./kg. There was minimal responding by the dogs during the timeout periods. Vomiting was occasionally seen during or shortly after the daily sessions, particularly at the two highest dose levels.

The second dog study is being performed with a progressive ratio reinforcement schedule. Two dogs have been studied so far, both with considerable progressive ratio experience. Dogs were given access to response-contingent drug infusions during three experimental sessions each day; each session lasted a maximum of 1 hr. with a minimum intersession interval of 3 hr. Only one infusion could be obtained during each session. The response requirement was increased daily until the dog failed to complete the necessary fixed-ratio; that is, until he reached the "break-point." Dogs were tested on saline and four doses each of nicotine and cocaine and treatment order was randomized. All doses of cocaine and nicotine maintained self-administration behavior at FR values well above those of saline. For both drugs there appeared to be a biphasic relationship between dose and break-point. Cocaine was a more effective reinforcer than nicotine under this schedule, attaining break-points several hundred responses greater than the maximum obtainable with nicotine.

Monkey Studies

The monkey studies were the result of a joint collaboration between Drs. Goldberg of the ARC and Roger Spealman of the Harvard Medical School. In the monkey studies, four animals with chronic venous catheters were used; three were experienced and one naive. A second-order schedule of reinforcement was used; experimental sessions were carried out with the subjects sitting in a chair equipped with a response lever and two stimulus lights and enclosed in a sound-attenuated chamber. At the beginning of each experimental session, a green stimulus light was turned on and every 10th lever pressing response during a 1 or 2 min. fixed interval changed the light from green to amber for 1 sec. The first FR10 unit completed after the FI elapsed turned off the green light and produced both the 1 sec. amber light and an i.v. injection of 30 ug./kg. of nicotine. A 3 min. timeout period then followed. Each session ended after the 12th timeout period or 90 min., whichever occurred first.

Stable responding developed in all subjects within 30 sessions and showed the pattern of responding typical of this reinforcement schedule. Overall response rates were consistently high, averaging 0.81 to 1.58 resp./sec.; local rates (from the first to the last response in each FR unit) were even higher, averaging from 1.22 to 4.77 resp./sec. Substitution of saline for nicotine usually resulted in a rapid decline of response rate, which returned rapidly to high rates on reinstitution of nicotine infusions. Tn one monkey, when the rate of responding failed to fall consistently during saline substitution, the brief light presentations during the interval were omitted and the rates of responding fell; the response rate stayed low when the brief amber lights were again presented during saline substitution and did not return to high rates until nicotine infusions were resumed. Pretreatment 30 min. prior to the session with 1 mg./kg. mecamylamine, i.m., caused a decrease in response rates similar to those seen after saline substitution. Overall response rates under the present second-order fixed-interval schedule with brief stimulus presentations were considerably higher than in a previous study using a simple fixed-interval schedule with no stimulus presentations during the interval, although the frequency of nicotine injection was about the same in the two studies. To further explore the role of the brief visual stimulus in maintaining high rates of responding, the amber light presentations were entirely omitted during the interval in two subjects. The amber light was presented only in conjunction with the i.v. nicotine infusion at the end of each interval. Omission of the visual stimulus was followed by a drop in response rates to about one-half the previous rate; and the hign rate returned when the brief stimulus presentations were resumed. These results indicate that nicotine can function as an effective reinforcer under a second-order schedule of drug self-administration and that environmental stimuli associated with nicotine intake can contribute importantly to the maintenance of drug-seeking behavior The second-order schedule of nicotine injection in the squirrel monkey appears to be a sensitive laboratory method for evaluation of both pharmacologic and environmental factors which may play a role in the maintenance of tobacco use by man.

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Evidence for the Release of Endogenous Opiates by Morphine

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Many, many papers have been published on the mechanism of antinociceptive action of morphine and other narcotic analgesics. Yet , the extent of our knowledge of the exact mechanisms by which morphine relieves pain is meager. Certainly the information presented in this report will not clarify the elusive mechanisms involved in pain relief. Hopefully, the approach taken in our laboratory along with the other approaches being carried out in other laboratories at this time will be useful in expanding our knowledge in this area, Cur experiments are based on the hypothesis that morphine and other narcotic analgesics release endogenous opiates which play an intricate and important role in the manifestation of pain relief. The pharmacology of the endogenous opiates resembles that of morphine in most aspects. A good correlation has been shown between the distribution of endogenous opiates and stereospecific opiate-binding sites in brain. However, little evidence has appeared in the literature to suggest that opiates do in fact release endogenous opiates from brain tissue. Puig and Musacchio and their colleagues (4) have shown that extensive stimulation of the isolated guinea pig ileum causes the release of endogenous opiates into the isolated organ bath. We chose to test our hypothesis by studying the concentration of endogenous opiates in cerebrospinal fluid following the injection of antinociceptive doses of morphine.

The mouse was used in the first series of experiments in which we studied the effects of various types of spinalizations on the activity of morphine. The results of these studies have been published in detail (2). Essentially we found that spinal ligation, like cauterized transection, caused a marked reduction in the efficacy of morphine in increasing tail-flick latency. These results showed that morphine’s action in this test system emanated from a supra spinal level. The activity of morphine was not altered when only the neural component of the spinal cord was disrupted. These results suggested that the humoral component

(CSF) was more important than the neural component of the spinal cord for the transmission of the effect of morphine in the brain to inhibition of the tail-flick reflex at the lower spinal level. If in fact this were true, disruption of the flow of CSF down the spinal cord should cause a decrease in the activity of morphine. This was tested by carefully removing a portion of the dura mater at the lower thoracic level of the cord which allowed some of the CSF to leak out rather than be transported to lower portions of the spinal cord. This surgical procedure reduced the antinociceptive activity of morphine by more than fifty percent. These results were confirmed in an experiment in which an opening was made in the cisterna magna and the mice were maintained head down-tail up at a 60-70° angle immediately prior to the injection of morphine and until the post injection tail-flick latency was determined. Wetness of the fur at the opening in many mice confirmed that the CSF was "leaking out" rather than being transported to the lower spinal levels. The activity of morphine was reduced significantly in this experiment.

Our conclusion at this point was that spinalization by cautery, ligation or removal of a portion of the spinal cord blocked the antinociceptive activity of morphine, suggesting that the supra spinal structures are essential for morphine's activity. This conclusion supports the work from many laboratories which shows that a higher concentration of stereospecific opiate-binding sites .exists in the mid or hind brain than in the spinal cord. It has also been shown that although morphine and other narcotic analgesics produce antinociception when administered directly into the spinal cord, the threshold for activity is much lower in a number of sites in the brain stem.

The second conclusion which we drew from these initial experiments was that the humoral component of the mouse spinal cord (CSF) was more important than the neural component for transmitting the effect of morphine in the brain to the actual inhibition of the tail-flick reflex in the lower spinal cord. The existence of stereospecific opiate-binding sites in the spinal cord was essential to our hypothesis that endogenous opiates were released in the brain, transported in the CSF and acted on spinal neurons to inhibit the tail-flick reflex.

We tested our hypothesis that endogenous opiates were released into CSF by morphine by quantitating the opiate-like activity of rabbit CSF taken prior to and after morphine injection in two bioassays, the when para-phenylquinone writhing test and the coaxially stimulated guinea pig ileum. The methods used and the results of these experiments have been published in more detail elsewhere (3). CSF taken from rabbits prior to the injection of morphine caused an inhibition of writhing (26%) indicating that opiate(s) exist in normal CSF. The inhibition was reproducible and significant and was antagonized by naloxone, suggesting that

it was an opiate effect. Much greater inhibition of writhing (60%) was found when CSF taken 1 hour after morphine was injected into the lateral cerebroventricle of mice. This effect was also antagonized by pretreating the mice with naloxone.

CSF taken prior to the administration of morphine to the rabbit caused an inhibition of the coaxially stimulated guinea pig ileum, an assay routinely used to quantitate opiate activity. This modest but reproducible inhibition was antagonized by naloxone. Considerably more inhibition of the coaxially stimulated guinea pig-ileum was seen following the addition of CSF taken after the injection of morphine to the rabbit. Again, this inhibition was reversed by naloxone.

Pretreating the rabbit with 2 mg/kg naloxone apparently blocked the release of endogenous opiates since CSF taken 1 hour following morphine in naloxone-pretreated rabbits did not inhibit writhing or block the twitch induced by coaxial stimulation of the guinea pig ileum. These results are not surprising, since naloxone probably antagonized the binding of the morphine to the opiate-sensitive binding sites on the cells which released the endogenous opiate.

An obvious alternate hypothesis to explain our data was that morphine itself existed in the CSF in sufficient quantities to activate opiate-sensitive binding sites in the spinal cord and block the tail-flick reflex, inhibit paraphenylquinone-induced writhing and block the coaxially stimulated guinea pig ileum. This possibility was tested by administering ^{3}H-dihydromorphine and in another experiment ^{3}H-morphine to rabbits,taking CSF one-hour after administration and quantitating the radioactivity per sample of CSF. In this way we quantitated both the parent compound and all metabolites which may have opiate effects. The results of these experiments are presented in Tables 1 and 2.

The data presented in these tables caused us to conclude that the opiate-like activity of CSF taken after the administration of morphine was not due to the presence of morphine and/or its metabolites in CSF. This conclusion was based on the fact that the total amount of radioactivity in the 5 ul of CSF, the volume injected per mouse, was approximately one-fiftieth the minimal effective dose of morphine in the writhing test and the concentration of radioactivity in 0.4 ml CSF was approximately 75 percent of the minimally effective dose of morphine in the coaxially stimulated guinea-pig ileum assay. The existence of opiate-like material in the CSF of untreated rabbits supported this conclusion.

Further support for this position was generated from a study of the stability of the opiate-like material in CSF. A sample of

TABLE 1

Relationship Between Morphine Levels in Cerebrospinal Fluid of Rabbits Injected with 10 mg/kg Radiolabelled Morphine Sulfate or Dihydromorphine and Effective Doses of Morphine in the Wriching Test

Radiolabelled Drug Administered	Animals #	Morphine Equivalents in CSF (ng/ml)	Morphine Equivalents in 5 µl CSF (ng)
^{3}H-dihydro-morphine	1	190	0.95
	2	130	0.65
^{14}C-morphine	3	128	0.64
	4	134	0.67
	5	134	0.67
$\overline{x}$ ± S.E.M.		143.8 ± 11	0.71 ± 0.06

Minimal effective dose of morphine given i.v.t. in the writhing test - 10 ng

ED-50 of morphine given i.v.t. in the writhing test - 50 ng

TABLE 2

Relationship Between Morphine Levels in Cerebrospinal Fluid of Rabbits Injected with 10 mg/kg Radiolabelled Morphine Sulfate on Dihydromorphine and Effective Doses of Morphine in the Guinea Pig Ileum Assay

Radiolabelled Drug Administered	Animal #	Morphine Equivalents in CSF (ng/ml)	Morphine Equivalents in in 400 µl CSF Diluted to 10 ml (moles/l)
^{3}H-dihydromorphine	1	190	1×10^{-8}
	2	130	7×10^{-9}
^{14}C-morphine	3	128	7×10^{-9}
	4	134	7×10^{-9}
	5	134	7×10^{-9}
$\bar{x}$ ± S.E.M.		143.8 ± 11	7.6×10^{-9}

Minimal effective concentration of morphine in guinea pig ileum assay 1×10^{-8}

ED-50 of morphine in guinea-pig ileum assay 1×10^{-7}

CSF, taken from a rabbit one hour after the injection of morphine, was injected into the lateral cerebroventricle of mice to test for its ability to inhibit paraphenylquinone-induced writhing immediately after it was taken from the rabbit. Another aliquot of the same sample was placed in a vial at room temperature and two hours later injected into the lateral cerebroventricle of other mice and tested for its ability to block writhing. Morphine was added to CSF taken from an untreated rabbit in sufficient amount to inhibit paraphenylquinone-induced writhing to an extent similar to that seen in the CSF taken from the morphine-treated rabbit. An aliquot of the CSF to which morphine was added was also stored at room temperature for 2 hours and then injected into the lateral ventricle of mice and tested for its ability to inhibit paraphenylquinone-induced writhing. The results of this experiment are presented in Table 3.

TABLE 3

Comparison of the Stability of Endogenous Opiate-Like Material and Morphine in Rabbit CSF

	Percent Inhibition of PPQ Writhing	
Sample	No Incubation Period	2 Hr Incubation at Room Temperature
CSF from a rabbit treated with 10 mg/kg morphine	60	0
Morphine added to CSF from a drug naive rabbit	89	96

The data presented in Table 3 convinced us that the opiate material in CSF taken after morphine treatment to the rabbits was not morphine itself. As a matter of fact, the stability of morphine in control CSF as quantitated in the writhing bioassay exceeded 8 hours.

The data presented in this manuscript and data submitted for publication elsewhere cause us to propose that morphine stimulates the release of endogenous opiates which are an important step in the manifestation of the antinociceptive action of morphine. The endogenous materials diffuse into intercellular fluid (CSF) and are carried throughout the central nervous system in CSF. The results of our experiments suggest to us that these endogenous opiates cause the inhibition of the tail-flick reflex in mice. It is our proposal that the released endogenous opiates interact with stereospecific opiate-binding sites on neurons in the brain, and possibly the spinal cord, of many other species

including man, to produce analgesia. The release of endogenous opiates by morphine has been reported by other workers (1). On a more global basis, it is our working hypothesis that all manipulations including drugs, acupuncture, stress and others, that relieve pain do so by releasing endogenous opiates. The observation that naloxone blocks the analgesia induced by each of these modalities supports our hypothesis. The isolation, characterization and eventual identification of these endogenous opiates is the main goal of our current research efforts.

REFERENCES

1. Same, Y., Gothilf, Y. and Weissman, B.A. Endogenous and Exogenous Opiate Agonists and Antagonists. New York: Pergamon Press Inc., 1980. 317 pp.

2. Dewey, W.L., Fu, T.C., Izazola-Conde, C. and Halenda, S.P. Characteristics and Function of Opioids. New York: Elsevier North-Holland, Inc., 1978. 271 pp.

3. Fu, T.C. and Dewey, W.L. Morphine antinociception: Evidence for the release of endogenous substance(s). Life Sciences, 25:53-60, 1979.

4. Puig, M.M., Gascon, P., Craviso, G.L. and Musacchio, J.M. Endogenous opiate receptor ligand: Electrically induced release in the guinea pig ileum. Science, 195:419, 1977.

   Puig, M.M., Gascon, P., Musacchio, J.M. Endorphin release: Cross tolerance to morphine. Eur. J. Pharmacol., 45:205, 1977.

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Comparison of the Effects of Buprenorphine and Methadone on Opiate Self-Administration in Primates

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The primate drug self-administration model was used to compare the relative efficacy of buprenorphine and methadone in suppressing opiate self-administration. Although the value of this model in predicting drug abuse liability has been repeatedly demonstrated (cf. Griffiths et al. 1980), it has seldom been used to evaluate the efficacy of phannacotherapies for the treatment of heroin addiction.

Buprenorphine is a new mixed opiate agonist-antagonist drug which significantly suppressed heroin self-administration by heroin addicts in controlled clinical studies (Mello and Mendelson,1980). Buprenorphine has 25 to 40 times the analgesic potency of morphine and similar subjective effects, but it does not produce significant physical dependence after prolonged administration (Houde, 1979; Jasinski et al. 1978; Lewis et al. 1981). Buprenorphine's antagonistic properties can effectively block the effects of high doses of morphine for 24 to 36 hours (Jasinski et al. 1978). The antagonistic component appears to preclude buprenorphine overdose (Lewis et al. 1981).

Methadone, an opiate agonist, has been used to treat heroin addiction for over 15 years. It induces cross-tolerance to the euphoric effects of other opiates and after abrupt termination, a protracted morphine-like withdrawal syndrome occurs. Despite its demonstrated clinical utility, methadone abuse has been associated with overdose deaths (Kreek, 1978). Clinical studies have consistently shown that methadone reduces but seldom completely eliminates opiate use (Martin et al. 1973; Jones and Prada, 1975) . Moreover, some methadone-maintained patients engage in a diverse pattern of polydrug use.

METHODS

The effects of maintenance on methadone or buprenorphine on opiate and food self-administration were studied. An ascending and descending 'series of doses of methadone (0.179 to 4.73 mg/kg/

day) and buprenorphine (.014 to .789 mg/kg/day) were compared with saline control and drug free baseline conditions. Each successive dose of buprenorphine or methadone was studied for 20 sessions over 5 consecutive days. Buprenorphine and methadone doses were extrapolated on a mg/kg basis from doses shown to be clinically effective in suppressing opiate self-administration in man (Martin et al. 1973; Mello and Mendelson, 1980). Methadone doses were comparable to 12.5 to 330 mg/day in man. Buprenorphine doses were comparable to 1 to 56 mg/day in man.

This report describes the effects of a single ascending dose series of methadone or buprenorphine on opiate and food self-administration in two groups of monkeys; the descending dose series on the same maintenance drug is still in progress. Subsequently, the buprenorphine maintenance group will be studied under methadone maintenance conditions and the methadone maintenance group will be studied under buprenorphine maintenance conditions in a single cross-over design.

Data are reported on 5 male monkeys that weighed between 5.3 and 8.4 kg. Four monkeys had a long history of opiate agonist and mixed agonist-antagonist self-administration. One experimentally naive monkey (A420) was trained to self-administer dilaudid (.02 mg/kg/inj) for 25 days, then heroin (.01 mg/kg/inj) was substituted for dilaudid. Three monkeys were rhesus and 2 monkeys (A389 and A429) were pigtail macaques. Monkeys were maintained at ad lib weight and were given multiple vitamins, fresh fruit and vegetables to supplement a banana pellet diet.

Monkeys worked at an operant task for food (1 gm banana pellet) and for either dilaudid (.02 mg/kg/inj) or heroin (.01 mg/kg/inj). Food and drug self-administration were maintained under a second-order schedule of reinforcement (FR 4 (VR 16:S)). An average of 16 responses on a variable ratio schedule (VR 16) produced a brief colored stimulus light (S+). However, a drug injection or a food pellet was delivered only after a fixed ratio of 4 (FR 4) of the VR 16 response requirements had been completed; i.e., each food pellet or drug injection required an average of 64 responses. Second-order schedules were used to minimize the possible sedative effects of drug infusions on operant responding.

Four periods of food availability and of drug availability occurred each- day. A 1-hour food session was followed by a 1-hour drug session and 2 hours of time-out when responses had no programmed consequences. The conditions of food and drug availability and time-out periods each were associated with a different colored stimulus light (S+) projected on a translucent response key on an operant panel. Drug injections were limited to 20 per session or 80 per day and food pellets were limited to 65 per session or 260 per day. Experiments continued 24 hours a day, 7 days a week.

Each monkey was surgically implanted with a double lumen catheter under aseptic conditions. Opiates were self-administered

through one lumen and maintenance drug solutions were injected through the second lumen so that there was no confounding of the two drug administration procedures. Buprenorphine, methadone and saline control solutions were given intravenously at 9:30 a.m., 2½ hours before the first daily drug session and 13½ hours before the last daily drug session. A single daily methadone or buprenorphine injection corresponds to the frequency with which these drugs are used clinically to suppress illicit opiate self-administration.

Methadone, heroin (3-6 diacetylmorphine), dilaudid and buprenorphine hydrochloride solutions were diluted to the appropriate concentration for individual monkeys and doses are expressed in terms of salts. All drug solutions were passed through millepore filters to remove pyrogens.

RESULTS AND DISCUSSION

Buprenorphine and methadone had divergent effects on both opiate and food self-administration over a dose range shown to be clinically effective in suppressing opiate use in opiate addicts. Buprenorphine significantly suppressed opiate self-administration, whereas methadone was associated with increased opiate self-administration at doses equivalent to 130 to 240 mg/day in man. Buprenorphine maintenance was associated with increased food self-administration which was often significant at higher dose levels whereas methadone maintenance was associated with decreased food self-administration.

Table 1 shows that *buprenorphine* at doses of .170 mg/kg/day (equal to 12 mg/day in man) produced a significant suppression of opiate self-administration in comparison to baseline in 3 monkeys. However, it was necessary to increase the daily dose of buprenorphine to the equivalent of 24-32 mg/day in man to achieve a 71% to 86% suppression of heroin self-administration in a monkey (A389) taking high baseline levels of opiates. An 83% to 97% suppression of opiate self-administration was achieved at lower buprenorphine doses in a monkey (B205) with a lower baseline level of opiate intake. After a transient suppression of opiate self-administration at buprenorphine doses of .170 to .226 mg/kg/day, Monkey A420 self-administered significantly more heroin than during baseline conditions at buprenorphine doses of .254 to .504 mg/kg/day . Significant sustained suppression of opiate self-administration by 79% to 95% required .675 to .789 mg/kg/day of buprenorphine, equivalent to 48 to 56 mg/day in man. Monkey A420 differed from Monkeys A389 and B205 in two respects: he was experimentally naive when these studies began, and he worked for heroin instead of dilaudid.

Considerably higher doses of buprenorphine were required to suppress opiate self administration in monkey than in man. A daily buprenorphine dose of 8 mg SC suppressed heroin self-administration by 95% to 98% in 4 subjects and by 69% to 84% in 2 subjects, whereas placebo maintenance subjects took between 93%

TABLE I - BUPRENORPHINE EFFECTS ON OPIATE SELF-ADMINISTRATION [INJECTIONS PER DAY (X ± S.E.)]†

Buprenorphine Dose (mg/kg/day)	Base-line	Saline	.028	.056	.087	.114	.142	.170	.198	.226	.254	.282	.336	.390	.447	.504	.561	.618	.675	.732	.789
Dose Equivalent In Man (mg/day)			2	4	6	8	10	12	14	16	18	20	24	28	32	36	40	44	48	52	56
Monkey A389 Dilaudid .02 mg/kg/inj	68.87 ±3.81	80.0 ±0	80.0 ±0	72.60 ±4.53	64.60 ±7.14	64.60 ±7.01	38.40*** ±2.69	46.80** ±6.04	48.20** ±4.96	50.60** ±7.62	30.20*** ±7.86	37.20*** ±4.05	18.0*** ±3.0	20.0*** ±6.50	9.20*** ±4.66						
Monkey B205 Dilaudid .02 mg/kg/inj	10.07 ±1.67	7.40 ±3.17	5.00 ±3.79	10.60 ±4.12	9.00 ±4.92	9.60 ±8.15	5.00 ±4.27	3.00* ±2.28	2.80* ±1.59	6.20 ±3.44	1.80* ±1.56	0.60** ±0.40	0.40** ±0.24	1.60* ±0.75	2.40* ±1.44						
Monkey A420 Heroin .01 mg/kg/inj	53.87 ±2.07	58.80 ±1.85	63.00 ±7.78	60.0 ± 0	57.40 ±7.49	65.00* ±4.45	60.00 ±6.17	35.60* ±14.36	45.00 ±7.48	38.40** ±6.39	71.40*** ±3.47	63.0 ±5.74	68.20* ±2.25	74.80*** ±3.09	61.40 ±3.85	63.20* ±1.83	47.80 ±4.13	37.40* ±8.67	11.20*** ±3.21	7.00*** ±4.12	2.80*** ±2.08

TABLE II - METHADONE EFFECTS ON OPIATE SELF-ADMINISTRATION [INJECTIONS PER DAY (X ± S.E.)]†

Methadone Dose (mg/kg/day)	Base-line	Saline	.179	.357	.714	1.07	1.43	1.58	1.73	1.88	2.03	2.18	2.33	2.63	2.93	3.23	3.53	3.83	4.13	4.73
Dose Equivalent In Man (mg/day)			12.5	25	50	75	100	110	120	130	140	150	160	180	200	220	240	260	280	330
Monkey A105 Heroin .01 mg/kg/inj	42.73 ±4.10	40.00 ±4.07	53.80 ±3.79	51.60 ±2.32	56.80 ±6.85	57.60 ±7.78	35.40 ±5.73	36.0 ±1.0	40.60 ±2.42	50.20 ±2.54	61.80* ±0.49	64.60** ±1.54	60.00 ±9.02	73.80*** ±3.59	64.60 ±6.36	80.0*** ±0.0	55.40 ±5.99	40.60 ±4.86	36.80 ±7.02	50.20 ±5.11
Monkey A319 Heroin .01 mg/kg/inj	30.53 ±3.13	25.40 ±1.86	16.80 ±7.90	17.80 ±1.32	25.60 ±1.50	29.80 ±1.16	28.60 ±1.08	30.60 ±0.98	42.00 ±0.89	41.60 ±1.75	41.60 ±2.48	39.80 ±2.13	38.20 ±2.08	40.80 ±2.23	37.00 ±1.30	37.80 ±1.83	35.00 ±1.26	39.20 ±1.82	41.60 ±1.17	54.20*** ±3.54

†Each data point equals 20 sessions over 5 days except drug free baseline which equals 60 sessions over 15 days

*Different from baseline ($p < .05$); **Different from baseline ($p < .01$); ***Different from baseline ($p < .001$)

and 100% of all the heroin available (Mello and Mendelson, 1980).

These data do not confirm an earlier report that pre-treatment with buprenorphine over a dose range of .003 to .30 mg/kg had no significant effect on morphine self-administration in monkey (Downs and Harrigan, 1978). Downs and Harrigan (1978) observed significant increases in morphine self-administration during continuous infusion of buprenorphine at doses of .020 and .040 mg/kg/hr in monkeys not physiologically dependent on morphine. However, no comparable increases in opiate self-administration at relatively low doses of buprenorphine (.014 to .087 mg/kg/day) were seen in the present study.

In contrast to buprenorphine, which produced dose-related decrements in opiate self-administration, maintenance on *methadone* was associated with increased heroin self-administration (Table 2). At methadone doses equivalent to 120 to 240 mg/day in heroin self-administration increased by 14% to 87%. At methadone doses equivalent to 260 to 330 mg/day in man, heroin self-administration remained higher (A319) or equivalent to baseline levels (A105). The most parsimonious interpretation of these data appears to be that methadone over a dose range of .179 to 4.73 mg/kg/day did not induce sufficient cross tolerance to significantly attenuate the reinforcing properties of heroin. Analysis of the distribution of heroin injections across daily drug sessions, 2½ to 13½ hours after methadone administration, showed no significant differences in number of drug injections taken during the first two and last two sessions each day. This suggeststhatpossible differences in the duration of action of methadone in monkey and man did not significantly influence data obtained.

Increased heroin self-administration during methadone maintenance was associated with suppressed food intake which was significantly below baseline levels in Monkey A105 (Table 3). However, there were no significant changes in body weight across the dose-range studied. Maintenance on increasing doses of buprenorphine was associated with increased food self-administration (Table 4). These increases were often significantly above baseline at higher buprenorphine doses, Buprenorphine appears to antagonize the usual depressant effects of opiates on food self-administration. These data confirm our previous observations that chronic buprenorphine self-administration at daily dose levels of 1.0 to 3.0 mg/kg was usually associated with significant increases in food self-administration (Mello et al. 1981).

In conclusion, these data suggest that buprenorphine may be more effective than methadone in suppressing heroin self-administration. However, controlled clinical comparisons of these drugs remain to be done. These data are consistent with a clinical evaluation of buprenorphine in heroin addicts (Mello and Mendelson, 1980). Persistence of heroin self-administration during methadone maintenance is consistent with the composite clinical experience (Martin et al. 1973; Jones and Prada, 1975) as well as animal studies (Griffiths, 1976; Jones and Prada, 1977).

TABLE III - METHADONE EFFECTS ON FOOD SELF-ADMINISTRATION [BANANA PELLETS PER DAY (x ± S.E.)]†

Methadone Dose (mg/kg/day)	Base-line	Saline	.179	.357	.714	1.07	1.43	1.58	1.73	1.88	2.03	2.18	2.33	2.63	2.93	3.23	3.53	3.83	4.13	4.73
Dose Equivalent In Man (mg/day)			12.5	25	50	75	100	110	120	130	140	150	160	180	200	220	240	260	280	330
Monkey A105 Heroin .01 mg/kg/inj	197 ±17	198 ±13	162 ±50	151 ±17	107* ±22	160 ±13	167 ±17	144 ±4	99** ±25	78** ±21	114* ±6	136 ±7	97* ±21	148 ±23	123* ±9	184 ±10	170 ±22	191 ±13	158 ±30	159 ±13
Monkey A319 Heroin .01 mg/kg/inj	141 ±11	187* ±5	92 ±23	144 ±14	124 ±15	111 ±7	104 ±6	116 ±11	87 ±30	107 ±11	124 ±9	110 ±5	96 ±14	87* ±17	98 ±11	90** ±6	82** ±11	81** ±13	90** ±6	174 ±21.76

TABLE IV - BUPRENORPHINE EFFECTS ON FOOD SELF-ADMINISTRTAION [BANANA PELLETS PER DAY (X ± S.E.)]†

Buprenorphine Dose (mg/kg/day)	Base-line	Saline	.014	.028	.056	.087	.114	.142	.170	.198	.226	.254	.282	.336	.390	.447	.504	.561	.618	.675	.732	.789
Dose Equivalent In Man (mg/day)			1	2	4	6	8	10	12	14	16	18	20	24	28	32	36	40	44	48	52	56
Monkey A389 Dilaudid .02 mg/kg/inj	128 ±10	173* ±13	144 ±9	110 ±5	136 ±13	95 ±9	89 ±21	117 ±8	102 ±21	127 ±33	142 ±14	180* ±23	165* ±11	169** ±5	129 ±22	145 ±13						
Monkey B205 Dilaudid .02 mg/kg/inj	32 ±8	64 ±14	92* ±9	42 ±21	88 ±8	103*** ±6	99*** ±9	116*** ±7	111*** ±3	137*** ±9	123*** ±7	109*** ±7	103*** ±9	116*** ±3	121*** ±10	111*** ±6						
Monkey A420 Heroin .01 mg/kg/inj	93 ±6	92 ±10	68 ±15	97 ±5	109 ±13	110 ±9	122* ±14	112 ±8	114 ±17	188*** ±47	168** ±13	180*** ±10	173*** ±10	143*** ±11	100 ±14	101 ±11	100 ±7	79 ±1	98 ±22	120 ±5	113 ±12	114 ±15

Each data point equals 20 sessions over 5 days except drug free baseline which equals 60 sessions over 15 days.

*Different from baseline ($p < .05$); **Different from baseline ($p < .01$); ***Different from baseline ($p < .001$)

REFERENCES

Downs, D.A. *and Harrigan, S.* Preclinical pharmacologic and toxicologic evaluation of compounds used in the treatment of narcotic addiction. Section I: Pharmacologic evaluation of antagonists. Contract Report: NIDA 271-77, 3421, Personal Communication, 1978.

Griffiths, R.R., Bigelow, G. and Henningfield, J.E. Similarities in animal and human drug taking behavior. In: Mello, N.K., ed. Advances in Substance Abuse, Behavioral and Biologic Research, Vol. 1, Greenwich: JAI Press, Inc., pp. 1-90, 1980.

Griffiths, R.R., Wurster, R.M. and Brady, J.V. Discrete trial choice procedure: Effects of naloxone and methadone on choice between food and heroin. Pharmacological Reviews, 27(3):357-365,1976

Houde, R.W. Analgesic effectiveness of the narcotic agonist-antagonists. Br J Clin Pharmac, (Suppl No 3) 297-308, 1979.

Jasinski, D.R., Pevnick, J.S. and Griffith, J.D. Human pharmacology and abuse potential of the analgesic buprenorphine. Arch Gen Psychiatry, 35:601-616, 1978.

Jones, B.E. and Prada, J.A. Drug seeking behavior during methadone maintenance. Psychopharmacologia (Berl.), 41:7-10, 1975.

Jones, B.E. and Prada, J.A. Effects of methadone and morphine maintenance on drug seeking behavior in the dog. Psychopharmacology, 54:109-112, 1977.

Kreek, M.J. Medical complications in methadone patients. In: Kissin, B., Lowinson, J. and Millman, R., eds. Recent Developments in Chemotherapy of Narcotic Addiction, Ann New York Acad Sci, 311:110-134, 1978.

Lewis, J., Rance, M.J. and Sanger, D.J. The pharmacology and abuse potential of buprenorphine, a new antagonist analgesic. In: Mello, N.K., ed. Advances in Substance Abuse, Behavioral and Biological Research, Vol. 3, Greenwich: JAI Press, Inc., (in press), 1981.

Martin, W.R., Jasinski, D.R., Haertzen, C.A., Kay, D.C., Jones, B. E., Mansky, P.A. and Carpenter, R.W. Methadone - a re-evaluation. Arch *Gen Psychiatry,* 28:286-295, 1973.

Mello, N.K. and Mendelson, J.H. Buprenorphine suppresses heroin use by heroin addicts. Science, 207-657-659, 1980.

Mello, N.K., Bree, M.P. and Mendelson, J.H. Buprenorphine self-administration by rhesus monkeys. Pharmac Biochem Behav, (in press), 1981.

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Oral Self-Administration of Phencyclidine (PCP) and PCP Analogs and Tolerance to PCP's Behavioral Effects

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Phencyclidine (PCP) has been demonstrated to serve as a potent reinforcer when self-administered orally by rhesus monkeys (Carroll and Meisch, 1980). The oral preparation is well-suited for the study of PCP's behavioral effects, since it is a common mode of human PCP abuse. The oral preparation lasts the life of the animal, allowing for a series of within-subject comparisons and a model of chronic drug abuse. In addition, with the oral route, it is possible to offer a choice between two or more substances.

The present paper summarizes the results of three studies. In the first study, methods were developed for rapidly establishing PCP as a reinforcer, without using a food reinforcement schedule or food 'deprivation to induce PCP drinking. In previous work whereby orally-delivered ethanol (Meisch and Henningfield, 1977, etonitazene (Carroll and Meisch, 1978) and pentobarbital (Meisch et al., 1981) were established as reinforcers, schedule-induced polydipsia or food-induced drinking procedures were used. These procedures require food depriving the animal and presenting the daily food ration while only the drug is available to drink. In the second study, two PCP analogs (PCE and TCP) were substituted for PCP and compared for their reinforcing effects. There have been previous comparisons of the PCP analogs with respect to discriminative stimulus properties (Brady and Balster, 1981; Brady et al., 1980; Shannon, 1980) and effects on schedule-controlled behavior (Brady and Balster, 1980); however, their relative reinforcing potential has not yet been determined. In the third study, the acquisition and loss of tolerance were examined in monkeys self-administering orally-delivered PCP.

Methods

Fourteen adult male rhesus monkeys served as subjects. Daily 3-hr drug self-administration sessions began at 11:00 a.m. Each session was preceded and followed by a 1-hr timeout when no liquids or stimulus conditions were presented. During the 19-hr

intersession period water was freely available. Each experimental chamber contained a panel on one wall with two drinking spouts and a large jeweled stimulus light above each. A green light signaled water, a blinking green light, PCP and a yellow light, saccharin. Liquid deliveries (0.5 ml) were contingent upon lip-contact responses on solenoid-operated drinking spouts under a fixed-ratio (FR) schedule. The number of lip-contact responses required for a liquid delivery varied between 1 and 16. PCE (N-ethyl-1-phencyclohexamine), PCP (1- 1-phencyclohexyl) pipiridine and TCP (1- 1-(2-thienyl) cyclohexyl pipiridine) HCI (NIDA: Research Triangle Institute) concentrations are expressed in terms of the salt. Further details of the procedure and apparatus have been previously reported (Carroll and Meisch, 1980; Carroll et al., 1981b; Henningfield and Meisch, 1976).

Experiment 1: Rapid Acquisition of PCP-Reinforced Behavior. Two procedures were tested: food deprivation and food satiation, and there were four monkeys in each group. All monkeys were experimentally naive except M-A1 and M-G who had previous i.v. drug self-administration experience in another laboratory. The specific procedure and results are described in tables 1 and 2. Experimental conditions were run sequentially as they are listed from left to right at the top of the table. Each condition was held constant until five sessions of stable behavior were obtained.

The first group of monkeys (table 1) was initially food satiated and water was available from both drinking devices under an FR 1 schedule. A PCP (0.25 mg/ml) solution was then substituted for water at both drinking devices during the session. When behavior stabilized, the monkeys were food deprived by allowing them access to only 75 g of food after the daily 3-hr session. The FR was then gradually increased from 1 to 8. At FR 8 concurrent water was introduced, and side positions were reversed daily. The FR for both PCP and water was then increased to 16. Table 1 shows that food deprivation increased drug self-administration nearly two-fold. Similar results have been previously reported (e.g., Carroll et al., 1979, 1981a). When the FR was increased from 1 to 8, the number of liquid deliveries (vs. water) under the concurrent FR 8 schedule indicated that the drug was serving as a reinforcer. An increase in the FR to 16 resulted in a greater contrast between drug and water. The mean number of sessions of drug availability before PCP was demonstrated to serve as a reinforcer was 37.2.

The procedure used in the second group (table 2) was similar to the first except that the monkeys were food satiated throughout the acquisition phase. Table 2 shows that baseline drinking rates were much lower in this group, and when PCP was substituted for water, liquid deliveries increased. However, liquid deliveries decreased only slightly as the FR was increased. After a mean of 25.9 drug sessions, it was clearly demonstrated PCP was serving as a reinforcer. Thus, it appeared that food-induced drinking (e.g., polydipsia) conditions and food deprivation were not necessary to establish PCP as a reinforcer. The number of

liquid deliveries in the food satiated group nearly doubled when the monkeys were food deprived after the acquisition procedure.

Table 1: Mean** Session Liquid Deliveries

Feeding Condition	Food Satiated		Food Deprived							
Fixed Ratio	1	1	1	2	4	8	8	8*	16	16*
Concentration	0	.25	.25	.25	.25	.25	.25	& 0	.25	& 0
Monkey										
M-C	619.4	1039.8	1676.6	1283.6	893.2	428.4	420.0	233.2	291.2	54.5
M-E	795.8	794.4	2122.6	1658.6	801.2	389.6	477.0	131.6	190.6	6.6
M-J	615.6	539.8	903.8	965.6	876.4	600.0	435.6	154.6	376.0	47.6
M-R2	1042.8	1073.8	1438.4	1176.5	801.0	357.4	206.8	72.0	270.4	38.2
Mean (N=4)	768.4	861.8	1535.4	1270.9	842.9	443.8	384.9	147.8	282.1	36.7
Mean S.E.s	64.1	70.1	59.1	49.8	68.8	20.7	31.9	58.5	15.9	8.2
Mean Total Sessions	7.3	9.7	9.8	6.5	5.7	5.5	7.3		10.3	

* Phencyclidine (0.25 mg/ml) and water (0) were concurrently available.
** Individual means are calculated from the last five sessions at each condition.

Table 2: Mean** Session Liquid Deliveries

Feeding Condition	Food Satiated									Food Deprived	
Fixed Ratio	1	1	2	4	8	8	8*	16	16*	16	16*
Concentration	0	.25	.25	.25	.25	.25	& 0	.25	& 0	.25	& 0
Monkey											
M-A1	427.0	521.0	550.2	554.3	535.0	405.2	262.3	240.2	131.2	355.6	9.8
M-B1	153.2	158.0	123.0	102.6	56.4	87.4	56.4	100.2	17.4	267.0	25.3
M-G	527.6	212.8	214.8	186.4	141.0	206.6	89.0	249.8	20.8	302.6	18.6
M-H	563.0	271.0	339.2	289.0	247.6	217.8	136.2	122.2	64.0	205.8	65.2
Mean (N=4)	417.7	290.5	306.8	283.1	245.0	229.3	135.9	178.1	58.4	282.8	29.7
Mean S.E.s	51.8	28.3	33.4	16.7	16.2	18.1	9.2	12.3	6.2	15.4	6.4
Mean Total Sessions	8.5	9.0	7.0	4.7	5.2	6.5		8.3		14.0	

* Phencyclidine (0.25 mg/ml) and water (0) were concurrently available.
** Individual means are calculated from the last five (or less in the case of M-A) sessions at each condition.

Experiment 2: Substitution of PCP Analogs for PCP. A separate group of three rhesus monkeys (M-B, M-M1 and M-R1) was used in this experiment. They had been trained according to food-induced drinking procedures previously described (Carroll and Meisch, 1980). After a stable baseline was obtained under a concurrent FR 16 schedule with PCP (0.25 mg/ml) and water, a range of concentrations was tested according to the following sequence: 0.25, 0.5, 0.25, 0.125, 0.25, 0.0625, 0.025, 0.0312, 0.25, 0.0156, 0.25. Each concentration was held constant until at least five sessions of stable behavior were obtained. An identical procedure was used with PCE. A mean of approximately 6

sessions was necessary to obtain stable behavior; there did not appear to be any tolerance to self-administration behavior. When TCP was substituted for PCP at 0.25 mg/ml, two of the monkeys (M-M1 and M-R1) showed marked muscle rigidity, and signs of severe ataxia were present for over 24 hr. The monkeys were then given access to the following TCP concentration series: 0.0625, 0.125, 0.25, 0.5, 0.0625, 0.0312, 0.0156, 0.0625, 0.25 mg/ml.

The results shown in Figure 1 indicate that all compounds were self-administered in excess of water; thus they served as effective reinforcers over a range of concentrations. PCE appeared to be considerably less potent than PCP, and TCP was the most potent of the three drugs tested. Behavioral observations revealed that PCE had very little effect, but PCP and TCP produced severe behavioral disruptions (e.g. ataxia, anesthesia) at the higher concentrations. These effects lasted 4 to 6 hr with PCP, but only 10 to 15 minutes with TCP. That TCP was more potent and shorter acting might suggest that it would serve as a more effective reinforcer. The comparison of potency of these three compounds in a self-administration test agrees with a report of their effects on suppression of operant responding in squirrel monkeys (Brady et al., 1980). However, the present results differ from relative potencies found with effects on fixed-interval performance in rhesus monkeys (Brady et al., 1980) motor performance in mice (Balster, 1981; Pinchasi et al., 1978) and tests of the discriminative stimulus properties of the three compounds (Brady and Balster, 1980; Shannon, 1980).

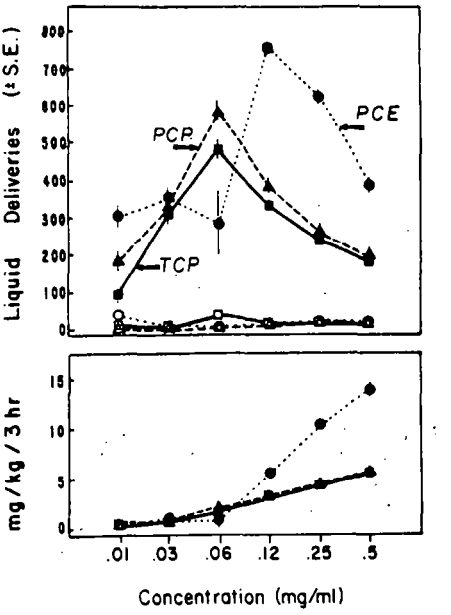

Figure 1. Mean liquid deliveries (upper frame) and mg/kg intake (lower frame) are presented for PCE (circles, dotted lines), PCP (triangles, dashed lines) and TCP (squares, solid lines) over a range of concentrations. Open symbols refer to concurrent water deliveries. Each point represents the mean of 15 observations: 3 monkeys x the last five sessions of stable behavior at each concentration. Vertical bars represent the mean (N = 3) standard errors (2) of the mean.

Tolerance to the Effects of Orally Self-Administered Phencyclidine on Saccharin-Maintained Behavior. Three additional monkeys (M-A, M-R, M-M2) were used. PCP (0.25 mg/ml) or water was available on the left drinking device and a saccharin solution (0.05% wt/vol) was available on the right. A five component schedule was used (see Figure 2). During the first component (20 min), the saccharin solution was available from the right drinking spout under an FR 8 schedule. This component was used as a control for nonspecific changes in saccharin-maintained behavior. The second component was a 5-min timeout when all stimulus conditions were off and responses in the drinking spouts had no consequences. In the third component (30 min), phencyclidine (0.25 mg/ml) was available from the left drinking spout under an FR 1 schedule. An oral dose of 4, 8 or 16 mg/kg was determined by limiting the number of liquid deliveries. PCP doses were tested in descending order. The fourth component was another 5-min timeout, and the fifth component was identical to the first, except it lasted 2 hr. After a stable baseline (5 sessions) was reached under these conditions, water was substituted for PCP during the third component for 4 sessions, and PCP was subsequently reinstated at the same dose for at least 6 sessions.

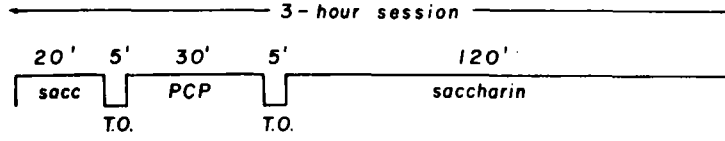

Figure 2. Tolerance procedure.

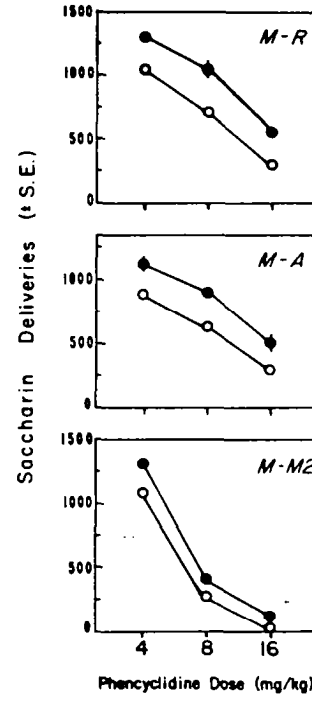

Figure 3. Saccharin deliveries during the last component - (2-hr) are presented as a function of PCP dose for the three monkeys. Filled circles are the means (+ S.E.) for the last 5 sessions and open circles represent the first session PCP was available after 4 sessions of water substitution.

Figure 3 shows that the dose response functions for the three monkeys were shifted to the right nearly two-fold when PCP was available daily indicating tolerance had developed. An example of the patterns of responding for saccharin and PCP is shown in Figure 4. Saccharin-maintained (FR 8) responding in the first component showed no systematic changes. PCP-maintained responding (FR 1) during the second component began immediately at the onset of the component and continued at a high rate until the liquid delivery limit was reached. Saccharin-maintained (FR 8) responding in the last component began at high rate, but it became disrupted at the two higher doses about 30 min after PCP consumption. At all doses the disruptions were always greater after the four sessions of water substitution. When saccharin deliveries during the last component (after PCP access) were compared to saccharin deliveries after water access, they were lower at 16 mg/kg, the same at 8 mg/kg, and considerably higher than at 4 mg/kg.

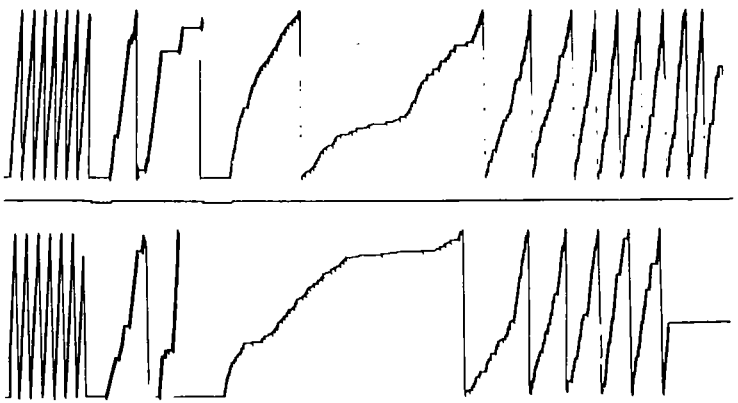

Figure 4. Two cumulative records are presented for monkey M-A at the 16 mg/kg PCP dose. The upper record was taken from the last session when PCP was available daily, and the lower record was obtained from the first session PCP was reinstated after 4 sessions of water substitution. The event pen (lower line) was deflected downward during the two time out periods. The stepping pen marked liquid responses, and it reset at about 500 responses.

After the dose-effect relationship was established, the monkeys were maintained at a 12 mg/kg dose of PCP (with PCP access under an FR 1 schedule and saccharin access under an FR 16), and the number of sessions of water substitution was varied from 1 to 16 to examine the rate of tolerance development and loss of tolerance. The results (Figure 5) indicate that tolerance is acquired within 4-5 days and a considerable amount of tolerance is lost by 8 days. These results are similar to those that have been previously reported concerning the effects of parenterally administered PCP on schedule-controlled behavior (Balster and Chait, 1976; Chait and Balster, 1978; Murray, 1978; Ruffing and Domino, 1980).

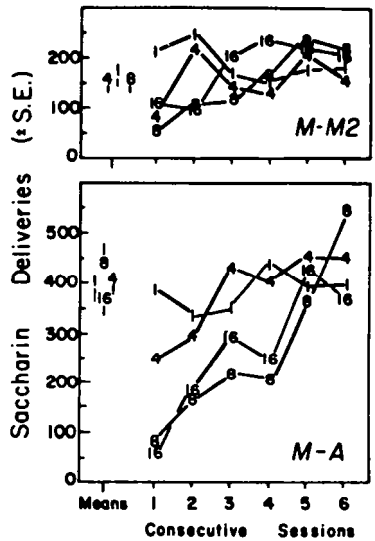

Figure 5. Mean saccharin deliveries (FR 16) during the final 2-hr component are presented for the last 5 sessions (when PCP was available daily) before 1, 4, 8 or 16 sessions of water substitution. Connected points: saccharin deliveries for 6 consecutive sessions after PCP (12 mg/kg) was reinstated.

Summary

The major findings of these studies were that phencyclidine can be rapidly established as a reinforcer without using food to induce drinking. Food deprivation is also not necessary to produce PCP self-administration, but it does increase the rate of responding by nearly two-fold. The PCP analogs, PCE and TCP were also self-administered. TCP was slightly more potent and much shorter acting than PCP, and PCE was considerably less potent than PCP. Finally, tolerance to the behavioral effects of PCP was rapidly acquired and lost, and a two-fold shift in the dose response curve was found.

References

Balster, R.L. The effects of phencyclidine and three analogues on motor performance in mice. Pharmacology, 20:46-51, 1980.

Balster, R.L., and Chait, L.D. The behavioral pharmacology of phencyclidine, Clin Tox, 9(4):513-528, 1976.

Brady, K.T., and Balster, R.L. Discriminative stimulus properties of phencyclidine and five analogues in the squirrel monkey. Pharmac Biochem Behav 14(2):213-218, 1981.

Brady, K.T., Balster, R.L., Meltzer, L.T., and Schwertz, D. Comparison of phencyclidine and three analogues on fixed-interval performance in rhesus monkeys. Pharmac Biochem Behav, 12(1):67-71, 1980.

Carroll, ME., France, C.P., and Meisch, R.A. Food deprivation increases oral and intravenous drug intake In rats. Science, 205:319-321, 1979.

Carroll, ME., France, C.P., and Meisch, R.A. Intravenous self-administration of etonitazene, cocaine and phencyclidine in rats during food deprivation and satiation. J Pharmacol Exp Ther, 217:241-247, 1981a.

Carroll, ME., and Meisch, R.A. Oral phencyclidine (PCP) self-administration in rhesus monkeys: Effects of feeding conditions. J Pharmacol Exp Ther, 214:339-346, 1980.

Carroll, ME., Senti, P.A., and Rudell, R.L. A microcomputer system for the control of behavioral experiments. Pharmac Biochem end Behav, 14:415-417, 1981b.

Chait, L.D., and Balster, R.L. The effects of acute and chronic phencyclidine on schedule-controlled behavior in the squirrel monkey. J Pharmacol Exp Ther, 204:77-87, 1978.

Henningfield, J.E., and Meisch, R.A. A drinking device for rhesus monkeys. Pharmac Biochem Behav, 4:609-610, 1976.

Meisch, R.A., Kliner, D.J., and Henningfield, J.E. Pentobarbite! drinking by rhesus monkeys: Establishment and maintenance of pentobarbital-reinforced behavior. J Pharmacol Exp Ther, 217:114-120, 1981.

Meisch, R.A., and Henningfield, J.E. Drinking of ethanol by rhesus monkeys: Experimental strategies for establishing ethanol as a reinforcer. Adv Exp Med Biol, 85B:443-463, 1977.

Murray, T.F. The effects of phencyclidine on operant behavior in the rat: Biphasic effect and tolerance development. Life Sci, 22:195-202, 1978.

Pinchasi, J., Maayani, S., Egozie, Y., and Sokolovsky, M. On the interaction of drugs with the cholinergic nervous system. II Cross-tolerance between phencyclidine derivatives and cholinergic drugs. Psychopharmacology, 56:37-40, 1978.

Ruffing, D.M., and Domino, E.F. First dose behavioral tolerance to phencyclidine on food-rewarded bar pressing behavior in the rat. Psychopharmacology, 69:1-4, 1980.

Shannon, H.E. Evaluation of phencyclidine analogues on the basis of their discriminative stimulus properties in the rat. J Pharmacol Exp Ther, 216:543-551, 1981.

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WHO Response to International Treaty Obligations

Dr. Inayat Khan, M.B., B.S., Ph.D.

It is a great pleasure for me to speak to you and to give you information on the activities of the World Health Organization during the past year since we met at Cape Cod last June.

I wish to convey that, keeping in view WHO's programme for health for all by the year 2000, drugs will continue to play an important role. WHO's evolutionary efforts to establish a list of essential drugs will always contain some drugs which act on the central nervous system and may have dependence liabilities; thus it is essential that the limited number of drugs be thoroughly investigated, and thus the work of the CPDD has become more important.

1. EVALUATION OF PSYCHOACTIVE DRUGS FOR INTERNATIONAL CONTROL

A WHO group reviewed nine anorectic drugs and concluded that phendimetrazine, phentermine, benzphetamine and mazindol be controlled under Schedule IV of the 1971 Convention. This recommendation of WHO was accepted by the UN Commission on Narcotic Drugs which met in February of 1981 in Vienna.

2. Under the 1971 Convention, parties can exempt from certain control measures those combination products containing more than a controlled psychotropic substance compounded in such a way that presents no or negligible risk of abuse and that it cannot be recovered by readily applicable means in a quantity liable to abuse. During the September 1980 Review Meeting, the lists provided by the Governments of Mexico and Bulgaria were examined. Certain products did not deserve exemption granted by the authorities. The UN Commission reviewed WHO's recommendations and approved them. This subject has become of great practical importance since the 70 countries who have so far ratified the 1971 Convention have a large number of such products which require review by WHO. This year

notifications from these countries are being reviewed.

3. DEVELOPMENT OF GUIDELINES IN THE CONTEXT OF THE INTERNATIONAL TREATIES FOR THE CONTROL OF NARCOTIC AND PSYCHOTROPIC DRUGS

You will recall that in 1981 the UN Commission on Narcotic Drugs, the Economic and Social Council, and the 33rd World Health Assembly (WHA/33.27) requested that WHO develop such guidelines for the help of Member States. WHA/33.27 in Paragraph 7.(3) requested the Director General of WHO, "to promote the initiation and strengthening of national and international programmes for the assessing, scheduling, control and appropriate use of narcotic and psychotropic substances, including those of plant origin and to support such programmes by the development of appropriate guidelines." WHO has initiated a project with funds from the Government of the Netherlands and UNFDAC, and we have begun undertaking an in depth study of the situation in six countries who have obtained a reasonable level of control of psychoactive substances. This will enable us to formulate guidelines for presentation to the Executive Board of WHO in January of 1984. A team has already visited Malaysia in March of this year and another team will soon begin a visit to Panama the day this Committee ends its deliberations. The other four countries to be visited in 1982 are Kuwait, Thailand, Morocco and Nigeria. WHO's concern is to try to develop guidelines which are simple and pragmatic.

4. A WHO Expert Committee on the implementation of the 1971 Convention on Psychotropic Substances met in September of 1980 and reviewed the methodology for assessing the public health and social problems associated with the use of psychotropic drugs. This was essential since the 1971 Convention requires this type of data as an essential for the evaluation of the benefit/risk ratio of a psychotropic drug (WHO Technical Report Series, No. 656, 1981). This Committee was headed by Prof. Harold Kalant from Toronto. It recommended that a mechanism be established for monitoring the non-medical use of psychotropic substances and for assessing the associated public health and social problems. The Committee also noted that many developing countries have only limited resources and because of other priorities do not have the finances, personnel, technological capacity or the training facilities to collect reliable data. On the other hand, many of the psychotropic drugs are being exported in large quantities in these countries where national control measures are inadequate. The Committee recommended a number

of steps to remedy the situation -- including making available research findings in a form that can be readily utilized and also the sponsoring of national and international workshops and seminars. The Committee also recommended that WHO should expeditiously begin to review the various groups of the numerous psychotropic substances which are widely used for possible control. It also requested WHO to strengthen its programme for investigating the relationship between alcohol and psychotropic substances on the one hand and injury, disability and death from road traffic accidents on the other. The Committee also recommended that the knowledge and methodology developed for this purpose be extended to investigations of industrial and other accidents.

Yet another recommendation was that governments be urged to require studies of the effects of drugs and drug interactions in driving ability as a pre-condition for licensing new psychotropic drugs for use in their countries. WHO and the National Institute for Drug Abuse of the U.S. have already reviewed this subject; a meeting entitled "Strategies for the Control of Drugs as Related to Traffic Safety" took place in Washington in April of this year under the leadership of Dr R. Willette. A report of this meeting will soon be available.

WHO has taken yet another practical step to utilize the information contained in this Expert Committee Report and convened a workshop in Finland in June of this year where 12 participants from developing countries and a large number of experts from within and outside Finland, WHO and UNFDAC took part. The goal of the workshop was the development of a manual for use in developing countries in establishing the role of psychotropic drugs in specific areas in public health where psychotropic drugs can and have created problems. The group recommended further study in a general hospital in developing countries.

5. Continuing WHO's efforts to encourage Member States to adhere to the 1971 Convention and to use this Convention as an instrument to use psychotropic drugs rationally, two national and two regional workshops were organized. The two national workshops on the use and misuse of psychotropic drugs were held in London and Bangkok. The regional workshops were held in Manila and Buenos Aires. The latter was especially for Portuguese and Spanish speaking participants. Later this year a Third Travelling Seminar on the Safe Use of

Psychotropic and Narcotic Substances will take place in Moscow and Tashkent in October. English, Russian and French speaking participants have been invited. One of the goals of this seminar is the development of guidelines for registration of psychoactive drugs with dependence liability.

6. This year we have planned two meetings for review of psychoactive substances -- in September for the opioid agonists and antagonists and in November for review of a number of benzodiazepines which are already on the market.

7. I wish to comment on the excellent paper presented by Professor Everette May while receiving Nathan B. Eddy Memorial award during the last part of his address referring to the future role of CPDD. I may add yet another role which is related to cooperation between CPDD and WHO in developing base line data from animal studies on certain groups and representative psychotropic drugs which is lacking today. I have already taken up this issue with Professor Joe Cochin, Chairman of CPDD. Yet another area worthy of attention to this committee is to draw up a paper elucidating further cooperation between the pharmaceutical industry and the national and international authorities and in particular WHO as it relates to the implementation of the international treaty obligations. I made this point at the last meeting of the UN Commission on Narcotic Drugs held in Vienna in February 1981 and was supported by the Executive Director of the UN Fund for Drug Abuse Control.

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Structure-Activity Relationships of Oxygenated Morphinans. III. An Exploration of the Effect of the Aromatic Oxygen and 6-Keto Group on Antinociceptive Activity, Receptor Affinity, and Narcotic, Antagonism

A. E. Jacobson, H. Schmidhammer, F.-L. HSU, M. D. Rozwadowska, L. Atwell, A. Brossi, M. D. Aceto, L. S. Harris, J. L. Katz, J. H. Woods, and F. Medzihradsky

We have, previously, reported on the synthesis of 4-hydroxy-N-methylmorphinan (1) (Hsu et al. 1979; Rozwadowska et al. 1980; Hsu, Rice, and Brossi 1980), 4-hydroxy-N-methylmorphinan-6-one (2) and 4-methoxy-N-methylmorphinan-6-one (3) (Hsu et al. 1979; Rozwadowska et al. 1980). Our comparison between the antinociceptive activities of 2 and 2 with those of 3-deoxydihydromorphine (4) and 3, 6-dideoxydihydromorphine (5) (Reden et al. 1979) initiated further work at NIH on a wide variety of oxygenated morphinans (figure 1) (Jacobson et al. 1981; Schmidhammer et al. 1981) in an attempt to ascertain the influence which oxygen atoms, in the morphinan skeleton, have on binding to the opiate receptor and on in vivo activity.

4-Methoxy-N-methylmorphinan (6) was found to be essentially equlpotent with morphine as an antinociceptive, emphasizing the fact that a c-3 hydroxyl function was unnecessary for in vivo antinociceptive activity in this set of opiate-like molecules. An oxygen atom in the C-4 position could be, apparently, "recognized" by the opiate receptor. If an hydroxyl function was returned to the C-6 position of a 4-oxygenated morphinan, either as the C-6alpha (7) or C-6beta (8) compound, to make it structurally more comparable to the morphine molecule, antinociceptive potency was markedly reduced. However, conversion of the 6-hydroxyl moiety in 7 or 8 to a ketone produced a much more potent compound (2). Conversion of 2 to its methyl ether produced 3, which had an ED50=0.9 µmol/kg; 3 was more than three times as potent as morphine. That discovery, in 1979, pointed to the idea that it was, generally, best to mask the aromatic hydroxyl group at C-4. Conversion to compounds without a phenolic or C-6 hydroxyl group obviates the possibility of involvement of the hydroxyl group in hydrogen bonding to some macromolecule in vivo. This theoretical idea that molecules with a C-4 or C-6 hydroxyl group could hinder macromolecules involved in the process leading to antinociception led us to the preparation of various morphinans, some of which will be discussed in this paper; others will be published elsewhere.

FIGURE 1

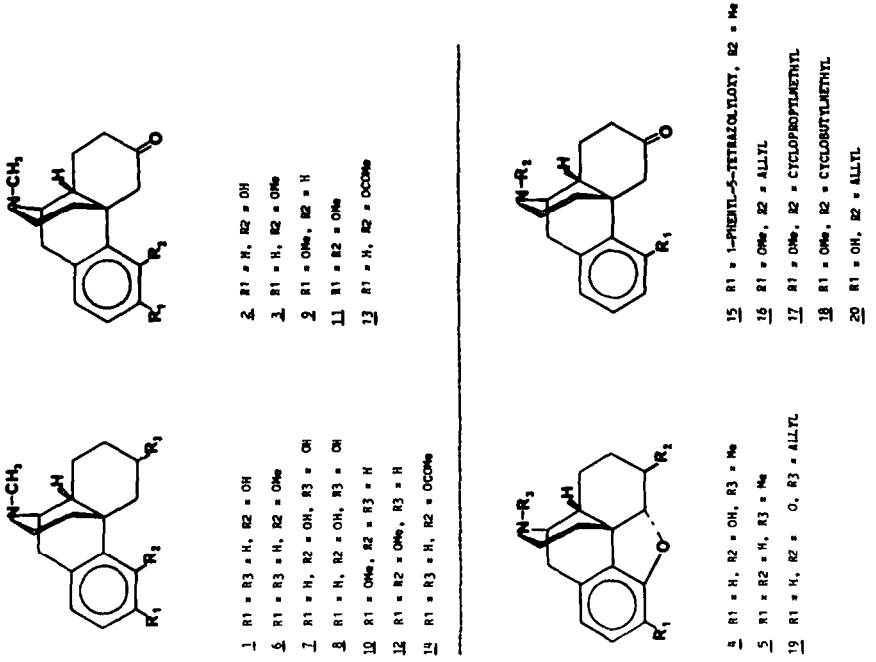

TABLE 1

Antinociceptive Activity of Selected Levo Enantiomers of Morphinans. Morphinan-6-ones and Reference Drugs in the Hot Plate Assay

Compound	ED50[a] SC	ED50[a] PO
(1) 4-Hydroxy-N-methylmorphinan	4.7 (3.5-6.8)	17.1 (12.9-22.1)
(2) 4-Hydroxy-N-methylmorphinan-6-one	4.4 (3.5-6.8)	8.6 (6.6-11.3)
(3) 4-Methoxy-N-methylmorphinan-6-one	0.9 (0.7-1.1)	5.6 (3.7-8.1)
(4) 3-Deoxy-6beta-hydroxydihydromorphine	2.1 (1.5-2.8)	13.9 (10.1-18.9)
(5) 3,6-Dideoxydihydromorphine	1.3 (0.89-1.85)	
(6) 4-Methoxy-N-methylmorphinan	3.1 (2.2-4.2)	
(7) 4,6alpha-Dihydroxy-N-methylmorphinan	59.8 (44.9-79.9)	
(8) 4,6beta-Dihydroxy-N-methylmorphinan	51.8 (37.3-71.7)	
(9) 3-Methoxy-N-methylmorphinan-6-one	3.9 (3.2-4.9)	8.5 (6.3-11.6)
(10) Levomethorphan	2.8 (1.8-4.4)	
(11) 3,4-Dimethoxy-N-methylmorphinan-6-one	1.1 (0.9-1.5)	4.1 (3.0-6.0)
(12) 3,4-Dimethoxy-N-methylmorphinan	1.0 (0.6-1.6)	31.4 (23.7-41.7)
(13) 4-Acetoxy-N-methylmorphinan-6-one	3.0 (2.6-3.5)	7.0 (5.1-11.2)
(14) 4-Acetoxy-N-methylmorphinan	5.1 (3.6-6.8)	18.2 (13.7-24.4)
(15) N-Methyl-4-(1-phenyl-1H-5-tetrazolyloxy)-morphinan-6-one	5.8 (4.6-7.0)	
(16) N-Allyl-4-methoxymorphinan-6-one	Inactive[b]	
(17) N-Cyclopropylmethyl-4-methoxymorphinan-6-one	60.0 (49.5-72.7)	
(18) N-Cyclobutylmethyl-4-methoxymorphinan-6-one	Inactive[b]	33.3 (25.3-43.9)
(19) N-Allyl-4,5-epoxymorphinan-6-one	21.7 (14.9-32.2)	
(20) N-Allyl-4-hydroxymorphinan-6-one	6.1 (5.0-7.4)	60.9 (44.4-83.4)
Levorphanol Tartrate	0.5 (0.2-0.7)	8.6 (6.6-11.5)
Morphine Sulfate	2.9 (2.5-3.3)	18.9 (14.1-24.9)
Codeine Phosphate	17.1 (11.3-26.)	34.0 (24.4-47.)

a) Dose at which half the mice are affected, in μmol/kg. The parenthesized numbers are 95% standard error limits determined by computerized probit analysis. The salts were introduced in aqueous solution; the bases in an Emulphor EL620 mixture;
b) Insufficient activity at 50mg/kg for statistical analysis.

METHODS

Chemistry: All of the prepared compounds had elemental analyses, mass, infrared and proton nuclear magnetic resonance spectra in accord with their designated molecular structures.

Assay procedures: The hot plate assay was described in Atwell and Jacobson (1978). The phenylqulnone writhing, tail flick and tail flick antagonism vs. morphine procedures were described by Dewey et al. (1970), and Dewey and Harris (1971).

Binding to Opiate Receptors: This assay was described in Valentino et al. (1981) and Woods et al. (1979).

Monkey Studies: Single dose suppression and precipitated withdrawal in rhesus monkeys was carried out as described in Aceto et al. (1981) and Woods et al. (1981), and references therein.

RESULTS & DISCUSSION

Generally, the most potent compounds in table 1 were those which had a 4-methoxy group either with, or without, an additional methoxy group at position 3 on the aromatic ring (compounds 3, 6, 11 and 12). The 6-keto compounds (2, 3, 11 and 13) were either equipotent with, or perhaps somewhat -more potent than, comparable compounds with a non-oxygenated C-ring (compounds 1, 6, 12 and 14). Compounds with 3-methoxyl groups, with or without a 6-keto moiety, were about as potent as morphine (9 and 10) but were much less potent than the comparable C-3 phenolic morphinan (levorphanol). Phenols are almost always more potent than their comparable ethers in the 3-substituted opiates (e.g. - morphine vs. codeine). However, the introduction of a second methoxyl group, at C-4 on the aromatic ring (11, 12), increases potency three fold. It is striking to note that the 4-Methoxy-N-methylmorphinan-6-one (3) and the 3,4-dimethoxy compounds (11, 12) are significantly more potent than their comparable phenolic relatives. The 4-acetoxyl compounds (13, 14) are essentially equipotent with the 4-hydroxyl compounds 1 and 2. Presumably, the phenolic esters are cleaved in vivo in a manner similar to that of the phenolic ester in heroin.

Some of the compounds had good oral (PO) activity in the hot plate. assay (3, 9, 11, 13). Compounds 3 and 11, orally, are almost as potent as sc administered morphine, in that assay. The ratio of sc to oral potency of 2 and 13 appears to be better than that ratio in morphine, and equivalent to that in codeine. The possible narcotic antagonists (16, 17, 18, 19, 20) had, as might be expected, little activity in the hot plate assay, with the exception of compound 20. Some have been examined for their narcotic antagonist activity in mice and in monkeys (table 2).

TABLE 2

Antinociceptive and Narcotic Antagonist Activity of Selected N-Substituted Compounds

CMPD.	ED50[a]			SDS[b]	NW[c]
	PPQ[d]	TF[e]	TFA[f]		
1	-	-	-	CS[g]	-
5	1.2 (0.5-2.9)	8.2 (3.1-22.6)	I	CS[g]	-
16	3.5 (2.6-4.8)	16.5 (6.5-41.9)	No D-R[h]	NS[i]	PW[j]
17	3.3 (0.8-11.3)	I[k]	1.1 (0.3-4.4)	NS[i]	PW[l]
18	1.9 (0.8-4.8)	26.6 (6.7-107.)	I	CS[m]	
19	7.8 (3.7-16.9)	I	I	-	-
20	~1.3	2.4 (1.0-5.4)	I	-	-
Pentazocine	5.8 (3.5-8.8)	I	63 (43-91)	PS[n]	-
Nalorphine	1.7 (0.7-4.1)	I	7.5 (2.0-2.8)	NS	PW
Morphine	0.7 (0.6-0.8)	17.3 (17-17.7)	I	CS[g]	-

a) Dose (sc) at which half the mice are affected, in µmol/kg. Parenthesized numbers are 95% confidence limits; b) Single dose suppression, in morphine-dependent rhesus monkeys: c) Precipitated withdrawal in morphine-dependent rhesus monkeys: d) Phenylquinone writhing assay in mice; e) Tail flick assay in mice: f) Tall flick antagonism vs. morphine in mice; g) Complete substitution at 1-4mg/kg: h) No dose-response relationship; i) No substitution (exacerbates withdrawal at 1-3mg/kg); j) Precipitates withdrawal at 0.1-3mg/kg, ca. 1/3 to 1/10 the antagonist-potency of nalorphine: k) Inactive: 1) Precipitates withdrawal at 0.1-3mg/kg, ca. 1/3 the antagonist potency of nalorphine; m) Complete substitution at 3, 5.6 and 10mg/kg; n) Partial substitution for morphine.

It was apparent from our former data on receptor binding affinity (Reden et al. 1979) that oxygen atoms on the aromatic ring, or on the C-ring, were unnecessary for binding to the opiate receptor. 3,6-Dideoxydihydromorphine (5) had ca. one-third the binding affinity of morphine for the receptor. The affinity the compound displayed for the receptor was remarkable in that the C-3 phenolic hydroxyl might have been, a priori, considered to be critical for the binding. Although the phenolic hydroxyl group can now be said to aid in the binding of the antinociceptive drug to a receptor, it is not critical to that event. The 4-methoxy-N-methyl-morphinan-6-one (3) (table 3) has the same relative affinity to the presumed µ receptor as does 5, when compared with the binding affinity of morphine. The greater in vivo relative potency compared to in vitro relative potency of 3 might be explained simply by more facile transport to the receptor sites. Metabolism of 3 to 2 probably need not be invoked to explain the in vivo antinociceptive potency of 3, in contrast with other phenolic ethers (e.g. - codeine). It is apparent from the data in table 3 that the 6-keto group in the 4-methoxyl series (2 vs. 1 and 3 vs. 6) enhances interaction with the receptor. Further, al though the

binding affinity of the 4-methoxy-N-methylmorphinan-6-one (3) is somewhat lower than that of the comparable 4-hydroxy compound 2, this is markedly different from the usual binding affinity of phenols and their ethers in C-3 substituted opiates (e.g. - codeine vs. morphine). Thus, there are two very unusual characteristics of some of the 4-methoxy-6-keto morphinans. Their binding affinity to the opiate receptor in rat brain membranes is extraordinary for aromatic ethers, and they appear to be considerably more potent in vivo than their phenolic counterparts.

The N-methyl derivatives appear, in general, to be morphine-like in their capacity to suppress withdrawal in SDS in morphine-dependent monkeys, which is in agreement with the +Na/-Na ratios they display in binding experiments to opiate receptors in rat brain membranes. Some of the 4-methoxyl compounds were successfully converted to agonist-antagonists. using N-moieties similar to those which are known to convert C-3 oxygenated opiates to their antagonists (table 2). The N-allyl (16) and N-cyclopropyl (17) analogs were found, in non-withdrawn monkeys, to exhibit narcotic antagonist activity. Compound 17 had ca. one-third the potency of nalorphine.

TABLE 3

Potency of Selected Morphinans, Morphinan-6-ones and Comparison Drugs in Displacing Stereospecifically Bound ^{3}H-Etorphine in Membrane Preparations From Rat Brain

Compound	EC50 (nM)		
	-Na	+Na	+Na/-Na
(1) 4-Hydroxy-N-methylmorphinan	150.	513.	3.4
(2) 4-Hydroxy-N-methylmorphinan-6-one	54.5	120	2.2
(3) 4-Methoxy-N-methylmorphinan-6-one	161.	488.	3.0
(6) 4-Methoxy-N-methylmorphinan	510.	889.	1.7
(13) 4-Acetoxy-N-methylmorphinan-6-one	112.	645.	5.8
Levorphanol[a]	14.	20.	1.4
Morphine[a]	60.	142.	2.6
Codeine[a]	17800.	34700.	1.9

a) From Woods, et al., 1979.

REFERENCES

Aceto, M.D., Harris, L.S., Dewey, W.L., and May, E.L. Dependence studies of new compounds in the rhesus monkey (1980). In: Harris, L.S., ed. Problems of Drug Dependence 1980. National Institute on Drug Abuse Research Monograph 34. Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., 1981. pp. 297-326.

Atwell, L. and Jacobson, A. E. The search for non-dependence producing analgesics in man: Ode to a mouse. Lab Animal, 7:42-47, 1978.

Dewey, W.L., Harris, L.S., Howes, J.F., and Nuite, J.A. The effects of various neurohumoral modulators on the activity of morphine and the narcotic antagonists in the tall-flick and phenyqulnone tests. J Pharmacol Exp Ther, 175:435-442, 1970.

Dewey, W.L. and Harris, L.S. Antinociceptive activity of the narcotic antagonists analogues and antagonistic activity of narcotic analgesics in rodents. J Pharmacol Exp Ther, 179:652-659, 1971.

Hsu, F-L., Jacobson, A.E., Rice, K.C., and Brossi, A. The dihydromorphine-morphinan-3-deoxydiydromorphine triangle. Amer Soc of Pharmacognosy, Abstract 35, July 29-August 3, 1979, Purdue University, West Lafayette, Indiana.

Hsu, F.-L., Jacobson, A.E., Rice, K.C., and Brossi, A. Partial synthesis of 3-deoxydihydromorphine from (-)-4-hydroxy-6-keto-N-methylmorphinan. Heterocycles, 13:259-261, 1979.

Hsu, F.-L., Rice, K.C., and Brossi, A. Total synthesis of (-)-3-deoxy-7,8-dihydromorphine. Helv Chim Acta, 63:2042-2045, 1980.

Jacobson, A.E., Hsu, F.-L., Rozwadowska, M.D., Schmidhammer, H., Atwell, L., and Brossi , A. Structure-activity relationships of oxygenated morphlnans. I. 4-Mono- and 3,4-dimethoxy-N-methylmorphinans and morphinan-6-ones with unusually high antinociceptive potency. Helv Chim Acta, in press, 1981.

Reden, J., Reich, M.F., Rice, K.C., Jacobson, A.E., and Brossi, A. Deoxymorphines: Role of the phenolic hydroxyl in antinociception and opiate receptor interactions. J Med Chem, 22:256-259. 1979.

Rozwadowska, M.D., Hsu, F.-L., Jacobson, A.E., Rice, K.C., and Brossl , A. Synthesis of (-)-4-hydroxy-6-keto-N-formylmorphinan, a versatile lntermediate for the synthesis of 3-deoxyopioids. Amer Chem Soc, 179th. National Meeting, Abstract 17 of Medicinal Chem Section, March 23-28, 1980, Houston, Texas.

Rozwadowska, M.D., Hsu, F.-L., Jacobson, A.E., Rice, K.C., and Brossi, A. (-)-4-Hydroxy-N-formylmorphinan-6-one, a versatile intermediate for the synthesis of 3-deoxyopioids. Can J Chem, 58:1855-1859. 1980.

Schmidhammer, H., Jacobson, A.E., Atwell, L., and Brossi, A. Structure-activity relationships of oxygenated morphinans. II. Synthesis and biological properties of 4-methoxy-6-ketomorphinans with narcotic antagonist side-chains. Heterocycles, in press, 1981.

Woods, J.H., Smith, C.B., Medzihradsky, F., and Swain, H.H. Preclinical testing of new analgesic drugs. In: Beers, R.F. and Bassett, E.G., ed. Mechanisms of Pain and Analgesic Compounds. New York: Raven Press, 1979. pp. 429-445.

Woods, J.H., Medzihradsky, F., Smith, C.B., Young, A.M., and Swain, H.H. Evaluation of new compounds for opioid activity (1980). In: Harris, L.S., ed. Problems of Drug Dependence, 1980. National Institute on Drug Abuse Research Monograph 34. Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., 1981. pp. 327-366.

Valentino, R.J., Herling, S., Woods, J.H., Medzihradsky, F., and Merz, H. Quaternary naltrexone: Evidence for the central mediation of discriminative stimulus effects of narcotic agonists and antagonists. J. Pharmacol Exp Ther, 217:652-659, 1981.

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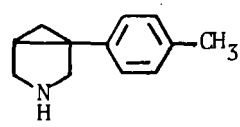
Bicifadine: Non-Narcotic Analgesic Activity of 1-Aryl-3-azabicyclo[3.1.0] hexanes

J. W. Epstein, A. C. Osterberg, B. A. Regan

Bicifadine (USAN 1979) (1) CL 220,075 [1-(4-methylphenyl)-3-azabicyclo[3.1.0]hexane], is undergoing clinical trials as a non-narcotic analgesic. It has a greater potency than aspirin, and a greater therapeutic index than codeine, pentazocine, or propoxyphene in a variety of tests in rats and mice (Epstein et al. 1981). It was essentially inactive in the high-intensity rat tail-flick procedure (Gray et al. 1970) and by the mouse hot plate method (59° C) (Eddy et al. 1950). It did not show physical dependence liability when tested by a subcutaneous pellet implant procedure (Way et al. 1969) or by using an incremental intraperitoneal dosing schedule (with naloxone challenge) (Saelens et al. 1971). Also, it had no in vitro opiate receptor binding properties using tritiated dihydromorphine. Single-dose substitution studies in morphine-dependent rhesus monkeys (Aceto et al. 1979) produced transitory effects that did not necessarily imply morphine-like properties. In a private communication, Aceto et al. (1979) reported that primary dependence studies in rhesus monkeys over a period of 40 days did not produce morphine-like physical dependence . Relatively little tolerance was seen to develop. It does not show anti-inflammatory activity, nor in vitro prostaglandin synthetase inhibition.

Bicifadine is being evaluated in its racemic form; however, the (1R, 5S)- (+) enantiomer has been shown to be the active component.



1, bicifadine

PHARMACOLOGICAL METHODS

Inflamed Rat-Paw Reversal of Abnormal Gait. A modification of the procedure of Atkinson and Cowan (1974) was used as the primary assay. Brewers' yeast was injected into the plantar surface of

the left hind paw of each rat, and 3 hours later a pre-drug assessment was determined for each rat (range: 0 = normal gait to 2 = maximum abnormal walking behavior). Rats with a gait score of 2 were then treated with vehicle or test compound, and post-drug scores were determined at selected time intervals; A > 50% reduction of abnormal gait was considered a positive analgesic response; the dose estimated to reduce the gait score from 2 to 1 in 50% of the rats was defined as the ED_{50}.

Phenylquinone Mouse Anti-Writhing Method. A modification of the procedure of Hendershot and Forsaith (1958) was used.

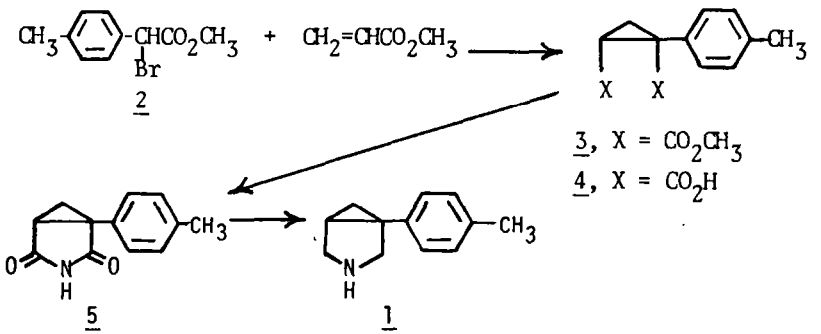
Inflamed Rat-Paw-Pressure Threshold Method. A modification of the method of Randall and Selitto (1957) was used to measure the pain threshold of rats whose paws were made sensitive to pressure by the injection of a 20% aqueous suspension (0.1 mL) of brewers' yeast into the plantar surface of the left hind paw.

Statistics. ED_{50}'s and 95% confidence limits were calculated according to the linear arc sine transformation method (Finney 1964).

CHEMICAL SYNTHESIS

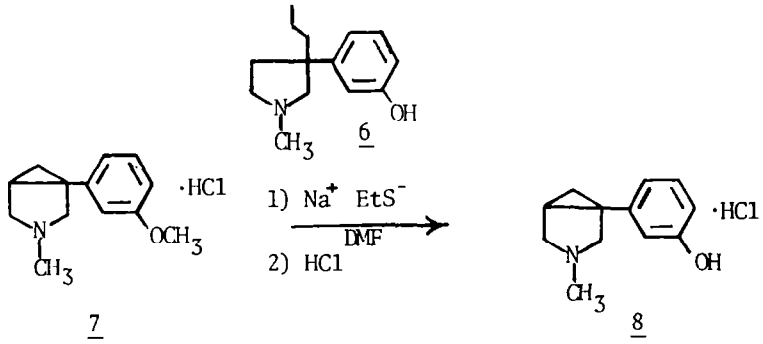
The general synthesis of 1-aryl-3-azabicyclo[3.1.0]hexanes is outlined in scheme I (Epstein et al. 1981) using the synthesis of bicifadine (1) as an example. The cyclization of bromoester (2) and methyl acrylate using sodium hydride in ether gave cis-cyclopropane dicarboxylate (3), which was then hydrolyzed to diacid (4). Cyclization of diacid (4) with urea gave imide (5), which was subsequently reduced with a hydride to the title amine (1).

SCHEME I



The optical resolution was achieved at the diacid 4 stage using optically active α-methyl-1-naphthalenemethylamine. The absolute configuration of the (+)-enantiomer 12 was determined by single-crystal X-ray analysis. Eschweiler-Clark (CH_2O, HCO_2H) reaction of 1 gave the N-methyl derivative 33, while reaction of 1 with allyl bromide and bromomethylcyclopropane gave the N-allyl, and N-cyclopropylmethyl derivatives 34 and 35 respectively.

The profadol (Bowman 1969) (6) analog 8 was prepared by demethylating the m-methoxyphenyl compund, 7, using sodium ethyl mercaptide in N,N-dimethylformamide. Compounds 26 and 27 were likewise prepared from 19 and 20 respectively by this general method.



PHARMACOLOGY

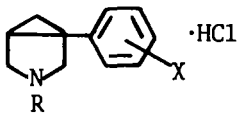
The results of analgesic tests are presented in table 1. A structure-activity relationship was derived by examining the "abnormal gait" data. For the substituents CH_3, Cl, and OCH_3 the para substituted compounds 1, 14 and 19, respectively, were more potent than the corresponding meta substituted 10, 15 and 20. The ortho substituted 11 and 16 were inactive. The particular substituent effect that governs potency in this test is not evident; however, it can be seen that p-alkyl substituents such as CH_3 (1) and C_2H_5 (28) impart the greatest degree of activity of the substituents studied.

Potency diminished for compounds in which the alkyl group was larger than ethyl, e.g. isopropyl (29) and n-hexyl (31), while the p-tert-butyl analog 30 was inactive. The effect of optical isomerism clearly discernible from the greater potencies of the (1R, 5S)-(+) enantiomers 12 and 17, as compared to the relative inactivity of the (1S, 5R)-(-) antipodes 13 and 18.

The effects of N-alkylation are not uniform. For the p-C1 analog 14, activity is diminished in going to the N-Me derivative 36, whereas for the p-CH_3 analog 1, conversion to the N-Me derivative 33 is accompanied by no loss in potency. However, when the allyl and cyclopropylmethyl groups were incorporated into 1 to give 34 and 35 respectively, there was a considerable loss of analgesic potency, and these compounds were not morphine antagonists. These groups are generally used as N-substituents for narcotic-antagonist-type analgesics (Bowman et al. 1973).

A comparison of the analgesic activity of the N-methyl-m-hydroxyphenyl congener 8 with profadol 6 shows that the incorporation of these two structiiral features which are generally found in agonist-antagonist analgesics, resulted in a compound of minimal activity. The p-tolyl analog 1 was chosen for further study as an analgesic

Table 1. Analgesic Activities of 1-Aryl-3-azabicyclo[3.1.0]hexanes



Cpd.	X	R	Abnormal Gait	Paw Pressure	Writhing
1	p-CH_3	H	18(11-31) [4(3-7)s.c.]	11(3-28	13(6-29)
6	profadol	-	Active [d]	NT	NT
7	m-OCH_3	CH_3	>100[b]	NT	NT
8	m-OH	CH_3	> 50[b]	~25s.c.[a]	50[b]
10	m-CH_3	H	> 50[a]	~25	18(13-25)
11	o-CH_3	H	> 50[b]	NT[c]	>50[b]
12	(+)-p-CH_3	H	17(10-31)	<25[a]	NT
13	(-)-p-CH_3	H	>200[a]	>25[a]	NT
14	p-Cl	H	31(21-45)	21(15-28)	21(13-34)
15	m-Cl	H	>50[a]	~50	34(24-48)
16	o-Cl	H	>100[b]	NT	NT
17	(+)-p-Cl	H	25(17-37)	~13	19(14-25)
18	(-)-p-Cl	H	>150[b]	>50[b]	<100[a]
19	p-OCH_3	H	24(11-61)	49(27-86)	4(2-9)
20	m-OCH_3	H	~177	NT	NT
21	p-F	H	>50[a]	14(6-33)	34(19-60)
22	m-F	H	>50[a]	~67	21(13-34)
23	p-Br	H	~141	NT	NT
24	p-CF_3	H	38(28-52)	~40	>100[b]
25	m-CF_3	H	28(21-37)	~50	29(13-64)
26	p-OH	H	>200[a]	NT	NT
27	m-OH	H	16(11-23)s.c.	>25s.c.[b]	NT
28	p-C_2H_5	H	13(9-19)	~25	24(13-45)
29	p-$CH(CH_3)_2$	H	9(6-15)s.c.	>25s.c.[b]	30(22-40)
30	p-$C(CH_3)_3$	H	>200[b]	NT	NT
31	p-(n-C_6H_{13})	H	50[b]	NT	NT
32	H	H	70(44-111)	71(24-206)	<100
33	p-CH_3	CH_3	20(16-25)	24(18-34)	16(11-23)
34	p-CH_3	e	>50[b]	NT	NT
35	p-CH_3	f	>50[b]	NT	NT
36	p-Cl	CH_3	>50[b]	60	<100[a]

[a] Highest dose tested, active. [b] Highest dose tested, inactive.

[c] NT = not tested. [d] 50 mg/kg, 4/5 reversed. [e] Allyl.

[f] Cyclopropylmethyl.

based on its uniform potency in all three screening tests. A study of oral therapeutic indices in rats (table 2) showed that bicifadine (1) compared favorably with aspirin, while it was significantly better than codeine, pentazocine and propoxyphene.

In conclusion, bicifadine (1) is an orally active analgesic. It is structurally distinct from the general class of agonist-antagonist analgesics and shows little or no physical dependence liability.

Table 2. Oral Therapeutic Indices in Rats

Compound	ED_{50} mg/kg P	G	LD_{50} mg/kg	Ratio P	LD_{50}/ED_{50} G
Bicifadine (1)	11	18	370	34	21
Aspirin	150	74	1466	10	20
Codeine	43	51	252	6	5
Pentazocine	90	125	246	2.7	2
Propoxyphene	21	41	55	2.6	1.3

P = paw-pressure method. G = abnormal gait method.

REFERENCES

Aceto, M.D., Harris, L. S., Dewey, W. L., and May, E. L., Annual Report: Dependence Studies of New Compounds in the Rhesus Monkey (1979). In: Harris, L. S., ed. Problems of Drug Dependence: 1979. National Institute on Drug Abuse Research Monograph 27. DHEW Pub. No. [ADM] 80-901. Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., 1980, p, 341.

Aceto, M.D., Harris, L. S., Dewey, W. L., and May, E. L., Committee on Problems of Drug Dependence, Inc.: private communication, 1979.

Atkinson, D. C., and Cowan, A. Reversal of yeast-induced motor impairment in rats as a test for narcotic and non-narcotic analgesics. J. Pharm Pharmacol, 26:727-729,1974.

Bowman, R. E. Profadol - A new, potent analgesic. Chem. Ind. (London), 1077, 1969.

Bowman, R. E., Collier, H. 0. J., Hattersley, P. J., Lockhart, I. M., Peters, D. J., Schneider, C., Webb, N. E., and Wright, M. Analgetics Based on the Pyrrolidine Ring. 8. J. Med. Chem. 16: 1177-1180, 1973.

Bowman, R. E., Collier, H. 0. J., Lockhart, I. M., Schneider, C., Webb, N. E., Wright, M. Analgetics Based on the Pyrrolidine Ring. 9. J. Med. Chem. 16:1181-1183, 1973.

Eddy, N. E., Touchberry, C. F., and Lieberman J. E. Synthetic analgesics. I. methadone isomer and derivatives. J. Pharmacol. Exptl. Therap. 98:121-317, 1950.

Epstein, J. W., Brabander, H. J. , Fanshawe, W. J. , Hofmann, C. M. -McKenzie, T. C., Safir, S. R., Osterberg, A. C., Cosulich, D. B., and Lovell, F. M. 1-Aryl-3-azabicyclo[3.1.0]hexanes, a New Series of Non-narcotic Analgesic Agents. J. Med. Chem. 24:481-490, 1981.

Finney, D.J. Statistical Methods in Biological Assay, 2nd Ed. New York: Hafner, 1964. p 454.

Gray, W. D., Osterberg, A. C., and Scuto, T. J. Measurement of the analgesic efficacy and potency of pentazocine by the D'Amour and Smith method. J. Pharmacol. Exptl. Therap. 172:154-162, 1970.

Hendershot, L. C. and Forsaith, J. Antagonism of the frequency of phenylquinone-induced writhing in the mouse by weak analgesics and non-analgesics. J. Pharmacol. Exptl. Therap. 125:237-240, 1958.

Randall, L. 0. and Selitto, J. J. A method for measurement of analgesic activity on inflamed tissue. Arch. int. Pharmacodyn. 111:409-419, 1957.

Saelens, J. K., Granat, F. R., and Sawyer, W. K. The mouse jumping test - a simple screening method to estimate the physical dependence capacity of analgesics. Arch. int. Pharmacodyn. 190:213-218, 1971.

United States Adopted Name. J. Am. Med. Assoc. 242:1912, 1979.

Way, E. L., Loh, M. M., and Shen, F. S. Simultaneous quantitative assessment of morphine tolerance and physical dependence. J. Pharmacol. Exp. Therap. 167:1-8, 1969.

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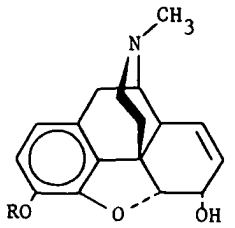
Synthetic Opium Alkaloids and Derivatives 2. Efficient Total Synthesis of (-)-Dihydrocodeinone and Congeners

Kenner C. Rice

The remarkable pharmacological effects of opium were recognized in ancient times and for many centuries this substance was the mainstay of the practicing physician. Even today, natural (-)-morphine (1), (-)-codeine (2) and other opium derivatives are still an important, if not indispensable group of drugs for the effective practice of modern medicine (Schwartz, 1980). The rising U.S. annual production and use of opium derivatives currently stands near 60,000 kg, with worldwide consumption at about 200,000 kg/year of which about 90% is codeine (2) (Schwartz, 1980). In this country, the sole source of these drugs has been extracts of the opium poppy, Papaver somniferum, purchased abroad, principally from India. The consequences of total dependence on foreign sources of a natural product were graphically illustrated during the opium shortage of 1973-5, when the U.S. Government was forced to release large portions of the strategic materials reserves of opium to domestic processors in order that requirements of this country could be met (Schwartz, 1980). Practical production of opium derivatives by total synthesis is thus a desirable capability, which could render this country independent of foreign sources, and would afford a number of new options, particularly in the event of armed conflict in the areas of poppy production or in the case of national emergency. A number of other ramifications of such a capability, as in the area of illicit heroin control, can also be envisioned. Herein is described straightforward methodology for synthesis of intermediates which could be utilized for production of medical opiates by total synthesis.

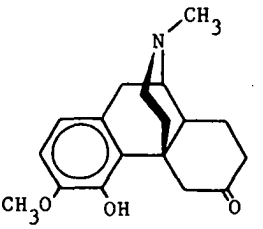
Since the correct formulation of the gross structure of morphine (1) and codeine (2) by Gulland and Robinson (1925), which followed the brilliant degradative work of Pschorr, Knorr and others (Holmes, 1952) in earlier attempts at structural elucidation, these alkaloids have been the subject of numerous synthetic studies. The relatively complex, unsymmetrical structures of morphine and codeine first yielded to the elegant synthetic efforts of Gates and Tschudi (1952). Later successes (Barton et al., 1963; Beyerman et al., 1976; Beyerman et al., 1978; Elad and Ginsberg, 1954; Grewe and Friedricksen,

1967; Kametani et al., 1969; Lie et al., 1979; Morrison et al., 1967; Rice, 1980; Schwartz and Mami, 1975; Szantay, 1980) afforded dihydrothebainone (3), which had been converted to morphine and codeine by Gates and Tschudi (1952), or other intermediates previously converted to these alkaloids.

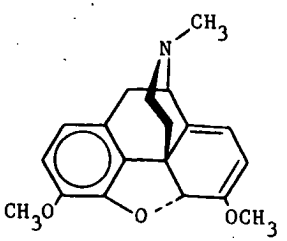


1. R = H, (-)-Morphine

2. R = CH_3, (-)-Codeine



(-)-3.



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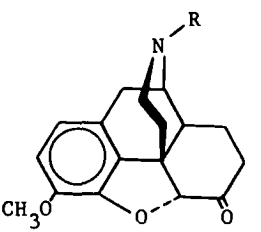


5. R = CH_3

6. R = H

Most efforts at total synthesis of opium alkaloids have utilized either a biomimetic route (Barton et al., 1963; Schwartz and Mami, 1975; Szantay et al., 1980) in which a phenolic 1-benzyltetrahydroisoquinoline is oxidized to a morphinandienone convertible to thebaine (4) and thence to morphine, or a Grewe-type (Beyerman et al., 1976; Beyerman et al., 1978; Grewe and Friedrichsen, 1967; Lie et al., 1979; Rice, 1980) electrophilic reaction of a suitably functionalized 1-benzylhexa or octahydroisoquinoline to form the mor-

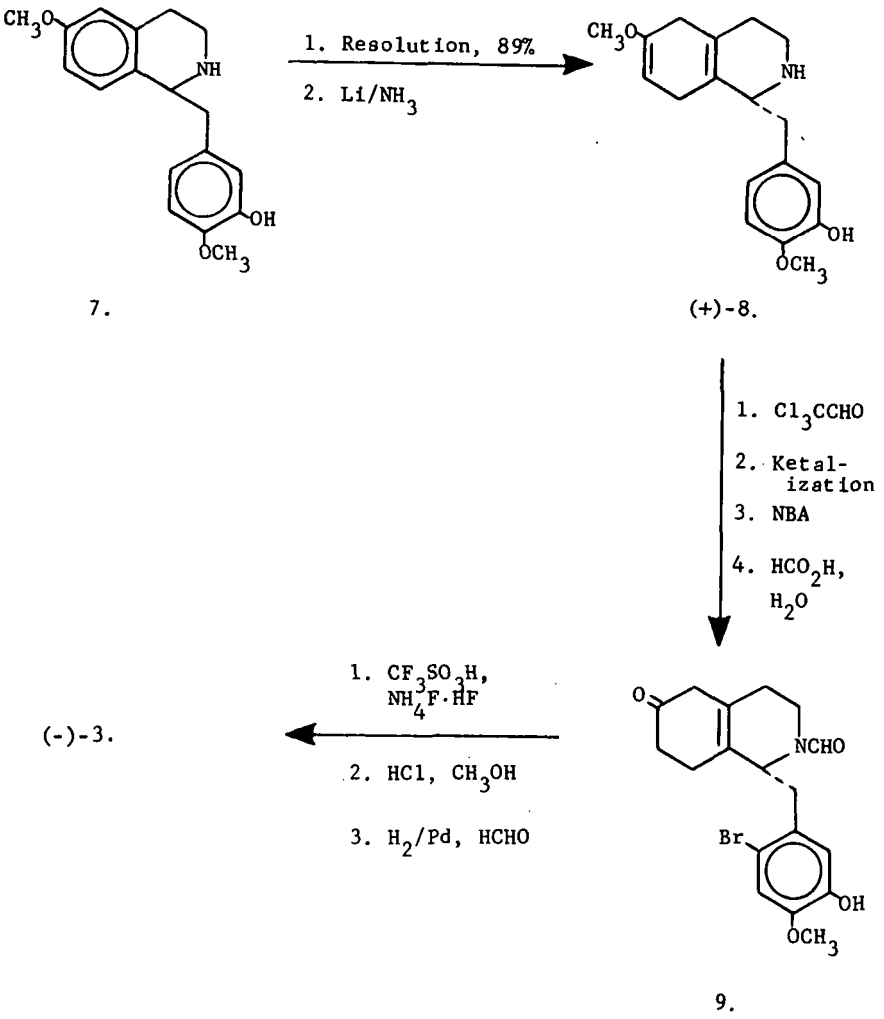
phinan carbon-nitrogen skeleton. In the former approach, control of the product distribution ratio, and the lability of the desired morphinandienone to secondary transformations have been major problems. In the Grewe approach, dihydrothebainone (3) has been a frequent objective for reasons described below; however, predominant cyclization to morphinans with an undesired oxygenation pattern, failure of Grewe cyclization with suitably blocked (to undesired cyclization) intermediates and lengthy routes employing symmetrical 1-benzyl substituents have rendered these attempts unfeasible for large scale synthesis.

In contrast to these results, a preliminary disclosure (Rice, 1980) from this laboratory recently described the successful execution of a modified Grewe-type synthesis of racemic dihydrothebainone (3), nordihydrocodeinone (5) and dihydrocodeinone (6) in 37, 30 and 29% overall yield respectively, from m-methoxyphenethylamine. This route utilized free phenolic intermediates, obviating the several additional steps for protecting and deprotecting the hydroxyl which are usually needed. It required isolation of only six intermediates (that were obtained sufficiently pure for further transfomation) and optionally afforded access to either the N-methyl or N-nor series. The (-)-enantiomer of dihydrothebainone (3) has been converted (Weller and Rapoport, 1976) to natural codeine in 68% overall yield without isolation of intermediates, to natural thebaine (4) in somewhat higher yield, and conversion of codeine (2) to morphine (1) in 90% yield has been described (Rice, 1977). Thus, the recent dihydrothebainone synthesis appeared to be a particularly promising lead for total synthesis of all medically valuable opium-derived morphinan derivatives, since the entire spectrum of this series consists of morphine (1), codeine (2), their transformation products and the drugs based on thebaine (4).

I would now like to describe extension of the route I used earlier in the racemic series to the efficient synthesis of the (-)-enantiomers of dihydrothebainone (3), dihydrocodeinone (5) and nordihydrocodeinone (6). Racemic tetrahydroisoquinoline 7 available from m-methoxyphenethylamine in 82% overall yield was readily resolved with (-)-tartaric acid to afford (+)-7 in 89% yield. The optical purity of (+)-7 was readily demonstrated by selective conversion to the corresponding urea derivative with optically pure a-methylbenzyl isocyanate followed by HPLC or NMR analysis. The former method proved to be at least an order of magnitude more sensitive in this system. Birch reduction of (+)-7 (30g scale) easily afforded essentially pure (+)-8 by TLC in 97% yield.

Selective N-formylation of (+)-8 occured essentially quantitatively by TLC as in the racemic series (Rice, 1980), however solubility properties of the crystalline N-formyl derivative of (+)-8 did not permit high recovery, in contrast to the racemic series. Thus, N-formylation of (+)-8 with chloral in THF, ketalization with ethylene glycol, regioselective bromination and deketalization without purification of the intermediates afforded crude octahydroisoquinoline 9. Cyclization of 9 as in the racemic series (Rice, 1980) gave crystalline (-)-1-bromo-N-formylnordihydrothebainone that was

identical in every respect with a sample prepared by degradation of naturally derived (-)-dihydrocodeinone (5). The combined yield of this N-formyl derivative and the parent base, isolated after acid hydrolysis of the filtrates was 40 % from (+)-8. The observation that (+)-7 affords (-)-1-bromo-N-formylnordihydrothebainone identical with that derived from natural (-)-codeine confirms the absolute configuration of (+)-7 previously assigned (Rice, 1980) on the basis of NMR arguments. Transformation of (-)-1-bromo-N-formylnordihydrothebainone to (-)-dihydrothebainone (3), (-)-dihydrocodeinone (5) and (-)-nordihydrocodeinone (6) was accomplished



7.

(+)-8.

(-)-3.

9.

in high yield as in the racemic series. Further work dealing with transformation of (+)-8 to (-)-3, (-)-5 and (-)-6 is in progress, and the results of these investigations will be reported. Based on data accumulated thus far, and in light of the work of Weller and Rapoport (1976), it now appears that overall yields of (-)-morphine (1) and (-)-codeine (2) from m-methoxyphenethylamine will be in the range of 10-30%.

REFERENCES

Barton, D. H. R., Kirby, G. W., Steglich, W., and Thomas, G. M. The Biosynthesis and Synthesis of Morphine Alkaloids. Proc Chem Soc, 203-204, 1963. See also: Barton, D. H. R., Bhakuni, D. S., James, R. and Kirby, G. W. Phenol Oxidation and Biosynthesis. Part XII. Sterochemical Studies Related to the Biosynthesis of the Morphine Alkaloids. J Chem Soc, (c), 128-132, 1967.

Beyerman, H. C., Lie, T. S., Maat, L., Bosman, H. H., Buurman, E., Bysterveld, E. M. J. and Sinnige: H. J. M. A Convenient Synthesis of Codeine and Morphine, Recl Trav Chim Pays-Bas, 95: 24-25, 1976.

Beyerman, H. C., van Berkel, J., Lie, T. S., Maat, L., Wessels, J. c. M., Bosman, H. H., Buurman, E., Bysterveld, E. M. J. and Sinnige, H. J. M. Synthesis of Racemic and Optically Active Codeine and Morphine via the N-Formylnordihydrothebainones. Recl Trav Chim Pays-Bas, 97: 127-130, 1978.

Elad, D. and Ginsberg, D. The Synthesis of Morphine. J Am Chem. Soc., 76: 312-313 (1954). See also: Elad, D. and Ginsberg, D. Synthesis in the Morphine Series. Part VI. The Synthesis of Morphine. J Chem Soc, 3052-3056, 1954.

Gates, M. and Tschudi, G. The Synthesis of Morphine. J Am Chem Soc, 78: 1380-1393, 1956. See also: Gates, M. and Tschudi, G. The Synthesis of Morphine. J Am Chem Soc, 74: 1109-1110, 1952.

Grewe, R. and Friedrichsen, W. The Cyclization of Octahydroisoquinoline Derivatives to Morphinan Ring Systems. Synthesis of Dihydrothebainones. Chem Ber, 100: 1550-1558, 1967.

Gulland, J. M. and Robinson, R. The Constitution of Codeine and Thebaine. Mem Proc Manchester Lit Phil Soc, 69: 79, 1925.

Holmes, H. L., The Morphine Alkaloids. I. In: Manske, R. H. F. and Holmes, H. L., Eds. The Alkaloids, New York: Academic Press Inc., 1952. pp. 1-159.

Kametani, T., Ihara, M., Fukomoto, K. and Yagi, H. Studies on the Synthesis of Heterocyclic Compounds. Part CCC. Synthesis of Salutaridine, Sinoacutine and Thebaine. Formal Total Synthesis of Morphine and Sinomenine. J Chem Soc (C), 2030-2033, 1969. See also: Kametani, T., Nemoto, H., Nakono, T., Shibuya, S. and Fukomoto, K. Total Synthesis of Salutaridine by Photolysis. Chem Ind (London), 788, 1978.

Lie, T. S., Maat, L. and Beyerman, H. C. Synthesis of Racemic and Chiral Codeine and Morphine via the Dihydrothebainones. Recl Trav Chim Pays-Bas 98: 419-420, 1979.

Morrison, G. C., Waite, R. O. and Shavel, J. An Alternate Route in the Synthesis of Morphine. Tetrahedron Lett, 4055-4056, 1967.

Rice, K. C. A Rapid High-Yield Conversion of Codeine to Morphine. J Med Chem 20: 164-165, 1977.

Rice, K. C. Synthetic Opium Alkaloids and Derivatives. A Short Synthesis of (±)-Dihydrothebainone, (±)-Dihydrocodeinone and (+)-Nordihydrocodeinone as an Approach to a Practical Synthesis of Morphine, 'Codeine and Congeners. J Org Chem, 45: 3135-3137, 1980. (Paper 1 in this series).

Schwartz, M. A. Prescription Drugs in Short Supply, Chapter 2, New York: Marcel Dekker, 1980.

Schwartz, M. A. and Mami, I. S. A Biogenetically Patterned Synthesis of the Morphine Alkaloids. J Am Chem Soc 97: 1239-1240, 1975.

Szantay, C., Blasko, G., Barczai-Beke, M., Pechy, P. and Dornyei, G. Studies Aiming at the Synthesis of Morphine II. Studies on Phenolic Coupling of N-Norreticuline Derivatives. Tetrahedron Lett, 21: 3509-3512, 1980.

Weller, D. D. and Rapoport, H. A Practical Synthesis of Codeine from Dihydrothebainone. J Med Chem, 19: 1171-1175, 1976.

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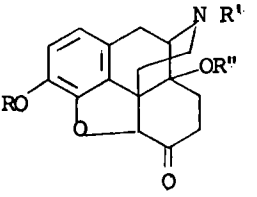
14-Alkoxy Dihydrocodeinones, Dihydromorphinones, and Morphinanones—A New Class of Narcotic Analgesics

Anil C. Ghosh, Rosemary L. Lavoie, Patricia Herlihy, John F. Howes, and Raj K. Razdan

INTRODUCTION

It is well dccmented that in morphinan-like narcotics, the region of the electrophilic nitrogen plays an imporatant role during the interaction of the drug with the opiate receptors (Blumberg and Dayton 1974; Leow and Berkowitz 1978; Pachter 1974). It has also been demonstrated that introduction of 14ß-hydroxy group in close proximity of the N- substituent group leads to compunds possesing potent pharmacological activity as agonists or mixed agonist antagonists or pure narcotic antagonists (Blumberg and Dayton 1974; Pachter 1974; Jasinski et al. 1967; Kosterlitz and watt 1968).

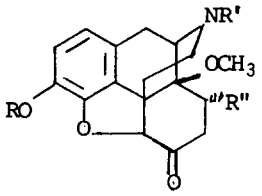
Thus oxymorphone (1a) is nearly ten times as potent as morphine as a narcotic analgesic. On the other hand, naloxone (1b) is a potent antagonist, and the corresponding N-cyclobutyl analog 1c is a mixed agonist antagonist.

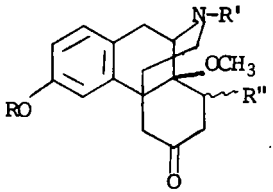


1a R=H R'=CH_3 R"=H
1b R=H R'$CH_2CH{=}CH_2$ R"=H
1c R=H R'=CH_2  R"=H
1d R=CH_3 R'=CH_3 R"=Cinnamoyloxy

In our search for nonaddictive analgesics, we wished to study effect of introducing an electrondonating group such as alkoxyl in the vicinity of the N-substituents in the morphine and

morphinan skeleton. This has led to a series of potent narcotic agonist antagonists having excellent potential as nonaddictive analgesics. This new class of compounds are represented by the structures 2-9.





2 R=H R'=CH_2▱ R"=H
3 R=H R'=CH_2▱ R"=CH_3
4 R=H R'=CH_2△ R"=H
5 R=H R'=CH_2△ R"=CH_3

6 R=H R'=CH_2▱ R"=H
7 R=H R'=CH_2△ R"=H
8 R=H R'=CH_2△ R"=α-CH_3
9 R=H R'=CH_2△ R"=β-CH_3

It may be pointed out that these 14-alkoxy derivatives, unlike the well documented 14-acyloxy analogs, are not likely to be converted to the corresponding 14-hydroxy derivatives. The 14-cinnamoyloxy derivative (1d) is a potent analgesic but shows significant physical dependence properties (Buckett 1965; Buckett 1966).

METHODS

Chemistry

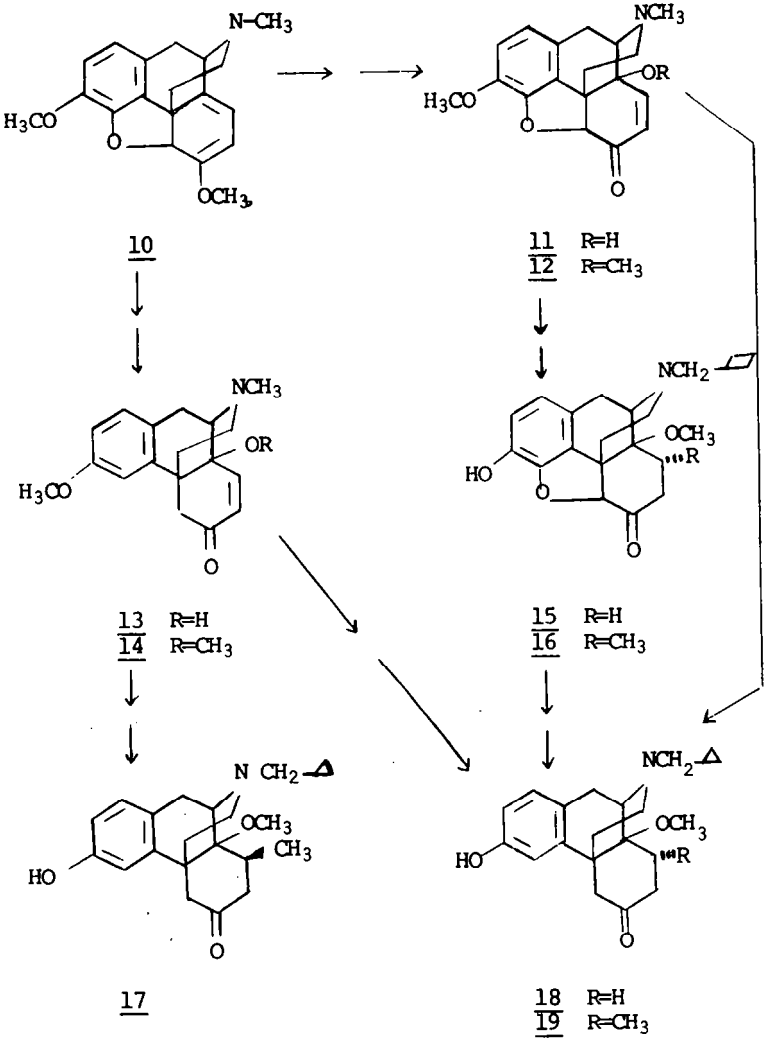
The starting material for compoubds of type 2-9 was the baine (10) (Scheme I), which was converted (Iijima et al. 1977) into 14-hydroxycodeinone (11) by treatment with m-chloroperbenzoic acid in CF_3COOH-AcOH-H_2O. Reaction of 11 with methyl iodide in presence of sodium hydride led to 14-methoxycodeineone (12). Catalytic hydrogenation led to 14-methoxy dihydrocodeineone, which was converted into compounds such as 15, 16, 18 and 19 in several steps. In another series of studies 10 was converted into 13. Structural modifications of 13 led to compounds 14, 17, 18 and 19. Introduction of the 8-alkyl substitution was accomplished by treatment of 12 and 14 with $(CH_3)_2$ Culi to give 3-methoxy-N-methyl analogs of 16 and 17, respectively.

Pharmacology

a) Mouse Acetic Acid Writhing Test

Male albino CD-1 mice (18-22g) were used for this study. A modification of the Whittle procedure (Whittle 1964) was used. The testdrugwas given by subcutaneous injection 15 minutes prior to an intraperitoneal injection of 0.5% acetic acid (0.4ml). The number of writhes per group of five mice were counted for 20 minutes starting five minutes after the acetic acid injection. Analgesic

SCHEME I


N-CH3
H3CO
O
OCH3
10
NCH3
OR
H3CO
O
O
11 R=H
12 R=CH3
NCH3
OR
H3CO
O
13 R=H
14 R=CH3
NCH2
OCH3
R
HO
O
15 R=H
16 R=CH3
N CH2
OCH3
CH3
HO
O
17
NCH2
OCH3
R
HO
O
18 R=H
19 R=CH3

potency was calculated from the difference between the test groups and their controls.

b) Rat Tail-flick Procedure (for Narcotic Antagonist Activity)

Male albino Wistar rats (lOO-15Og). were used for this study. The method described by Harris and Pierson (1964) was used.

Two control reaction times were determined thirty minutes apart and prior to intraperitoneal injection of the test drug. Ten minutes later an ED_{80} dose of morphine was administered subcutaneously and reaction times were then determined twenty minutes later. The narcotic antaqonist activity was determined from the difference between the groups and control groups which received morhpine alone.

RESULTS AND DISCUSSION

The antinociceptive properties of various compounds in the morphine series are shown in Table I. The following trends in SAR are noteworthy.

The introduction of a substituent to the 14 position of morphine-like molecules has resulted in the formation of compounds whose pharmacological profile differs significantly from the unsubstituted molecule (Blumberg and Dayton 1974; Leow and Berkowitz 1978; Pachter 1974). Thus, 14-hydroxy hydromorphine (oxymorphone) and l4-hydroxyhydrocodone (oxycodone) are more potent than hydromorphone and hydrocodone respectively. N-cyclopropylmethylnoroxymorphone (Naltrexone) is a more potent antagonist than its unsubstituted analogs but lacks agonist activity.

In N-cycloalkyl substituted 4,5-epoxymorphinan series, replacement of 14-H with 14-methoxy resulted in compounds with weaker agonist and antagonist actions. Additional introduction of an 8α-methyl group led to more active series of compounds, such as TP5162. This compound caused morphinelike symptomology in rodents

A number of interesting compunds were obtained in the l4-methoxymorphinan series (Table II).

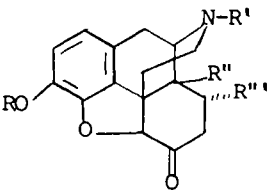
In the cyclobutylmethyl series, introduction of l4-methoxy group led to 5306 having potent agonist activity with no antagonist activity. A combination of 14-methoxy and N-cyclopropylmethyl group, however, provided compounds 5305 and 5400 with excellent agonist-antagonist ratio and good activity. Compund 5400, in view of its potency, as well as excellent agonist/antagonist ratio, has been selected as a potential clinical candidate.

When an 8α-methyl group was introduced to the 17-cyclobutylmethyl-14-methoxy morphinan skeleton, compound 5249 with good mixed agonist-antagonist properties was obtained.This compound supported morphine-like physical dependence in the rat. On the other hand, introduction of a 8ß-methyl group in l4-methoxy morphinan led to pure narcotic antagtists. Thus,compound 5210 is an extremly

potent narcotic antagonist. In this series, even the N-cyclobutylmethyl compound were potent antagonists with little or no agonist activity. This lack of agonist properties with cyclobutyl series is interesting, as it is in contrast to what has been generally observed in opiods.

TABLE I

Analgesic and Narcotic Antagonist Activities of Dihydrocodeinone and Dihydromorphinones

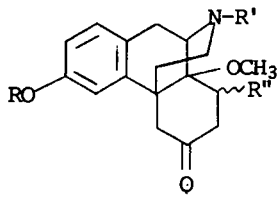


Compound No.	R	R'	R"	R"'	ED_{50} Mouse Writhing (mg/kg,s.c.)	AD_{50} Rat Tail Flick (mg/kg, i.p.)
5099	CH_3	CH_3	H	H	1.06	
5101	CH_3	CH_3	OH	H	0.50	
5251	CH_3	CH_3	OCH_3	H	0.09	
5121	CH_3	CH_3	OCH_3	CH_3	0.21	
5108**	CH_3	CH_2 	H	H	8.8	>3.0
5128	H	CH_2	H	H	0.07	1.7
5474	H	CH_2 	OH	H	7.0	0.40
5253*	CH_3	CH_2 	OCH_3	H	I	I
5259*	H	CH_2 	OCH_3	H	1.91	5.8
5158*	CH_3	CH_2 	OCH_3	CH_3	6.9	2.5
5162*	H	CH_2 	OCH_3	H	0.04	0.46
5118	H	CH_2	H	H	1.34	0.19
5460	CH_3	CH_2 	OH	H	I	0.26
5469	H	CH_2	OH	H	I	0.07
5252*	CH_3	CH_2 	OCH_3	H	I	1.02
5258*	H	CH_2	OCH_3	H	I	0.24
5157*	CH_3	CH_2 	OCH_3	CH_3	I	0.46
5179*	H	CH_2	OCH_3	CH_3	I	0.5

* = HCl salt ** = HBr salt
I = Inactive at 10mg/kg

TABLE II

Analgesic and Narcotic Antagonist Activities of Morphinanones



				ED_{50} Mouse Writhing (mg/kg,s.c.)	AD_{50} Rat Tail Flick (mg/kg, i.p.)
5287	CH_3	CH_3	H	0.033	
5421	CH_3	CH_3	α-CH_3	0.094	
5316	CH_3	CH_3	β-CH_3	0.35	
5296*	CH_3	CH_2 	H	0.77	I
5306*	H	CH_2 	H	0.007	I
5219*	CH_3	CH_2 	α-CH_3	15.1	I
5249	H	CH_2 	α-CH_3	0.018	6.1
5211*	CH_3	CH_2 	β-CH_3	I	0.41
5212*	H	CH_2 	β-CH_3	I	0.18
5305*	CH_3	CH_2 	H	0.98	1.50
5400	H	CH_2 	H	0.89	0.64
5327*	CH_3	CH_2 	α-CH_3	1.85	I
5284*	H	CH_2 	α-CH_3	I	@2.0
5209*	CH_3	CH_2 	β-CH_3	I	0.45
5210*	H	CH_2 	β-CH_3	I	0.004

* = HCl salt
I = Inactive at 10mg/kg

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REFERENCES

Blumberg, H., and Dayton, H.B. In: Braude, M.C., Harris, L.S., May, E.L., Smith, J.P., and Villarreal, J.E., eds. Narcotic Antagonists. Vol. 8. New York: Raven Press, 1974. pp. 33-43.

Buckett, W.R. Some pharmacological studies with l4-cinnamoyloxy codeinone. J Pharm Pharmacol, 17 (11): 759-60, 1965.

Buckett, W.R. The physical dependence producing capacity (PDC) of 14-cinnamoyloxy codeinone. Neuro-Psycho-Pharmacol,Proc Int Congress. Coll Int Neuro-Psycho-Pharmacol., 5th, Washington, D.C., 1966, 1243-6 Chemical Abstracts, 68, 103752e (1968).

Harris, L.S., and Pierson, A.K. Some narcotic antagonists in the benzomorphan series. J Pharmacol Exp Ther, 143 (2): 141-148, 1964.

Iijima, I., Rice, K.C., and Brossi, A. The Oxidation of thebaine with m-chloroperbenzoic acid. Studies in the (+) morphinan series. Helv Chim Acta, 60 (7): 2135-2137, 1977.

Jasinski, D.R., Martin, W.R., and Haertzen, C.A. The human pharmacology and abuse potential of N-allylnoroxymorphone (naloxone). J Pharmacol Exp Ther, 157: 420-426, 1967.

Kosterlitz, H.W., and Watt, A.J. Kinetics parameters of narcotic agonists and antagonists with particular reference to N-allylnoroxymorphone (naloxone). Brit J Pharmacol, 33: 266-276, 1968.

Leow, G.H., and Berkowitz, D.S. Quartum chemical studies of N-substituent variation in oxymorphone series of opiate narcotics. J Med Chem, 21 (1): 101-105, 1978.

Pachter, I.J. In: Braude, M.C., Harris, L.S., May, E.L., Smith, J.P., and Villarreal, J.E., eds. Narcotic Antagonists. vol. 8. New York: Raven Press, 1974. pp. 57-62.

Whittle, B.A. The use of changes in capillary permeability in mice to distinguish between narcotic and nonnarcotic analgesic. Brit J Pharmacol, 22: 246-253, 1964.

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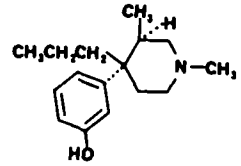
Structural Requirements for Affinity and Intrinsic Activity at the Opiate Receptor Defined in 4-Phenylpiperidine and Related Series

D. M. Zimmeman, S. E. Smits, M. D. Hynes, B. E. Cantrell, M. Reamer, and R. Nickander

In previous reports (Zimmerman and Nickander, 1977; Zimnerman et al. 1978a; 1978b), the structure-activity relationships of a series of 1,3,4-trialkyl-4-phenylpiperidines, containing potent narcotic antagonists, were explored. The importance of 3-methyl substitution for this antagonist activity was demonstrated and the narcotic agonist and antagonist properties of LY150720 were described. Since that time the pharmacology of LY150720 has been extensively evaluated and the results of these studies are the subject of an accompanying report.



(d,ℓ) - LY150720, HCL SALT
(ℓ) - LY97436
(d) - LY97435

LY150720 is a racemic mixture whose resolution results in a highly unique stereospecific separation of narcotic agonist and antagonist activity. The partial agonist properties of LY150720 are a consequence of the potent morphine-like agonist activity of the d-isomer and nalorphine-like antagonist activity of the l-isomer.

Though there have been previous reports of stereospecific separation of analgesic activity from physical dependence liability for certain benzomorphan analogs (Ager et al., 1969) and 5-m-hydroxyphenyl-2-methylphenylmorphan (May and Takeda, 1970), in no case was the degree of separation of pharmacological activities achieved as seen with LY150720.

In this paper, a series of SAR studies is described in an attempt to further characterize this unique class of opiate partial agon-

ists. The structural requirements for both affinity and intrinsic activity and the possible importance of conformational binding modes on the opiate receptor in the 4-phenylpiperidine and 4-phenyl-2-pyrindine series are described.

CHEMISTRY

The synthesis of the 1,3,4-trialkyl-4-phenylpiperidines (U.S. Patent No. 4,081,450), the 1,2,3,4-tetraalkyl-4-phenylpiperidines (U.S. Patent No. 4,228,288) and the cis- and trans-phenylpyrindines (U.S. Patent No. 4,236,009; Evans et al., 1980) have been previously reported. The isomeric configurations were confirmed by 360 MH_z - ^1H NMR and ^{13}C NMR analysis.

METHODS

The method for the acetic acid-induced mouse writhing analgesic test was similar to that previously described (Nickander et al., 1977). The ED_{50} value, defined as the dose required for a 50 percent reduction in the frequency of writhing, was computed by "The Use of the Regression Line in Reverse" (Brownlee, 1965).

The method for the rat tail heat analgesic test has been previously described (Nickander et al., 1977; Robbins, 1955). The ED_{2sec} value is defined as the dose requied for a 2-sec increase in reaction time and was computed by "The Use of the Regression Line in Reverse" (Brownlee, 1965).

The ability of the test compound to reduce or antagonize the analgesic effect of morphine was measured in the rat tail heat test (Zimmerman and Nickander, 1977). The test antagonist was administered 20 min before the administration of morphine sulfate (10 mg/kg, s.c.) and the analgesic effect of morphine was measured 10 min later. The AD_{50} value, computed by "The Use of the Regression Line in Reverse" (Brownlee, 1965) was that dose required for a 50-percent reduction in the analgesic response to morphine.

The affinity for opiate receptors of rat brain homogenates was measured by assaying the displacement of ^3H-naloxone from specifically bound sites as described before (Pasternak et al., 1975).

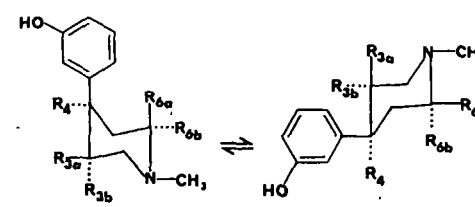
RESULTS

Narcotic agonist and antagonist measures for LY150720, its d-isomer (LY97435) and its l-isomer (LY97436) are shown in table 1, while opiate receptor biiiding affinities are given in table 2. The ED_{50} values in the mouse writhing test for LY150720 and LY97435 were comparable to that of morphine, while LY97436 was 1/10 as potent. In the rat tail heat test the analgesic potencies of LY150720 and LY97435 were again similar to that of morphine; however, LY97436 failed to produce a significant analgesic effect in this test. Inspection of table 2 shows that the potency difference between the enantiomers, LY97435 vs. LY97436, was not primarily due to differences in affinity for opiate receptors, as is normally the case. Both compounds had opiate receptor binding affinities similar to

that of morphine. In addition, LY97436 had a low sodium ratio compared to that of LY97435 and morphine (3.7, 26.7 and 20.0, respectively), inferring that LY97436 has properties of a partial agonist. In accord with this, LY97436 antagonized the analgesic response of morphine with an AD_{50} value 1/4 that of pentazocine, and 8 times that of nalorphine. These data indicate that LY97436 has low intrinsic activity (i.e., a reduced ability to stimulate the opiate receptor). Comparison of LY150720 and its d- and l-isomers with compound 1, figure 1, revealed that 3-methyl substitution on either enantiotropic edge of the piperidine ring had relatively little effect on opiate receptor affinity, table 2. These results coupled with their narcotic agonist and antagonist activities, table 1, indicate that loss of intrinsic activity at the opiate receptor is associated only with substitution on the enantiotropic edge leading to the l-isomer.

FIGURE 1.

Compound	R_4	R_{3A}	R_{3B}	R_{6A}	R_{6B}
1	Propyl	H	H	H	H
2	CH_3	CH_3	H	H	H
3	CH_3	H	CH_3	H	H
4	CH_3	CH_3	H	H	CH_3
5	CH_3	H	CH_3	H	CH_3
6	CH_3	H	CH_3	CH_3	H
7	CH_3	CH_3	H	CH_3	H



AXIAL-PHENYL EQUATORIAL-PHENYL

In an attempt to determine the conformational binding mode (axial-phenyl or equatorial-phenyl, figure 1) (Portoghese, 1965) responsible for the narcotic antagonist activity seen with the 1,3,4-trialkyl-4-phenylpiperidines, a series of 1,3,4,6-tetramethyl-4-phenylpiperidines was synthesized.

The energy difference between the two conformations shown in figure 1 is relatively small for the 1,3,4-trialkyl-4-phenylpiperidines, though the equatorial-phenyl conformation appears to be favored for compounds 2 and 3. Consequently, a conformational change of the ligand might be induced during the course of a drug-receptor interaction. With the 1,3,4,6-tetraalkyl-4-phenylpiperidines this event would seem less likely because of the additional energy barriers involved. For example the axial-phenyl conformer would appear to be favored in compounds 4 and 5 because of severe 1,3-diaxial interactions in the equatorial-phenyl conformer. Similarly for compounds 6 and 7 the equatorial-phenyl conformation would be favored.

Tables 1 and 2 show that substitution of methyl for hydrogen at $R_{6\,b}$ in compound 2, predicted to cause an equatorial to axial-phenyl con, formational change, transforms a pure antagonist to a potent, morphine-like agonist (compound 4). This transformation results in a 12-fold increase in opiate receptor binding affinity in the absence of sodium; however, affinity is reduced two-fold in the presence of sodium. In contrast, the addition of a methyl at R_{6a}, to

compound 2, giving compound 7, in which the equatorial-phenyl conformer would be further energetically favored, reduces opiate receptor affinity two-fold with no effect on intrinsic activity (i.e., narcotic antagonist activity is retained). These results strongly indicate that the narcotic antagonist activity in the 1,3,4-trialkyl-4-phenylpiperidine series is mediated through an equatorial-phenyl conformer receptor interaction. Similar observations with compounds 3, 5 and 6 are in accord with these conclusions.

The relationships of the cis-phenylpyrindines (compounds 8, 9 and 10), the trans-phenylpyrindines (compounds 11, 12 and 13) and the 5-phenyl-2-methylmorphans (May *et al.*, 1955; 1970) (compounds 14, 15 and 16) to LY150720 were explored. As shown in figure 2, the trans-4α-phenyl-2-pyrindines have an axial constrained phenyl group while the 5-phenyl-2-methylmorphans have the phenyl ring fixed in the equatorial position. However, with the cis-4α-phenyl-2-pyrindines, as with LY150720, both axial and equatorial phenyl conformations are possible.

TABLE 1

Compound	Agonist Measures: Mouse Writhing ED_{50} (mg/kg, s.c.)	Agonist Measures: Rat Tail Heat ED_{2sec} (mg/kg, s.c.)	Antagonist Measures: Rat Tail Heat AD_{50} (mg/kg, s.c.)
LY150720	1.6 (1.4-1.9)	1.8 (1.1-2.6)	41[a]
LY97436	8.1 (5.1-13)	>100	4.4 (2.6-7.4)
LY97435	0.76 (0.56-1.0)	0.78 (0.66-0.90)	Add.
1	1.3 (0.94-1.6)	0.89 (0.67-1.2)	Add.
2	>50	>50	0.24 (0.13-0.50)
3	15 (6.7-32)	33 (20-53)	31 (21-46)
4	1.6 (1.2-2.0)	1.6 (1.0-2.1)	Add.
5	>20[b]	-[b]	-[b]
6	1.2 (0.94-1.4)	1.8 (0.66-2.9)	Add.
7	>80	>80	0.40 (0.27-0.53)
8	1.2 (0.97-1.4)	0.28 (0.14-0.42)	Add.
9	1.8 (1.4-2.3)	1.1 (0.44-1.7)	Add.
10	0.19 (0.11-0.32)	0.26 (0.17-0.35)	Add.
11	1.06 (0.87-1.2)	0.48 (0.29-0.67)	Add.
12	3.4 (2.8-3.6)	4.5 (3.1-6.0)	Add.
13	0.45 (0.34-0.60)	0.76 (0.25-1.2)	Add.
14	1.8 (1.4-2.2)	0.87 (0.63-1.1)	Add.
15	3.1 (1.5-4.8)	3.3 (0.97-5.7)	Add.
16	1.0 (0.78-1.3)	0.39 (0.35-0.45)	Add.
17	27 (20-35)	>80	1.3 (1.2-1.6)
Morphine	0.89 (0.68-1.1)	0.71 (0.54-.92)	-
Meperidine	3.2 (2.8-3.6)	3.1 (2.3-3.9)	-
Pentazocine	2.0 (1.4-2.9)	2.6 (1.8-3.7)	20 (14-27)
Nalorphine	0.65 (0.39-1.1)	>80	0.32 (0.23-0.45)
Naloxone	>80	>80	

a) Pretreatment time was 170 minutes prior to the administration of morphine sulfate.
b) Insufficient sample for complete analysis. There was a 38 ± 6 percent inhibition of the number of writhes at 20 mg/kg, s.c.

As shown in table 1, compound 11 is a potent morphine-like agonist. Furthermore, resolution of compound 11 shows the d-isomer (compound 13) to be 10 times as potent as the l-isomer (compound 12) in both the mouse writhing and rat tail heat-analgesic tests. Inspection of table 2 shows that the potency difference between these two enantiomers can be explained on the basis of opiate receptor affinities. In addition the high intrinsic activity of both compounds is confirmed by their ability to completely suppress withdrawal symptoms in morphine-dependent monkeys (Woods *et al.*, 1981).

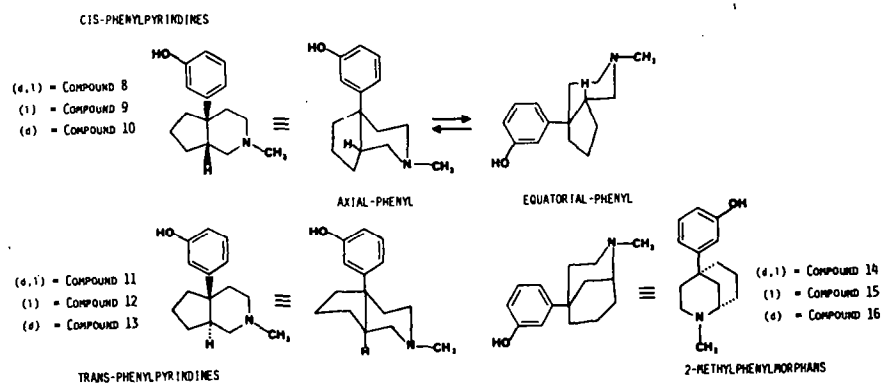
Similarly, compound 8 appears to be a potent morphine-like agonist; however, separation of its d- and l-isomers shows compound 8 to be quite different from compound 11. Its d-isomer (compound 10) is approximately 5-10 times more potent than the l-isomer (compound 9, LY150342) as an analgesic. However, receptor binding measures, table 2, show compound 10 to have only twice the affinity for opiate receptors and suggest that compound 10 has higher relative intrinsic activity.

TABLE 2

Compound	IC_{50} (nM) Values[a] +NaCl[b]	-NaCl	Na Ratio (+NaCl/-NaCl)
LY150720	55	7.5	7.3
LY97436	32	8.5	3.7
LY97435	120	4.5	26.7
1	130	9.0	14.5
2	100	160	0.6
3	1800	250	7.2
4	220	13	16.9
5	1400	75	18.7
6	220	15	14.7
7	200	380	0.5
8	550	20	27.5
9	700	35	20.0
10	300	16	18.8
11	56	8.0	7.0
12	160	16	10.0
13	50	2.7	18.5
14	320	22	14.5
15	250	46	5.4
16	560	17	32.9
17	230	54	4.3
Morphine	130	6.5	20.0
Naloxone	4	3	1.3
Pentazocine	123	15.2	8.1

a) The data present the concentration (nM) of each compound inhibiting the stereospecific binding of ^{3}H-naloxone by half.
b) The concentration of NaCl was 100 μM.

FIGURE 2

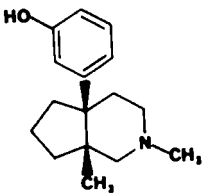


Although compound 9 fails to block the analgesic effects of morphine, its partial agonist activity has been demonstrated by its ability to precipitate withdrawal in morphine-dependent monkeys (Aceto et al., 1980) and rats, its failure to suppress withdrawal symptoms in morphine-dependent monkeys (Woods et al., 1980; Aceto et al., 1980), and its relatively small effect on mouse locomotor activity. In addition, respiratory depression studies in conscious rats show compound 9 to have a reduced depressant effect.

The agonist and antagonist measures and affinity values for compounds 14, 15 and 16 are given in tables 1 and 2. These data and published reports on compounds 14, 15 and 16 (Ong et al., 1974) show the cis-4**α**-phenyl-2-pyrindines and the 5-phenyl-2-methylmorphans to have similar pharmacological profiles.

In an attempt to more closely establish the structure-activity relation of the 3,4-dialkyl-4-phenylpiperidines with the 4**α**-phenyl-2-pyrindine series, the synthesis of the cis-9-methyl-4**α**-phenyl-2-pyrindine (compound 17) was undertaken.

COMPOUND 17



As shown in table 1, compound 17 was found to be a relatively pure narcotic antagonist, in striking contrast to the potent agonist activity of its des-9-methyl analog, compound 8. Table 2 shows both compounds 8 and 17 to have comparable opiate receptor affinities, indicating that g-methyl substitution gives a compound with reduced intrinsic opiate receptor activity. The effect of 9-methyl substitution on compound 8 is highly comparable to the effect of 3-methyl substitution on the 4-alkyl-4-phenylpiperidines and infers a strong similarity of action between the two series at the opiate receptor.

CONCLUSIONS

The effect of 3-methyl substitution in the 4-alkyl-4-phenyl-piperidine series has been shown to be primarily related to a loss of intrinsic activity rather than affinity at the opiate receptor and, as seen with LY150720, this effect can be highly stereospecific.

Comparisons of the 1,3,4-trimethyl- with the 1,3,4,6-tetramethyl-4-phenylpiperidines suggest that this loss of intrinsic activity, and resulting narcotic antagonist activity, is mediated through an equatorial-phenyl conformational binding mode. Furthermore, the pharmacological changes arising from 2-methyl substitution in the 1,3,4,6-tetramethyl-4-phenylpiperidines appear to be the result of a change induced in the conformational binding mode by steric interactions.

The cis-phenylpyrindines, like the 1,3,4-trialkyl-4-phenyl-piperidines and the 2-methylphenylmorphans, appear to bind to the opiate receptor and exert their pharmacological actions in the equatorial-phenyl binding mode. Consequently, factors affecting receptor affinity and intrinsic activity in these series are related.

These results further substantiate the existence and importance of at least two distinct bind ing modes at the opiate receptor postulated by Portoghese (1965). In the equatorial-phenyl binding mode the 3 position of the piperidine has been characterized as a stereospecific site that alters intrinsic activity, producing antagonist activity.

REFERENCES

Aceto, M. D., Harris, L. W., Dewey, W. L. and May, E. L. Committee on Problems of Drug Dependence 1980. In: NIOA Research Monograph 34, p. 297, 1981.

Ager, J. H., Jacobson, A. E. and May, E. J. J Med Chem 12:288. 1969.

Brownlee, K. A. In: Statistical Theory and Methodology in Science and Engineering, 2nd ed., New York, John Wiley and Sons, Inc., 1965.

Evans, O. A., Mitch, C. H., Thomas, R. C., Zimmerman, D. M. and Robey, N. L. J Am Chem Soc 102:5955, 1980.

May, E. L. and Murphy, J. G., Jr. Org Chem 20:1197. 1955.

May, E. L. and Takeda, M. J Med Chem 13:805, 1970.

Nickander. R., Smits, S. and Steinberg, M. J Pharmacol Exp Ther 200:245, 1977.

Ong, H. H., Oh-Ishi, T. and May, E. L. J Med Chem 17:133, 1974.

Pasternak, G. W., Wilson, H. A. and Snyder, S. H. Molecular Pharm 11:340, 1975.

Portoghese, P. S. J Med Chem 8:609, 1965.

Robbins, E. B. J Am Pharm Assoc 44:497, 1955.

Woods, J. H., Katz, J. L., Medzihradsky, F., Smith, C. B., Young, A. M. and Winger, G. O. Reported at the 43rd Annual Scientific Meeting of the Committee on Problems of Drug Dependence, 1981.

Woods, J. H., Katz, J. L., Medzihradsky, F., Smith, C. B., Young, A. M. and Swain, H. H. Committee on Problems of Drug Dependence 1980. In: NIDA Research Monograph 34, p. 327, 1981.

Zimmerman, D. M. and Nickander, R. Proc 39th Ann Mtg, Committee on Problems of Drug Dependence, 1977.

Zimmerman, O. M., Nickander, R., Horng, J. S. and Wong, D. T. Nature 275:332-334, 1978.

Zimmerman, D. M., Smits, S. and Nickander, R. Proc 40th Ann Mtg Committee on Problems of Drug Dependence, 1978, p. 237.

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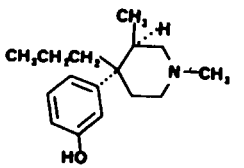
Preclinical Pharmacology of Lilly Compound LY150720, A Unique 4-Phenylpiperidine Analgesic

M. D. Hynes, S. E. Smits, B. E. Cantrell, R. Nickander, and D. M. Zimmerman

The idea of using a mixture of morphine and nalorphine for the relief of pain with the hope of minimizing the side effects associated with morphine was explored more than 25 years ago. Adverse effects associated with nalorphine precluded clinical utility. However, the concept that a mixture of a morphine-like agonist and a nalorphine-like antagonist would be a useful analgesic had considerable merit which warranted further investigation.

An agent with such properties is Lilly compound LY150720, a racemic mixture of a d-optical isomer with potent morphine-like agonist activity and an l-optical isomer exhibiting nalorphine-like activity. LY150720 is an N-methyl-4-phenylpiperidine derivative, a unique structure for a narcotic with agonist-antagonist properties It is a member of a series of 1,3,4-trialkyl-4-phenylpiperidines, the discovery of which led to the definition of a new class of narcotic antagonists (Zimmerman and Nickander 1977; Zimmerman et al. 1978a, 1978b). This paper reports the results of the preclinical studies with LY150720 and its stereoisomers.



(d,l) • LY150720, HCL SALT
(l) • LY97436
(d) • LY97435

MATERIALS AND METHODS

Mouse Writhing Analgesic Test. The writhing response was determined for each of 5 mice observed simultaneously beginning 5 min after the injection of a 0.6 percent solution of acetic acid as previously described (Nickander et al. 1977).

Rat Tail Jerk Analgesic Test. The tail of the rat was held near a nichrome resistance wire which was heated by the passage of a 6.5 amp current (AC). Radiant heat from the wire becomes aversive to a

normal rat within 6 to 7 sec, at which time the rat attempts to jerk away from the heat source (Nickander et al. 1977; Robbins, 1955).

Narcotic Antagonist Measurement in Mice. The ability of a test compound to reduce morphine-induced (46 mg/kg) Straub tail reaction and increase in motor activity was determined. The presence or absence of these behaviors was scored. When both signs were present a score of 2 was assigned, whereas mice showing one or the other were scored 1, and those showing neither sign received a score of 0.

Narcotic Antagonist Measurement in Rats. The ability of the test compound to antagonize the analgesic effect of morphine was measured in the rat tail heat analgesic test as described above. The stimulus intensity was increased to 7 amp, which enhances the likelihood of detecting morphine antagonism (Zimmerman and Nickander 1977).

Mouse Locomotor Activity. Mouse locomotor activity was measured in circular wire mesh cages 2 inches high and 11 inches in diameter. Two mice were placed in each cage and allowed to acclimatize for one hour before being injected subcutaneously. One count was registered each time the light beam passing through the center of the cage was interrupted. The total number of counts was recorded for a 4-hour period following injection.

Single Dose Suppression of Spontaneous Withdrawal in Morphine-Dependent Rats. Rats were made dependent by administration of increasing doses of morphine. Withdrawal signs including diarrhea ptosis, jumping and body shakes, were observed 16 to 20 hours after' the last morphine injection.

Respiratory Depressant Measures in Conscious Rats. Experiments were conducted on rats fitted with permanently-indwelling arterial catheters. On the day of the test blood was drawn anaerobically from this catheter and blood gas values determined. Rat arterial blood samples were analyzed on an Instrumentation Laboratory 513 pH/Blood Gas Analyzer that measured pH, pCO_2 and pO_2 directly (Smits et al. 1981).

Affinity for Opiate Receptors in Rat Brain Homogenates. Interaction of test compounds with ooiate receptors of freshlv prepared rat brain homogenate was measured by assaying the. displacement of 0.25 μM ^{3}H-naloxone (50 Ci/mmole. New England Nuclear) or 0.75 μM ^{3}H-D-Ala-D-Leu-enkephalin (31 Ci/μmole, Amersham). Following incubation, the samples were filtered through Whatman glass fiber filters (GF/C) and washed twice with buffer. Filters were subsequently placed in vials and, after adding 10 ml of Phase Combining System (Amersham), counted by liquid scintillation spectrophotometry.

RESULTS

Mouse Writhing Analgesic Test. Compound LY150720 inhibited acetic acid-induced writhinq in mice following both oral and subcutaneous administration. The-ED_{50} values are presented in reference to standard narcotic analgesics in Table I. Following-subcutaneous administration, compound LY150720 was twice as active as meperidine, equivalent to pentazocine and about 1/4 as potent as morphine.

Comparison of writhing inhibition following oral administration showed that compound LY150720 was more active than pentazocine, equivalent to meperidine and less active than morphine. The analgesic effects of LY150720 in the writhing test were blocked by the narcotic antagonist naloxone.

TABLE 1
Analgesic Activity of LY150720 in the Mouse Writhing Test

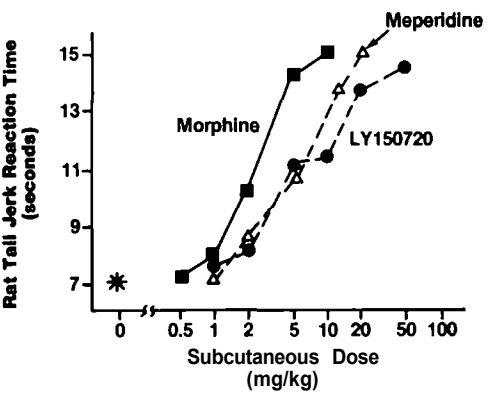
	Inhibition of Mouse Writhing[a] ED_{50} (95 Percent Confidence Limits)	
Treatment	Subcutaneous	Oral
LY150720	2.4 (1.8 - 3.2)	18.0 (15.0 - 23.0)
Morphine	0.5 (0.3-0.8)	4.4 (3.6 - 5.3)
Meperidine	4.9 (4.2-5.9)	15.8 (11.5 - 21.7)
Pentazocine	2.0 (1.4-2.9)	46.0 (38.0 - 56.0)

a. The mouse writhing ED_{50} values are expressed in mg/kg.

The two optical isomers of compound LY150720 were examined for their analgesic activity in the mouse writhing assay. Following subcutaneous administration, the d-isomer, compound LY97435, dose dependently inhibited writhing and-was calculated to have an ED_{50} value of 0.76 (0.56-1.0) mg/kg. The l-isomer, compound LY97436, also inhibited writhing, but had an ED_{50} value of 8.1 (5.1-13) mg/kg, which is 10 times that observed for the d-isomer.

Rat Tail Jerk Analgesic Test. Dose response data for compound LY150720 in the rat tail jerk test following subcutaneous administration are shown in Figure 1. Compound LY150720 produced a dose-related analgesia in rats as evidenced by a prolongation of rat tail jerk reaction times. A comparison of the dose-response curves for morphine, meperidine and LY150720 indicated some differences. For example, the dose response for morphine had a steep slope which reached the cut-off time of 15 seconds at a 10 mg/kg dose. At the lower end of the dose response curve, compound LY150720 was approximately half as potent as morphine and equipotent with meperidine. However, beginning at about 20 mg/kg, there was only a slight increase in effect with larger doses of LY150720. The effect of compound LY150720 was still slightly below the cut-off value at doses as high as 50 mg/kg.

FIGURE 1.
Analgesic activity of LY150720 in the rat tail jerk analgesic test



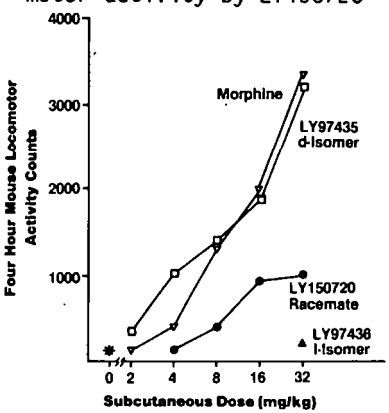
The optical isomers of LY150720 were also examined for analgesic activity after subcutaneous administration in the rat tail jerk test. The d-isomer was comparable with morphine in potency, shape of the dose-response curve, and duration, whereas the l-isomer exhibited little if any effect even at very high doses. These results suggest that the analgesic activity of the racemate resides in the d-optical isomer. The l-isomer appears to limit the analgesia of the d-isomer when the racemate is given, suggesting that the l-isomer may have some narcotic antagonist properties.

Narcotic Antagonist Measures in Mice. The ability of compound LY150720 and its l-isomer, compound 97436, to block the morphine-induced Straub tail reaction and increased locomotor activity in mice was determined in comparison to nalorphine and pentazocine. All four agents produced a dose-related antagonism of the above effects of morphine. The dose of nalorphine that caused a 50 percent antagonism of these effects (AD_{50}) was calculated to be 0.46 mg/kg. Correspondingly, AD_{50} values for LY97436, pentazocine and LY150720 were 5.9, 19 and 45 mg/kg, respectively. Thus, the l-isomer of LY150720 was approximately 1/10 as potent as nalorphine and slightly greater than 3 times more potent than pentazocine in blocking the narcotic effects of morphine. Compound LY150720 exhibited weak morphine antagonist activity in this test in that greater than 70 percent antagonism was not achieved. Morphine antagonism is much easier to demonstrate for the l-isomer alone than when the d-isomer is present, as is the case with the racemate.

Narcotic Antagonist Measures in Rats. Dose response data for the antagonism of morphine by compounds LY150720 and LY97436 in the rat tail jerk test were then generated. The pretreatment times were 30 min for compound LY97436 and 180 min for compound LY150720, the time of peak antagonist activity for each compound. Morphine analgesia was effectively antagonized by both compounds in a dose-dependent manner. The AD50 (95 percent confidence limits) values were 4.4 (2.6-7.4) mg/kg for compound LY97436 and 41 (18-91) mg/kg for compound LY150720.

Mouse Locomotor Activity. Morphine is well known for its ability to dose-dependently stimulate locomotor activity in mice as can be seen from the data depicted in Figure 2. In contrast to morphine, LY150720 produced dose-related increases in locomotor activity from 4 to 16 mg/kg, while the effects following doses of 16 and 32 mg/kg were similar. Thus, the maximum degree of stimulation obtainable with LY150720 appears to be similar to that seen with a morphine dose of between 4 and 8 mg/kg. The results for the two optical isomers are also given in Figure 2. There was a dose-related increase in activity

FIGURE 2.
Stimulation of mouse locomotor activity by LY150720

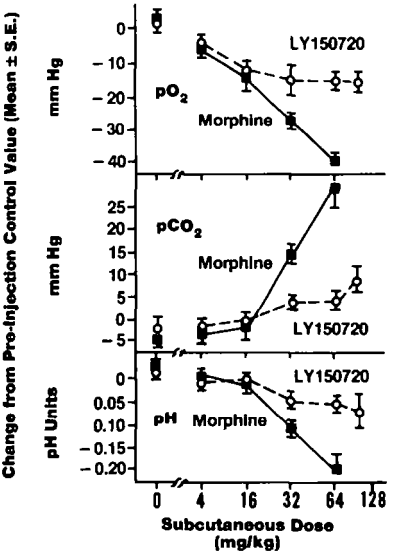


when the d-isomer, compound LY97435, was administered. As can be seen from-this figure the effect of a 32 mg/kg dose was only slightly less than that observed with morphine at the same dose. Thus, the d-isomer appears to be a morphine-like agonist in this procedure. In marked contrast to these results, the 32 mg/kg dose of the l-isomer was without effect on activity levels in mice. This marked difference in the effect of the two isomers provides an explanation for the plateau in effect observed with the racemate.

Single Dose Suppression of Spontaneous Withdrawal in Morphine-Dependent Rats. Morphine, meperidine and LY150720 were investigated for their ability to suppress the signs of spontaneous withdrawal in morphine-dependent rats. Morphine and meperidine produced a dose-related suppression of withdrawal and were calculated to have ED_{50} values of 4.9 and 17.3 mg/kg, respectively. In marked contrast, compound LY150720 did not suppress withdrawal at doses as high as 64 mg/kg. At the lowest dose tested, 0.5 mg/kg, there was a significant increase in the severity of withdrawal. These data clearly distinguish compound LY150720 from the standard narcotic agonists, such as morphine and meperidine, and suggest a low abuse potential.

Respiratory Depressant Measures in Conscious Rats. Morphine and LY150720 were compared for their ability to produce respiratory depression in conscious rats. The respiratory depressant effects of LY150720 as measured by arterial blood pCO_2, pO_2 and pH are shown in Figure 3 in reference to those produced by morphine. Subcutaneous administration of LY150720 or morphine to conscious rats depressed respiratory function, as indicated by the decrease in arterial blood pO_2. The depressant effects of morphine increased in a dose-dependent manner from 4 to 64 mg/kg, whereas administration of compound LY150720 in doses of 4 and 16 mg/kg produced a dose-related respiratory depression. However, the administration of compound LY150720 at doses greater than 32 mg/kg only slightly decreased blood pO_2, producing a maximum achievable effect for LY150720 equivalent to that of approximately 16 mg/kg morphine. Changes in pCO_2 and pH were consistent with those seen for arterial blood pO_2. These data suggest that respiratory depression in man could be less of a problem with LY150720 than with morphine.

FIGURE 3.
Changes in arterial blood gases following LY150720 or morphine administration



Affinity of LY150720 and its Isomers for In Vitro Opiate Receptors Labeled with [^{3}H]-Naloxone and [^{3}H]-D-Ala-D-Leu-Enkephalin. The data summarized in Table 2 show the IC_{50} values for LY150720 and its optical isomers for inhibiting ^{3}H-naloxone and ^{3}H-D-Ala-D-Leu-enkephalin binding in rat brain homogenates. These IC_{50} values were then compared to give a μ/δ ratio. As expected, morphine and fentanyl were found to exhibit a marked preference for the μ receptor. Conversely, D-Ala-D-Leu-enkephalin was found to have a higher affinity for the delta site as indicated by ^{3}H-D-Ala-D-Leu-enkephalin displacement. Compound LY150720 was found to hav good affinity for both receptors, with a slight preference for the ^{3}H-naloxone site. The μ/δ ratio was calculated to be 0.6, which is almost 10-fold greater than observed for morphine. Compound LY97435 was found to have equal affinity for the ^{3}H-naloxone and ^{3}H-D-Ala-O-Leu-enkephalin site. Although its affinity at the δ site was not as great as that observed for D-Ala-D-Leu-enkephalin it had a significantly higher affinity for this site than either morphine or fentanyl. In fact the activity of the d-isomer was 16 times greater than that observed for morphine and 40 times that for fentanyl. The l-isomer also exhibited good affinity for the D-Ala-D-Leu-enkephalin site, but not as good as that seen for the d-isomer.

TABLE 2
Affinity of LY150720 and its Isomers for Opioid Receptors

Compound	IC_{50} Values[a] (nM)		μ/δ
	^{3}H-Naloxone	^{3}H-D-Ala^2-D-Leu^5-Enkephalin	
Morphine	6.5	75	0.08
Fentanyl	4.8	196	0.02
D-Ala^2-D-Leu^5 Enkephalin	42.1	1.9	22.15
LY150720 Racemate	7.5	12.3	0.6
LY97435 d-Isomer	4.5	4.5	1
LY97436 l-Isomer	8.5	16	0.5

a. The data present the concentration (nM) of each compound inhibiting the stereospecific binding by half.

DISCUSSION

Good analgesic activity was observed in rodent assays following administration of the structurally unique partial opiate agonist LY150720. Pharmacological evaluation of the two optical isomers of this racemate revealed that the d-isomer, compound LY97435, was a potent morphine-like narcotic agonist, whereas the l-isomer, compound LY97436, was a partial opiate agonist. Apparently the antagonist activity of the l-isomer limits the extent to which the

d-isomer can exert its narcotic character when the racemate, LY150720, is administered. Acute toxicity determinations in rodents indicated a good margin of safety which was supported by the limited depression of respiration produced by LY150720.

The fact that LY150720 did not suppress morphine withdrawal in rodents distinguishes it from standard narcotic agonists and suggests a low liability for abuse (Zimmerman et al., 1978b). This contention is supported by studies in monkeys conducted under the auspices of the Committee on Problems of Drug Dependence. In single-dose suppression studies in morphine-dependent rhesus monkeys undergoing spontaneous withdrawal, LY150720 caused only mild CNS depression at doses up to 40 mg/kg and did not suppress or precipitate morphine abstinence. Primary dependence studies in monkeys revealed an abstinence syndrome of mild to moderate severity following chronic LY150720 administration which was not typical of morphine or related opioids (Aceto et al. 1981; Woods et al. 1981).

The good therapeutic index of LY150720 in rodents, coupled with its unique binding properties and low physical dependence liability, suggests that it mav have a clinical profile distinctly different from other partial agonists.

REFERENCES

Aceto, M. D., Harris, L. W., Dewey, W. L. and May, E. L. Committee on Problems of Drug Dependence 1980. In: NIDA Research Monograph 34, (ed. L. S. Harris), p. 297, 1981.

Nickander, R., Smits, S. and Steinberg, M. J Pharmacol Exp Ther 200:245, 1977.

Robbins, E. B. J Am Pharm Assoc 44:497, 1955.

Smits, S. E., Nickander, R Booher, R. N., Zimmerman, D. M., Wong, D. T., Hynes. M. D. and pohland, A. Committee on Problems of Drug Dependence 1980. In: NIDA Research Monograph 34 (ed. L. S. Harris), p. 75, 1981.

Woods, J. H., Medzihradsky, F., Smith, C. B., Young, A. M. and Swain, H. H. Committee on Problem; of Drug Dependence 1980. In: NIOA Research Monograph 34 (ed. L. S. Harris), p. 327, 1981.

Zimnerman, O. M. and Nickander, R. Proc 39th Ann Mtg, Committee on Problems of Drug Dependence, 1977.

Zimmerman, D. M. and Nickander, R., Horng. J. S. and Wong, D. T. Nature 275:332, 1978a.

Zimmerman, O. M., Smits, S. and Nickander, R. Proc 40th Ann Mtg Committee on Problems of Drug Dependence, 1978b.

AUTHORS

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A Structure Activity Relationship Study of the Cyclohexyl and Aromatic Rings of Phencyclidine (PCP)

Edward Cone, Harlan Shannon, Bruce Vaupel, Tsung-Ping Su, and Roy McQuinn

The pharmacology of PCP has been studied extensively; however, the mechanism of action at the molecular level remains poorly understood. We have undertaken studies on PCP directed toward defining the structural requirements for pharmacological activity. A consideration of the PCP molecule reveals that it is a semirigid structure consisting of a cyclohexane ring (C) geminally substituted with an aromatic ring (A, benzene) and a basic ring (B, piperidine). It can be conveniently represented by the symbol, A–C–B. The unique pharmacology of this compound has already engendered several structure activity studies (Maddox et al., 1965; Kalir et al., 1969; Geneste et al., 1979; Kalir et al., 1978). The focus of these studies has been the substitution of various functional groups for the A, B and C rings, with the majority of new compounds representing A or B substitutions: groups that are believed to be mainly responsible for PCP's activity.

We directed our studies to an examination of the pharmacologic importance of the C ring of PCP and to alterations of electronic and spatial relationships of the A and B rings. Since the steric relationship between the A and B rings is determined by the size of the cycloalkane ring (C), the systematic alteration of the size of ring C would result in predictable changes in the distance between rings A and B (see table 1). Alteration of the distance between A and B also could be accomplished by "insertion" of methylene linkages [-(CH_2)n-] between rings A and C. A third structural change considered was the enlargement of the aromatic ring system of A, thereby extending conjugation and altering the electronic profile of the A ring and, consequently, the entire molecule.

This report describes the synthesis and pharmacological activity of two series of PCP derivatives (see figure 1). In Series 1, the size of the C ring was varied from C3 (cyclopropyl) to C8 (cyclooctyl). In Series 2, compounds were prepared which represent methylene "insertions" between the A and C rings. Other members of the latter series were prepared which represent

FIGURE 1

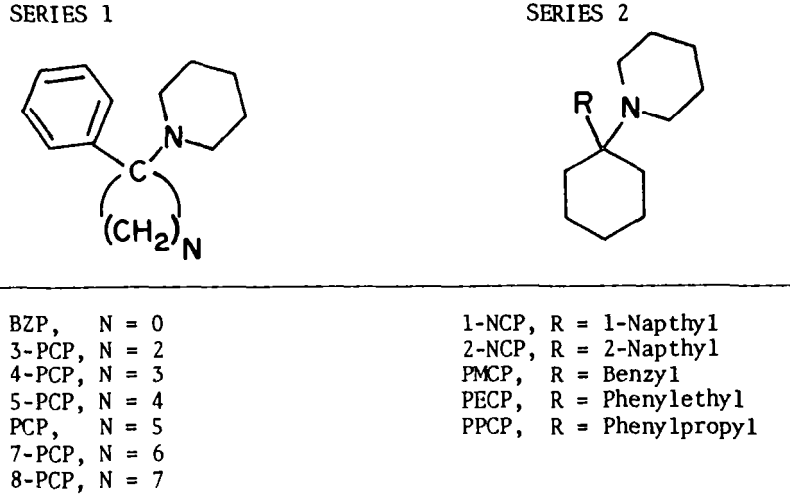


Figure 1. Structures of phencyclidine derivatives

simple substitution of the A ring by napthyl groups. Pharmacological activities of these compounds were measured by the rat discriminative stimulus and the mouse rotarod assay. In vitro testing was performed with the ^{3}H-PCP binding assay.

METHODS

Syntheses of Phencyclidine Derivatives

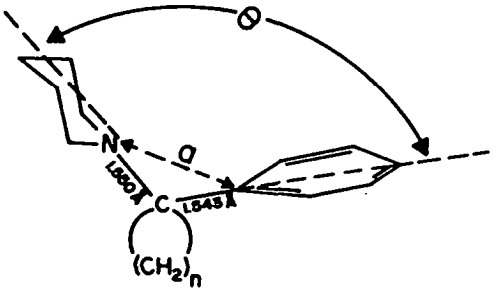
The procedures for the preparation of PCP derivatives by Kalir et al. (1969) was used with appropriate modifications for the syntheses of 4-PCP, 5-PCP, 7-PCP, 1-NCP, 2-NCP, PMCP, PECP and PPCP. BZP was made in good yield by refluxing benzylamine in the presence of 1,5-dibromopentane and potassium carbonate in dimethylformamide. 3-PCP was prepared by the method of Kaiser et al. (1962). 8-PCP was synthesized by a modification of the method of Geneste et al. (1979) for the preparation of PCP derivatives. The structure and purity of all compounds were confirmed by elemental analyses, thin-layer chromatography, mass spectrometry and nuclear magnetic resonance.

Discriminative Stimulus Assay

Male, Fischer-derived CDF rats were trained to discriminate between PCP and saline in a two choice, discrete-trial avoidance task similar to that described in detail elsewhere (Jasinski et al., 1980). Pupil diameter was measured photographically with a Polaroid CU5 close-up camera. The pupils were photographed immediately before the rats were injected (control) and again immediately before the start of the test session 30 min later.

Table 1

Effect of cycloalkyl ring size on the bond angle and interatonic distance between the nitrogen atom (N13) and the C1 carbon of the benzene ring in phencyclidine derivatives.



COMPOUND	n	CYCLOALKYL RING	θ (DEGREES)[a]	a(ANGSTROM
3-PCP	2		116	2.623
4-PCP	3		111	2.549
5-PCP	4		109.5	2.526
PCP	5		109	2.518
7-PCP	6		109	2.518
8-PCP	7		109	2.518

[a] The angle θ for compounds where n = 6,7 was assumed to be equal to that of phencyclidine. For compounds where n = 2,3,4 the angle θ was obtained from Coulson and Moffitt, Phil. Mag. 40, 1 (1949).

^{3}H-PCP Binding Assay

The binding assay was performed as described by Zukin and Zukin (1979) with the exception that the glass fibre filter was pre-treated with water saturated with t-amyl alcohol to reduce non-specific binding.

Mouse Rotarod Test

Relative potencies of PCP-like compounds and their precursors were determined in male ICR Swiss mice by measuring ataxia using the rotarod method of Dunham and Miya (1957). Each mouse was tested sequentially at 6-min intervals for 1 hr after injection according to the modification of Kalir et al. (1969).

RESULTS

Two series of phencyclidine derivatives were synthesized and characterized by standard chemical and physical means. The structures of these compounds are illustrated in figure 1. All were tested in the rat discriminative stimulus (DS) assay and the ^{3}H-PCP binding assay. Activities of the Series 1 compounds also were measured in the mouse rotarod (RR) assay. The results are shown in table 2.

In the rat DS assay, rats were trained in a two-choice discrete-trial avoidance procedure to discriminate between saline and 3.0 mg/kg of PCP administered intraperitoneally 30 min before the start of the session. PCP produced dose-related increases in the percentages of trials completed on the PCP-appropriate choice lever. 4-PCP, 5-PCP and 7-PCP also were effective in producing at least 90 percent PCP-appropriate choice responding, although they were much less potent. The remainder of the compounds of Series 1 and 2 were inactive up to the highest dose tested (table 2). Pupillary miosis was observed for PCP, but the remainder of the compounds produced mydriasis or no change.

In the ^{3}H-PCP binding assay, PCP was the most potent of the Series 1 compounds followed by 8-PCP with a relative potency (RP) of 0.72 (PCP = 1.0). There were only slight differences in binding for the other members of this series. In the Series 2 compounds, conversion of the aromatic ring (A) to that of a napthyl group reduced relative potency by one-fifth (2-NCP) and by one-half (1-NCP). For the methylene "insertion" compounds, binding affinity rose dramatically from the weakly binding PMCP' (RP = 0.24) to PPCP (RP = 1.35) with PECP (RP = 0.52) exhibiting intermediate activity.

The Series 1 compounds were tested in the mouse rotarod assay for impairment of gross motor performance. Although all compounds were active (with the exception of 8-PCP which was too toxic to obtain a dose response curve), valid bioassays using PCP as the standard were obtained only for 3-PCP, 4-PCP and BZP. All compounds were less active than PCP.

TABLE 2

Pharmacological activities of phencyclidine derivatives

Compound	Rat Discriminative[a] Stimulus Assay	Pupillary Effects (Rat)	Mouse Rotarod[a] Assay	^{3}H-PCP[a,b] Binding Assay
BZP	IA(30 mg/kg)	0	0.11(±0.05)	0.02
3-PCP	IA(56 mg/kg)	0	0.04(±0.03)	0.07
4-PCP	0.17(±0.07)	↑	0.31(±0.08)	0.08
5-PCP	0.37(±0.12)	↑↑	0.57[c]	0.12
PCP	1.0	↑	1.0	1.0
7-PCP	0.07(±0.05)	↑↑	0.13[c]	0.23
8-PCP	IA(30 mg/kg)	↑	--[d]	0.72
1-NCP	IA(100 mg/kg)	↑	NT	0.47
2-NCP	IA(30 mg/kg)	↑↑	NT	0.19
PMCP	IA(30 mg/kg)	↑	NT	0.24
PECP	IA(30 mg/kg)	↑↑	NT	0.52
PPCP	IA(30 mg/kg)	↑	NT	1.35

[a] Values represent relative potencies where the number listed indicates the number of μM of PCP equivalent to 1 μM of the compound. Numbers in parentheses represent the 95% confidence limits or, if the compound was inactive (IA), represent the highest dose tested. NT = not tested.

[b] The IC_{50} of unlabeled PCP was 270 nM.

[c] A parallel line bioassay was not obtained.

[d] This compound was too toxic (seizures) to obtain a dose-response curve.

DISCUSSION

The geometric and electronic similarity of PCP to acetylcholine has been proposed as an explanation of PCP's in vitro activity (Kalir et al., 1978). The positive charge on the protonated nitrogen (B ring) is said to mimic the trimethyl ammonium group and the region of high electron density (aromatic ring, A) mimics the ester oxygen of acetylcholine. Overlap of these groups is readily apparent by inspection of Dreiding models and it has been emphasized that the distances between the positive charge (nitrogen) and the region of high electron density (benzene) is a critical factor for overlap (Weinstein et al., 1973). Deviations from this critical distance should presumably prevent overlap and binding with the cholinergic receptor. Clearly, the cyclohexyl ring (C) offers rigidity to the PCP molecule and also determines the distance between rings A and B by nature of its SP^3 hybrid bonding orbitals. By reducing the size of the C ring in a stepwise fashion, the distance between rings A and C should increase from 2.518 A for PCP as measured between N13 and C7, table 1) to a maximum of 2.623 A for 3-PCP as a result of the required changes in bonding orbitals for smaller ring systems. The effect of this stepwise decrease in the size of ring C was to decrease both in vivo activity (rat DS assay and mouse RR assay) and in vitro activity (^{3}H-PCP binding assay).

Alternate molecular changes were also made to increase the size of ring C to seven- and eight- membered rings. For these compounds, it is presumed that the bonding orbitals would remain equivalent to those of PCP with the distances between rings A and B also being equal. Despite these predictions, their activities were greatly reduced or completely abolished. Also, severe toxicity became the limiting factor in testing 8-PCP in the mouse RR assay. It is obvious from these data that the cycloalkyl ring serves more pharmacological purpose than providing rigidity and defining the spatial relationship between rings A and B. It appears likely that the cyclohexyl ring (C) plays an integral role in the activity of PCP, serving not only as the main steric determinant in the molecule, but also as a hydrophobic attachment site. This view is supported by the lack of activity of BZP, a compound which lacks the C ring but possesses both A and B rings needed for overlap with acetylcholine.

The lack of activity of 1-NCP and Z-NCP in the rat DS assay indicates that the potential for overlap with acetylcholine does not necessitate the appearance of PCP-like activity. These compounds have similar molecular features with PCP, the only change being in the size and electronic properties of the aromatic ring (A). It is possible that the napthyl groups would present changes in the electrostatic potential pattern sufficient to account for their lack of activity; however, this remains to be determined. This would also serve to explain the lack of activity of the methylene "insertion" compounds in the rat DS assay.

There was good correspondence between the in vivo activity-measures (rat DS assay and mouse RR assay) and the in vitro ^{3}H-PCP binding assay within the Series 1 cycloalkyl. compounds. There was, however, a complete lack of agreement between the results of the rat DS assay and the ^{3}H-PCP binding assay for the Series 2 compounds. There are a number of possible explan tions for the discrepancy between these assays. The original ^{3}H-PCP binding assay has been criticized for its high binding to the glass fiber filter (Maayani and Weinstein, 1980). The assay used in these studies is a modification of the original procedure (Zukin and Zukin, 1979) by pretreatment of the filter with t-amyl alcohol, a step which reduces binding to the filter but does not eliminate it. Consequently, the relative potencies of these compounds could be distorted by high background. Another possible explanation for these discrepancies would be an antagonistic component for the Series 2 compounds, in which case they would show high binding affinities and low in vivo activities. This, however, appears not to be the case basis of preliminary experiments in which the impairment of gross motor performance induced by PCP was not reversed by these co ounds. An alternate and possibly more viable explanation would that the binding of PCP derivatives encompasses a wider range of potential pharmacological effects than those elicited by PCP alone. Some credence is given to this proposal by the obvious overlap of effects elicited by the Series 1 compounds, 4-, 5- and 7-PCP, with PCP in the rat DS assay, but with divergent pupillary effects. A lack of parallelism with PCP in the dose response curve also was seen with the 5- and 7-PCP compounds in the mouse RR assay. Other potential explanations of the differences in the in vivo and in vitro results include possible differences in rates of metabolism, distribution and excretion.

In summary, the requirements for PCP-like activity a pear to necessitate the inclusion of a cyclohexyl ring (ring C) in new derivatives. Although relative potency measures were obtained for other compounds without this structural feature, a lack of correspondence in other pharmacological measures was evident. For compounds in which the phenyl ring (A) was spatially located further away Erom the cyclohexyl ring by methylene "insertion" and those compounds in which a napthyl group was substituted for the A ring, a complete lack of PCP-like activity was found by the rat DS assay, but moderate to high activity was seen in the ^{3}H-PCP binding assay.

REFERENCES

Dunham, N.W., and Miya, T.S. A note on a simple apparatus for detecting neurological deficit in rats and mice. J Amer Pharm Assoc 46:208-209, 1957.

Geneste, P., Kamenka, J. M., Ung, M. S. N., Herrman, P., Goudal, R., and Trouiller, G. Determination conformationnelle de derives de la phencyclidine en vue d' une correlation structure-activite. Eur J Med Chem 14:301-308, 1979.

Jasinski, D.R., Shannon, H.E., Cone, E.J., Vaupel, D.B., Risner, M.E., McQuinn, R.L., Su, T.-P., and Pickworth, W.B. Interdisciplinary studies on phencyclidine. In: Domino, E.F., ed. PCP-Historical and Current Perspectives. Ann Arbor, MI: NNP Books, 1980, in press.

Kaiser, C., Lester, B. M., and Zirkle, C. L. 2-Substituted cyclopropylamines. I. Derivatives and analogs of 2-phenylcyclopropylamine. J Med Chem 5:1243-1265, 1962.

Kalir, A., Edery, H., Pelah, Z., Balderman, D., and Porath, G. 1-Phenylcycloalkylamine derivatives. II. Synthesis and pharmacological activity. J Med Chem 12:473-477, 1969.

Kalir, A., Maayani, S., Rehavi, M., Elkavets, R., Pri-Bar, I., Buchman, O., and Sokolovsky, M. Structure-activity relationship of some phencyclidine derivatives: in vivo studies in mice. Eur J Med Chem 13:17-24, 1978.

Maayani, S., and Weinstein, H. "Specific binding" of ^{3}H-phencyclidine: artifacts of the rapid filtration method. Life Sci 26:2011-2022, 1980.

Maddox, V.H., Godefroi, E.F., and Parcell, R.F. The synthesis of phencyclidine and other 1-aryl-cyclohexylamines. J Med Chem 8:230-235, 1965.

Weinstein, H., Maayani, S., Srebrinik, S., Cohen, S., and Sokolovsky, M. Psychotomimetic drugs as anticholinergic agents. II. Quantum-mechanical study of molecular interaction potentials of 1-cyclohexylpiperidine derivatives with the cholinergic receptor. Molec Pharmacol 9:820-834, 1973.

Zukin, S.R., and Zukin, R.S. Specific [^{3}H] phencyclidine binding in rat central nervous system. Proc Natl Acad Sci USA 76:5372-5376, 1979.

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The Effects of Centrally Acting Peptides on the Chronic Actions of Buprenorphine in the Rat

Hemendra N. Bhargava, Ph.D.

INTRODUCTION

Buprenorphine is a potent analgesic dry with rapid onset and long duration of action (Cowan et al., 1977a). This drug belongs to mixed opiate agonist-antagonist analgesic. It also possesses low physical dependence liability (Cowan et al., 1977b; Jacob et al., 19791. A recent report indicated that buprenorphine suppressed the self-administration of heroin in heroin dependent subjects and it had an advantage over methadone since its use did not result in opiate abstinence syndrome following its termination (Mello and Mendelson, 1980).

In spite of its beneficial properties as a potent analgesic and as a pharmacotherapeutic agent for the treatment of heroin addiction, buprenorphine suffers from a major disadvantage, which is the develop nent of tolerance to its analgesic action when administered chronically (Cowan et al., 1977b). Previous studies from these laboratories have indicated that certain hypothalamic peptide hormones, like melanotropin release inhibiting factor (Pro-Leu-Gly-NH_2 MIF) and its analog cyclo (Leu-Gly), block the tolerance to morphine in mice and rats (Bhargava, 1980; 1981a, b; Bhargava et al., 1980) and to human ß-endorphin in the rat (Bhargava, 1981c,d). Because of the importance of buprenorphine as a therapeutic agent, in this report the effects of MIF and cyclo (Leu-Gly) on tolerance to buprenorphine in the rat are described.

METHODS

Male Sprague-Dawley rats weighing 150 to 200 g obtained from King Animal Laboratories, Oregon, Wis., were used. The rats were acclimated to the laboratory for at least 4 days prior to being used. Food and water were continuously available.

MIF was obtained as a gift from the Abbott Laboratories, N. Chicago, Illinois, through the courtesy of Dr. A.O. Geiszler. Cyclo (Leu-Gly) was synthesized in these laboratories as described previously (Bhargava, 1981b). Dr. A. Cowan of Temple University, Philadelphia, kindly furnished a sample of buprenorphine. The peptides and

buprenorphine were dissolved in distilled water and injected subcutaneously in a volume of 1 ml/kg of body weight.

Induction and assessment of tolerance to buprenorphine

The tolerance to buprenorphine was induced in the rat by twice daily injections of buprenorphine (0.5 mg/kg SC) for 4 days. The tolerance to analgesic and hyperthermic effect of buprenorphine was assessed on day 5 by measuring the intensity of the two responses following a challenge dose (0.5 mg/kg) of buprenorphine. The analgesic response was measured by using a tail-flick apparatus as described previously (Bhargava, 1981a). The tail-flick latencies to thermal stimulation were determined prior to and at various times after buprenorphine injection. The basal latencies were found to be 1.8 ± 0.1 sec (S.E.). A value of 10 sec. for the tail-flick reaction time was used as the cut-off point to avoid damage to the tail. The analgesic reponse for each rat was calculated according to the following formula.

$$\% \text{ analgesia} = \frac{T-C}{10-C} \times 100,$$

were C and T represent the tail flick reaction times in seconds prior to at a specified time after buprenorphine injection. The data are expressed as mean % analgesic response ± S.E.M.

The rectal temperature of each rat was measured prior to and at various times after buprenorphine injection by using a rectal probe and a telethermometer (Yellow Spring Instrument Co., Yellow Springs, Ohio). The change in rectal tmeperature at each time interval was calculated. The data are expressed as mean increases in rectal temperature, °C ± S.E.M.

Effect of MIF and cyclo (Leu-Gly) on tolerance to buprenorphine

To study the effect of peptides on tolerance to buprenorphine, rats were divided into three groups. The groups received injections of water (vehicle), MIF (2 mg/kg) or CLG (2 mg/kg), respectively. Each treatment group was further divided into two subgroups. One hour after the water or peptide injection, rats in one subgroup received the vehicle for buprenorphine (water) while those in the second subgroup received buprenorphine (0.5 mg/kg). The injections of buprenorphine and its vehicle were repeated in their respective groups in p.m. The various treatments were repeated every day for 4 days. On day 5, all the rats were injected with buprenorphine (0.5 mg/kg) and the analgesic and therrnic responses were determined as described above.

Statistics

The differences in the means of various treatment groups were analyzed by analysis of variance followed by Scheffe's 'S' test. The difference was considered significant when the p value was less than 0.05.

RESULTS

Analgesic and thermic responses to buprenorphine

The administration of buprenorphine produced a dose-related analgesia and hyperthermia in the rat. As shown in Figure 1 A, buprenorphine 0.25 mg/kg, produced 46.7% analgesia at 30 min, and this level of analgesia was maintained for 90 min. Buprenorphine at 0.5 mg/kg dose produced 100% analgesia for 90 min and for the next 90 min was maintained at 45% level.

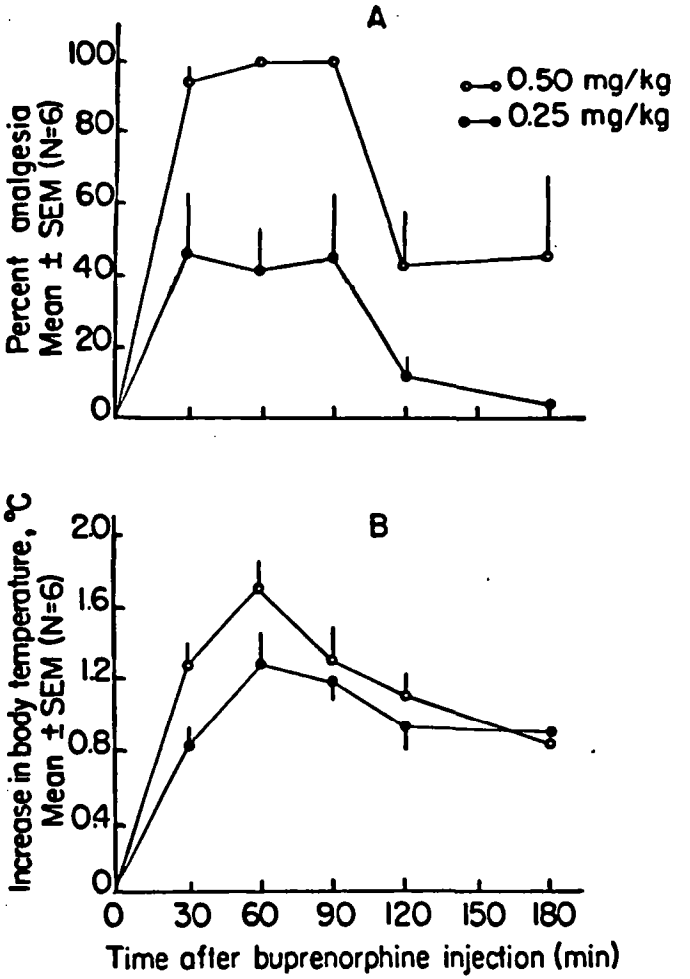

Figure 1 Effect of buprenorphine on the analgesic and thermic response in the rat

The administration of buprenorphine produced a hyperthermic response in the rat. As shown in Figure 1 B. The hyperthermia produced by 0.25 and 0.5 mg/kg doses lasted for more than three hours.

Effect of peptides on tolerance to buprenorphine

Based upon the initial studies, a dose of 0.5 mg/kg of buprenorphine was selected for tolerance studies. Chronic administration of buprenorphine (0.5 mg/kg SC twice a day for 4 days) resulted in the development of tolerance to its analgesic effect. This tolerance was inhibited by daily injections of MIF or cyclo (Leu-Gly). The administration of buprenorphine (0.5 mg/kg) to rats treated chronically with water (vehicle) produces 88.8, 77.8 and 34.3% analgesia at 30, 60 and 90, respectively after its injection. This analgesic response was not modified by daily injections of either MIF or cyclo (Lew Gly). In contrast to 88.8% analgesia at 30 min after buprenorphine injection in water-treated rats, only 14.1% analgesia was observed in rats treated chronically with buprenorphine. The analgesia was practically absent (1.5%) at 60 and 90 min after buprenorphine injection in buprenorphine-tolerant rats. The administration of buprenorphine produced significantly higher level of analgesia at each time interval in buprenorphine tolerant rats which were given daily injections of MIF or cyclo (Leu-Gly).

Chronic administration of buprenorphine also resulted in the development of tolerance to its hyperthermic effect. As shown in Thirty min after the buprenorphine (0.5 mg/kg) injections, the body temperature of nontolerant rats rose by 1.76°C, whereas, in buprenorphine tolerant rats, an increase of only 0.97° C was noted. Daily injections of MIF or cyclo (Leu-Gly) did not alter the hyperthermic effect in buprenorphine naive rats. However, the injections of peptides completely blocked the tolerance to the hyperthermic effect of buprenorphine. The increase in body temperature after buprenorphine (0.5 mg/kg) in buprenorphine-naive and buprenorphine-tolerant rats injected with peptides did not differ.

DISCUSSION

The present studies indicate that buprenorphine produces dose-dependent analgesia and hyperthermia in the rat. Whereas, morphine produced its peak analgesic effect at 30 min after administration (Bhargava, 1980) and had short duration of action, buprenorphine (0.5 mg/kg) produced intense (100%) analgesic response for 90 min and a fair degree of analgesia was maintained for a 3-hour observation period. Similarly, the hyperthermic effect lasted for 3 hours. This suggests that buprenorphine is a potent drug which has a long duration of action.

Chronic administration of buprenorphine resulted in the development of tolerance to its analgesic and hyperthermic effects in the rat. Tolerance to the analgesic effect has been reported in the mouse previously (Cowan et al., 1977a). Although Cox et al., (1976) failed to observe tolerance to the hyperthermic effect of opiate agonists, like morphine, others have shown that tolerance does develop to the hyperthermic effects of both the endogenous and the exogenous opiates

(Huidobro-Toro and Way, 1980; Bhargava,1981 d,e). The present study demonstrates that tolerance also develops to buprenorphine-induced hyperthermia.

Daily administration of MIF or cyclo (Leu-Gly) inhibited the development of tolerance to both the analgesic and the hyperthermic effects of buprenorphine.

The precise mechanism by which the peptides inhibit the development of opiate-induced tolerance is not clear. It is possible that these peptides are acting as narcotic antagonists since narcotic antagonists, like naloxone and naltrexone, have been shown to prevent the development of narcotic tolerance and dependence (Mushlin and Cochin, 1976; Bhargava, 1978; Huidobro-Toro and Way, 1980). Indeed MIF possesses naloxone-like activity in some tests. For instance MIF antagonizes morphine-induced analgesia; however, unlike naloxone, MIF was inactive in reversing the Straub-tail reflex, or the inhibition of electrically induced contraction of the vas deferens (Kastin et al., 1979).

Chronic administration of opiates induced supersensitivity of brain dopamine receptors (Lal, 1975; Bhargava, 1980, 1981 a; Ritzmann et al., 1979). The supersensitivity results from chronic depression of dopaminergic transmission. The opiate-induced supersensitivity of dopamine receptors is blocked by MIF and cyclo (Leu-Gly) (Bhargava, 1980, 1981; Ritzmann et al., 1979). The administration of buprenorphine elevates the forebrain homovanillic acid concentration which suggests its interaction with dopaminergic neurons (Cowan et al., 1976). Since MIF is known to potentiate the behavioral effects of l-dopa (Huidobro-Toro et al., 1974), it is possible that inhibition of buprenorphine tolerance by MIF and cyclo (Leu-Gly) may involve central dopaminergic systems.

In summary, the present studies indicate that the hypothalamic peptide MIF and its analog cyclo (Leu-Gly) inhibit buprenorphine-induced tolerance. Therefore these peptides may find use as adjuncts to the pharmacotherapy of pain and narcotic addiction when buprenorphine or other opiates are used.

ACKNOWLEDGEMENTS

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REFERENCES

Bhargava, H.N.: The effects of naltrexone on the development of physical dependence on morphine, European J. Pharmacol. 50, 193-202, 1978.

Bhargava, H.N.: Cyclo (leucylglycine) inhibits the development of morphine induced analgesic tolerance and dopamine receptor supersensitivity in rats, Life Sci. 27, 117-123, 1980.

Bhargava, H.N.: The effect of melanotropin release inhibiting factor and cyclo (Leu-Gly) on tolerance to morphine induced antinociception in the rat: a dose response study Br. J. Pharmacol. 72, 707-714, 1981 a.

Bhargava, H.N.: The effect of peptides on tolerance to the cataleptic and hypothermic effect of morphine in the rat. Neuropharmacology 20, 385-390, 1981 b.

Bhargava, H.N.: Effects of Pro-Leu-Gly-NH_2 and cyclo (Leu-Gly) on tolerance to the pharmacological actions of human beta endorphin in the rat. Fed. Proc. 40, 304, 1981 c.

Bhargava, H.N.: Inhibition of tolerance to the pharmacological effects of human beta endorphin by prolylleucyglycinamide and cyclo (leucylglycine) in the rat. J. Pharmacol. Exp. Ther. 218, 404-408, 1981 d.

Bhargava, H.N.: Structure activity relationship studies with hypothalamic peptide hormones Effect on opiate induced tolerance. Pharmacologist 23, 120, 1981 e.

Bhargava, H.N., Walter, R. and Ritzmann, R.F.: Development of narcotic tolerance and physical dependence: effects of Pro-Leu-Gly-NH_2 and cyclo (Leu-Gly). Phamacol. Biochem. Behav. 12, 73-77, 1980.

Cowan, A., Dettmar, D.W. and Walter, D.S.: The effect of acute doses of buprenorphine on concentrations of homovanillic acid (HVA), 5-hydroxyindole-acetic acid (5HIAA) and 3-methoxy-4-hydroxy-phenylglycol (MHPG) in the rat forebrain. Br. J. Pharmacol. 58, 275P, 1976.

Cowan, A., Doxey, J.C. and Harry, E.J.R.: The animal pharmacology of buprenorphine, an oripavine analgesic agent, Br. J. Pharmacol. 60, 547-554, 1977 a.

Cowan, A., Lewis, J.W. and Macfarlane, I.R.: Agonist and antagonist properties of buprenorphine, a new antinociceptive agent, Br. J. Pharmacol. 60, 537-546, 1977 b.

Huidobro-Toro, J.P., de Carolis, A.S. and Longo, V.G.: Actions of two hypothalamic factors (TRH, MIF) and of angiotensin II on behavioral effects of L-DOPA and 5-hydroxytryptophan in mice, Pharmacol. Biochem. Behav. 2, 105-109, 1974.

Huidobro-Toro, J.P. and Way, E.L.: Rapid development of tolerance to the hyperthermic effect of ß-endorphin. European J. Pharmacol. 65, 221-231, 1980.

Jacob, J.J.C., Michaud, J.M. and Tremblay, E.C.: Mixed agonist opiate and physical dependence, Br. J. Clin. Pharmacol. 7, 291 S, 1979.

Kastin, A.J., Olson, R.D., Ehrensing, R.H., Berzas, M.C., Schally A.V., and Coy, D.H.: MIF-1's differential actions as an opiate antagonist, Pharmacol. Biochem. Behav. 11, 721-723, 1979.

Lal, H.: Narcotic dependence, narcotic action and dopamine receptors, Life Sci. 17, 483-496, 1975.

Mello, N.K. and Mendelson, J.H.: Buprenorphine suppresses heroin use by heroin addicts, Science 207, 657-659, 1980.

Mushlin, B.E. and Cochin, J.: Tolerance to morphine in the rat: its prevention by naloxone, Life Sci. 18, 797-802, 1976.

Ritzmann, R.F., Walter., R., Bhargava, H.N. and Flexner, L.B.: Blockage of narcotic-induced dopamine receptor supersensitivity by cyclo (Leu-Gly), Proc. Natl. Acad. Sci. 76, 5997-5998, 1979.

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Interactions Between Tetrahydrocannabinol (THC) and Morphine in Rats

F. Cankat Tulunay, I. H. Ayhan, and S. B. Sparber

INTRODUCTION

Because of the possibility that narcotic analgesics and marijuana my be used together in various doses and sequences, it is important to study their interactions. Tolerance develops to several of the effects of morphine and (-)trans-Δ^9-tetrahydrocannabinol (THC), the primary psychoactive constituent of marijuana (McMillan et al., 1971; Jones et al., 1976; Tulunay et al., 1980, 1981; Uran et al., 1980), in both man and animals. It has also been shown that THC can produce tolerance and dependence within a few days (Ulku et al., 1980; Uran et al., 1980; Tulunay et al., 1980,1981; Kaymakcalan et al., 1977) and the irreversible long-acting narcotic antagonist, chlornaltrexamine, effectively blocks development of tolerance to and dependence upon THC in rats (Tulunay et al., 1981).

In the present study, we have investigated the interactions between THC and morphine on locomotor activity and autoshaped behavior of rats during tolerant and dependent states.

MATERIAL AND METHODS

Male white rats (Ankara University Medical School strain) 150-200 g were used in locomotor activity studies. Male Holtzman rats, initial body weight 325-345 g, were used in autoshape behavior studies.

The locomotor activity of rats was counted by Animex activity meter (Farad, Sweden). The locomotor activity of rats was counted 2½ hr after THC or solvent, 45 min after morphine and 5 min after naloxone injections for 30 min.

In another series of experiments, mature male rats SD-Holtzman, (Madison WI) were partially food deprived to 80 percent of their free-feeding weights and conditioned to an operant autoshape

response in a manner described in detail elsewhere (Hughes and Sparber, 1978).

All subjects in this experiment were implanted with either morphine rods (12.5 mg) or placebo rods and injected with either THC or its solvent for several days prior to being injected with naloxone to precipitate opiate-type withdrawal abstinence.

Specially prepared 75 mg morphine base pellets (two pellets/rat) were implanted s.c. without ansthetics for locomotor activity studies.

Except total latency times, square-root transformations were applied to all parameters in order to decrease variability of data to homogeneity of variances (total lever contact, total lever press, total strip contact and locomotor activity). Total latency time was evaluated as mean min ± SEM. The other figures represent mean square root ± SEM. Student's t-test was used for statistical comparisons and p value set to 0.05 for significance.

RESULTS

Motor Activity. As shown in table 1, acute treatment of animals either by morphine (20 mg/kg) or THC (40 mg/kg) produced a significant decrease in motor activity. When 5 mg/kg of naloxone was injected 2½ hr after THC and 45 min after morphine, morphine-induced decreased activity reversed canpletely, but THC-induced depression reversed partially.

Solvent treatment (group I) did not produce any significant changes during the experiment. On the second day of THC treatment partial tolerance and on the third day complete tolerance developed to the locomotor inhibitory action of THC. Naloxone produced (group II/b) a significant depression in chronic THC-treated animals and produced typical withdrawal symptoms (for details, see Tulunay et al., 1980, 1981). On the fourth day of treatment when animals were challenged with 20 mg/kg of morphine (group II/a), motor activity was significantly depressed and this depression was not significantly different than with the test dose of morphine. In other words, there was no cross-tolerance to morphine.

The test dose of morphine produced a significant depression in rats and tolerance to this effect developed within four days. When morphine-pelleted animals were challenged with naloxone, motor activity increased significantly when compared to naloxone (group I/b) controls and THC+naloxone (group II/b) groups. In morphine-pelleted animals, partial cross-tolerance was observed to the depressant action of THC (group III/c versus test dose THC).

Results are summarized in table 2.

TABLE 1

THE ACUTE EFFECTS OF THC AND MORPHINE ON LOCOMOTOR ACTIVITY OF RATS AND THEIR INTERACTIONS WITH NALOXONE

Groups	Locomotor activity (mean ± SEM)	N
Solvent	15.1 ± 1.58	9
THC 40 mg	4.5 ± 0.99[a]	9
Morphine 20 mg/kg	6.3 ± 1.30[a]	9
THC 40 mg/kg + NLX	8.5 ± 1.37[a,b]	9
Morphine 20 mg/kg + NLX	13.3 ± 1.19[b]	9

a - $p < 0.05$ when compared with solvent group; b - $p < 0.05$ when compared with THC and morphine groups.

TABLE 2

LOCOMOTOR ACTIVITY CHANGES DURING TOLERANT AND DEPENDENT STATES

Day/Group	Solvent (I)	THC (II)	Morphine (III)
1st day	15.4 ± 1.10	4.5 ± 0.99	6.3 ± 1.30
2nd day	14.8 ± 0.77	10.0 ± 1.88	-
3rd day	14.5 ± 1.88	16.1 ± 2.14	-
4th day	a) 14.9 ± 1.24 (solvent)	a) 7.6 ± 1.04 (M)	a) 15.7 ± 2.77 (M)
	b) 15.8 ± 1.12 (NLX)	b) 9.9 ± 1.22 (NLX)	b) 20.4 ± 1.36 (NLX)
		c) 16.8 ± 2.28 (THC)	c) 8.0 ± 1.19 (THC)

TABLE 3

OPERANT BEHAVIOR RESULTS

Groups*	Total Lever Contact**	Total Lever Press**	Total Strip Contact**	Total Latency Time (min ± SEM)
I. Placebo rods-solvent				
a. 20 hr after implantation	4.42 ± 0.03	22.67 ± 2.27	4.97 ± 1.39	0.85 ± 0.11
b. 90 min after 1st dose solvent	4.47 ± 0.00	26.38 ± 5.01	3.02 ± 0.56	0.59 ± 0.18
c. 5th day (5th dose) of THC	4.47 ± 0.00	29.87 ± 4.80	1.98 ± 0.87	0.46 ± 0.16
d. NLX withdrawal (10th session)	4.47 ± 0.00	32.94 ± 6.50	2.44 ± 0.90	0.27 ± 0.06
II. Placebo rods-THC				
a. 20 hr after implantation	4.46 ± 0.02	23.21 ± 4.25	4.45 ± 0.43	0.72 ± 0.17
b. 90 min after 1st dose	4.06 ± 0.17[a,b]	7.42 ± 0.89[a,b]	0.89 ± 0.55[a,b]	1.76 ± 0.47[a,b]
c. 5th day (5th dose)	4.45 ± 0.02	17.45 ± 3.02[b]	2.61 ± 1.77	0.52 ± 0.10
d. NLX withdrawal	3.34 ± 0.51[a,b]	8.47 ± 1.30[a,b]	0.97 ± 0.46[a,b]	2.65 ± 0.53[a,b]
III. Morphine rods-solvent				
a. 20 hr after implantation	4.42 ± 0.03	14.51 ± 2.67	3.31 ± 0.56	0.90 ± 0.11
b. 90 min after 1st dose	4.35 ± 0.04	14.32 ± 3.20	1.00 ± 0.63	0.90 ± 0.16
c. 5th day (5th dose)	4.40 ± 0.04	16.85 ± 5.40	2.13 ± 0.78	0.66 ± 0.23
d. NLX withdrawal	4.38 ± 0.07	9.87 ± 1.53[a]	1.77 ± 0.56[a]	0.74 ± 0.15
IV. Morphine rods-THC				
a. 20 hr after implantation	4.40 ± 0.03	13.91 ± 2.90	3.81 ± 1.73	0.92 ± 0.18
b. 90 min after 1st dose	3.96 ± 0.35	8.25 ± 2.11[a,b]	1.85 ± 1.13	1.79 ± 0.39[a,b]
c. 5th day (5th dose)	4.42 ± 0.03	11.13 ± 2.21	2.86 ± 2.30	0.95 ± 0.22
d. NLX withdrawal	2.44 ± 0.81[a,b]	3.70 ± 0.99[a,b]	0.60 ± 0.40[a,b]	3.30 ± 0.81[a,b]

a = 3rd session; b = 4th session; c = 9th session; d = 10th session evaluations.

* - 5 animals in each group; ** - square roots ± SEM

(a) - significantly different their 3rd sessions; (b) - significantly different their corresponding solvent values (Group II versus I and Group IV versus III).

Autoshape Behavior. After 3-8 sessions, all animals made maximum correct lever contacts (20 times in 20 min). The injection of 5 mg/kg THC significantly lowered their lever contact, lever presses and strip contacts and increased total latency time. On the fifth day of the experiment (fifth dose of THC), tolerance developed to these effects. When chronic THC-treated animals were challenged with naloxone, these parameters were again significantly decreased; total latency increased.

when THC was injected into the morphine pelleted (MP) animals, significant decreases in autoshaped responding and lever presses were observed. After five injections of THC, partial tolerance developed to these effects. On the fifth day of the experiment, animals were challenged with naloxone and an obvious opiate-like abstinence syndrome was observed. While lever contacts, lever presses and strip contacts significantly decreased, total latency, expectedly, increased. Results are summarized in table 3.

DISCUSSION

A number of papers have appeared in recent years describing the interactions between THC and opiate agonists and/or angatonists. For example, THC has been shown to potentiate morphine-induced Straub tail reaction and hyperactivity in mice (Buxbaum et al., 1972; Ayhan et al., 1979; Ulku et al., 1980) and analgesia in rats and mice (Buxbaum et al., 1972; Kaymakcalan and Deneau, 1972). Narcotic antagonists have been found to be effective in blocking some pharmacological actions of THC or other cannabinoids such as analgesia, hypothermia, increase in the synthesis of catecholamines and development of tolerance to the analgesic and hypothermic effects and dependence on THC. As with morphine, tolerance also develops to the effects of THC (Uran et al., 1980; Tulunay et al., 1981). Moreover, THC has been shown to produce an attenuation of naloxone-precipitated abstinence in morphine-dependent rats (Hine et al., 1975). In addition, naloxone has also been found to precipitate an abstinence syndrome in THC tolerant-dependent rats (Kaymakcalan et al:, 1977; Tulunay et al., 1980, 1981); Recently, Tulunay et al. (1981) have shown that chlornaltrexamine, a selective, irreversible opiate antagonist, inhibits THC-induced analgesia, hypothermia, hypothermic tolerance and dependence in rats. These studies suggest there may be sane common receptor mechanism for THC and opiates for certain effects of both drugs such as analgesia. On the other hand, some effects develop in the opposite direction. In the same strain of rats it has been found that THC always produces hypothermia (0.6-40 mg/kg) while morphine produces hyperthermia (2.5-160 mg/kg) (Tulunay, 1980; Uran et al., 1980). Another difference found in this experiment was that there is increased motor activity during morphine withdrawal while there is decreased motor activity in THC withdrawal.

Several aspects of our results deserve special consideration. First, THC can produce opiate-like physical dependence within a

short time in rats which is detectable with naloxone. Second, cross-tolerance develops to the locomotor depressive action of THC in morphine tolerant rats but not to morphine in THC-tolerant rats. Third, even very small doses of morphine potentiate the development of dependence in chronic THC-treated rats. Fourth, naloxone effectively antagonizes the depressant actions of both drugs in acute experiments. The possible relationship of these interactions with the enkephalin/endorphin systems should be considered.

REFERENCES

Ayhan, I.H., Kaymakcalan, s., and Tulunay, F.C. Interaction between Δ^9-tetrahydrocannabinol and morphine on the motor activity of mice. Psychopharmacology, 63:169-172, 1979.

Buxbaum, D.M. Analgesic activity of Δ^9-tetrahydrocannabinol in the rat and mouse. Psychopharmacologia, 25:275-277, 1972.

Gellert, N.F., and Sparber, S.B. A comparison of the effects of naloxone upon body weight loss and suppression of fixed-ratio operant behavior in morphine-dependent rats, J Pharmacol Exp Ther, 201:44-54, 1977.

Hine, B., Friedman, E., Torrelio, M., and Gershon, S. Morphine dependent rats. Blockade of precipitated abstinence by tetrahydrocannabinol. Science, 187:443-335, 1975.

Hughes, J.A., and Sparber, S.B. d-Amphetamine unmasks postnatal consequences of exposure to methylmercury in utero: Methods for studying behavioral teratogenesis. Pharmac Biochem Behav, 8:365-375, 1978.

Jones, R.T., Benowitz, N., and Bachman, J. Clinical studies of cannabis tolerance and dependence. Ann NY Acad Sci, 282:221-239, 1976.

Kaymakcalan, S., and Deneau, G. Some pharmacological properties of synthetic Δ^9-tetrahydrocannabinol. Acta Med Turc 9:19-23, 1972.

Kaymakcalan, S., Ayhan, I.H., and Tulunay, F.C. Naloxone-induced or postwithdrawal abstinence signs in Δ^9-tetrahydrocannabinol-tolerant rats. psychopharmacology, 55:243-249, 1977.

McMillan, D.E., Harris, L.E., Frankenheim, J.M., and Kennedy, J.S. 1-Δ^9-trans-tetrahydrocannabinol in pigeons: tolerance to the behavioral effects. Science, 169:501-503, 1970.

Sparber, S.B. Use of learned behavior in testing for neurotoxicity. In: Gryder, R.M., and Frankos, V.H. Effects of Foods and Drugs on the Development and Function of the Nervous System: Methods for Predicting Toxicity. HHS Publication No. (FDA) 80-1076,1980. pp. 49-61.

Tilson, H.A., Squibb, R.E., Meyer, O.A., and Sparber, S.B. Postnatal exposure to benzene alters the neurobehavioral functioning of rats when tested during adulthood. Neurobehav Toxicol, 2:101-106, 1980.

Tulunay, F.C. The effects of morphine and various narcotic antagonist type analgesics on body temperature in rats. Life Sci, 27:511-520, 1980.

Tulunay, F.C., Uran, B., Ayhan, I.H., Ulku, E., and Kaymakcalan, S. Development of physical dependence in short-term tetrahydrocannabinol treated rats. Res Comm Subs Abuse., 1:151-158, 1980.

Tulunay, F.C., Ayhan, I.H., Portoghese, P.S., and Takemori, A.E. Antagonism by chlomaltrexamine of some effects of Δ^9-tetrahydrocannabinol in rats. Eur J Pharmacol, 70:219-224, 1981.

Ulku, E., Ayhan, I.H., Tulunay, F.C., Uran, B., and Kaymakcalan, S. Effect of Δ^9-tetrahydrocannabinol on the morphine-induced hyperactivity of mice. Psychopharmacology, 69:201-205, 1980.

Uran, B., Tulunay, F.C., Ayhan, I.H., Ulku, E., and Kaymakcalan, S. Correlation between the dose and development of acute tolerance to the hypothermic effect of THC. Pharmacology, 21:391-395, 1980.

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Interaction of Ca++ With. Normorphine and ß-Endorphin on the Guinea Pig Ileum

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Considerable evidence indicates that calcium may have an important biochemical role in the actions of morphine and its surrogates. In vitro, only a few attempts have been carried out to characterize the pharmacologic interactions between calcium and the opiates. In the guinea pig ileum, the classical in vitro preparation for studies on opiate action (Paton, 1957; Schaumann, 1957), it has been well documented that the ability of opiates to inhibit the twitch caused by electrical stimulation of the ileum correlates well with antinociceptive potency (Kosterlitz and Waterfield, 1975). However, the effect of Ca++ on this opiate inhibitory response has scarcely been studied. Our laboratory (Hu et al., 1980) and Opmeer and van Ree (1979) in a short communication stated that Ca++ produced competitive antagonism of the morphine effects on the guinea pig ileum. More recently, Opmeer and van Bee (1980) reported that modifications in the external calcium concentrations altered the sensitivity to the opiate-like inhibitory response produced by high frequency of electrical stimulation. However, these findings are not consistent with the studies on opiate binding where divalent cations have been reported to increase the binding of opiate agonists. Since calcium, magnesium, nickel and especially manganese increased the binding of opiates to brain membranes (Pasternak et al., 1975) or to membrane preparations derived from neuroblastoma x glioma hybrid cells (Blume, 1978) one might infer that these cations should enhance opiate action. These inconsistencies prompted a detailed examination of the interaction of normorphine and B-endorphin with calcium on the isolated preparation of the guinea pig ileum.

EXPERIMENTAL PROCEDURES

Chemicals

Nonmorphine sulfamate was generously supplied by Dr. E.L. May from the National Institutes of Health. Acetylcholine, choline chloride, noradrenaline and adrenaline bitartrate, adenosine diphosphate so-

dium salt, were purchased from Sigma Chemical Co. B-Endorphin was a generous gift of Professor C.H. Li (UCSF).

Bioassay preparation

The longitudinal muscle myenteric plexus preparation of the guinea pig ilea was dissected according to Puig et al., (1978). The tissues were maintained on a modified Ringer solution as detailed by Huidobro-Toro et al. (1981). Segments of about one inch in length wer mounted in a 10-ml organ bath containing Ringer solution at 37°C and bubbled with a mixture of 95% O_2 and 5% CO_2 isometric muscular contractions were registered by means of a force displacement transducer (model FT 03C) coupled to a Grass polygraph recorder. Intestinal strips were stimulated electrically through two ring platinum electrodes with supramaximal pulses (80 volts, 5 msec duration) at a frequency of 0.1 Hz.

Quantification of the response to acetylcholine and to opiate

Before electrical stimulation was initiated, each preparation was challenged with 15 nM acetylcholine (Ach). Most strips responded immediately with a vigorous contraction of about 1 g. After the contractions Became uniform, a dose-response curve for Ach was determined. The maximal contraction, considered to be a 100% response, was generally achieved with 5.0 uM Ach. A plot (% response vs. log Ach) was performed for each strip, and the median effective dose (ED_{50}) was determined by interpolation.

Upon application of electrical pulses to the strips the preparations reactedwith regular twitchings. Normorphine, or B-endorphin, were added for a period of two minutes, after which the preparations were washed three to four times with the Ringer solution and allowed to stand for about 20 minutes prior to the next drug application. Activity was expressed as the percentage of inhibition of the electrically induced muscular twitch as detailed previously (Huidobro-Toro et al., 1978). The concentration of nomorphine, B-endorphin or other neurochemicals to inhibit the muscular twitching by 50% (IC50) was estimated by interpolation from log dose response curves.

Effect of calcium on inhibitory effects of opiates and other drugs

To study the effect of calcium on the opiate responses, the calcium concentration in the Ringer was varied between 1.25 mM and 5.0 mM. All of the other conditions were unchanged. Dose-effect curves to the inhibitory response of opiates, catecholamines, or adenosine diphosphate were determined in strips equilibrated in Ringer containing 1.25, 2.5, 3.75, or 5 mM Ca++.

Development and assessment of morphine tolerance and cross opiate tolerance

Guinea pigs were made tolerant-dependent on morphine by the subcutaneous implantation of six pellets containing 75 mg morphine base each. Four pellets were implanted on the first day and two were implanted 48 hours later. The animals were sacrificed approximately 72 hours after the first implant. The intact ileal strip preparations were mounted as described previously. For the control experiments, guinea pigs were implanted with placebo pellets, but otherwise were treated identically to the morphine group. To prevent in vitro opiate withdrawal from the ileum of the tolerant-dependent animals, the Ringer solution was supplemented with lOO nM morphine, as recommended by Schulz and Herz (1976). Dose-effect curves for Ach and opiates were determined as already described.

RESULTS

Effect of Ca++ on the opiate responses

Calcium produced a concentration-dependent antagonism of the inhibitory effect of normorphine to electrical stimulation. Increasing the Ca++ concentration in the Ringer caused a marked decrease in the sensitivity to nonmorphine or to B-endorphin. As shown in Figure 1, the normorphine IC_{50} increased linearly more than 100-fold with changes in Ca++ between 1.25 and 5 mM. In striking contrast the relative change in Ach sensitivity was much less, the ED_{50} increasing modestly four-fold. Opiates were considerably more sensitive to the Ca++ blockade than other agents that cause inhibition of the twitching response of the ileum. A four-fold increase in Ca++ (from 1.25 to 5 mM) caused only a minor reduction of the inhibitory potency of norepinephrine (5.21 fold), epinephrine (2.25 fold) or adenosine diphosphate (6.23 fold) as com-, pared to that of the opiates, which was about 100-fold for normorphine or about 60-fold for Bendorphin.

The antiopiate effect of Ca++ was quite selective since other divalent metal cations did not mimick the action of calcium. Mg++ or Mn++ for example increased in a dose-dependent fashion the sensitivity of the intact ileum to normorphine. This effect of Mg++ occurred without altering the sensitivity to Ach, but with Mn++ there was considerable decrease in the sensitivity of the preparations to Ach.

Effect of calcium on the opiate responses of morphine tolerant-dependent strips

Ileum strips obtained from guinea pigs implanted with morphine pellets exhibited cross tolerance to the in vitro responses of normorphine or B-endorphin as compared to tissues obtained from placebo-treated animals. During the resting period prior to

the electrical stimulation, segments from tolerant animals showed considerably more spontaneous activity than those from controls.

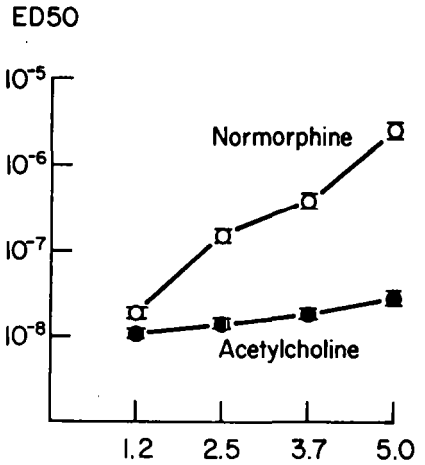

Figure 1

Effect of Ca++ on the responses of normorphine and acetylcholine

Normorphine inhibition of the twitching response of the ileum to electrical stimulation and the contractile effect of acetylcholine were measured at varying Ca++ concentrations. The ED_{50} values were interpolated from dose-effect curves and are expressed in molar concentrations in the ordinate. Symbols refer to the mean value obtained in eight separate experiments, bars to the S.E.M.

As can be noted in figure 2, cross-tolerance between morphine and nomorphine was demonstrated by nearly a twenty-fold increase in the IC_{50} for normorphine. Despite the high degree of opiate tolerance, the antiopiate action of Ca++ was still very much in evidence as indicated by a four-to eight-fold displacement of the normorphine dose-effect curves to the right at all Ca++ concentrations. Maximal agonist response was always observed at the highest opiate concentrations. Similar results were obtained for Bendorphin. Figure 2 shows about a 10-fold degree of crossed morphine-B-endorphin tolerance. In addition, raising the concentration of calcium in the media caused a marked reduction in the potency of Bendorphin to inhibit the electrically induced neuromuscular twitching in both the control, non-tolerant strips, and in the ileum strips derived from animals chronically treated with morphine.

Tolerance development did not alter the sensitivity to exogenously applied Ach. The Ach ED_{50} was not significantly modified in strips of ileum obtained from guinea pigs implanted with morphine pellets when compared to that of the placebo-treated animals. Nor

was the Ach ED_{50} of the two groups altered by changing the external Ca++ from 2.5 to 3.75 mM. The Ach ED_{50} at 2.5 mM Catt was 7.2 + 0.9 nM in the morphine-treated preparations as compared to 8.3 + 0.4 nM in the preparations obtained from placebo-treated animals. At 3.7 mM Ca++,the Ach ED_{50} was 8.3 + 0.4 and 8.1 + 1.1 nM in the morphine-treated and non-treated preparations respectively.

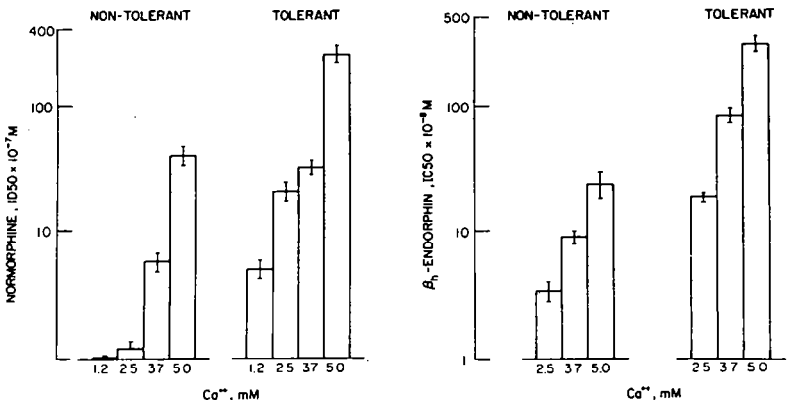

Figure 2

Effect of Ca++ on the inhibitory responses of nomorphine and B-endorphine in non-tolerant and tolerant guinea pig ileum

Guinea pigs were rendered tolerant on morphine, by the s.c. implantation of six morphine Pellets containing 75 mg morphine base. Placebo-pellet-treated animals served as controls. Ilea from the morphine-tolerant guinea pigs were incubated with 100 mM morphine to prevent opiate withdrawal. The normorphine ID_{50} values were determined in preparations containing 1.2, 2.5, 3.75 or 5 mM Ca++. See panel on the left. The B-endorphin IC_{50} was calculated at 2.5, 3.75 and 5 mM Ca++ in non-tolerant and morphine-tolerant tissues (right panel). Columns indicate the mean ID_{50} value; bars represent the S.E.M. (n=8) for each condition.

DISCUSSION

The present results demonstrate that Ca++ reduces the inhibitory effect of nomorphine and Bendorphin in the longitudinal muscle myenteric plexus preparation of the guinea pig. In general, at the lower and intermediate calcium concentrations, the normorphine response curves show parallelism, suggesting a competitive interaction between Ca++ and the opiate. At the highest calcium concentration the parallelism was lost. Opiates are far more sensitive to the Ca++ antagonism than other types of neurally active agents such as catecholamines or adenosine derivatives that also cause inhibition of neuromuscular twitching. The high degree of specificity of the blockade by opiates is indicated by the fact

that the contractile response to Ach was reduced only to minor degree by a very high concentration of Ca++. The specificity of Ca++ in antagonizing the opiate action was also evidenced by the fact that other divalent cations failed to elicit a similar effect. Mn++ and Mg++ both increased the sensitivity of the ileum to the inhibitory effect of nonmorphine (Huidobro-Toro et al., 1981). In the case With Mg++ the augmentation in opiate action was achieved Without any alteration in sensitivity to Ach. This suggests that the effect with Mg++, my have been achieved by enhancement of the inhibitory effects of normorphine on Ca++ uptake. A similar conclusion may also hold for Mn++ but the fact that Mn++ also reduced sensitivity to Ach clouds the tissue.

The precise site of action of opiates in the guinea pig-ileum has not yet been determined. Since the work of Schaumann (1957) and Paton (1957), it has been generally accepted that morphine and derivatives decrease the release of Ach from the nerve terminals in the myenteric plexus Which causes the inhibition of the twitching evoked by electrical stimulation. The present results suggest that the antagonism of Ca++ on the opiate responses is presynaptic in origin. This conclusion is supported by the fact that the contractile effect of exogenous Ach was modified only to a minor extent by changes in Ca++ that caused dramatic reductions in the effects of nonmorphine. Moreover, normorphine decreased the release of radioactive Ach in isolated intestinal strips, and this action was significantly reduced by increasing the external Ca++(Huidobro-Toro et al., 1981).

The development of tolerance to normorphine does not appear to alter the responses to acetylcholine or the antiopiate effect of Ca++ in a major manner. Implantation of morphine pellets to render animals tolerant resulted in about a 10-to 20-fold increase in the nomorphine and B-endorphin IC_{50} for inhibiting the electrically stimulated contractile response of the ileum but the sensitivity of the preparation to exogenous acetylcholine was essentially unaltered. Also, despite the high degree of tolerance, Ca++ retained its ability to antagonize the inhibitory response to these two opiates in a dose-dependnet manner. This would suggest that the site for Ca++-opiate acute effects is not materially affected by the development of tolerance. Such a conclusion is compatible With our earlier studies (Loh et al., 1969), where we noted that an inhibitor of protein synthesis (cycloheximide)could block the development of tolerance to morphine Without altering its acute response to morphine. We suggested that the macromolecules responsible for tolerance and physical-dependence develop ment Were different from those concerned With acute opiate effects and Were turning over a more rapid rate.

lb explain the effects of Ca++ in the present experiments on the guinea-pig ileum, it appears reasonable to draw upon the results of in vivo studies showing that Ca++ antagonizes morphine antinociception and that morphine acutely lowers neuronal Ca++ at nerve endings and elevates it after chronic administration (Kakunaga et

al., 1966, Harris, et al., 1975, 1976, 1977, Cardenas and Ross 1975, 1976, Yamamoto et al., 1978 and Guerrero-Munoz et al., 1979a, 1979b). Based on these studies and the close correlation noted between the potency of opiates to produce antinociception and to depress the electrical twitch of the fleum (Kosterlitz and Waterfield, 1975), we suggest that opiates act to block the calcium uptake at the terminals of the opiate-sensitive neurones of the myenteric plexus. As a result of the decreased calcium influx in the presence of opiates, less neurotransmitter is released from the nerve terminals, and this effect results in a depression of the neurotransmission. Increasing the extracellular Ca++ facilitates an increase in the Ca++ uptake following the electrical depolarization, which in turn causes an increase in the acetylcholine release to oppose the inhibitory effect of normorphine. Also, during tolerance, assuming there is an increase in the intrasynapto somal Ca++ content analogous to that in the brain, one might expect the increased Ca++ to oppose the opiate effects. Thus, tolerance would be evidenced as an increase in the opiates IC_{50} by the present data as well as by earlier findings (Goldstein and Schulz, 1973; Ward and Takemori, 1976). In this connection, it is of importance to cite also the observation of Mattila et al. (1962) who first reported that ilea from tolerant-dependent guinea pigs showed an increase in the spontaneous activity of the preparation. Our present findings confirm this report and suggest that this effect may be due to an accumulation of Ca++ during the development of morphine tolerance. Further experiments are in progress to assess the release of Ach by other opiates and to extend these observations to other endogenous opioid-like peptides in the guinea-pig ileum bioassay.

Blume, A.J.: Interaction of ligands with the opiate receptors of brain membranes: Regulation by ions and neucleotides. Proc. Natl. Acad. Sci. (USA). 75: 1713-1717, 1978.

Cardenas, H.L. and Ross, D.H.: Morphine induced calcium depletion in discrete regions of rat brain. J. Neurochem. 24: 487-493, 1975.

Cardenas, H.L. and Ross, D.H.: Calcium depletion of synaptosomes after morphine treatment. Brit. J. Pharmacol. 57: 521-526, 1976.

Goldstein, A. and Schulz, R.: Morphine tolerant-longitudinal muscle strip from guinea-pig ileum. Brit. J. Pharmacol. 48: 655-666, 1973.

Guerrero-Munoz, F., Cerreta, K.V., Guerrero, M.L. and Way, E.L.: Effect of morphine on synaptosomal Ca++ uptake. J.Pharmacol. Exp. Ther. 209: 132-136, 1979a.

Guerrero Munoz, F., Guerrero, M.L., Way, E.L. and Li, C.H.: Effect of B-endorphin on calcium uptake in the brain. Science (Washington): 206, 89-91, 1979b.

Harris, R.A., Loh, H.H. and Way, E.L.: Effect of divalent cations, a cation chelator and an ionophore on morphine analgesia and tolerance. J. Pharmacol. Exp. Ther. 195: 488498, 1975.

Harris, R.A., Loh, H.H. and Way, E.: Antinociceptive effects of lanthanum and cerium in non-tolerant and morphine tolerant-dependent animals. J. Pharmacol. Exp. Ther. 196: 288-297, 1976.

Harris, R.A., Yamamoto, H., Loh, H.H. and Way, E.L.: Discrete changes in brain calcium with morphine analgesia, tolerance-dependence; and abstinence. Life Sci. 20: 501-506, 1977.

Hu, J. Huidobro-Toro, J.P. and Way, E.L.: Calcium antagonism of opiate action in the non-tolerant and tolerant guinea pig ileum. In: Endogenous and exogenous opiate agonists and antagonists, ed. by E. Leong Way, pp. 263-266, Pergamon Press, New York, 1980.

Huidobro-Toro, J.P., Foree, B. and Way, E.L.: Single dose tolerance and cross tolerance studies with the endorPhins in the isolated guinea pig ileum. Proc. West. Pharmacol. Soc. 21: 381-386, 1978.

Huidobro-Toro, J.P., Hu, J. and Way, E.L.: Calcium antagonism of the inhibitory effect of normorphine on the ileum of the morphine-tolerant and non-tolerant guinea pig. J. Pharmacol. Exp. Ther. 218: 84-91, 1981.

Kakunaga, T., Kaneto, H. and Kano, K.: Pharmacological studies on analgesics. VII. Significance of the calcium ion in morphine analgesia. J. Pharmacol. Exp. Ther. 153: 134-141, 1966.

Kosterlitz. H.W. and Waterfield. A.A.: In vitro models in the study of structure-activity relationships of narcotic analgesics. Ann. Rev. Pharmacol. 15: 29-47, 1975.

Loh, H.H., Shen, F.H. and Way, E.L.: Inhibition of morphine tolerance and physical dependence development and brain serotonin synthesis by cycloheximide. Biochem. Pharmacol. 18:, 2711-2721, 1969.

Mattila, M.: The effect of morphine and nalorphine on the small. intestine on normal and morphine tolerant rat and guinea pig. Acta Pharmacol. Toxicol. 19: 47-52, 1962.

Opmeer, F.A. and van Ree, J.M.: Competative antagonism of morphine action in vitro by calcium. Europ. J. Pharmacol, 53: 395-397, 1979.

Opmeer, F.A. and yan Ree, J.M.: Differential involvement of calcium in acute and chronic opiate action in the guinea-pig ileum in vitro. J. Pharmacol. Exp. Ther. 213: 188-195, 1980.

Pasternack, G. W., Snowman, A. and Synder, S.: Selective enhancement of ^{3}H-opiate agonist binding by divalent cations. Molec. Pharmacol. 11: 735-744, 1975.

Paton, W.D.M.: The action of morphine and related substances on contraction and on acetylcholine output of coaxially stimulated guinea pig ileum. Brit. J. Pharmacol. Chemother. 12: 119-127, 1957.

Puig, M.M.) Gascon, P. and Musacchio, J.M.: Electrically induced opiate-like inhibition of the guinea pig ileum: cross tolerance to morphine. J. Pharmacol. Exp. Ther. 206: 289-302, 1978.

Schaumann, w.: Inhibition by morphine of the release of acetylcholine from the intestine of the guinea-pig. Brit. J. Pharmacol. Chemother. 12: 115-118, 1957.

Schulz, R. and Herz, A.: Aspects of opiate dependence in the myenteric plexus of the guinea pig. Life Sci. 19: 117-1128, 1976.

Ward, A. and Takemori, A.E.: Studies on the narcotic receptors in the guinea pig ileum. J. Pharmacol. Exp. Ther. 199: 117-123, 1976.

Yamamto, H., Harris, R.A., Loh, H.H. and Way, E.L.: Effect of acute and chronic morphine treatments on calcium localization and binding in brain. J. Pharmacol. Exp. Ther. 205: 255-264, 1978.

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Localization of the Reward-Relevant Opiate Receptors

Michael A. Bozarth and Roy A. Wise

Recognition of the importance of the rewarding properties of opiates in establishing compulsive drug use (Eddy, 1973; Jaffe, 1975) has prompted a search for the identification of brain mechanisms subserving opiate reward. Oneofthe first steps is the neumanatomical localization of the reward-relevant opiate receptors, but attempts to identify the brain site of rewarding drug action have been subject to serious limitations of current paradigm (Bozarth, 1982).

The most powerful method to demonstrate that a drug is acting at a particular brain site is to show that the drug is self-administered directly into that site. This can identify the initial target of rewarding drug action and thus neuroanatomically define the population of receptors mediating this effect. Another method for studying drug reward is the conditioned place preference paradigm (Rossi & Reid, 1976). In this paradigm, animals are confined to a normally nonpreferred portion of a test chamber following drug'injections. They are subsequently tested in the drug-free condition to determine if a learned preference or aversion has developed to the place where the drug was experienced. This technique can potentially reveal the affective consequences of the drug experience: increases in the amount of time spent in the portion of the test chamber associated with the drug experience suggest that the drug has positive affective consequences. Thisparadigmhasthe advantage of not making any response demands on the animal in the drugged condition, so it avoids the problem of sedative side-effects of some drug treatmnts.

The present paper reports the results of experiments using the intracranial self-administration and conditioned place preference paradigms. Rats quickly learned a lever-pressing response to inject morphine directly into the ventral tegmental area but did not self-administer morphine into other brain regions. This rewarding effect of morphine was confirmed using the conditioned place preference paradigm. The reward produced by systemically injected heroin, as assessed by the conditioned place preference paradigm, was blccked by dopamine receptor blockade. These studies suggest that the rewarding properties of opiates are dependent on a dopaminergic mechanism probably activated through opiate receptors in the ventral tegmental area.

INTRACRANIAL SELF-ADMINISTRATION STUDIES

The usefulness of the intracranial self-administration paradigm rests on the demonstration of behavioral, pharmacological, and anatomical specificity of the effect. First, it must be established that the animals are working for the rewarding properties of the drug injections, and that responding is not merely the consequence of nonspecific behavioral arousal. Second, it is necessary to demonstrate that the rewarding effects of central drug injections are dependent on the same receptor mechanism that mediates systematic drug reward. Third, it must be determined if the intracranial self-administration of a drug is localized to restricted brain regions or is an effect which is demonstrable throughout the brain. It is in the localization of the reward-relevant opiate receptors that intracranial self-administration can make its most important contribution to the understanding of the mechanisms of opiate reward and abuse.

Experimentally naive, male Long-Evans rats were unilaterally implanted with 22-gauge guide cannulae stereotaxically aimed at one of several brain regions. Obturators were fitted to a depth of 0.5 mm beyond the guide cannula. The rats were tested in a 27 x 38 x 39 an box housed in a dimly illuminated, sound-attenuating chamber. An operant lever was mounted on one wall of the test box. Drug injections were delivered using an electrolytic microinfusion transducer (EMIT) system. In these experiments, a 200-µA current applied for 5 seconds was used to deliver 100 nl of drug solution. For methodological details of the EMIT system, see Bozarth and Wise (1980).

Experiment I: Reward From Ventral Tegmental Morphine Injections

The first experiment was designed to determine if experimentally naive rats would learn to press a lever to inject morphine directly into the ventral tegmental area. To control for accidental lever contacts, a yoked control procedure was used. Each morphine-reward rat was paired with a yoked-control animal such that lever-presses by the experimental rat produced concurrent infusions in both animals. Lever-presses by the yoked-control rat were recorded but did not produce infusions. Using this procedure, the influence of increased locomotor activity on response measures could be assessed.

Rats implanted with guide cannulae in tbe ventral tegmental area were randomly assigned to either a morphine-reward, yoked control, or Ringer's control group. For the morphine-reward group, each lever-press produced a l00-nl infusion of morphine sulfate dissolved in 100 nl of Ringer's solution. Yoked-control animals received the same injections as their experimental partners. The Ringer's-control group received response-contingent vehicle only. The rats were tested for lever-pressing in three four-hour sessions on alternate days. Rats in the morphine-reward group were tested in a fourth session in which naloxone hydrochloride (10 mg/kg, i.p.) was injected one hour into the session.

The morphine-reward group rapidly learned the lever-pressing response making significantly more responses than the yoked or Ringer's-control groups ($p<.01$). Naloxone, injected one hour into the last test session, effectively blocked morphine self-administration.

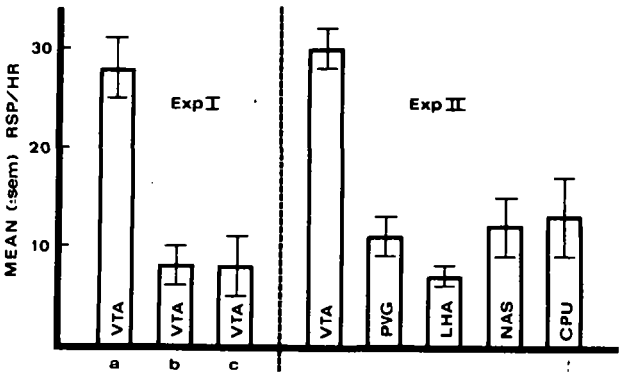

FIGURE 1: Mean (±standard error) number of response/hour across all three sessions. Exp. I: all rats were implanted with, cannulae in the ventral tegmental area (VTA); (a) morphine-reward, (b) yoked control, (c) Ringer's control, n=5/group (adapted from Bozarth & Wise, 1981). Exp. II: all rats received response-contingent morphine; cannulae were implanted in the VTA, periventricular gray substance (PVG), lateral hypothalamic area (LHA), nucleus accumbens septi (NAS), or caudate nucleus (CPU), n=6 to B/group.

These data suggest that morphine injected into the ventral tegmental area can serve as a reward for a lever-pressing response. Since the response rates of the morphine-reward group were reliably greater than those of the control group, the lever-pressing was not due to nonspecific behavioral arousal. The fact that intracranial self-administration was blocked by naloxone (data not illustrated) suggests that the rewarding action of these microinjections was dependent on an opiate-receptor mechanism and notthe consequence of some nonspecific changes in local osmolarity, pH, or calcium flux.

Several observations suggest that the dopaminergic cells of the ventral tegmentum mediated the rewarding effects of these microinjections. First, opiate receptors appear to be located on these dopaminergic cells or their afferents (Schwartz, 1979) and microinjections of morphine into this region cause an increase in the single unit activity of these cells (Finnerty & Chan, 1980). Second, morphine microinjected into the ventral tegmental area has been reported to increase locomotor activity (Joyce & Iversen, 1979; Pert et al., 1979), and this effect was observed in both the morphine-reward and yoked-control animals of the present study. Stimulation of locomotor activity seems to be dependent on a dopaminergic substrate with cell bodies located in the ventral tegmental area (Joyce & Iversen, 1979, 1980). Furthermore, since the rewarding injections were unilateral, the increased locomotor activity was asymmetrical and resulted in circling: the direction of circling was contralateral to the side of injection indicating that dopamine release was enhanced at the terminal fields of these cells (Ungerstedt, 1971a).

Experiment II: Lack of Morphine Reward From Other Injection Sites

To determine if other brain sites would support intracranial self-administration, rats were unilaterally implanted with guide cannulae in the following brain regions: ventral tegmental area, periventricular gray substance, lateral hypothalamic area, nucleus accumbens, or caudate nucleus. Experimentally naive animals were tested every other day for three four-hour sessions. Each lever-press resulted in a 100-ng infusion of morphine as in the first experiment.

Acquisition of the lever-pressing response was found only in rats with cannulae in the ventral tegmental area. The lack of self-administration into the periventricular gray substance is of particular significance since it eliminates the possibility that morphine injected into the ventral tegmentum is rewarding because of diffusion up the guide cannula to the cerebral ventricles (the anterior-posterior and medial-lateral stereotaxic coordinates for these two sites were the same). The failure to obtain morphine self-administration into the lateral hypothalamic area is in conflict with previous reports (E. Stein & J. Olds, 1977; M. Olds, 1979). There are two methodological differences that deserve particular attention. First, intraventricular self-administration of opioids has been demonstrated (Amit et al., 1976; Belluzzi & L. Stein, 1977). The studies reporting morphine self-administration into the lateral hypothalmic area used guide cannulae that were much larger than used in the present study. This can facilitate drug spread up the guide shaft and into the cerebral ventricles (Routtenberg, 1972) resulting in diffusion to a distal site of action. Second, the reports of lateral hypothalamic self-administration have involved rats previously trained to lever-press for brain stimulation reward. Lateral hypothalamic morphine injections might be capable of maintaining an already learned response but not capable of establishing a new habit; this might be expected if lateral hypothalamic injections were slowly diffusing to a distal site of action and serving as a weak reward. Regardless of the explanation for the lateral hypothalamic self-administration reported by others, it is apparent that ventral tegmental morphine injections are a much more potent reward than are microinjections into the other brain regions tested in this study.

CONDITIONED PLACE PREFERENCE STUDIES

The conditioned place preference paradigm can make several important contribution to the study of drug reward. It offers an independent method of assessing a drug's rewarding properties which is not susceptible to behavioral debilitating effects of various drugs or lesions. Also, conditioning variables have been implicated in the maintenance of drug-seeking behavior (Schuster & Woods, 1968), and this paradigm allows a direct comparison of these conditioning variables across different drugs and parameters of conditioning. Finally, this paradigm is extremely quick and easy to use.

Place preference was measured in a shuttle box (25 x 36 x 35 cm) with a wood floor on one side and a wood floor covered with wire mesh on the other. The amount of time rats spent on each side of the box was automatically recorded in 15-minute sessions for five consecutive

preconditioning days Next, the animalss received daily drug injections for four days in which they were restricted to the nonpreferred side of the box for 30 minutes. Finally, the animals were retested for place preference during access to the entire shuttle box.

Experiment III: Place Preference From Central Morphine Injections

In intracranial self-administration studies, the animal controls the number of infusions and thus the total dose and volume of drug injeced. .Since the field of effective drug spread varies as a function of response rate, it is difficult to estimate the distance of the cannula placements to the reward-relevant receptors (Bozarth, 1982). This problem can be overcome by injecting each animal with the same volume of drug and assessing reward using the conditioned place preference paradigm. Cannula placements can then neuroanatomically map the region of the reward-relevant receptor Population.

Rats were injected with 250 ng of morphine sulfate into the ventral tegmental area immediately before each of the four conditioning trials. The infusions were delivered over 28 seconds in 500 nl of Ringer's solution using the EMIT method (Bozarth & Wise, 1980).

Rats with cannulae in the same region as those supporting self-a&inistration in the earlier experiments developed a conditioned place preference for the side of the box associated with morphine injections. Rats with cannulae placed caudal to this region failed to acquire such a preference. Preliminary estimates suggest that the

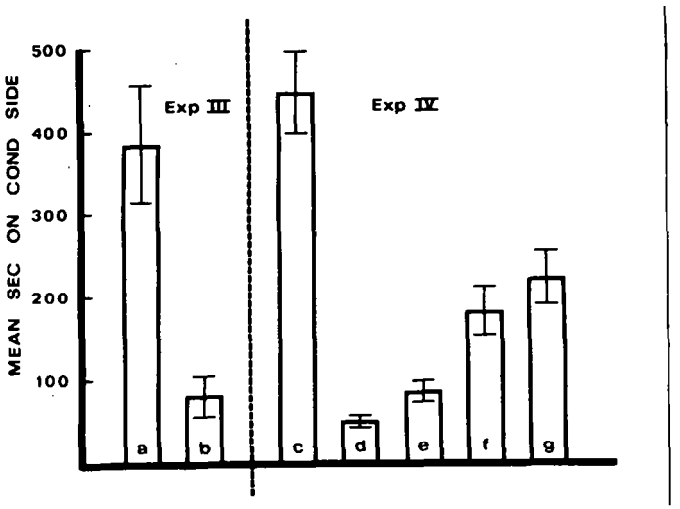

FIGURE 2: Mean (± standard. error) number of seconds on the side of putative conditioning. Exp. III: (a) cannulae 2.8 to 3.8 mm posterior to bregma, n=11, (b) cannulae 4.2 to 4.8 mm posterior to bregma, n=8; histological verification was based on Pellegrino et al. (1979); between group difference, p<.01. Exp. IV: (c) heroin plus saline, (d) heroin plus naloxone, (e) heroin plus pimozide, (f) saline plus naloxone, (g) saline plus pimozide, n=11/group.

caudal limit of the reward-relevant receptor population corresponds to the boundary of the ventral tegmental dopamine-cell group.

Experiment IV: Neuroleptic challenge of Heroin Reward

Ihe conditioned place preference paradigm avoids some of the problems of lever-pressing experiments by assessing drug reward in the drug-free state. Thus, this paradigm is not sensitive to the response depressant or excitatory effects of drugs or brain lesions. In the next experiment, the conditioned place preference produced by systemic heroin injections was challenged with the dopmine-receptor blocker pimozide and the opiate antagonist naloxone.

Five groups of rats were tested. Three group received heroin (0.5 mg/kg, s.c.) preceded by either saline (1.0 ml/kg, i.p.), naloxone (3.0 mg/kg, i.p.), or pimozide (0.5 mg/kg, i.p.), One group was injected with naloxone alone and another with pimozide only. All drugs were injected immediately before the conditioning trials except pimozide which was injected four hours prior to conditioning.

Animals injected with heroin plus saline showed a shift in place preference similar to that seen after intracranial morphine injections ($p<.01$). Pretreatment with either naloxone or pimozide blocked the development of a heroin-induced place preference, while treatment with either naloxone or pimozide alone had no effect.

These results are concordant with self-administration studies suggesting an attenuation of opiate reward following neuroleptic treatment (Hanson & Cimini-Venema, 1972; Pozuelo & Kerr, 1972). Since place preference is tested in drug-free animals, pimozide's blockade of heroin reward cannot be attributed to a general sedative effect that could confound lever-press measures.

GENERAL DISCUSSION

The use of the intracranial self-administration paradigm in Experiments I and II has provideda direct demonstration of the rewarding action of morphine delivered into the ventral tegmental area. The fact that the rats learn to lever-press rapidly suggests that the rewarding effects of these injections occur soon after the drug infusions. Rats would not be expected to learn this response as rapidly if the rewarding impact of the infusions were delayed, as would be the case if the rewarding effects were dependent on the diffusion of drug to a distal site of action.

The rewarding action of morphine injected into the ventral tegmental area has been confirmed using the conditioned place-preference paradigm. In a similar study, place preference was established with bilateral morphine injections into the ventral tegmentum but not with injections dorsal to it (Phillips & LePiane, 1980). Experiment III extended these results showing that unilateral injections are also effective and that injections caudal to the ventral tegmental area are not effective.

The failure to find intracranial self-administration into the brain sites tested in Experiment II suggests a neuroanatomical seperation of the rewarding, analgesic, and sedative properties of opiates. The periventricular gray substance has been implicated in opiat-induced analgesia (Jacquet & Lajtha, 1976; Pert & Yaksh, 1974; Sharpe et al., 1974; Yaksh et al., 1976) and sedation (Pert et al., 1978), while the rewarding properties of morphine appear to be dependent on an action in the ventral tegmental area. The site of action for opiate-induced physical dependance is less clearly defined,but it seems to involve receptors in the thalamus and periventricular gray region (Wei et al., 1973; Wei & Loh, 1976; Wei, 1981). These studies suggest that the ability of an opiate to produce analgesia, sedation, and physical dependence may be neuroanatomically separable from its rewarding properties.

The importance of dopamine-containing cells in the regulation of food, water, and brain stimulation reward is well established (Ungerstedt, 197lb; Wise, 1978; 1980). An important role for dopaminergic cells projecting to the nucleus accumbens has also been demonstrated in psychomotor stimulant reward(Roberts et al., 1980). The fact that reward from systemic heroin appears to be dependent on a dopaminergic mechanism (Experiment IV)suggests that it may share a common neural substrate with these other sources of reward. The localization of the reward-relevant opiate receptors in the ventral tegmental area makes this a likely place for opiate reward to interface with a dopaminergic substrate of reward.

REFERENCES

Due to space limitations, references are available from the authors.

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Endogenous Opioids May Mediate Ethanol's Effects on the Hypothalamic-Pituitary-LH Axis

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ABSTRACT

There has been a good deal of speculation regarding the possibility that endogenous opioids participate in the effects of ethanol on the central nervous system. Thus far, however, this relationship has been very difficult to establish. Ideally, an appropriate model to employ to examine the interaction between the CNS actions of ethanol and endogenous opioid-containing neuronal elements would satisfy two criteria: first, that a role for opioid peptides in the system has been established; and, second, that the actions of ethanol on the system are also well-defined. The hypothalamic-pituitary-luteinizing hormone (LH) axis satisfies both of these criteria and was employed in the present studies. We found that naloxone substantially attenuated the inhibitory effects of ethanol on serum LH levels and, similarly, that ethanol effectively antagonized naloxone-induced increases in serum LH levels. The results thus support the hypothesis that ethanol exerts some of its effects through opioid containing neuronal elements in the CNS.

INTRODUCTION

It has been suggested that ethanol exerts sane of its effects by interacting with endogenous opioids in the CNS. This hypothesis is based upon two observations: first, there are a number of similarities between the pharmacological and physiological actions of ethanol and the narcotics and, second, naloxone has been shown to antagonize a number of the CNS effects of ethanol (e.g., Blum et al. 1980; Ho and Ho 1979; Jeffcoate et al. 1979; Triana et al. 1980; Lorens and Sainati 1978; Middaugh et al. 1978).

An inspection of the literature, however, suggests that a definitive relationship between the CNS actions of ethanol and endogenous opioids has not as yet been established. For example, similarities between the actions of ethanol and the narcotics need not imply a common mechanism of action. Moreover, it is difficult to interpret

many of those studies in which naloxone has been found to antagonize ethanol's effects because endogenous opioids have not been clearly shown to be involved in the complex behaviors that have been examined. Thus, it is uncertain whether naloxone blocks the effects of ethanol by a specific antagonism of ethanol-induced alterations in endogenous opioids or by sane other action. Ideally, the best model to employ in examining the CNS actions of ethanol should satisfy two criteria: that a definitive role for endcgenous opioids in the function of the system has been clearly established and, in addition, that the effects of ethanol on the system have also been well-defined. The hypothalamic-pituitary-LH axis seems to provide a model preparation that satisfies these two criteria since it has been clearly established that endogenous opioids play a prominent role in regulating activity in this axis (see Cicero 198Oa; Meites et al. 1979. for reviews) and that ethanol depresses serum LH levels in the male of several species in a dose-dependent fashion, apparently by inhibiting the release of LH-RH (see Cicero 1980b for a review). This system was employed in the present studies to examine whether ethanol reduced serum LH levels by interacting with opioid-containing systems in brain.

METHODS

Effects of Naloxone on Ethanol-Induced Depressions in Serum LH

Groups of rats were injected with saline or naloxone (0.25 mg/kg), subcutaneously; half of the animals in each group were simultaneously (<15 sec) injected with saline or various doses of ethanol. The animals were killed 2 hours later, and hypothalamic-LH-RH content (Nett et al. 1973) and pituitary and serum LH levels (Niswender et al. 1969) were determined.

Effects of Ethanol on Naloxone-Induced Increases in Serum LH

To determine whether ethanol would antagonize the effects of naloxone on serum LH, rats were injected with saline or ethanol (1.0 g/kg) 30 min prior to the injection of sufficient doses of naloxone to construct appropriate dose-response curves with respect to increasesin serum LH. The rats were killed 20 min after the naloxone or saline injections (50 min after the ethanol injection). Brains, pituitaries and bloods were obtained fran the animals in both studies for the determination of hypothalamic-LH-RH content and pituitary and serum LH levels.

Opiate Binding Studies

[^{3}H]-naloxone binding assays were performed essentially as describedpreviously (Smith and Simon 1980). Binding assays were carried out in the presence or absence of ethanol ($1x10^{-6}$ to $2x10^{-1}$ M, final concentration. In all of the experiments reported in this paper, specific [^{3}H]-naloxone binding represented 75-80% of the total binding.

RESULTS

Effects of Naloxone on Ethanol-Induced Inhibitions of Serum LH

The effects of naloxone on ethanol-induced depressions in serum LH levels are shown in table 1. It is apparent that naloxone substantially antagonized the effects of ethanol on serum LH. In fact, at doses of ethanol up to 1.5 g/kg, serum LH levels were significantly elevated in naloxone-ethanol treated animals when compared to saline-ethanol-treated rats. It is important to note that naloxone itself, at this dose and time interval, had no effect on serum LH levels.

TABLE 1

The effects of saline or naloxone (0.25 mg/kg) on ethanol-induced changes in serum LH levels (ng/ml).

Ethanol Dose (g/kg)	Saline	Naloxone
0	34.2 (±4.8)	32.5 (±3.6)
0.75	22.3 (±3.1)*	58.7 (±8.9)†
1.00	18.0 (±1.9)*	59.4 (±6.8)†
1.50	12.5 (±1.4)*	27.5 (±2.4)
2.00	8.8 (±0.9)*	14.2 (±1.2)*

* significantly ($p<.01$) lower when compared to control;
† significantly ($p<.01$) higher when compared to control.

Effects of Ethanol on Naloxone-Induced Increases in Serum LH

The effects of 1.0 g/kg ethanol on the naloxone dose-response curve, with respect to increases in serum LH, are shown in table 2. As can be seen, ethanol markedly reduced naloxone-induced in-

TABLE 2

The effects of ethanol on naloxone-induced increases in serum LH levels (ng/ml).

Naloxone Dose (mg/kg)	Saline	Ethanol
0	23.6 (±1.2)	24.3 (±2.8)
0.067	48.9 (±4.8)	---
0.125	62.4 (±3.4)	---
0.25	82.5 (±7.9)	48.3 (±1.9)*
0.375	102.4 (±7.9)	---
0.50	116.5 (±6.8)	60.9 (±5.4)*
0.75	117.8 (±4.3)	68.9 (±4.6)*
1.0	113.4 (±5.6)	82.1 (±2.3)*
2.0	---	102.5 (±6.4)
5.0	118.7 (±4.6)	116.5 (±3.2)

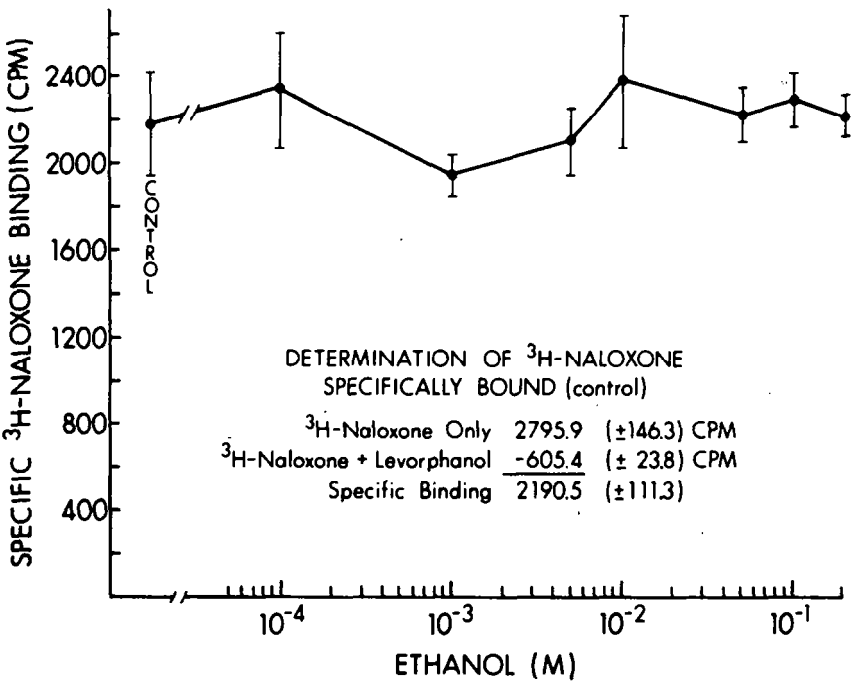
All serum LH levels in naloxone-treated animals were significantly ($p<.01$) higher than those found in the respective control group. *Significantly ($p<.01$) lower than saline-treated rats.

creases in serum LH levels and appeared to shift the dose-response curve significantly to the right when compared to controls. Although the data shown in table 2 represent the effects of only one dose of ethanol, similar results were obtained with other doses as well. Ethanol itself did not depress serum LH levels at this relatively low dose, and short time interval.

Opiate Binding Studies

As shown in figure 1, ethanol had no effect on specific [^{3}H]-naloxone binding to rat brain membranes at concentrations up to $2x10^{-1}$M.

FIGURE 1



Specific [^{3}H]-naloxone binding (CPM) as a function of the ethanol concentration in the incubation medium. The determination of specific binding is given as an inset in this figure. Values are mans (±SEM) of at least three experiments carried out in triplicate.

DISCUSSION

Previous research has demonstrated that endogenous opioid peptides are involved in regulating the normal activity of the hypothalamic-pituitary-LH axis and may mediate the negative feedback control of this axis by testosterone (see Cicero, 1980a, for a review). The present results demonstrated that pretreatment with a low dose of naloxone substantially blocked ethanol-induced depressions in serum

LH. In addition, ethanol markedly attenuated naloxone-induced increases in serun LH levels. Thus, these data indicate that naloxone and ethanol mutually antagonize each other's effects on serum LH. Moreover, this antagonisn appears to take place at a suprasellar site, presumably in those areas of brain regulating LH-RH release, since it has been found that LH-RH readily overcomes ethanol's inhibition of naloxone-induced increases in serun LH (unpublished observations) and that naloxone and ethanol do not interfere with the response of the pituitary to LH-RH under in vivo or in vitro conditions (Cicero, 198Oa, b; Meites et al. 1979). These results, therefore, are compatible with the hypothesis that ethanol depresses serum LH levels by activating endogenous opioid peptide systems in the hypothalamus that normally inhibit LH-RH.

There are several mechanisms, other than direct mediation by opioid peptides, that could explain the interaction between ethanol and naloxone observed in this and other studies. These should be discussed.

First, it could be that the antagonism between ethanol and naloxone observed in the present studies is "physiological" as opposed to "pharmacological." Although it is difficult to completely rule out "physiological" antagonisn, it can be minimized by employing a standard dose of the test drug (i.e., ethanol or naloxone), that is known to elicit a physiologically relevant response and then attempting to antagonize its effects by using dosage and time intervals at which the competing drug has no observable effect of its own. If antagonism is observed under these conditions, the likelihood that physiological antagonism can fully explain the observed antagonistic interaction between the two drugs is diminished. In the present studies, we found that naloxone and ethanol were capable of antagonizing each other's effects on serum LH levels at doses and time intervals at which neither drug itself affected LH. Thus, although "physiological" antagonism cannot be ruled out entirely, and this possibility should be borne in mind, the present data would seem to argue against this interpretation and suggest that some other mechanism is involved.

A second mechanism that could be involved in the interaction between ethanol and naloxone is that ethanol or its highly reactive metabolite, acetaldehyde, might influence opiate-receptor mechanisms in some way under in vivo conditions. In the presentp sent studies, the possibility that ethanol directly inhibited [^{3}H]-naloxone binding under in vitro conditions was excluded, but it is quite possible that under in vivo conditions ethanol, or some consequence of its metabolism, including the generation of acetaldehyde, could influence opiate-receptor processes in sane fashion.

As a final possibility, acetaldehyde could react with endogenously occurring compounds in brain to form substances that have an affinity for the opiate receptor and thereby exert significant biological activity of their own. Support for this conclusion has been provided by two sets of observations. First, acetaldehyde reacts with several endogenous opioids to form compounds that compete for opiate receptors in the brain and the guinea pig ileum (Summers and

Hayes, 1980). Second, acetaldehydereadily condenses with indoleamines to form iscquinoline alkaloids, similar in structure to a number of opium alkaloids (Weiner, 1979). Since these compounds have been shown by a number of investigators to bind to opiate receptors and elicit a number of effects after their administration (Lasala et al. 1980; Nimikitpaisan and Skolnick, 1978; Siggins and French, 1979), it may not be unreasonable to speculate that acetaldehyde condenses with a number of compounds in brain that could in turn influence opiate binding and/or exert opiate like effects themselves.

In conclusion, the studies described in this paper strongly reinforce previous suggestions that ethanol exerts sane of its effects by interacting with opioid-containing systems in brain. In these earlier studies, this conclusion was based upon similarities between the acute and chronic actions of the two drugs and several reports that naloxone can prevent some of the actions of ethanol. Inferences can be misleading, however, and unfortunately those studies showing an antagonism of ethanol's effects by naloxone have been somewhat difficult to interpret. In the present studies, however, we have been able to demonstrate an apparent interaction between opioid-containing systems and ethanol.

REFERENCES

Blum, K., Briggs, A.H., Elston, S.F.A., Hirst, M., Hamilton, M.G., and Verebey, K. A common denominator theory of alcohol and opiate dependence: review of similarities and differences. In: Rigter. H., and Crabbe, J.C., eds. Alcohol Tolerance and Dependence, Amsterdam: Elsevier/North-Holland Biomedical Press. 1980. pp. 371-

Cicero, T.J. Effects of exogenous and endogenous opiates on the hypothalamic-pituitary-gonadal axis in the male. Fed Proc, 39: 2551-2554, 1980a.

Cicero, T.J. Cannon mechanisms underlying the effects of ethanol and narcotics on neuroendocrine function. In: Mello, N.K., ed. Advances in Substance Abuse. Greenwich, Conn: JAI Press, 198Ob. pp. 201-254.

Ho, A.K., and Ho, C.C. Toxic interactions of ethanol with other central depressants: antagonism by naloxone to narcosis and lethality. Pharmacol Biochem Behav, 11:111-114, 1979.

Jeffcoate, W.J., Herbert, M., Cullen, M.H., Hastings, A.G., and Walder, C.P. Prevention of effects of alcohol intoxication by naloxone. Lancet, 1-1157-1159, 1979.

Lasala, J.M., Cicero, T.J., and Coscia, C.J. The opiate-like effects of norlaudanosolinecarboxylic acids on the hypothalamic-pituitary-gonadal axis. Biochem Pharmacol, 29:57-61, 1980.

Lorens, S.A., and Sainati, S.M. Naloxone blocks the excitatory effect of ethanol and chlordiazepoxide on lateral hypothalamic self-

stimulation behavior. Life Sci, 23:1359-1364, 1980.

Meites, J., Bruni, J.F., Van Vugt, D.A., and Smith, A. Relation of endogenous opioid peptides and morphine to neuroendocrine functions. Life Sci, 24:1325-1336, 1979.

Middaugh, L.D., Read, E., and Boggan, W.O. Effects of naloxone on ethanol-induced alterations of locomotor activity in C57BL/6 mice. Pharmacol Biochem Behav, 9:157-160, 1978.

Nett, T.M., Akbar, A.M., Niswender, G.P., Hedlund, M.T., and White, W.F. A radioimmunoassay for gonadotropin-releasing hormone (Gn-RH) in serum. J Clin Endocrinal Metab, 36:880-885, 1973.

Nimikitpaisan, Y., and Skolnick, P. Catecholamine receptors and cyclic AMP formation in the central nervous system: effects of tetrahydroiscquinoline derivatives. Life Sci, 23:375-382, 1978.

Niswender, G.P., Reichert, L.E., Midgley, A.R., and Nalbandov, A.V. Radioimmunoassay for bovine and ovine luteinizing hormone. Endocrinology, 84:1166-1173, 1969.

Siggins, G.R., and French, E. Central neurons are depressed by iontophoretic and micropressure application of ethanol and tetrahydropapaveroline. Drug Alcohol Depend, 4:239-243, 1979.

Smith, J.R., and Simon, E.J. Selective protection of stereospecific enkephalin and opiate bindings against inactivation by N-ethyl-male imide: evidence for two clases of opiate receptors. Proc Nat1 Acad Sci, 77:281-284, 1980.

Summers, M.C., and Hayes, R.J. Acetaldehyde-enkephalins: pronounced changes in the opiate activity of methionine-enkephalin and leucine-enkephalin on reaction with-acetaldehyde. FEBS Lett, 113:99-101, 1980.

Triana, E., Frances, R.J., and Stokes, P.E. The relationship between endorphins and alcohol-induced subcortical activity. Am J Psychiatry, 137:491-493, 1980.

Weiner, H. Acetaldehyde metabolism. In: Majchrowicz, E., and Noble, E.P., eds. Biochemistry and Pharmacology of Ethanol. New York: Plenum Press, 1979. pp. 125-133.

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Evidence for a Single Opioid Receptor Type on the Rat Deferens

Richard J. Freer, Alan R. Day, and Chung Shin Liao

INTRODUCTION

There is no doubt that there exist in nature several distinct populations of opioid receptor sub-types (Martin et al. 1976, Chang and Cuatrecasas 1979 and Lord et al. 1977). This fact is formally stated in the "Multiple Receptor Theory" of opioid action first espoused by Martin et al. (1976). In fact, opioid drugs are now invariably categorized based on their selectivity for the various receptor sub-types. However, as more data has accumulated it has become necessary, in order to preserve the classifications defined under the multiple receptor theory, to postulate the co-existence of more than one type of opioid receptor within a single target tissue. An alternative explanation, however, is that there is but a single receptor type in each target tissue which is capable of multiple modes of binding. This concept, first proposed by Portoghese. (1965), could also explain the heterogeneous responsiveness of single-target tissues to opioid drugs. It is, of course, important that the question of multiple receptors versus multiple modes of binding be resolved since one must think quite differently when dealing with several binding complexes rather than a single macromolecular system.

The rat vas deferens (RVD) is an unusual tissue in that it is quite unresponsive (only producing approximately 20% of the maximum response) to the archetype opioid alkaloid, morphine (Lemaire et al. 1978, Schulz et al. 1979, Wuster et al. 1980). This has been intrepreted to mean that there is in the RVD a low density of morphine-sensitive mu (μ) receptors. However, the published data are also consistent with the possibility that morphine is a partial agonist in this preparation. If that were the case, the same effect (i.e., decreased maximum response) would be observed but only a single type of opioid binding site would be necessary to explain these results. The experiments described below were designed therefore to determine if morphine is a partial agonist in RVD and, if so, whether the data are consistent with the presence of a single opioid receptor type in this tissue.

METHODS

Vas deferens were dissected from Sprague-Dawley rats (250-400 g) and mounted in 10 ml jacketed organ baths (Metro Scientific) containing Kreb's solution at 37 C. The Krebs had the following composition (mM) : NaCl, 118; KCl, 4.7; $CaCl_2$, 2.5; KH_2 PO_4, 0.93; $NaHCO_3$, 25 and glucose, 11. The solution was continually gassed with a mixture of 95% O_2/5% CO_2 The RVD was placed between two parallel platinum electrodes (separated by 5 mm) and adjusted to a resting tension of 200 mg. Field stimulation was applied at 100V, 0.1 HZ, with 2-msec duration as described previously (Liao et al, 1980) and the twitch response recorded isometrically using a Beckman Dynograph system. The field stimulation was validated as being due to pre-junctional nerve stimulation since 10 M tetrodotoxin could block the twitch response but did not affect post- junctional sensitivity to serotonin. The ID_{50} concentration (i.e. the concentration necessary to inhibit the twitch response by 50%) of the various agonists were obtained from a full dose-response curve, and antagonists were tested against that concentration. Antagonists were added to the bath 3 min before challenge with the agonist.

The synthesis of D-Ala^2-$N1e^5$ (des-COOH)-enkephalin has been described (Day et al, 1978). Human ß-endorphin was purchased from Peninsula Laboratories. Morphine sulfate, oxymorphone hydrochloride, etorphine hydrochloride, naloxone hydrochloride and sufentanil citrate were kindly supplied by Dr. William Dewey, Medical College of Virginia. Ketobemidone hydrochloride and ɤ-(+)-N-allyl-normetazocine hydrobomide were the generous gift of Dr. Everette May, Medical College of Virginia.

RESULTS

Our experiments on RVD with ß-endorphin, etorphine and sufentanil showed these drugs to be full agonists with ID_{50}'s of 28, 38 and 48 nM respectively. This is consistent with previous data in the literature (Lemaire et al, 1978, Schulz et al, 1979, Wuster et al, 1980) as was our finding that morphine produced only a slight inhibition (20% at 10^{-5}M) of the twitch response. We have extended these studies to look further at opioids which have been classified as being selective for μ (oxymorphone and etonitazine, ketobemidone) ,δ [D-Ala -Nle (des-COOH) -enkephalin] ,σ (α- (+) -N-allyl-normetazocine) receptors (Figure 1). Of this group the etonitazine and enkephalin were full agonists (ID_{50}'s of 0.15 and 2 μM respectively) while oxymorphone only reduced the twitch response by 10% at 10^{-5}M. Ketobemidone and α-(+)-allyl-normetazocine were inactive at concentrations up to 10^{-5}M.

On inspection of our dose-response curves as well as those in the literature (Lemaire et al, 1978) it seemed possible that the low responsiveness of RVD to morphine and its congener, oxymorphone, could be due not to a low concentration of a particular receptor typebuttothefactthatthesedrugs arepartialagonists. By definition a partial agonist should competitively antagonize a full agonist

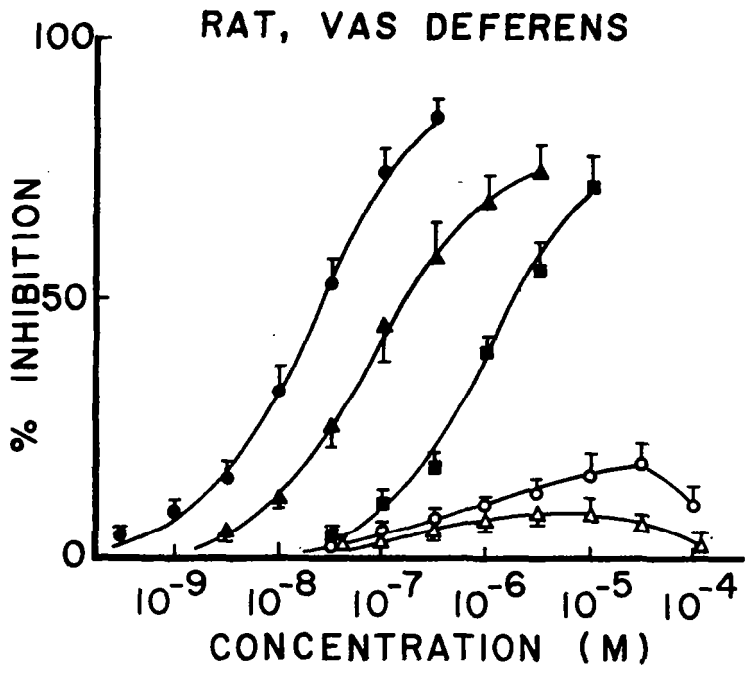

FIG. 1

Inhibition of field stimulated rat vas deferens by opioids. ß-endorphin (●), etonitazine (▲) D-Ala^2-Nle-(des-COOH)-Enkephalin (■), morphine (○) and oxymorphone (△). Each point is the average ± SEM of 6-10 determinations.

acting on the same receptor site. Therefore, to investigate the possibility that ß-endorphin and morphine interacted with the same receptor site, morphine was tested as an antagonist of ß-endorphin. As shown in Fig. 2 (right) and Table 1, morphine (10^{-5}M) clearly antagonized ß-endorphin in a dose-dependent manner. As one would expect with a true partial agonist, the concentration of morphine necessary to produce blockade of ß-endorphin was identical to those which produced its weak agonist activity (compare to Figure 1). The morphine congener oxymorphone behaved in the same way and was, in fact, a slightly more effective antagonist of ß-endorphin (Fig 2 right, Table 1). For comparison the antagonism produced by 10^{-7}M nalo one is also shown in Fig. 2 (left). In addition both morphine (10^{-5}M) and oxymorphone (10^{-3}M antagonized D-Ala^2-Nle5- (des-COOH)-enkephalin while oxymorphone (10^{-5}M) also antagonized etorphine and sufentanil. The magnitude of the antagonism of ß-endorphin, enkephalin, etorphine and sufentanil was very similar (dose ratio of

30-100 fold) in the presence of 10^{-5} oxymorphone, again suggesting that all the drugs were reacting with the same binding site.

Finally, ketobemidone, α-(+)-N-allyl-normetazocine and ketocyclazocine were found also to inhibit ß-endorphin. These were, on a molar basis, equipotent with morphine and oxymorphone in this respect.

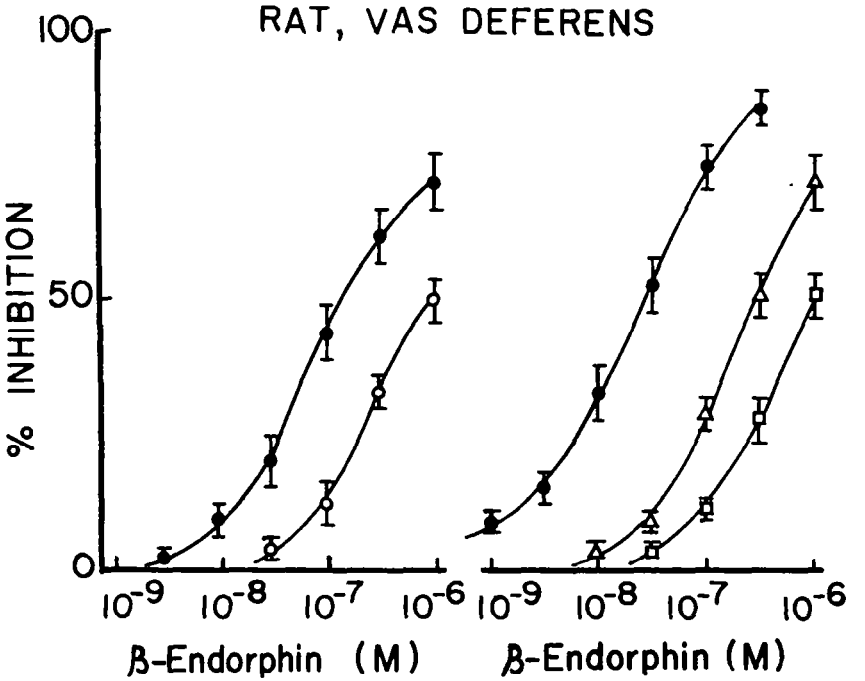

FIG. 2

Antagonism of ß-endorphin inhibition of field stimulated rat vas deferens. Left: control (●) and in the presence of 10^{-7}M naloxone (○). Right: control (●) and in the presence of 10^{-5}M morphine (△) or oxymorphone (□). Each point is the average ± SEM of 6-20 determinations.

DISCUSSION

In its basic form the multiple-receptor theory of opiate action predicts that there exists in Nature several distinct kinds of receptors which show differing selectivity for opioids of varying structure. This is undoubtedly true when one compares different species or different tissues within a single species, However, this concept of multiple receptors has been extended to individual tissues and

cells such that the presence of several different opiate receptors are postulated to be present within a single tissue. The principal evidence to support this notion comes from differing rank order potencies of opioid agonists and antagonists on different test systems . Using this kind of approach it has been suggested that the RVD contains predominantly σ and/or ε receptors within lesser numbers of μ receptors and few, if any, δ or κ receptors (Lemaire et al, 1978, Schulz et al, 1979, Wuster et al, 1980).

Table 1.

Antagonism by opiates of ß-endorphin inhibition of field stimulated rat vas deferens

ß-endorphin (M)	% Twitch Response* Control	Treatment	Antagonist (M)
10^{-7}	56 ± 5	88 ± 4	Naloxone (10^{-5})
3×10^{-8}	52 ± 5	86 ± 4	Morphine (10^{-5})
3×10^{-8}	52 ± 4	94 ± 1	Oxymorphone (10^{-5})
3×10^{-8}	56 ± 3	100 ± 1	Desomorphine (10^{-5})
3×10^{-8}	48 ± 4	99 ± 1	Ketocyclazocine (10^{-5})
3×10^{-8}	68 ± 3	88 ± 4	α-(+)-N-Allylnormetazocine (3×10^{-5})
3×10^{-8}	54 ± 3	87 ± 2	Ketobemidone (3×10^{-6})

*Data are the average ± SEM of 6-8 determinations.

There is, however, an alternate explanation to account for different pharmacological profiles amongst opioid target tissues. This was elaborated first in 1965 and again in 1978 by Portoghese. In its simplest form it says that the diverse responsiveness of opioid target tissues may be due to multiple modes of binding to a single binding site. It is this kind of mechanism which we feel best explains the data obtained in our study. It seems clear that there is only one binding site in the RVD, at least as measured pharmacologically in the field-stimulated preparation. The evidence for this is that there is complete interchangability between drugs selective for each of the major receptor classifications. For example there are full agonists from the δ and ε class [i.e. ß-endorphin and the D-Ala^2-Nle^{5}des-COOH)-enkephalin] and the μ class (etorphine, etonitazene and sufentanil). Other μ drugs (i.e. morphine and oxymorphone) are partial agonists but will inhibit the δ and ε class [i.e. ß-endorphin and D-Ala^2-Nle^5(des-COOH)-enkephalin] as well as other μ agonists (i.e. sufentanil, etorphine, and etonitazene). Finally drugs classified as a σ (α-(+)-N-allyl-normetazocine) or κ (ketocyclazocine) ligands will antagonize both the

δ and ε agonists. In short each drug tested was either an agonist, partial agonist or antagonist. None were inactive. It is interesting that a recent paper (Gillan et al, 1981) also reported similar data but chose to interpret their data under the multiple-receptor theory. Furthermore, they observed that a kappa(κ) ligand (ethylketocyclazocine) also is an antagonist in RVD.

Two additional points should be made to strengthen our contention that only a single binding site exists in this tissue. First is the fact that the partial agonists morphine and oxymorphone antagonize ß-endorphin in a concentration-dependent manner. This concentration range is virtually identical to that at which these drugs exhibit their weak agonist activity, suggesting that each effect is mediated via interaction with the same receptor site. The second point is that the oxymorphone antagonism is the same regardless of the nature of the agonist used. It will, for example, antagonize ε and δ drugs (ß-endorphin and enkephalin) to the same degree as it blocks μ drugs (etorphine and sufentanil). There is no discrimination based on drug classification, again suggesting a single binding site.

In conclusion, we believe that our data is consistent with the suggestion that the opiate receptor in the rat vas deferens is homogeneous. Our results have been interpreted within the framework of Portoghese's original concept of different binding modalities to a single receptor.

REFERENCES

Chang, K.J. and Cuatrecasas, P. J. Biol. Chem. 254:2610-2618, 1979.
Day, A.R., Carney, J.M., Rosecrans, J.A., Dewey, W.L. and Freer, R.J. Res. Commun. Chem. Pathol. Pharmacol. 20:59-68, 1978.
Gillan, M.G.C., Kosterlitz, H.W. and Magnum, J. Brit. J. Pharmacol. 72:13-15, 1981.
Lemaire, S., Magnan, J. and Regoli, D. Brit. J. Pharmacol. 64: 327-329. 1978.
Liao, C:S., Day, A.R. and Freer, R.J. Res. Commun. Chem. Pathol. Pharmacol . 31:173-176, 1981.
Lord, J.A.H., Waterfield, A.A., Hughes, J. and Kosterlitz, H.W. Nature (London) 267: 495-499, 1977.
Martin, W.R. , Fades, C.G. , Thompson, J.A., Huppler, R.E. and Gilbert, P.E. J. Pharmacol. Exp. Ther. 197:517-532, 1976.
Portoghese, P.S. J. Med. Chem. 8:609, 1965.
Portoghese, P.S. Acc. Chem. Res. 11:21-29, 1978.
Schulz, R., Faase, E., Wuster, M. and Herz, A. Life Sci. 24:843-850; 1979.
Wuster, M., Schulz, R. and Herz, A. In, E.L. Way, ed. Endogenous and Exogenous Opiate Agonists and Antagonists. New York Pergammon Press 1980, pp. 75-78.

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Autoradiographic Localization of the Phencyclidine/Sigma "Opiate" Receptor in Rat Brain

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In the past few years, phencyclidine ("Angel Dust", PCP) has become a major drug of abuse in the United States. The "psychosis" induced by PCP resembles schizophrenia and makes the question of its molecular mechanism of action one of considerable interest. Recently, classical ligand binding to brain homogenates with rapid filtration to reduce nonspecific binding has been used to demonstrate PCP receptors in rat brain (Vincent et al., 1979; Zukin and zukin, 1979). Using the new brain-slice technique (Herkenham and Pert, 1980), we now report specific [^{3}H]PCP binding to slide-mounted sections of fresh-frozen rat brain. Subsequently, using tritium-sensitive LKB film analyzed by computerized densitometry (Goochee et al., 1980), we visualized the distribution patterns of [^{3}H]PCP binding in rat brain and found a unique distribution which predominates in cortex and hippocampus. Furthermore, although morphine and opiate peptides fail to displace [^{3}H]PCP binding, opiates that produce psychotomimetic effects, classified as sigma (Martin et al., 1976), potently displace [^{3}H]PCP binding, suggesting that the sigma effects of opiates are mediated through the PCP binding site.

MATERIALS AND METHODS

Male Sprague-Dawley rats were decapitated and their brains ware rapidly immersed in isopentane at -40°C, mounted on cryostat chucks, and cut into 25 µm-thick coronal sections at -14°C. Sections were thaw-mounted near the edge of precleaned gelatin-coated slides, air-dried on ice about 2 h and then stored at -14°C for at least 48 h before use.

Frozen slide-mounted sections (one section per slide) were incubated for 45 min in 30 ml ml beakers in a volume of 10 ml consisting of 5.0 mM Tris-HCl buffer plus 50 mM sucrose, pH 7.4 at 0°C with 8.2 nM [^{3}H]PCP (400,000 cpn/ml; 48 Ci/mmol; New England Nuclear) or in the presence of nonradioactive PCP or other indicated drugs. At the end of the incubation, the slides were placed in racks holding 30 slides and transferred sequentially through six rinses (30 sec

in each) of 5.0 mM Tris-HCl buffer plus 50 mM sucrose, pH 7.4 at 0°C plus 1 percent bovine serum albumin. Binding of [^{3}H]PCP to the tissue slice was quantitated by counting the tissue-laden slide fragment in 10 ml Aquassure scintillation cocktail (New England Nuclear) after vigorously agitating the vial contents for 30 min. Specific binding was calculated as the difference in counts bound in the presence and absence of 0.1 mM PCP. Olfactory bulb slices were generally utilized because of the availability of many similar 25 µm-thick sections (60-70) from each brain.

Preparation of incubated slides for microscopic visualization was carried out as follows: at the end of the rinsing period, the slides were rapidly dried under a stream of cold air and then juxtaposed tiyhtly with tritium-sensitive film (Ultrafilm, LKB Instruments, Rockville, MD) and stored at room temperature for ten days. After this exposure, the film was processed in Kodak D19 at 22°C for 4 min and then fixed for 5 min. We utilized the Goochee et al. (1980) computer program, which codes optical density data along a color spectrum, to visualize the distribution of the PCP binding sites in rat brain.

In preliminary experiments, we have observed that the optimal signal-to-noise ratio was achieved by preincubating brain slices for 15 min at 0°C, in the presence of 20 mM NaCl in buffer, followed by a 45-min incubation in 5.0 mM Tris-HCl buffer plus 50 mM sucrose, pH 7.4 at 0°C without any added ions. Under these conditions, 60-70 percent of the total bindiny was displaced by 0.1 mM PCP when the concentraton of radiolabeled PCP was 8.2 nM. Saturation curves and Scatchard analysis of [^{3}H]PCP binding revealed a saturable single class of binding sites with a Kd = 46 mM and a Bmax = 10.5 fmol/slice. Figure 1 shows that a large number of PCP analogs displace [^{3}H]PCP in a broad range of concentrations.

FIGURE I

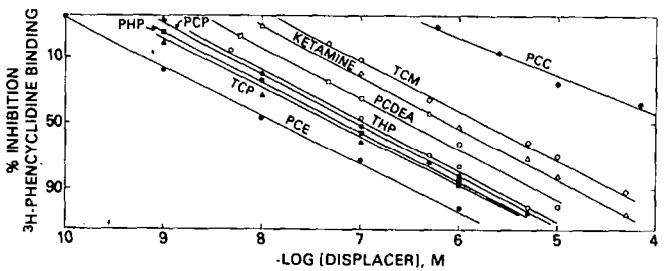

Figure 1. Displacement of [^{3}H] PCP by nonradioactive PCP and various analogs. Values are expressed as percent inhibition of specific binding of [^{3}H]PCP and are plotted as Log-Probit plots.

The most potent analog, PCE, displaced [^{3}H]PCP binding about six times more potently than PCP itself. By contrast, ketamine was 10 times less potent than PCP and PCC was a very weak displacer of [^{3}H]PCP binding. Also, while morphine, naloxone, and a number of

opiate peptides failed to significantly displace [^{3}H] PCP binding, a number of "sigma" opiate agonists potently inhibited [^{3}H] PCP binding (fig. 2). For the ten PCP analogs for which both biochemical and behavioral data were available, there is a rather precise correlation ($r = 0.98$; $p < 0.001$) between the ability of these ligands to displace [^{3}H] PCP binding from brain slices and to act in the PCP-discriminative stimulus test (fig. 3).

FIGURE 2

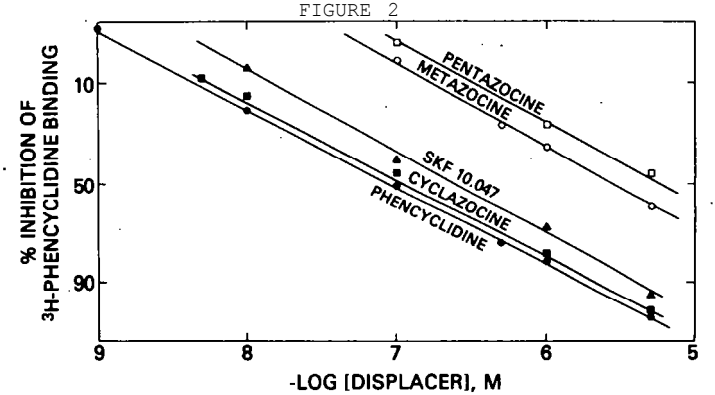

Figure 2. Displacement of [^{3}H] PCP by nonradioactive PCP and various opioid drugs. Values are expressed as percent inhibition of specific binding of [^{3}H] PCP and are plotted as log-Probit plots.

FIGURE 3

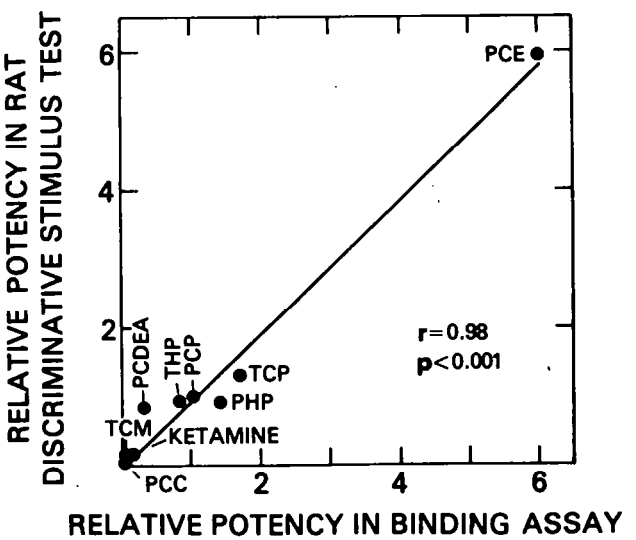

Figure 3. Relative potencies of a series of PCP analogs in displacing specifically bound [^{3}H] PCP vs. the relative potencies of these compounds in the rat discriminative stimulus test.

FIGURE 4

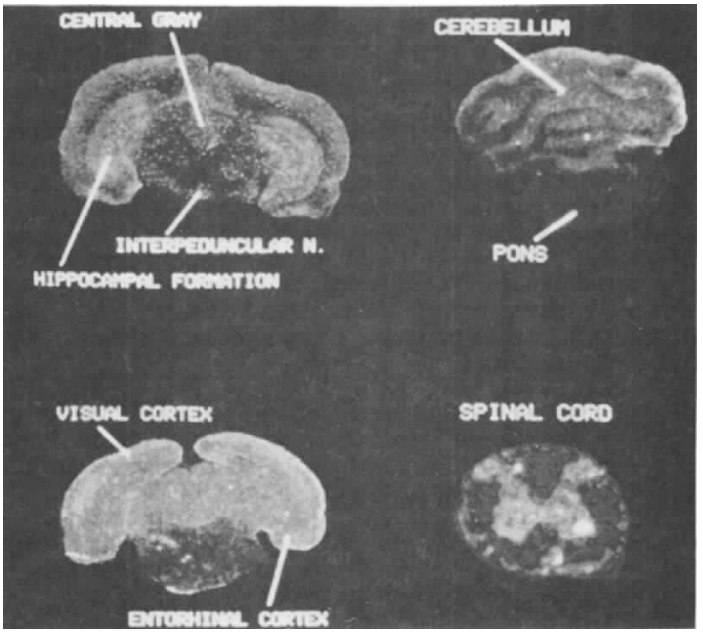

Figure 4. Pseudocolor reconstructions of [^{3}H] PCP autoradiographs of rat brain sections using the computerized densitometry and color coding technique. Each picture was obtained using the same color pattern.

As shown in fig. 4, the hippocampus and dentate gyrus contain the hiyhest levels of specific [^{3}H] PCP binding measured in this study; label predominates in layers superficial to the pyramidal and granule cell layers. In neocortex it is more dense in the outer five layers; in cerebellum it predominates in the molecular layer. Brainstem areas which stand out against low binding in adjacent structures are the central gray, substantia nigra and interpeduncular nucleus. These leave moderate [^{3}H] PCP receptor densities similar to those obtained in the gray matter of spinal cord.

DISCUSSION

Ligand specificity analysis of [^{3}H] PCP binding suggests that we are visualizing a unique and distinct population of binding sites which are very similar to those that mediate the pharmacological PCP effects in vivo.

Maayani and Weinstein (1980) have claimed that [^{3}H] PCP binding is a technical artifact of the rapid filtration technique. Since then, Vincent et al. (1980) have demonstrated that the importance of these technical problems has been overstated. In this study, using no filters at all, binding to the glass on which the slides were mounted was less than 5% of the total binding.

However, we feel that the strongest evidence for the specificity of the binding we have observed is the close correlation between the ligand selectivity pattern of [^{3}H] PCP displacement and the relative potencies of these drugs in a behavioral-test.

In this study, we have observed that a small number of benzomorphan opiates with peculiar psychotominetic "sigma" properties potently interact with [^{3}H] PCP binding sites. While an early study suggested that naloxone blocks these sigma effects (Martin et al., 1976), recent reports show that the behavioral (Holtzman, 1980; Shannon, 1981) and biochemical (Wood et al., 1980; Zukin and Zukin, 1981) action of PCP and/or sigma agonists in various species are not reversed by morphine or naloxone. These results suggest that the sigma effects of benzomorphan opiates are due to their interaction with the PCP receptor.

The PCP binding site may sometimes or always be a portion of the receptor-effector complex of other drug receptors. It is interesting that a synthetic drug like PCP is able to interact with a uniquely patterned population of binding sites in rat brain. At this time, we are uncertain whether this is due to an accidental structural similarity to an as yet undiscovered endogenous ligand or merely a fortuitous ability to interact with ions channels or other neurotransmitter receptor-effectors.

Finally, our results indicate that the PCP receptor seem to be a cortical and hippocampal receptor. This cortical distribution seems appropriate for a receptor of a drug with striking "schizophrenomimetic" properties (Snyder, 1980).

ACKNOWLEDGMENTS

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REFERENCES

Goochee, C., Rasband, W., and Sokoloff, L. Computerized densitometry and color coding of [^{14}C] Deoxyglucose autoradiographs. Ann Neurol 7:359-370, 1980.

Herkenham, M. and Pert, C.B. In vitro autoradiography of opiate receptors in rat brain suggests loci of "opiatergic" pathways. Proc: Natl Acad Sci USA 77:4469-4473, 1980.

Holtzman, S.G. Phencyclidine-like discriminative effects of opioids in the rat. J Pharmacol Exp Ther 214:614-619, 1980.

Maayani, S., and Weinstein, H. "Specific binding" of ^{3}H-phencyclidine: artifacts of the rapid filtration method. Life Sci 26:2011-2022, 1980.

Martin, W.R., Eades, C.G., Thompson, J.A., Huppler, R.E., and Gilbert, P.E. The effects of morphine and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. J Pharmacol Exp Ther 197:517-532, 1976.

Shannon, H.E. Evaluation of pnencyclidine analogs on the basis of their discriminative stimulus properties in the rat. J. Pharmacol Exp Ther 216:543-551, 1981

Snyder, S.H. Phencyclidine. Nature 285:355-356, 1980.

Vincent, J.P., Kartolovski, B., Geneste, P., Kamenda, J.M., and Lazdunski, M. Interaction of phencyclidine ("angel dust") with ε specific receptor in rat brain membranes. Proc Natl Acad Sci USA 76:4678-4682, 1979.

Vincent, J.P, Vignon, J., Kartolovski, B., and Lazdunski, M. Binding of phencyclidine to rat brain membranes: technical aspect. Eur J Pharmacol 68:73-77, 1980.

Wood, P.L., Stotland, M., Richard, J.W., and Rackham, A. Actions of mu, kappa, sigma, delta and agonist/antagonist opiates on striatal dopaminergic function. J Pharmacol Exp Ther 215:697-703, 1980.

Zukin, S.R., and Zukin, R.S. Specific [^{3}H]-phencyclidine binding in rat central nervous system. Proc Natl Acad Sci USA 76:5372-5376, 1979.

Zukin, R.S., and Zukin, S.R. Demonstration of [^{3}H] cyclazocine binding to multiple opiate receptor sites. Mol Pharmacol 1981, in press.

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Behavioral Dependence in Rhesus Monkeys with Chronic Phencyclidine Administration

Barbara Lord Slifer, William L. Woolverton, and Robert L. Balster

Phencyclidine (PCP) has been shown to function as a reinforcer to maintain operant responding. Monkeys will intravenously self-administer large quantities of PCP under unlimited-access conditions (Balster et al., 1973; Balster and Woolverton, 1980). In addition Balster and Woolverton (1980) recently reported the occurrence of withdrawal symptoms indicative of physical dependence following unlimited self-administration of phencyclidine for 20-30 days. While obvious physiological abstinence symptoms can be reliably measured, more subtle, less easily observed disruptions may be overlooked. Schedule-controlled responding has been successfully used to establish stable and sensitive baseline patterns *of* behavior. Such procedures are proving useful for qualitatively and quantitatively assessing the behavioral effects associated with discontinuation of chronic drug administration. In the past, marked alterations in schedule-controlled behavior, indicative of withdrawal, were demonstrated to occur upon cessation of chronic morphine administration to rhesus monkeys (Holtzman and Villarreal, 1973; Thompson and Schuster, 1964) and rats (Ford and Balster, 1976) and following abstinence from prolonged ethanol drinking in rats(Ahlenius and Engel, 1974) and THC administration in monkeys (Branch et al., 1980). In this study we report the use of the disruption of operant behavior to examine the effects of abstinence from chronic phencyclidine infusions in rhesus monkeys.

METHODS

Four adult, male rhesus monkeys (Macaca mulatta) served as subjects in this study. Two of the animals M566, M314) were experimentally naive, while the remaining two monkeys (M173, 7623) had previous experience in intravenous self-administration studies. The animals were individually housed in self-administration cubicles (0.8 x 0.8 x 1.0 m) and each wore a stainless steel tubular harness and springarm which was attached to the rear of the cubicle to restrain the animal and protect the catheter. This permitted free movement of the monkey within the chamber. The animals were surgically prepared with chronic indwelling

catheters under PCP-pentobarbital anesthesia. The silicone rubber catheter (0.8 mm lumen) was inserted into a jugular vein to the level of the right atrium. The distal end of the catheter was passed subcutaneously to an exit point on the animals back. The external catheter was then threaded through the springann and out the rear of the cubicle where it was connected to a syringe pump.

Within the cubicle, two response levers were located on the clear plexiglass door at the front of the chamber. Three red, 28V lamps were mounted above each lever. The food hopper for the externally mounted pellet feeder was located between the response levers. Events within the chamber were controlled and recorded by solid-state programming equipment located in an adjacent room.

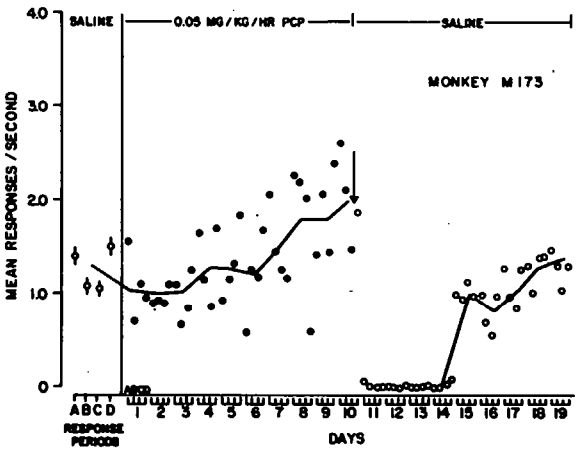
The naive monkeys were trained to respond for banana-flavored pellets on an FR1 schedule on the lever located to the right of the feeder by baiting the lever with a raisin. The FR response requirement was gradually incremented to a terminal value of 100 response (FR100) . Responses on the left lever had no programmed consequences. Once the FR100 had been established, the animals were given 30 min periods every 6 hrs during which they earned their daily food ration. These response periods occurred at 4:00 p.m. (period A), 10:00 p.m. (B), 4:00 a.m. (C), and 10:00 a.m. (D). During response periods the lights above the right response lever were illuminated. In addition each response period was signalled by a white noise alarm which was subject-terminated by the first response on the FR lever. Following the establishment of food-reinforced responding, the monkeys were started on continuous saline infusions via their catheters at a rate of 0.84 ml/hr. When responding for food reinforcement concurrent with saline infusions had stabilized, the saline was replaced by 0.05 mg/kg/hr PCP. All drug or saline substitutions took place at 8:00 a.m., 2 hours prior to response period D (10:00 a.m.). Following 10 days of PCP administration, saline was administered again.

Response rates and food intake in each response period were recorded between 2:00-3:00 p.m. In addition, during this time period the syringes and pellet feeders were refilled and the monkeys were given fresh water and a vitamin suppliment. If supplimentary feeding was required it was done at this time also. Routine morning housekeeping chores (cubicle cleaning, watering and routine checks) were performed between 7:00-8:00 a.m. daily.

RESULTS

The effects on response rates of the 10-day chronic administration and subsequent withdrawal of 0.05 mg/kg/hr PCP are illustrated in figure 1. This figure shows the response rates during each response period for monkey M173. The saline control is based on the 5 saline days preceding PCP substitution. It can be seen that during the first three days of PCP administration the mean response rates (indicated by the solid line), were at or below control rates. The daily rates then increased over the remaining

days of PCP administration to above saline control levels. On day 10 the arrow indicates saline substitution for PCP. Eight hours later during response period A the disruption in responding is apparent. The animals made very few responses during the period and even fewer during the following two periods. Operant responding in this animal was suppressed for 4 days before beginning recovery to baseline levels. Upon observation during the withdrawal period, the four animals showed signs of illness which included emesis and refusal of a preferred food. These signs were observed only during the first 12-24 hours after cessation of PCP administration.



The averaged data for all 4 monkeys are summarized in Table 1. The data are presented as overall mean response rates as percent of control responding. Saline control is again based on the 5 days preceding PCP infusions. Predrug saline control rates for the four monkeys averaged 1.90 (± .10) responses per second. The chronic drug regimen significantly increased the mean response rates above saline control levels and, concomitantly, the food pellets earned also increased. The animals were generally observed to consume all pellets earned during these periods. During PCP administration the monkeys were observably intoxicated, exhibiting such signs as ataxia, nystagmus and decreased aggressiveness.

The response rate disruption during PCP withdrawal illustrated in figure 1 was seen in all subjects (table 1). The other subjects also showed a gradual recovery and mean rates of responding did not return to control levels until day 7 or 8. The number of reinforcers earned was also suppressed during recovery and recovered over 9 days of withdrawal. Due to the few pellets earned during the early days of withdrawal, the subjects were given a small amount of supplemental food to maintain their health. Mild physical signs and symptoms were occasionally observed in most subjects during the first two days of withdrawal.

TABLE 1

Response Rates and Number of Reinforcers Earned

During Chronic Phencyclidine Infusion (.05 mg/kg/hr) and

Withdrawal in Four Rhesus Monkeys

Phase of the Experiment	Mean Response Rates[a] (% of Control ± S.E.M.)	Mean Food Pellets[b] Earned (± S.E.M.)
5 Days Saline Control	100 (±4)	158 (±10)
10 Days PCP Infusion	128 (±4)*	180 (±9)
Withdrawal Day 1	2 (±1)*	2 (±2)*
Withdrawal Day 2	6 (±2)*	7 (±5)*
Withdrawal Day 3	20 (±9)*	22 (±14)*
Withdrawal Day 4	36 (±14)*	44 (±33)*
Withdrawal Day 5	65 (±15)*	103 (±35)
Withdrawal Day 6	75 (±13)*	103 (±17)
Withdrawal Day 7	89 (±10)	137 (±6)
Withdrawal Day 8	97 (±10)	148 (±19)
Withdrawal Day 9	111 (±11)	177 (±12)

[a]Response rates for each animal for each response period were calculated as percent of the mean response rates for that animal for that period during the 5 days saline control. Numbers in the table are the means of these values for 4 monkeys.

[b]Mean food pellets earned across all four response periods for the days indicated. Values are the means of 4 monkeys.

*Significantly different from saline. $p < 0.05$

DISCUSSION

The response rate increases on the fixed-ratio schedule produced by chronic PCP administration differ from other studies which have reported only rate decreases in FR responding with PCP (Wenger, 1976; Wenger and Dews, 1976; Chait and Balster, 1978). These studies, however, were with species other than the rhesus monkey (e.g. pigeon, mouse, squirrel-monkey). In general, the overall response rate increases were due to a decrease in post-reinforcement pause duration. These increases are particularly interesting because of the very high baseline rates generated by the FR schedule. The effects of acute PCP on response rates in rhesus monkeys have been shown to be response-rate dependent (Brady et al., 1980), with response rates greater than 0.1 resp/sec generally decreased by PCP. The consistent increases we obtained in the present study with much higher baseline rates thus represent a qualitatively different effect of continuous-PCP administration than is seen with acute administration.

Following 10 days of PCP infusion at 0.05 mg/kg/hr (1.2 mg/kg/day), response rates were markedly disrupted by 8 hours after saline substitution. Average rates on the first day of withdrawal were only 2% of control values. Responding was also markedly affected for at least 7 or 8 days but did return to baseline values. We were surprised by the gradual recovery from the disrupting effects produced by the withdrawal of PCP. This was particularly interesting in light of the disappearence of the observable physiological signs of withdrawal distress within 24 hours following cessation of drug infusions. During the next few days following the initial withdrawal, the animals took and consumed banana pellets when offerred but would not work on the FR schedule to obtain them. This suggests the sensitivity of the quantitative behavioral measure to the subtle withdrawal effects of chronic PCP.

The suppression of responding upon removal of the drug was a reliable effect in all four subjects. This disruption in operant responding is evidence for a behavioral dependence as defined by Schuster and Thompson (1969); that is a disruption in behavior upon termination of chronic drug treatment. Reversal of the behavioral disruption by PCP administration would be further evidence for behavioral dependence. We are in the process of carrying out studies of the reversal of the withdrawal phenomenon by PCP administration. This definition of behavioral dependence is thus completely analogus to physical dependence except the behaviors rather than physical signs and symptoms are assessed. Therefore, based on the present study and our previous one (Balster and Woolverton, 1980), PCP has been shown to produce both behavioral and physical dependence.

REFERENCES

Ahlenius, S. and J. Engle. Behavioral stimulation induced by ethanol withdrawal. Pharmacol Biochem Behav 2:847-850, 1974.

Balster, R.L., C.E. Johanson, R.T. Harris, C.R. Schuster. Phencyclidine self-administration in the rhesus monkey. Pharmacol Biochem Behav 1:167-172, 1973.

Balster, R.L. and W.L. Woolverton. Continuous-access phencyclidine self-administration by rhesus monkeys, leading to physical dependence. Psychopharmacology 70:5-10, 1980.

Brady, K.T., R.L. Balster, L.T. Meltzer, D. Schwertz. Comparison of phencyclidine and three analogues on fixed-interval performance in rhesus monkeys. Pharmacol Biochem Behav 12:67-71, 1980.

Branch, M.N., M.E. Degring, D.M. Lee. Acute and chronic effect of Δ-9-tetrahydrocannabinol on complex behavior of squirrel monkeys. Psychopharmacology 71:247-256, 1980.

Chait, L.D. and R.L. Balster. The effects of acute and phronic phencyclidine on schedule-controlled behavior in the squirrel monkey. J Pharmac Exp Ther 204:77-87, 1978.

Ford, R.D. and R.L. Balster. Schedule-controlled behavior in the morphine-dependent rat. Pharmacol Biochem Behav 4:569-573, 1976.

Holtzman, S.G. and J.E. Villarreal. Operant behavior in the morphine-dependent rhesus monkey. J Pharmac Exp Ther 184:528-541, 1973

Schuster, C.R. and T. Thompson. Self-administration of and behavioral dependence on drugs. Ann Rev Pharmacol 9:483-502, 1969.

Thompson, T. and C.R. Schuster. Morphine self-administration food-reinforced, and avoidance behaviors in rhesus monkeys. Psychopharmacologia 5:87-94, 1964.

Wenger, G.R. The effect of phencyclidine and ketamine on schedule-controlled behavior in the pigeon. J Phannacol Exp Ther 196: 172-179, 1976.

Wenger, G.R. and P.B. Dews. The effects of phencyclidine, ketamine, d-amphetamine and pentobarbital an schedule-controlled behavior in the mouse. J. Pharmac Exp Ther 196:616-624, 1976.

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Comparison of Barbiturate and Benzodiazepine Self-Injection in the Baboon

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ABSTRACT

Self-injection of three barbiturates (amobarbital. pentobarbital, and secobarbital) and six benzodiazepines (clonazepam. clorazepate, diazepam, flurazepam, medazepam. and midatlom) was examined in baboons. Intravenous injections of drug were dependent upon completion of 160 lever presses (a 160-response fixed-ratio schedule). A three-hour time-out period followed each injection, pennitting a maximum of eight injections per day. Before testing each dose of drug, self-injection performance was established with cocaine. Subsequently, a test dose was substituted for cocaine. The three barbiturates maintained the highest levels of self-injection, which were similar to those maintained by cocaine, while the six benzodiaiepines maintained relatively modest levels of self-injection. Of the six benzodiazepines, the compound with the shortest duration of action, midazolam, produced the highest levels of self-injection. At the highest self-injected doses, the barbiturates produced anesthesia in contrast to the benzodiazepines, which produced only sedation. None of the drugs affected food intake.. The differences between the barbiturates and benzodiazepines with respect to the maintenance of self-injection correspond well with the results of previous animal and human drug self-administration studies.

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Experimental Induction of Benzodiazepine Physical Dependence in Rodents

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INTRODUCTION

The 20-year mass cultural use of benzodiazepines as minor tranquilizers in the practice of medicine has led to a growing concern for the possible risk of addiction. Hollister et al. (1961) demonstrated that benzodiazepines are capable of inducing physical dependence leading to withdrawal hyperexcitability in patients receiving 100 to 600mg chlordiazepoxide (8-20 times therapeutic dose). Little effort has been directed to reproducing this neuropathic state in animals, Only Yanagita and Takahashi' (1973) have reported the induction of dependence to chlordfazepoxide and diazepam culminating in nervous hyperexcitation including convulsions in the monkey.

Accordingly, we have engaged in chronic studies in rats and mice to develop a reliable model of benzodiazepine tolerance and physical dependence. Our efforts have focused on the "chronically equivalent maximally tolerable" dosing paradigm previously developed in cats (Okamoto et al. 1975). By this approach, the efficient induction of benzodiazepine dependence is sought by administering the drug in as large a dose as possible and as often as possible to insure continuous intoxication without impairment of self-sufficient health. Doses are individually selected to restore the same quantitative peak effect. This paper summarizes our pilot investigations with chlordiazepoxide administered fntragastrically by gavage in the rat. These studies led‘to the "chronically equivalent" chlordiazepoxide rat model (Ryan and Boisse, 1979; 1981). Initial attempts to apply this dosing paradigm to the mouse were unsuccessful; the mouse could not accept repeated gavage. Accordingly, we let the mouse take the drug orally via the drinking water.

METHODS

Chronic Chlordiazepoxide Dosing in the Rat by Gavage

Male Sprague-Dawley rats (Charles River) were treated with chlordiazepoxide hydrochloride (75 mg/ml). Before and at two-hour intervals after each morning dose a neurological exam was performed on each animal to quantify CNS depression. The exam consisted of ratings on

screen grip, ladder test, motor activity, walking, crawling, righting, wakefulness, arousability, respiration, wink reflex and flexor reflex. The grading system and an 11-point scale to quantftate CNS depression are described elsewhere (Ryan and Boisse, 1979; 1981).

To optimize dose-time coordinates optimal to induce severe dependence in rats, pilot experiments were conducted to explore the influence of dose level (anesthetic and ataxic peak effects), dosing fnterval, and chronicity of treatment upon the severity of the resultant wfthdrawal reaction. From acute dose-response explorations, the loading dose was 450 mg/kg for the ataxic and 900 mg/kg for the anesthetic endpoint. Subsequent doses were indfvidually adjusted in 25 mg/kg steps to restore the initial peak response. The dosing frequency was either once daily in the morning or twice daily at 7am and 5pm. Chronicity was varied from one to five weeks.

Chronic Chlordiazepoxide in the Mouse via the Drinking Water

Hale Charles River mice (CD-1) were individually housed. Since chlordfazepoxfde produced an aversion to drink, the initial concentration of the drug was low to deliver only 10 mg/kg/day. In addition, the drug was dissolved in tap water containing 0.5% sodium saccharin in an effort to mask the taste and encourage drfnkfng. Based on the suppression of water fntake for the preceding 3 or 4 days and general condition, the concentration in the drinking water was adjusted in 50 mg/kg steps to deliver doses that minimally depressed water consumption for 10 weeks.

Quantitative Evaluatfon of Chlordfazepoxide Withdrawal

Following chronic chlordfazepoxfde dosing in the rat, the drug was abruptly stopped and each animal was carefully observed for behavioral signs of wfthdrawal at least at 8am and 6pm untfl all signs disappeared. The characteristic signs are predominantly motor, autonomic and behavioral disturbances (Ryan and Boisse, 1979; 1981). Many signs were subjectively graded from 0 to 3 (maximum fntensfty.Some signs that could not be quantitated were recorded as present (+) or absent (0 or N) or by indicating the direction of change. Objectively measured withdrawal sfgns included body weight and food consumption. All animals were mafntafned in an activity device to monftor the occurrence of convulsions. The protocol was sfmilar in mice.

RESULTS

Chlordiazepoxide Dose-Time Relationships for Dependence in the Rat

Results of the pilot explorations of dose, dosfng frequency, and chronicity of treatment for induction of dependence is shown in Table 1. At least 4 rats survfved each of the seven treatment plans shown. Once daily dosing to an ataxic end-point for 5 weeks produced a mild wfthdrawal reaction based on both the number of withdrawal sfgns and their peak Intensity which did not exceed grade 1. Since once daily dosfng often failed to continually depress the CNS according to neurological criteria, twice daily ataxfc dosfng was explored. The influence of chronfcfty of dosing was also examined. As shown, wfthdrawal

severity increased from 1 to 5 weeks. Five weeks produced the most severe withdrawal reaction. Interestingly, the overall severity of the withdrawal reaction was about the same for once dafly anesthetic dosing and twice daily ataxfc dosing for 5 weeks. However, the survival rate was greater (100%) for ataxic dosing. Accordingly, twice dally ataxfc dosing for 5 weeks was adopted to develop our "chronically equivalent" chlordiazepoxide treatment plan.

Chronic Chlordiazepoxide in the Rat

Ffgure 1 summarizes the analysts of chronic dose and response throughout the 5 weeks. The criterion of "chronically equivalent" ataxfc peak effect was met as demonstrated by the constancy of the average peak CNS depression rating throughout treatment with a mean of means equal to 5.20 (± 1% S.E.). Since the total daily dose increased from an inftial maintenance dose of 163 mg/kg on day 2 to a final maintenance dose of 839 mg/kg on day 34, tolerance developed. The overall magnftude of this tolerance represented a 5-fold increase in total daily dose over the course of 5 weeks. Tolerance developed more rapidly over the first 3 weeks and then continued to develop more slowly for the remainder of the treatment.

Chronic Chlordiazepoxide in the Mouse

Figure 2 summarizes the analysis of chronic dose and response (water consumed) throughout the 10-weeks. Although drinking behavior is no doubt influenced by chlordfazepoxide in the drinking water as well as in the CNS, measurements of water consumption during chronic treatment provided a quantitative measurement of the action of this drug which limits dose increases and thus the utility of the approach. Since dose was increased as normal levels of water consumption were restored, dose increases reflect tolerance development. The top tracing in Figure 3 shows that the level of water consumption was fairly constant throughout treatment showing a slightly downward trend only from weeks 8 to 10. Mean of means for daily water consumption throughout treatment was 7.5 (± 0.30 S.E.) ml/mouse, which is not significantly different from a parallel saccharin free control (p> ;98). Mice drinkfng water containing only saccharin drank 8.8 ml/day. Since the delivered, dose increased from 9.4 mg/kg Initially (day 4 to 7) to 742 mg/kg at the-end of chronic treatment (day 66 to 70), tolerance apparently developed. Because the daily water consumptfon was not appreciably affected by the fnitial dose, inftfal and final dose comparisons may be exaggerating the actual magnitude of tolerance developed. Accordingly, these results in the mouse cannot be quantitatively compared to the rat data.

Chlordiazepoxide Withdrawal in the Rat and Mouse

All rats abruptly terminated from "chronically equivalent".chlordiazepoxfde dosing showed severe withdrawal. Signs seen in all rats include twitches, tremors, muscular hypertonus, arched back, high step, piloerection, apprehensive behavior, increased startle reaction and weight loss. These rats exhibited 15 different signs. None exhibited seizures. Figure 3 depicts the tfme-course of selected signs. The latency to onset varied from 2 to 5 days. Peak was maintained from

day 6 to 11. Recovery was usually complete 2 weeks after the last dose.

All mice abruptly tennfnated from 10 weeks exposure in the water exhibited withdrawal. Only 5 signs occurred in all mice: tremors, tail ereitfon, piloerectfon, apprehensive behavior, and increased startle reactions. No other sfgns were seen. The onset (Figure 3) was fairly abrupt from 12 to 24 hours after removal of the drug. Peak withdrawal persisted from 24 to 60 hours and recovery was complete wfthfn 4 to 5 days. Compared to the rat, chlordfazepoxfde withdrawal in the mouse was less severe, occurred earlier and within a shorter time frame.

DISCUSSION

Physical dependence culminating in withbrawal hyperexcitation can be induced in rats and mice. Like alcohol, barbiturates and opiates, the severity of the withdrawal reaction varies wfth the magnftude of chronic dose and duration of chronic treatment. The doses required to induce severe dependence fn rats were 300 to 400 times greater than the minimal anti-conflict effective dose (Cook and Davidson, 1973).

None of the rodents exhibited convulsion as has occasionally been reported in man. This outcome mfght be due to the sequential biotransformation of chlordiazepoxfde to pharmacologically active metabolites which accumulate, and essentially slow, the rate of elimfnatfon of active drug to facilitate neuronal re-adaptation before the drug is completely elfmfnated (cf. Bofsse and Okamoto, 1978b). These observations support the medical opinion that benzodiazepines are remarkably safe drugs from the standpoint of physical dependency.

The intragastric route in the rat is a more effective strategy to induce chlordfazepoxfde dependence than the oral route vfa the drfnkfng water in the mouse. The aversion of rodents to chlordfazepoxfde solutions limits the future application of this method.

REFERENCES

Boisse, N.R., and Okamoto, M. Physical dependency to barbital com pared to pentobarbital: Part I: "Chronically equivalent" dosing method, J Pharmacol Exp Ther, 204:497-506, 1978a.

Boisse, N.R., and Okamoto, M. Physical dependency to barbital compared to pentobarbital: Part IV: Influence of eliminatfon kinetics, J Pharmacol Exp Ther, 204:526-540, 1978b.

Cook, L., and Davidson, A.B. Effects of behaviorally active drugs in conflict-punishment procedure in rats. In: Gorattfnf. S., Messfnf. E., and Randall, E.O:. eds. The Benzodiazepines. New-York: Raven-Press, 1973 pp. 327-346.

Hollister, L.E., Motzenbecker, F.P., and Degan, R.O. Withdrawal reactions from chlordfazepoxfde ("Librium"). Psychopharmacologia 2:63-68, 1961.

Ryan, G.P., and Boisse, N.R. The production of benzodiarepfne physical dependence in rats. The Pharmacologist 21(3):50, 1979.

Ryan, G.P., and Boisse, N.R. Experimental induction of benrodiazepine tolerance and physical dependence. J Pharmacol Exp Ther (submitted), 1981.

Yanagita, T., and Takahashi, S. Dependence lfabflity of several sedatfve-hypnotic agents evaluated in monkeys: J Pharmacol Exp Ther 185:307-316, 1963

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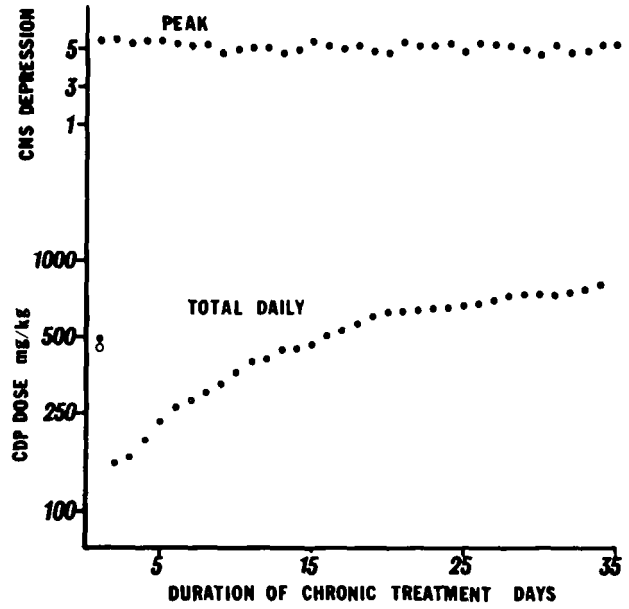
TABLE I

PILOT EXPLORATION OF DOSE AND TIME

FOR INDUCTION OF CHLORDIAZEPOXIDE DEPENDENCE IN RATS

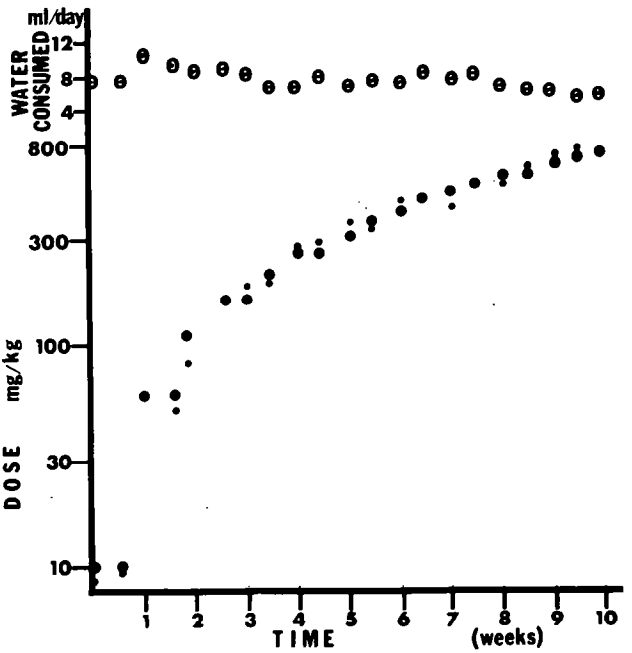
CHRONICITY OF TREATMENT	DOSING FREQUENCY	AVERAGE FINAL DOSE	DOSING CRITERION	WITHDRAWAL REACTION	
				OVERALL	# SIGNS/RAT OUT OF 20
5 weeks	once/day	650	ataxia	mild	9.8
1 week	twice/day	175	ataxia	moderate	11.7
2 weeks	twice/day	263	ataxia	moderate	12.7
3 weeks	twice/day	335	ataxia	moderate	12.0
4 weeks	twice/day	368	ataxia	moderate	12.5
5 weeks	twice/day	435	ataxia	severe	15.0
5 weeks	once/day	975	anesthetic	severe	14.5

FIGURE 1



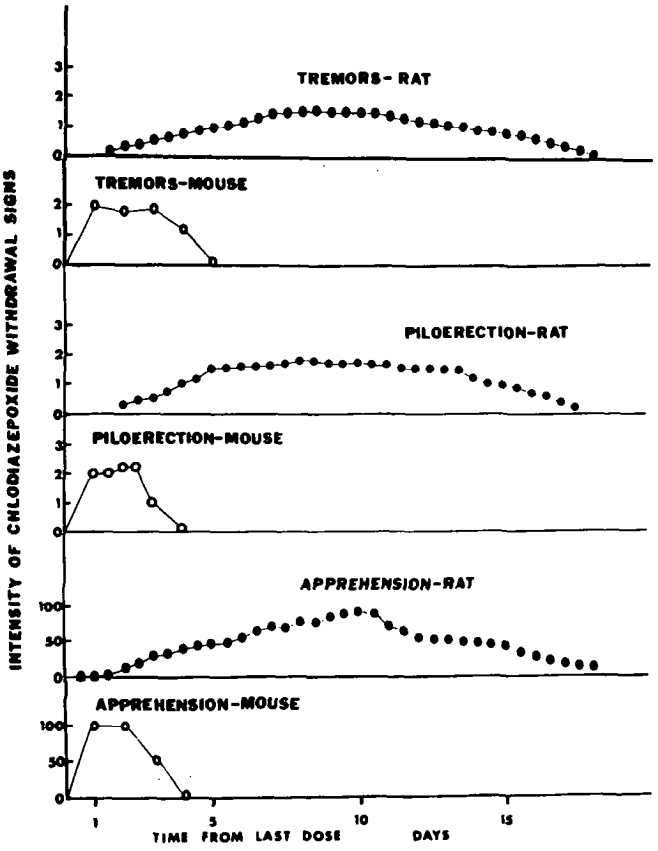
Equivalency of chronic chlordiazepoxide dosing in rat
Abscissa: time in days during chronic treatment
Ordinate, uppermost trace: the average peak depression rating after each morning dose of chlordfazepoxide
Ordinate, lowermost trace: average total daily dose of chlordiaz-epoxide.

FIGURE 2



Analysis of chronic chlordiazepoxide dose and water consumption in the mouse.
Abscissa: time in weeks during chronic treatment
Ordinate, uppermost trace: average mls of water consumed daily over 3 or 4 day (biweekly) intervals.
Ordinate, lowermost traces: (•) average daily dose actually consumed: (●) intended doses.

FIGURE 3



Time course of selected signs during chlordfazepoxfde withdrawal in rat and mouse
Abscissa: time in days from last dose of chlordiazepoxide
Ordinate, upper four traces: mean intensity of sign
Ordinate, lower two traces: incidence of apprehensive behavior
Solid dots (●) refer to rat; open circles (◉) refer to mouse.

The Etonitazene-Dependent Rhesus Monkey as a Model to Study Narcotic Agonist and Antagonist Activities

Andrew H. Tang

Rhesus monkeys were rendered tolerant to and physically dependent on the potent narcotic analgesic, etonitazene, when a solution of etonitazene was available as the only drinking fluid. To maintain a regular intake of the narcotic and to avoid overdose, the monkeys were trained to receive the drug solution by a limited-access, self-administration schedule. This procedure can be fully automated in operation, and withdrawal from etonitazene dependence has properties similar to that reported for morphine-dependent rhesus monkeys.

Narcotic agonists and antagonists were evaluated in the etonitazene-dependent monkeys by comparing their behavioral depressant effects with those in a separate group of nondependent monkeys. Cross-tolerance or precipitated abstinence in the dependent monkeys could be demonstrated, dependent on the balance of agonist versus antagonist properties.

INTRODUCTION

The morphine-dependent rhesus monkeys have been used for a number of years in the evaluation of substances with morphine-like physical-dependence capacity (Deneau and Seevers 1962). The same procedure is also useful for the identification of narcotic antagonist properties by the precipitated abstinence syndromes (Villarreal and Karbowski 1973). This procedure usually requires subcutaneous injections of morphine every 6 hours around the clock. In rodents, morphine dependence has been maintained with morphine-containing pellet implantation. Gellert and Holtzman (1978) were successful in producing stable morphine dependence in rats by limited access to morphine-drinking solutions. The last procedure has the advantage of requiring no regular handling for injections or surgical preparations. We have adopted the same concept of limited access to drinking of a narcotic solution in the rhesus monkeys, using the potent narcotic compound, etonitazene. The extreme potency of etonitazene makes it possible for a dilute solution to be acceptable to the monkeys (Carroll and Meisch

1978). The regularly spaced, limited-access schedule provided a relatively stable blood level of the drug. When the behavioral effects of drugs are compared between the dependent and nondependent animals, cross-tolerance to etonitazene or precipitated withdrawal could be demonstrated.

METHOD

Three adult male rhesus monkeys (body weights between 4 and 6 kg) were housed continuously in individual cages (18" x 24" x 30") in a small air-conditioned room with ceiling illumination regulated at 7 a.m. to 7 p.m. cycles. The cages were partitioned so that the monkeys could hear but not see each other. The room has a one-way viewing window open to an adjacent laboratory which housed programming and recording equipment. The experimental subjects were removed briefly each week for cage cleaning and weighing.

On the transparent plexiglass front doors of the cages were mounted the following: two large primate response levers about 8" above the floor and 8" between each other. Above each lever was a set of three small stimulus lights. The left lever was always for fluid reinforcement with the corresponding lights illuminated during the drinking sessions. The right lever was always for food reinforcement with the corresponding lights illuminated during the food sessions. Midway between the two levers was a receiving cup where the fluid or food pellets were dispensed in the corresponding sessions. Above each cage were two 75 watt light bulbs which were illuminated during either food or fluid sessions. In addition, each session was also accompanied by the presence of masking noise in the room.

Solutions of etonitazene HCl were dispensed from a bottle placed above each cage through a solenoid-controlled valve and which, when activated for 0.2 seconds, produced 1 ml of the fluid in the receiving cup. During food sessions, the reinforcement consisted of banana-flavored Noyes pellets (190 mg). Experimental schedules and data collection were controlled by standard programming equipment in the adjacent room. Two TV cameras were mounted on the wall facing-the front of the cages, and the behavior of the monkeys during precipitated abstinence was videotaped for later analysis.

The daily routine consisted of 6 drinking sessions and one food session. Each session lasted 15 minutes and was signaled by the presence of the overhead lights above each cage, the illumination of the stimulus light above the appropriate lever, and the white noise in the room. The drinking sessions were scheduled to commence at approximately 1 p.m., 5 p.m., 9 p.m., 1 a.m., 5 a.m., and 9 a.m. The food sessions always preceded the 1 p.m. drinking session. Since food intake from the scheduled session was relatively small, the animals were also fed regular monkey chow 10-15 pellets each afternoon about 3 p.m. No drinking water was available other than the etonitazene solution during the sessions.

In the drinking session, responses on the left lever produced the etonitazene solution on a FI-15 second schedule, i.e. the first response, after 15 seconds elapsed from the preceding reinforcement, produced another reinforcement. There was, therefore, a maximum of about 60 ml of drinking fluid for each drinking session. Responses on the right lever during this session had no consequence, but were recorded as such. In the food session, responses on the right lever produced food pellets in the receiving cup according to a FR-30 schedule, i.e. every 30th response was reinforced.

Training of the monkeys to lever-press for food and drink-took less than a week's time. The liquid reinforcement was initially tap water, which was changed to low concentrations of etonitazene (beginning at 0.3 µg/ml) as responses stabilized. The concentration of etonitazene was increased stepwise to the final concentration of 7.5 µg/ml after 3 weeks of training. Naloxone was injected i.m. at weekly intervals to evaluate the level of physiological dependence.

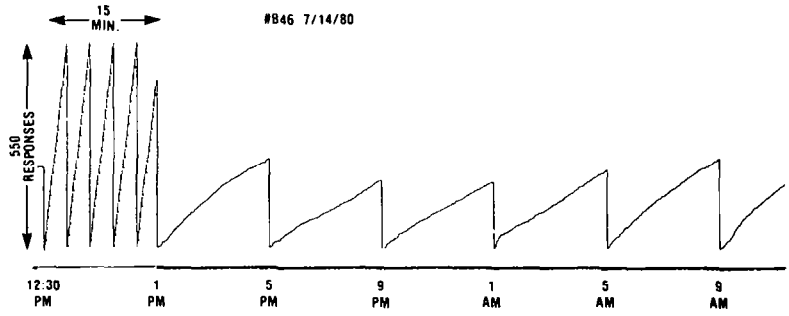
Drugs to be evaluated for cross-tolerance to etonitazene or precipitated abstinence were injected intramuscularly 15 minutes before the food-reinforced sessions. The disruption of food-reinforced behavior in the dependent monkeys was compared to that in 3 nondependent monkeys. These 3 other male rhesus monkeys (comparable body weights) lived in their home cages in an adjacent room with continuous access to drinking water. Each animal was given a 30-minute daily experimental session during which they were placed in a restraining chair. The chair was equipped with a response lever and pellet dispenser and was housed in a sound-attenuated chamber. These 3 monkeys were trained to lever-press on a VI-60 second schedule for food reinforcement (190 gm Noyes pellets). Once a week, a test drug was injected i.m. 15 minutes before the experimental session, and the disruption of this behavior was compared to the immediately preceding saline-injected sessions.

RESULTS

Figure 1 shows a representative daily record of the responses in the food and etonitazene-solution-reinforced sessions. The FR-30 schedule for food reinforcement (12:30 p.m.) generated a high rate of lever presses. In contrast, the FI-15 second schedule for drinking fluid produced schedule-appropriate lower rates. The average intake of etonitazene and volumes of fluid consumed in the 6 daily sessions are shown in Figure 2 for the 3 dependent monkeys. Except for the 9 a.m. drinking session which is most distant in time from feeding, the monkeys seldom missed a drinking session and usually received the maximum number of reinforcements allowed by the schedule. Computed according to body weights, the intake of etonitazene ranged between 350-550 µg/kg/day.

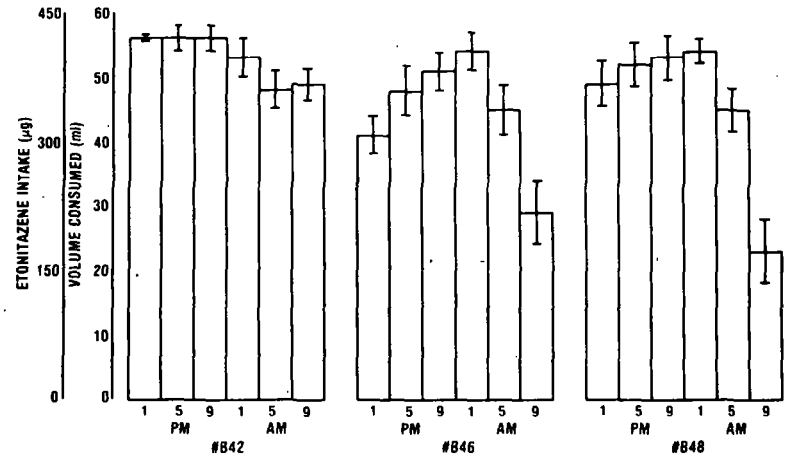
The dependent monkeys appeared to be completely tolerant to etonitazene at these maintenance doses as they were healthy and showed steady weight gain in the course of more than one year. Spontane-

Figure 1



Cumulative record for one monkey responding for food (12:30 p.m.) and etonitazene solution (15 minutes/4 hours). Each response moved the recording pen upward one step, producing food reinforcements (downward marks). Bottom pen marks fluid reinforcements (1 ml each). Paper did not advance between sessions.

Figure 2



Average fluid land etonitazene) intake on control days for the three dependent monkeys.

ous abstinence occasionally occurred when a monkey missed two or more consecutive drinking sessions. During the next 6 to 12 hours, such monkeys displayed withdrawal signs of salivation, irritability, stressful vocalization and other behaviors suggesting discomfort (laying on the floor, bearing of teeth, etc.). An i.m. injection of etonitazene (10/µg/kg) always restored normal behavior promptly.

Using the food-reinforced lever presses for quantitative evaluation, the behavioral disruptive effects of drugs injected i.m. were compared between these dependent and three nondependent monkeys. The dose-response relations of several narcotic agonists are shown in Figure 3. This group of compounds, including etonitazene itself, are less potent in the dependent animals, suggesting tolerance and cross-tolerance to this narcotic agent. In contrast, compounds known to have narcotic antagonist properties are much more potent in the dependent monkeys (Figure 4). Since the higher doses of these antagonists which disrupted the food-reinforced lever presses also produced signs of withdrawal, the effect on the operant behavior was probably the result of precipitated abstinence. The narcotic agonists and antagonists, therefore, have opposite patterns of effects in the two groups of monkeys.

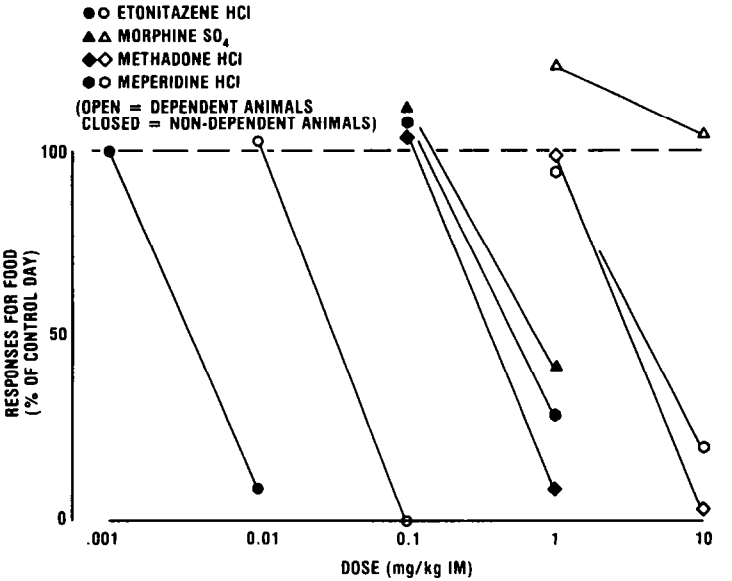
Figure 5 shows the results of several other opiate derivatives which disrupted the food-reinforced lever presses in both dependent and nondependent monkeys with comparable potencies. These compounds also produced an incomplete pattern of withdrawal syndromes. Salivation and overt sedation were the most common overt effects observed in both sets of monkeys.

DISCUSSION

Carroll and Meisch (1978) have shown that etonitazene solution presented for oral intake can serve as a reinforcer for lever presses in nonwater-deprived rhesus monkeys. There are significant differences in the two procedures since the dependent monkeys in the present study had no access to drinking fluid other than the etonitazene solution in the 6 daily drinking sessions. No attempt was made to demonstrate the reinforcing properties of etonitazene, Evidences suggest, in fact, that these 3 monkeys lever pressed for etonitazene solution solely for hydration. For instance, monkeys often did not work for all the available etonitazene solution in the 9 a.m. drinking session, a time period furthest removed from feeding. When a monkey was in a state of mild withdrawal, lever presses for the etonitazene solution were usually further disrupted rather than accelerated.

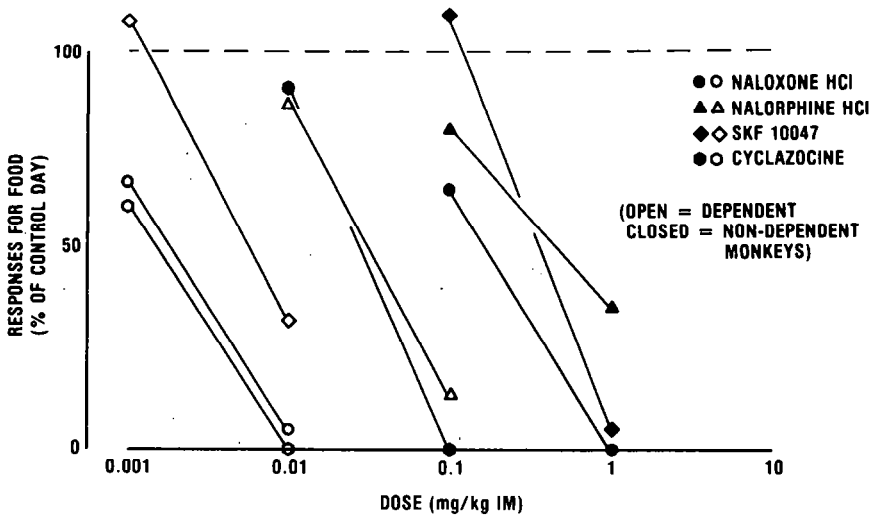
The self-administration paradigm in this procedure did provide a convenient and precise regimen for the intake of the narcotic agent, sufficient to maintain a stable state of tolerance and physical dependence. The quantitative comparison in behavioral effects between the dependent and nondependent monkeys separates compounds with predominantly narcotic agonist or antagonist properties.

Figure 3



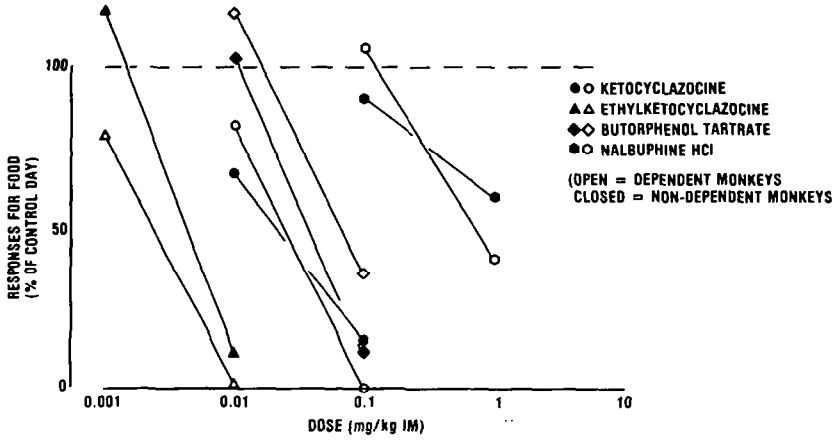
Disruption of food-reinforced lever presses by narcotic analgesics in the etonitazene-dependent and non-dependent rhesus monkeys. Each point represents the average of three monkeys.

Figure 4



Disruption of food-reinforced lever presses by narcotic antagonists in the etonitazene-dependent and non-dependent rhesus monkey. Each point represents the average of three monkeys.

Figure 5



Disruption of food-reinforced lever presses by some opiate derivatives in the etonitazene-dependent and non-dependent rhesus monkeys. Each point represents the average of three monkeys.

Opiate derivatives which have comparable potencies disrupting operant behaviors in both dependent and nondependent monkeys (Figure 5) belong to a third category. Two conditions could explain this phenomenon: For a mixed agonist-antagonist, behavioral disruption may have been produced in the nondependent monkeys by the narcotic agonist properties, whereas the same behavior was disrupted in the dependent animals by the narcotic antagonist properties (precipitated abstinence). Both properties are expressed at the same dose range so that the dose-response curves appear similar, although the mechanisms of action were different. Both butorphanol and nalbuphine are mixed agonist-antagonists with relatively weak antagonist potencies. The similarity of the dose-response curves may reflect their coincidental balance of the two properties. Ketazocine and ethylketocyclazocine, on the other hand, are known to have very weak antagonist activities. Both compounds have been found neither to suppress nor to precipitate abstinence syndromes in chronic spinal dogs (Martin et al. 1976) or rhesus monkeys (Woods et al. 1979), both made dependent on morphine. A kappa-type narcotic receptor distinct from the morphine (mu)-type was postulated to mediate the CNS effects of these two compounds. Results in this study are consistent with this explanation in that the behavioral depressant effects of ketazocine or ethylketazocine in the monkeys did not undergo cross-tolerance to

etonitazene as did other narcotic agonists. The possibility that butorphanol and nalbuphine may also possess this property in addition to their narcotic antagonist activities should also be considered.

REFERENCES

Carroll, M.E., and Meisch, R.A. Etonitazene as a reinforcer; oral intake of etonitazene by rhesus monkeys. Psychopharmacology, 59: 225-229, 1978.

Deneau, G.A., and Seevers, M.H. Evaluation of morphine-like physical dependence in the rhesus monkeys (Macaca Mulatta). Proc. Committee on Drug Addiction and Narcotics, 23rd Meeting, Addendum, 1962.

Gellert, V.F., and Holtzman, S.G. Development and maintenance of morphine tolerance and dependence in the rat by scheduled access to morphine drinking solutions. J Pharmacol exp Ther, 205:536-546, 1978.

Martin, W.R., Eades, C.G., Thompson, J.A., Huppler, R.E., and Gilbert, P.E. The effects of morphine- and nalorphine-like drugs in the non-dependent and morphine-dependent chronic spinal dog. J Pharmacol exp Ther, 197:517-532, 1976.

Villarreal, J.E., and Karbowski, M.G. The action of narcotic antagonists in morphine-dependent rhesus monkeys. Narcotic Antagonists Adv Biochem Psychopharm, 8:273-289, 1973.

Woods, J.H., Smith, C.B., Medzihradsky, F., and Swain, H.H. Preclinical testing of new analgesic drugs. Mechanisms of Pain and Analgesic Compounds. New York: Raven Press, 1979. 429 pp.

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Dependence Potential of Buprenorphine Studied in Rhesus Monkeys

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Buprenorphine hydrochloride is an analgesic developed by Reckitt & Colman, U.K.

The drug is an opiate partial antagonist having a high affinity for opiate receptors and is known to exhibit a strong and relatively long-lasting analgesic effect in animals and man.[1,2] Specifically, the analgesic effect in man is approximately 30 times that of morphine, while the effects of the drug continue longer than those of equipotent doses of morphine, pethidine, or pentazocine.[3] At the same time, the drug is a potent opiate antagonist, the effect of which is reported to be nearly equal to that of naloxone.[1]

METHODS

Experiment 1. Gross observation of the acute CNS effects of buprenorphine in normal rhesus monkeys. Single doses of buprenorphine at 4, 15, 60 and 250 ug/kg, 1.0 and 4.0 mg/kg were intravenously administered to 2 monkeys per dose level. In addition, single doses of the drug at 15 and 250 ug/kg, and 1.0 mg/kg to 2 monkeys per dose level, and at 4.0 and 16.0 mg/kg to 4 monkeys per dose level, were administered subcutaneously.

Experiment 2. Effects of buprenorphine on the morphine withdrawal signs of mophine dependent rhesus monkeys. Single dosesofbuprenorphine at 1 and 16 mg/kg,morphine at 3 mg/kg, and codeine at 16 mg/kg to 2 monkeys each, and physiological saline at 0.5 and 5.0 ml/kg to 1 monkey each as control, were subcutaneously administered in monkeys showing intermediate-grade withdrawal signs after having been made physically' dependent on morphine by repeated subcutaneous injection of morphine HCl at 3 mg/kg 4 times daily (roughly every 6 hr) and then withdrawn for 13-14 hr. The withdrawal signs were observed for during 2 hr following administration.

Experiment 3. Precipitation of withdrawal signs by single adninistration of buprenorphine in morphine-dependent rhesus monkeys. Using 8 of the morphine-dependent monkeys employed in experiment 2, single doses of buprenorphine at 15 and 60 ug/kg, pentazocine at 4.0 mg/kg, and physiological saline were subcutaneously administered to 2 monkeys each at 2 hr after their regular dosing of morphine, and the precipitation of morphine withdrawal sighs and their severity were observed for during 1.5-2.5 hr following adninistration.

Experiment 4. Physical dependence test in normal rhesus monkeys by repeated subcutaneous adninistration of buprenorphine. Buprenorphine at 1.0 mg/kg was subcutaneously administered to 4 normal monkeys 4 times daily (roughly every 6 hr) for 31 days. After a final administration at 1:00 pm on day 32, withdrawal observation was conducted for 5 days. Starting on day 36, the same pattern of repeated administration at 1.0 mg/kg was resumed for 31 days, and a second 5 days of withdrawal observation was begun after the final administration at 1:00 pm on day 67. Precipitation of withdrawal sighs by subcutaneous adninistration of naloxone at 1 mg/kg 2 hr after the 1:00 pm dosing of buprenorphine on days 14, 28, 49, and 63 was tried.

Experiment 5. Intravenous cross self-administration of buprenorphine with lefetamine and physiological saline in experienced rhesus monkeys. The course of the experiment followed a pattern of 4-hr daily self-administration sessions with the drug to be self-administered changing every 3 days; first, 3 sessions with the standard reinforcing drug lefetamine (SPA: 1-1, 2-diphenyl-dimethyl-aminoethane HCl) at a unit dose of 0.1 mg/kg; next, 3 sessions with physiological saline; and finally, 3 sessions with buprenorphine. The whole 9-session course was repeated 4 times with a different unit dose tested for buprenorphine each time, namely 0.25, 1, 4, and 15 µg/kg.

Experiment 6. Continuous intravenous self-administration of buprenorphine in rhesus monkeys. Using 2 monkeys each with and without previous experience in such experiments, self-administration of buprenorphine under the FR 1 schedule was observed. The unit dose of buprenorphine was shifted every 24 weeks upon necessity from among the doses of 4, 15, and 60 µg/kg/inj. Since monkey No. 983 failed to initiate active intake of the drug during this stage, timer-programmed forced adninistration of the drug every 2 hr at a unit dose of 60 g/kg/inj was performed for 2 weeks while self-administration was observed during and after this period.

Experiment 7. Progressive ratio test of intravenous self-administrtaion of buprenorphine and pentazocine. Four monkeys were trained ahead of time to self-administer lefetamine under a schedule of FR 100. The experiment consisted of 6 trials with each monkey, each trial beingmadeupof 7 days of responding under FR 100 and 1 progressive ratio trial beginning with self-administration at FR 100 followed by increase of this ratio by a

factor of $\sqrt[4]{2}$ for each succeeding drug administration until the monkey ceased attempting toobtainthe drug as determined by the criterion that the number of lever presses during the final 48 hr failed to surpass 50% of the number required for the previous administration, or that no administration had taken place during 72 hr, at which point the number of presses required for the final delivered administration was taken as the score for the trial. The order and type of trial in each monkey is shown in Table 4, where trials 1 and 6 are for saline, while trials 2-5 are for buprenorphine at 15 or 60 µg/kg or for pentazocine at 60 or 250 µg/kg. During all trials, 15 min of time-out followed each drug administration under either condition.

RESULTS

1. Acute CNS effects of buprenorphine in normal rhesus monkeys. Immediately after intravenous injection of 4 mg/kg, both monkeys showed depressed breathing and somewhat asthenic body posture while sitting on the perch. From several minutes after injection, eyes were half-closed, often closed, and when not closed the animals would stare fixedly while holding anunchangingposture, or engage in incessant skin scratching. This condition continued for about 3 hr. The dose level at each succeeding observaticn was l/4 of the previous, down to 4 µg/kg, with the overall result that eye-closing was seen at mg/kg as well, and decrease in responsiveness to man or other monkeys as well as to audio stimuli was found at doses of 15 µg/kg or more. At 4 µg/kg, only slightly increased skin-scratching was seen.

Subcutaneous adninistration of the drug produced nearly the same effect as intravenous. That is, skin-scratching and decreased responsiveness were seen at doses of 15 µg/kg or more. While at 1 and 4 mg/kg, eye-closing and marked depression were noted. Beyond this, at 16 mg/kg, such signs of motor impairment as loss of footing fmn the perch were also seen. The duration of the drug effect was slightly longer than for intravenous adninistration

2. Effect of buprenorphine on the morphine withdrawal signs. In morphine-dependent and withdrawn monkeys showing intermediate-grade signs, injection of 1 or 16 mg/kg of buprenorphine tended to worsen rather than suppress the signs. In contrast, 3 mg/kg of morphine as well as 16 mg/kg of codeine administered subcutaneously clearly suppressed the withdrwal signs.

3. Precipitation of withdrawal signs by single administration of buprenorphine. Within 30 min after subcutaneous injection of buprenorphine, withdrawal singsofthe intermediate gradewith 15 µg/kg and of the severe grade with 60 µg/kg were observed. Administration of pentazocine at 4 mg/kg produced withdrawal signs of approximately identical severity to those produced by 15 µg/kg of buprenorphine.

4. Physical dependence test in normal rhesus monkeys. Upon repeated administration of buprenorphine 1.0 mg/kg s.c., the depressant effects gradually weakened and, except for the skin scratching, almost completely disappeared by 2 weeks after the start, showing the development of tolerance.

In the naloxine tests on days 14 and 28, monkeys transiently exhibited the signs of abnormal posturing and restlessness, but as autonamic nerve manifestations and nervous irritibility were not present, these would be considered atypical as morphine-type withdrawal signs. During the 5-day natural withdrawal observation starting on day 32, no signs judged to be withdrawal signs were observed.

In the second 31 days of administration from day 36, no signs of drug effects other than slight weight loss in all 4 monkeys was noted. The withdrawal signs were not especially stronger than before in either naloxone test, and no withdrawal signs of any drug type noted during the final natural withdrawal test (Table 1).

Table 1. Development of Physical Dependence by Repeated Administration of Buprenorphine

Monkey	Body weight (kg)					Grade of withdrawal signs					
						Naloxone test (day)				Withdr. test	
	Initial	28th day	1st withdr.	63rd day	2nd withdr.	14th	28th	49th	63rd	1st	2nd
896	4.7	4.8	4.8	4.7	4.45	Mild	Mild	Mild	Mild	None	None
988	4.8	5.05	4.8	4.7	4.65	None	Mild	None	Mild	None	None
997	3.8	3.8	3.6	3.55	3.45	Mild	Mild	Mild	Mild	None	None
1008	4.75	4.65	4.4	4.35	4.1	None	Mild	Mild	Mild	None	None

5. Intravenous cross self-administration of buprenorphine with lefetamine and saline. The highest intake rates for buprenorphine were at 1 μg/kg/inj in 3 monkeys and 4 μg/kg/inj in the other 3. In spite of the large individual variation. a significant increase over the rates for saline was recognized at both doses (Table 2).

Table 2. Intravenous Cross Self-administration of Buprenorphine

Monkey	Average daily No. of self-administ. (4 hrs/day)	Percent ratio of self-administration rate, lefetamine as 100%				
	Lefetamine	Saline	Buprenorphine (μg/kg)			
	0.1(mg/kg)	0.25(ml/kg)	0.25	1	4	15
No. 634	107±17.2	14.6%	-%	53.3%	66.1%	40.5%
No. 838	162.3±23.4	3.0	-	10.5	20.9	14.4
No. 931	140.4±44.3	3.4	6.9	94.0	30.8	19.2
No. 981	168.6±28.2	3.6	-	16.6	48.6	7.9
No. 989	93.2±11.8	6.2	31.1	38.6	12.6	8.3
No.1002	102.3±18.2	19.6	-	42.0	24.4	28.6
Mean±S.D.		8.4±6.4	19.0±17.1	42.5±29.9	33.9±19.9	19.8±12.7

* : $P < 0.05$ against saline

6. Continuous intravenous self-administration of buprenorphine. The experiment was initiated in experienced monkeys, and because self-administration of the drug was clear in spite of individual difference, the experiment was repeated in the 2 naive monkeys. Again, both monkeys showed self-administration although No. 963 initiated only after the -forced administration (Table 3).

During the periods of buprenorphine intake, the monkeys exhibited some lessening of voluntary movement and decrease in responsiveness to the observer, but without marked depression or change in general physical condition. No clear withdrawal signs were noted during the saline period following active drug intake.

Table 3. Average Daily Number of Injection in continuous Intravenous Self-administraton of Buprenorphine

S: Saline, B: Buprenorphine, Dose: μg/kg/injection, (): period-2weeks each unless indicated

No. 808[a] F 4.3kg	S 3.0	B - 4 5.2	25.4	17.0	S(2 days) 1st:15 2nd:12	B - 15 12.9	13.7	B - 60 17.9	11.1	S(lw) 10.3		
No. 983[b] M 4.1kg	S 0.3	B - 4 0.4	B - 15 1.7	0.3	B - 60 0[c]	45.1	55.0	S(2 days) 1st:7 2nd:3	B - 60 37.3	23.8	S(lw) 2.3	
No.1018[a] F 4.6kg	S 4.1	B - 4 45.4	70.9		S(2 days) 1st:38 2nd:53	B - 15 82.6	57.4	72.7		S(lw) 38.7		
No.1045[b] M 5.2kg	S 3.9	B - 4 6.1	B - 15 5.2		B - 60 29.9	40.1	S(2 days) 1st:34 2nd:12	B - 60 41.9	39.4	S(lw) 4.1		

a) Experienced monkeys. b) Naive monkeys.
c) Programmed administration added at 60 μg/kg/inj. every 2 hours for 2 weeks.

7. Progressive ratio test of intravenous self-adninistration of buprenorphine and pentazocine. In contrast to the results with saline, comparatively large scores were obtained in the following trials for buprenorphine and pentazocine (Table 4). Specifically, all monkeys showed higher swres for the larger unit dose of pentazocine, while with buprenorphine, 3 out of 4 animals showed higher scores for the lower unit dose of 15 μg/kg/inj.

Table 4. Results of Progressive Ratio Test

Monkey	Saline 0.25ml/kg	Pentazocine(mg/kg) 0.06	0.25	Buprenorphine(mg/kg) 0.015	0.06	Saline 0.25ml/kg
No. 966(male)	100[1]	950[2]	1130[3]	1600[4]	950[5]	200[6]
No.1025(male)	100[1]	670[5]	6400[4]	1130[2]	2690[3]	120[6]
No.1029(female)	120[1]	570[2]	3200[5]	3810[4]	670[3]	1130[6]
No.1037(female)	170[1]	3200[5]	6400[4]	1350[3]	950[2]	1350[6]

The ratio attained for the last dose in the progressive ratio period. Trial order in each monkey indicated by numbers within brackets.

DISCUSSION

Tolerance and physical-dependence potential. Repeated administration of buprenorphine to rhesus monkeys showed that within 2 weeks the depressant effects as seen in the gross behavior of the monkeys became weak. In the self-adninistration experiment as well, the effects observed in the animals became less clear after the early stage, so that here as well the development of tolerance could be recognized. It has been reported that,while development of physical dependence on the drug has not been observed in the various animal studies performed to date[4,5]), weak withdrawal signs were observed during the withdrawal period in man[6]). In the present study, no cross-physical dependence to morphine was observed in the suppression test and no withdrawal sign was observed even in the second natural withdrawal test, but some minor atypical withdrawal sighs were precipitated in the naloxone tests which did not exhibit any strengthening in the sewnd test. Thus, from these results it remains unclear whether the drug possesses a morphine-like physical dependence potential or not, but even should there prove to be such a potential, it would have to be a very weak and prectically negligible one.

Reinforcing effect. In the intravenous cross self-administration experiment with lefetamine, buprenorphine was found to have clear reinforcing effect at the unit-doses of 4 μg/kg/inj or more. In the continuos self-adninistration experiment also, all 4 monkeys self-acbninistered the drug. In the progressive ratio test it was found that, in terms of the highest scores regardless of dose, 2 out of 4 monkeys scored higher on either drug. However, the monkeys showing the high swres of 6400 each for pentazocine respectively scored only 2690 and 1350 for buprenorphine, while on the other hand, the monkeys with higher buprenorphine scores respectively achieved 3810 and 1600 for buprenorphine versus 3200 and 1130 for pentazocine. These results my indicate that the reinforcing efficacy of buprenorphine is not as high as that of pentazocine.

Dose level and gross behavioral manifestations during the continuous self-adninistration experiment. The highest daily dose of buprenorphine self-administered by any monkey in any 2-week period during this experiment was 3.3 mg/kg, intaken by one of the naive monkeys (No. 983), while the highest daily doses self-administered by the other monkeys were 2.51, 1.24, and 1.07 mg/kg/day. These figures show a relatively wide individual variation in the average daily dose level but fall within a non-lethal dose range even if intravenously injected all in one dose. This may be attributed to be an extremely wide safety margin of buprenorphine in spite of the fact that its effects are produced even at very small doses. In addition, the fact that the monkeys, even though actively taking the drug, did not at any time self-administer the drug in excess of the tolerable dose level may be worthy of attention. Likewise, no monkey during self-administration exhibited

marked depression or stimulation, nor were any acute toxic manifestations noted. Taking these facts into consideration together with the result that the drug's reinforcing efficacy appearedtobe not so high, it is assumed that the psychological dependence potential of buprenorphine may be lower than that of pentazocine.

REFERENCES

1. Cowan, A., Lewis, J. W. and Macfarlane, I. R. Agonist and antagonist properties of buprenorphine, a new antinociceptive agent. Br J Pharmac 60:537-545, 1977.

2. D&kin, A. B., Esposito, B. and Philibin, C. Double-blind evaluation of buprenorphine for post-operative pain. Canad Anaesthetises' J 24:195, 1977.

3. Hovell, B. C. Comparison of buprenorphine, pethidine and pentazocine for the relief of pain after operation. Brit J of Anaesthesia 49:913, 1977.

4. Cowan, A. Evaluation in nonhuman primates evaluation of the physical dependence capacities of oripavine-the baine partial agonists in patas monkeys. Adv in Biochem Psychoph-armacology 8:427, 1974.

5. Martin, W. R., Eades, C. G., Thompson, J. A., Huppler, R. E. and Gilbert, P. E. The effects of morphine and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. J pharmacol Exp Ther 197:517-532, 1976.

6. Jasinski, D.R., Pevnick, J. S. and Griffith, J. D. Human pharmacology and abuse potential of the analgesic buprenorphine. Arch Gen Psychiatry 35:501-516, 1978.

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Development of Selective Tolerance to Particular Types of Opiate Receptors

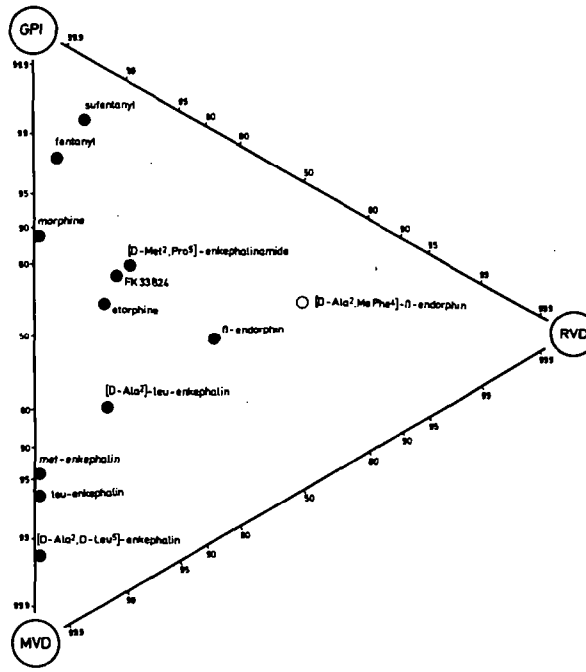
A. Herz, R. Schulz, and M. Wuster

The observation that certain opiates were unable to suppress the manifestation of morphine abstinence in the chronic spinal dog preparation led to the concept of multiple opiate receptors (Martin et al. 1976). This concept has subsequently been supported by the results of a number of in vitro binding studies, whith have demonstrated the existence of a heterogeneity of opioid binding sites within the central nervous system (CNS) (Chang and Cuatrecasas 1979; Robson and Kosterlitz 1979; Chang et al. 1980; Pasternak 1980; Snyder and Goodman 1980) and, most convincingly by the use of opioid-sensitive peripheral tissue preparations (Lord et al. 1977; Leslie and Kosterlitz 1979; Leslie et al. 1980; Hughes 1981). These latter studies were performed mainly upon the guinea-pig ileum preparation (GPI), which contains predominantly receptors which mediate the action of morphine-like compounds ('μ-receptors'), and the isolated mouse vas deferens (MVD) which displays a relatively higher sensitivity to enkephalin than to morphine and has, thus, been considered as a δ-receptor preparation (Lord et al. 1977).

It was recently discovered that the vas deferens of-the rat (RVD), which is almost insensitive to both morphine and enkephalin, is quite sensitive to ß-endorphin. This led to the suggestion of the term ε-receptor for this novel type of opiate receptor (Schulz et al 1979; Wuster et al. 1979).

The data obtained from these three different preparations (GPI, MVD, RVD) are incorporated into the framework of figure 1. The position of a compound in the triangle reflects its preferential interaction with the particular receptor type. Accordingly, the position of [D-Ala^2,D-Leu^5]-enkephalin (DADL) at 99.1 percent on the lower part of the MVD-GPI axis represents a 99.1

FIGURE 1



Relative potencies of various opioids in inhibiting electrically induced muscle contraction in the isolated myenteric plexus-longitudinalmuscle preparation of the guinea-pig ileum (GPI), the mouse vas deferens (MVD) and the rat vas deferens (RVD). The compounds are arranged in the triangle according to their potencies on the various preparations. The sides of the triangle represent relative potencies expressed on a percentage scale. To represent small differences between compounds a probit scale is employed for graduation (see Wuster et al 1979).

percent selectivity of the compound for the MVD and a 0.9 percent selectivity for the GPI. ß-Endorphin, located approximately in the center of the triangle has an about similar activity in all three preparations (for details see Wuster et al. 1979, 1980).

The interpretation of the data derived from the results obtained upon these in vitro preparations might be complicated by the possible heterogeneity of opiate receptors in the particular preparations. It has indeed previously shown by means of the technique radioreceptorassay that the MVD also contains p-receptors in addition

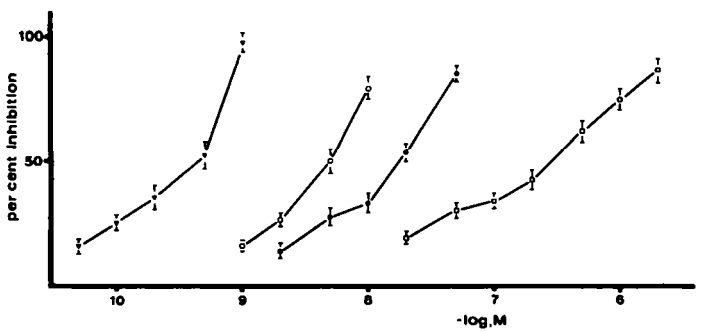
to δ-receptors (Leslie et al. 1980).

If a multiplicity of opiate receptors implies the independent occurrence of Certain receptor types, an essentially different approach to the study of these receptors may be achieved by means of their chronic activation proposed by Martin et al (1976). A prolonged selective activation of a particular receptor population should then induce the development of tolerance and dependence in only this specific population, leaving other opiate receptor types unaffected. It was expected that the MVD would provide a suitable preparation for the testing of this hypothesis.

Mouse vas deferens

Mice were chronically treated with particular opiate receptor agonists, e.g. the specific δ-receptor agonist DADL and the μ-receptor agonist sufentanyl (SUF). Long-term infusion of these drugs was accomplished by means of subcutaneously implanted minipumps. After 6 days infusion, the isolated vasa were set up in solutions containing concentrations of the respective drug appropriate to the maintenance of tolerance (Schulz et al. 1980a, b).

FIGURE 2



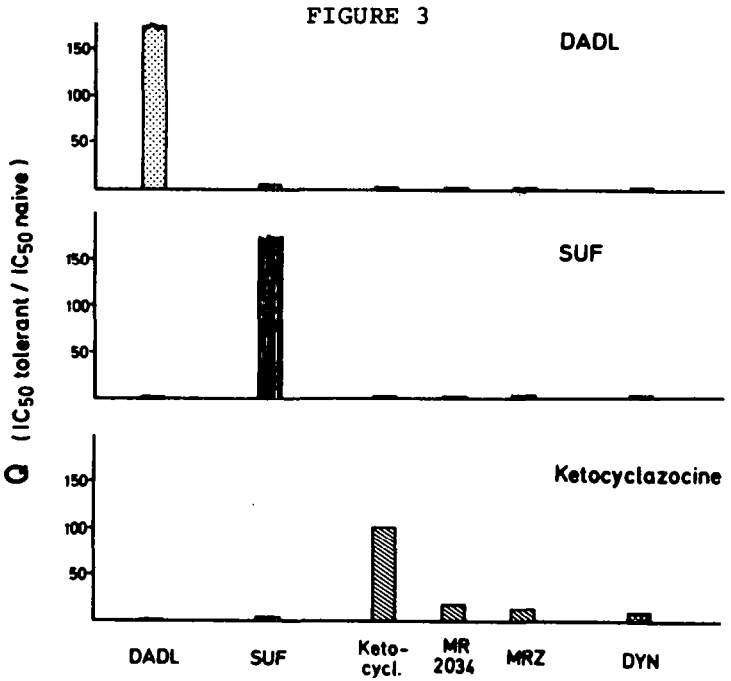
Dose-response curves for [D-Ala^2,D-Leu^5]-enkephalin (DADL) on the electrically stimulated isolated mouse vas deferens.
Data are for preparations from untreated mice (▼) and from mice infused with 0.5 g DADL per h (○) 1.5 g per h (●) and 5 g per h (□) for 6 days.

Figure 2 represents the dose-response curves of the vasa deferentia of these chronically treated mice for DADL in comparison to those obtained from vasa of naive mice. There is a tremendous shift of the dose-response curve to the right, indicating an about 800-fold degree of tolerance, whereas the dose-response curve- for SUF remains largely unchanged. In contrast, continuous infusion. Of the animals with SUF induced an about 1000-fold tolerance without changing sensitivity to DADL. The question arises whether the occurrence of further receptor types can be demonstrated in the MVD.

Figure 3 depicts the extension of this type of experiment in which, in addition to SUF and DADL, various κ-agonists (ketocyclazocine, MR 2034 and MRZ) were chronically applied by minipumps (Wuster et al. 1981); the vasa of these differently treated mice were then tested with the various opioids. The degree of tolerance revealed in these experiments is expressed as a quotient Q reflecting the ratio of the inhibitory dose for 50 percent inhibition (ED_{50}) of the tolerant preparation in comparison to the ED_{50} of the naive preparation. The higher this quotient, the higher the degree of tolerance. DADL-infused mice exhibit a high degree of tolerance when tested with DADL, but no cross-tolerance to SUF and various κ-agonists. SUF-infused mice lack cross-tolerance to both DADL and to κ-agonists. The various κ-agonists employed here also do not show cross-tolerance to SUF and DADL. Within this κ-group, however, varying degrees of cross-tolerance are seen, indicating that these κ-agonists themselves are not homogeneous. Interesting are the results obtained when these various preparations are tested with dynorphin (DYN), a recently detected opioid peptide exhibiting particularly high potency. There is no cross-tolerance either to μ- and δ-agonists. Summing up these data, the presence of at least three types of opiate receptors in the MVD - with these types not necessarily homogeneous with reference to κ-agonists - is indicated. There is an indication that the μ-receptors are also not an uniform population.

The question as to the mechanism this underlying selective tolerance arises. Attempts to resolve the question whether this high degree of tolerance is accompanied by changes in the number of binding sites for the particular ligand are hampered by methodological difficulties. Preliminary results seem to support the notion that this tolerance is not associated with a loss of specific opioid binding sites. Interestingly, in these highly tolerant preparations, naloxone completely failed to precipitate a withdrawal sign (Schulz et al. 1980b). This may be interpreted as an indication that the adaptational changes take place at the level of the opiate receptor and not at subsequent steps in the effector

FIGURE 3



Tolerance and cross-tolerance produced by different opiate receptor agonists in the mouse vas deferens. The degree of tolerance measured by calculating the quotient (Q) of the IC_{50} values of tolerant and naive preparations is plotted on the ordinate. Q = 1 indicates lack of tolerance. The drug chemically infused is indicated in each panel. Abscissa: Opioids tested for tolerance and cross-tolerance. Each column represents the quotient of the IC_{50} values of 6 experiments.

system. In this context, it seems to be important to note that the MVD does not contain somata and the receptors are located exclusively at the nerve terminals. This observation may be of significance since preparations where tolerance is accompanied by dependence, expressed as withdrawal signs do apparently contain somata.

Guinea-pig ileum

There are certain data indicating that the longitudinal muscle-myenteric plexus of the guinea-pig ileum ("strip") does not represent a pure μ-receptor preparation, but also contains κ-receptors while the possible presence of functional δ-receptors remains an open question (Leslie et al. 1980). In view of the fact that this

preparation develops tolerance which appears to be correlated with the development of dependence (Schulz and Herz 1976; Herz and Schulz 1979), it was of particular interests to investigate whether selective tolerance to various opioid agonists can be demonstrated in this preparation, too.

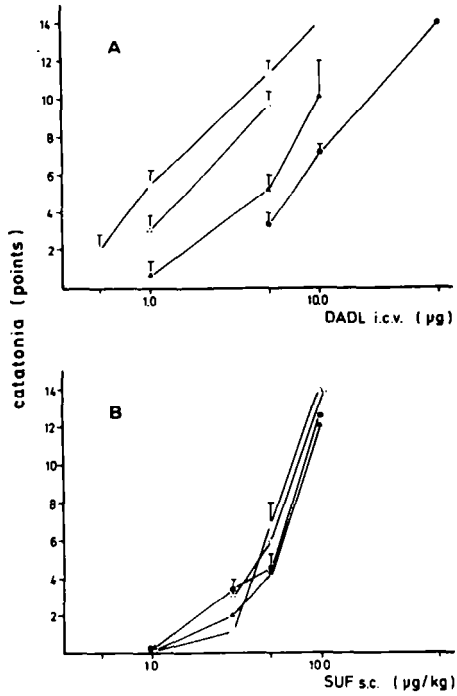
Guinea pigs were rendered highly tolerant by continuous infusion of various opioids via osmotic minipumps (a few compounds i.e. morphine, ethylketocyclazocine, which were not sufficiently soluble in water, were administered via subcutaneously implanted pellets). After 5 days, the "strip-preparations" were set up in solutions containing concentrations of the respective drug appropriate to maintain tolerance.

The development of tolerance selective to various opioid agonists, as was seen in the mouse vas deferens, was observed. There were, however, some remarkable differences. When strips obtained from guinea pigs chronically infused with fentanyl were tested against a series of opioid agonists, a high degree of cross-tolerance between various μ- and δ-agonists was evident, whereas the sensitivity to the various κ-agonists remained largely unchanged. Very similar results were obtained in DADL-infused guinea pigs. The various κ-agonists revealed a varying degree of cross-tolerance to μ- and δ-agonists. From this still incomplete data, it emerges that various types of opiate receptors, which can independently develop quite high degrees of tolerance, are present in the strip-preparation. It may be expected that a detailed investigation of the withdrawal precipitable in these preparations, showing selective tolerance to the various agonists, may reveal information as to how far the various receptors participate in the development of physical dependence.

Central nervous system

A similar approach was adapted for the investigation of the central nervous system (Schulz et al 1981). In rats, SUF was continuously infused by subcutaneously implanted osmotic minipumps and DADL by minipumps which delivered the drug directly into the 3rd ventricle. After 5 days, analgesia (vocalization response after electrical tall stimulation) and catatonia (estimated according to a scoring system) was tested by evaluation of dose-response curves for DADL (i.c.v. injection) and SUF (s.c. injection). There was a clear separation of the development of the tolerance to the particular drugs. As an example, figure 4 shows that DADL-infused rats developed a more than 10-fold tolerance for catatonia when tested with DADL, but not when tested with SUF. An opposite. pattern of results, was obtained in SUF-infused

FIGURE 4



Dose-response curves for the catatonic effect of [D-Ala^2,D-Leu^5]-enkephalin (DADL) (A) and sufentanyl (B) in control rats (0, saline-infused) and rats chronically infused with 5 µg DADL per hour (Δ), 10 g/h. (▲) and 50 g (●) for 7 days.

rats: 10-fold tolerance when acquired with SUF, lack of tolerance when tested with DADL. In principle, similar results were obtained for analgesia - although in this case, the separation of the effects induced by both drugs was somewhat smaller.

Thus, these experiments show that selective tolerance to various agonists may be developed in the central nervous system. It is, on the other hand, interesting to note that identical (or at least similar) effects, e.g. analgesia, may be obtained by activation of different types of receptors. This contrasts to some extent to some recent results which claim a close relationship between analgesia and µ-receptor activation (Goodman and Snyder 1980); they are, however, in accord with the recent findings showing that the primary afferent fibres

to the dorsal horn which carry nociceptive information contain μ- as well as δ-receptors (Fields et al. 1980). Much more work is, however, needed in order to get more convincing results for the highly complex central nervous system. There is no information available as to whether the withdrawal in rats, showing selective tolerance to the specific reseptor ligands, differ from each other.

Concluding Remarks

The significance of studies concerning the development of selective tolerance to different opioid receptor agonists in view of a differentiation of various types and subtypes of opiate, receptors is quite evident. Studies along this line may also offer a promising approach to an understanding of the problems related to the development of tolerance/dependence and the mechanisms underlying these phenomena. Answers to the questions as to tolerance and dependence are separable under certain conditions or whether effects mediated by different types of opiate receptors underly different adaptational changes, upon chronic drug supply may be answered by this methodology.

REFERENCES

References will be furnished upon request.

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Is Drug Abuse Treatment Effective?

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INTRODUCTION

The effectiveness of drug abuse treatments has been challenged in the popular and professional literature and by recent Federal funding decisions. Yet few evaluation studies have adequately assessed the effectiveness of these treatments using an appropriate range of reliable outcome measures, a representative sample of treatment modalities, or more than one perspective on treatment effectiveness. The present paper examines substance abuse treatment effectiveness from five perspectives, using a sample of 282 patients treated in 3 programs and evaluated at six month follow-up. The five areas examined include:

1. Do patients improve following treatment?
2. Are improvements confined to drug use, or more pervasive?
3. What are the sizes of these improvements in standardized terms?
4. How do these improvements compare with those from other treatments?
5. Are these improvements due to treatment?

Due to space limitations, only a summary of some of the salient findings will be presented. A more detailed account of the methodology and results for both our drug-abusing (N=282) and alcoholic (N=460) populations is available, from the senior author.

METHOD

Subjects - All male veterans who were admitted for drug abuse treatment at either the Coatesville or Philadelphia VA Medical Centers during 1978 were eligible for the study, There were no significant differences in demographic or background characteristics between patients in the two hospitals, and approximately 90 percent of all subjects *were* Philadelphia residents. There were no treatment admission criteria other than eligibility for veterans' benefits.

We initially evaluated 325 male veterans who were admitted to the three drug abuse rehabilitation programs at the Coatesville or Philadelphia VA Hospitals during 1978, and who remained in rehabilitation treatment at least five inpatient days or five outpatient visits. We were able to contact approximately 89 percent of the remaining patients six months after admission to treatment, thus, complete data were available on 282 subjects.

Treatment Programs - The drug abuse treatment network of the Veterans Administration in the Philadelphia area consists of 2 inpatient programs at the Coatesville VA Medical Center, plus an outpatient methadone clinic at the Philadelphia VA Medical Center. Patients were assigned to one of the rehabilitation programs on the basis of their personal requests, the clinical judgement of the admitting staff, administrative considerations such as bed census or patient visit criteria, and simple chance.

PROCEDURE

Admission - The admission and follow-up evaluations were based upon data from the Addiction Severity In&x (ASI) (McLellan et al. 1979). The ASI is a structured, 30-40 minute, clinical research interview designed to assess problem severity in six areas commonly affected by addiction. These areas include medical, legal, substance abuse, employment, family, and psychological problems. In each of the areas, objective questions are asked measuring the number, extent, and duration of problem symptoms in the patient's lifetime and in the past 30 days. The patient also supplies a subjective report of the recent (past 30 days) severity and importance of the problem area. The interviewer assimilates the two types of information to produce a rating (0-9) reflecting the extent to which treatment is needed by the patient in each area. These 10-point ratings have been shown to provide reliable and valid general estimates of problem severity for both alcoholics and drug addicts (McLellan et al. 1979), and the individual items offer a comprehensive basis for clinical and experimental assessment at the time of admission to treatment and at subsequent evaluation periods.

Follow-up - All follow-up evaluations were done through ASI interviews between an independent research technician and the patient, either in person or over the phone. No information from secondary sources was used and all data were closely monitored to preserve confidentiality. The validity of these data were of particular concern in this study and are discussed separately (McLellan et al. in press). The reader is referred to that source in the interests of space limitations.

Outcome Criteria - It was important for the aims of this study to have general measures of treatment outcome, since single- item measures can be inherently unreliable. We-therefore constructed criterion composites from sets of single items within each of the problem areas. Several items from each problem area were intercorrelated to exclude those which were unrelated, and the remaining items were standardized and tested for conjoint reliability. A set

TABLE 1

ADMISSION TO SIX-MONTH FOLLOW-UP CHANGE
IN MALE DRUG ABUSE PATIENTS

N=			282	
CRITERIA[a]	ADM.		6-MO.	D[b]
MEDICAL COMPOSITE	9.4		7.0	.08
Days Med. Probs.	8		5	.14
EMPLOYMENT COMPOSITE	12.1	**	-2.9	.60
Days Worked	3	**	11	.57
Money Earned	80	**	309	.43
ALCOHOL COMPOSITE	18.1	*	13.4	.26
Days Drinking	8		7	.14
Days Drunk	5	*	3	.23
DRUG COMPOSITE	27.2	**	5.8	.81
Days Opiates	12	**	4	.59
Days Depressants	5	*	2	.26
Days Stimulants	4	*	2	.17
LEGAL COMPOSITE	21.9	**	9.4	.48
Days Crime	9	*	3	.50
Illegal Income	394	**	91	.32
FAMILY COMPOSITE	14.2	**	9.6	.31
Days Family Probs.	10	*	6	.32
PSYCHOLOGICAL COMPOSITE	14.1	*	9.6	.34
Days Psych. Probs.	11	**	7	.28

* = $p < .05$
** = $p < .01$

[a]All criteria measured during 30 days prior to admission and six-month follow-up.

[b]D = Within-group effect size - .20 = Small change,
.50 = Moderate change,
.80 = Large change

of 3 to 5 objective items from each ASI problem area was selected using this procedure, and each set showed a standardized reliability coefficient of .73 or higher. Seven composites (medical problems, employment, drug use, alcohol use, legal status, family problems, and psychological function) were constructed in this manner and scores on each composite were calculated for all patients at admission and follow-up.

DISCUSSION

We examined the results of substance abuse treatment in a sample of male veteran alcoholics and drug addicts treated in our rehabilitation programs. Highly reliable composite measures were recorded at admission in seven areas commonly affected by addiction. These same measures were again recorded on an 89-percent follow-up sample, six months later by independent technicians. Results provided data on five different evaluation issues.

Do Patients Show Significant Improvement Following Substance Abuse Treatment? Based upon our within-group paired comparisons of admission and follow-up status (table 1), the answer is unequivocally "yes." Highly significant improvements were seen in both our composite criteria (indicating general problem status) and in the single- item measures.

Are Improvements Specific to Drug Use or More Pervasive? Results of both the within and between-group comparisons indicated significant improvements in most of the seven criterion areas. The most significant improvements were shown in the target area of drug use, but highly significant improvements were also shown in the areas of employment, legal, family and psychological status.

Perhaps the only clear exception to this general improvement was the area of medical status or physical health. We have no reason to believe that medical treatment was particularly poor for these patients but rather it is likely that many of the physical problems of these patients were underreported at treatment admission (due to the anaesthetic effects of drugs and alcohol) and that many of the medical problems which were reported by these, patients were chronic in nature, with little chance of significant remission.

What is the Magnitude of the Improvements? While tests for significance of difference measure the likelihood that a difference between two distributions of scores is due to chance, effect-size measures assess the amount of difference between the distributions. These effect-size measures are calculated in terms of the number of standard deviations (which can in turn be converted to Percentiles) between the admission and follow-up distributions and are presented in the last column of table 1.

As in the case of the paired t-test data, the greatest changes occurred in the target area of drug use but moderate to large changes also occurred in the areas of employment and legal status. In practical terms these improvements translated to a 67 percent

TABLE 2

	WITHIN-GROUP COMPARISONS						BETWEEN-GROUP COMPARISONS
	LONG-TERM 225			*SHORT-TERM* 57			
	ADM.		6-MO.	ADM.		6-MO.	POST ANCOVA[b]
MEDICAL COMPOSITE[a]	9.6		5.1	9.1		8.6	*
Days Med. Probs.	8		3	9		6	
EMPLOYMENT COMPOSITE	12.4	**	-2.7	11.6	**	-3.8	*
Days Worked	3	**	10	4	*	12	
Money Earned	88	**	341	77	**	268	*
Welfare	241	*	190	221	*	166	
ALCOHOL COMPOSITE	17.0	**	11.9	19.4		19.0	**
Days Drinking	8	*	5	9		11	**
Days Drunk	5	*	2	6		6	
Money for Alcohol	18	*	6	15		10	*
DRUG COMPOSITE	27.0	**	3.0	28.1	*	14.8	**
Days Opiate	13	**	3	11	*	7	**
Days Depressants	3	*	1	4		4	*
Days Stimulants	4	*	1	3		4	**
Money for Drugs	229	**	43	249	**	171	**
LEGAL COMPOSITE	20.1	**	3.0	22.8		23.2	**
Days Crime	10	*	1	7		8	*
Illegal Income	309	**	23	526	*	186	*
FAMILY COMPOSITE	15.1	*	9.4	9.6		9.7	*
Days Fam. Probs.	11	*	3	8		8	*
PSYCHOLOGICAL COMPOSITE	14.2	**	8.4	13.9	*	11.8	*
Days Psych. Probs.	11	*	7	12	*	7	

* = $p < .05$
** = $p < .01$

[a]All criteria were measured during 30 days prior to admission and prior to six-month follow-up.

[b]Covariates were age, race # prev. treatments, pretreatment score.

reduction in opiate use, a 50 percent reduction in stimulant tie, a 67 percent decrease in crime days and a 386 percent increase in earned income. Thus, the evidence here and from other studies suggests that the major improvements following drug abuse treatment are in illicit drug use but that there are several other areas which show moderate to major changes.

How Do Substance Abuse Treatments Compare With Other Psychological Treatments? A meta-analysis comparison of treatment effect-sizes was performed between the fully treated groups of the present study and data from Smith and Glass' (1980) study of 475 psychotherapy studies. Our drug abuse treatment effects were comparable to those shown by studies of professional psychotherapy in the criterion areas of drug use, employment, and legal status. However, the overall levels of treatment effect-sizes were generally higher in the psychotherapy treatments .

It seems likely that these differences are due in part to the tire specific orientations of substance abuse treament, in part to differences in the level of training between the therapists, and in part to differences in control groups. As indicated, the primary therapists in the present study were technicians doing rehabilitation counseling, while the majority of psychotherapy studies used doctoral- level therapists.

Is Patient Improvement Due to Treatment? We recognized that despite the significant improvements shown, there was no clear evidence that the changes were due to the treatment process. We had some indication that greater amounts of treatment were associated with better outcomes, but in order to evaluate this issue more closely we required an appropriate control group. In an attempt to provide such a group, we selected all subjects from our population who had received more than five but less than fifteen days of rehabilitation treatment and had received a favorable discharge.

These "shortterm" patients were not assigned to this group in a random manner. However, in several respects, this group provides an appropriate and conservative comparison. First, although the treatment assignments of the long and shortterm patients were not random, they were made on an equal basis. All patients were assigned to treatment on the basis of their personal requests, bed availability and other administrative factors. Since the distribution of treatment program assignments was not significantly different between the longterm and the shortterm patients, it is not possible to argue that the ST patients had entered into less-favored treatments or were assigned differently.

It is possible to argue that these shortterm patients had less motivation, thereby accounting for their shorter time in treatment. However, all ST patients completed five to fourteen days of rehabilitation therapy at their assigned program, Further, all had received favorable discharges, indicating that they had left with adequate discharge planning and were not ejected for disciplinary reasons. Finally, there was no evidence to suggest that these

patients had a poorer prognosis at the time of treament admission or at discharge. We cannot completely rule. out the possibility of differences in nwtivation between the two groups; however our prior work (Luborsky and McLellan, 1978; McLellan and Druley, 1977) has shown that neither staff nor patient ratings of motivation are systematically related to length of time in treatment or to type of discharge. We do not contend that the shortterm group is the optimum control group, only that it is a valid and unusually conservative comparison to the longterm group, providing a useful estimate of actual treatment effects.

The within-group comparisons of improvement in the LT and ST patients indicated more significant improvements, at higher levels of significance and at greater magnitude for the fully treated groups (see table 2). The between-groups analyses of covariance included adjustments for pretreatment differences in age, race, prior treatments and each admission criterion score, providing the most direct test possible of the extent to which greater treatment was associated with better outcome. The results from these analyses (last column, table 2) showed significantly better post-'treatment status in virtually all areas for the longterm patients. It is important to note that although the shortterm groups generally showed positive change, the longterm groups still showed significantly better outcomes and several large treatment effects in comparison. We would argue that these data provide a clear and valid demonstration of substance abuse treatment effectiveness. The important questions of cost-effectiveness and cost-benefit remain to be adequately assessed, and we will address these issues in future reports.

REFERENCES

Due to space limitations, a complete list of references may be obtained from the senior author.

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AUTHORS

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Withdrawal from Heroin in Three or Six Weeks: Comparison of LAAM Versus Methadone

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In this paper we abstract a clinical trial in outpatient detoxification with heroin addicts. A full report of the study will appear in the Archives of General Psychiatry, in an article of the same title.

One of the problems with drug treatment is that short-term detoxification is ineffective in encouraging heroin users to adopt a drug-free lifestyle, even though a three week time limit has been set by Federal law. Another problem is that outpatient detoxification programs require patients toattendaclinic everyday. There is some evidence that a longer detoxification may allow clients to give up opiates. In addition, a longer-acting opioid like levo-alpha acetylmethadol (LAAM) allow alternate-day clinic attendance. To sum up, both LAAM as an alternative to methadone and a withdrawal program longer than three weeks may be more useful than the standard 21-day methadone detoxification.

In this study 61 heroin addicts were randomized to one of four study groups: six weeks of LAAM, six weeks of methadone,three weeks of LAAM, or three weeks of methadone. The six-week procedures included three weeks of steady dosing before the dose decreased to zero. Outcome measures included length of stay in the program, use of illicit drugs, withdrawal symptoms, patient satisfaction, clinician ratings of global progress, and status at followup three months later.

As expected, subjects assigned to six weeks stayed in treatmnt longer, although subjects in the three-week LAAM group were most likely to stay until the end of active dosing. Most patients used heroin during treatmant,with few differences among experimental groups. Those assigned to six weeks were more likely to be opiate free in the third week of treatment. Comparisons among treatment groups on withdrawal discomfort showed no differences: Initial doses of LAAM suppressed withdrawal symptoms the same as initial doses of methadone, and withdrawal symptoms appeared in both LAAMM and methadone subjects at the end of dosing. The results did not support the idea that LAAM is "self-tapering."

Subjects in the six-week groups were rated more improved in their global progress and in halting the use of opiates. 86 percent of the subjects were reached for followup approximately three months after intake. The effects of treatment had not endured-only two subjects had remined continuously abstinent from heroin. Subjects who had received LAAM tended to return to heroin use more quickly than those who had received methadone.

To sum up, there were some temporary benefits to extending the time limit on detoxification to six weeks; however, the benefits did not endure. This wasthe first attempt to evaluate the use of LAAM in detoxification programs. LAAM performed similarly to methadone. Detoxification programs need many further improvements if they are to bring narcotic addicts to a drug-free state. Lengthening detoxification beyond 21 days may not improve the ultimate "abstinence rate" of patients, but it may improve effectiveness on more limited indicators of outcome.

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Self-Regulated Opioid Detoxification by Humans: Effects of Methadone Pretreatment

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Relatively little experimental attention has been devoted to study of the opioid detoxification process. Despite the fact that in clinical practice most detoxifications are conducted gradually, virtually all experimental data characterizing the opioid withdrawal syndrome involve abrupt termination of opioids (e.g., Martin et al. 1973).

The withdrawal syndrome is typically characterized as being subjectively severe but objectively mild (Senay et al. 1977), and adjunct medications frequently are prescribed to relieve insomnia and subjective discomfort of detoxifying patients (Jaffe 1980; Washton and Resnick 1980; Razani et al. 1975). Few data are available concerning the utility of such adjunct medications, however.

In the present experiment we have used an experimental human drug self-administration methodology to evaluate the effects of pharmacological pretreatments upon opioid drug-seeking and self-administration behavior, as well as upon the signs and symptoms of gradual opioid detoxification.

METHODS

Participants. Six male volunteers between the ages of 25 and 37 participated. All were methadone-maintenance patients requesting detoxification from methadone. Methadone-maintenance doses at enrollment ranged from 30 to 80 mg. Addiction histories ranged from 7 to 20 years duration (x = 12.0). Each patient gave written informed consent prior to participation.

General method. Within an eight-bed residential behavioral pharmacology research laboratory human drug self-administration methods were used to assess the effects of pretreatment with placebo and two doses of methadone upon methadone self-administration behavior and upon the signs, symptoms, subjective and behavioral effects of methadone detoxification. Patients engaged in

self-regulated methadone detoxification by engaging in operant responding to obtain 4-mg doses of methadone. Pharmacological pretreatments occurred on a randomized schedule as described below.

Instructions. Patients enrolled for a six-week study duration. They were informed that their methadone detoxification would be totally self-regulated, with their total daily methadone intake being determined by their own performance on the simple operant task described below. Patients were given no recommended schedule of detoxification except that they should plan to be totally drug-free for at least one week prior to their scheduled hospital discharge. Patients were informed that on some days they would receive pretreatment medication bottles which might contain either inactive placebo or various doses of methadone. Patients were informed that no drugs other than methadone would be administered either for experimental reasons or for relief of withdrawal discomfort.

Methadone self-administration. Daily six-hour sessions of methadone self-administration occurred between 12:00 p.m. and 6:00 p.m. During this period subjects could earn 4-mg doses of methadone-by completing a specified fixed number of responses on a portable radio transmitter operant-response console (fixed-ratio schedule). This hand-held operant-response console permitted patients to work for methadone while ambulatory within the research ward dayroom and while concurrently engaged in other activities. Each effective response on the console required that the button be depressed for one second. The fixed-ratio requirement was initially 300 (FR 300) and was increased as described below. Unless a pretreatment bottle was dispensed, the only methadone received was that earned during the daily self-administration session. The maximum dose available for self-administration each day was equal to the patient's maintenance dose or the next larger multiple of 4 mg. Methadone earned during the daily self-administration sessions was either dispensed in individual 4-mg doses as earned (three subjects) or accumulated and dispensed as a single dose at the end of the session (three subjects).

Methadone pretreatment. For each patient, days on which a pretreatment was administered alternated with days on which no pretreatment was administered. When two patients on the ward were participating in the study, only one received a pretreatment on any given day. On pretreatment days subjects were required to consume the contents of a bottle containing either placebo, 15 mg,. or 30 mg of methadone at 9:00 a.m., three hours prior to the start of the daily self-administration session. Procedures were double-blind, and neither the subjects nor the nursing staff were informed of the magnitudes of the doses under study. All doses were dispensed as liquid prepared from cherry-syrup solution (Methadose). To minimize the possibility that a subject could deduce either the presence or the dose of methadone given, dextromethorphan was used as a taste mask, and the total volume of liquid in any pretreatment bottle was varied in a randomized block fashion among 30, 60, or 90 cc so that no dose was correlated with any

given volume of medication.

Each of the three pretreatment conditions was administered five times to each patient. The order of administration was scheduled in randomized block fashion. No pretreatments were scheduled for at least the first five days of methadone self-administration. Then the effects of the first block of pretreatment doses were assessed while the FR requirement remained at 300 responses. Effects of the second, third, fourth, and fifth blocks of doses were assessed at FR requirements of 600, 1200, 1800, and 2400 responses, respectively.

Psychophysiological measures. For each patient, temperature, pulse, respiration rate, blood pressure, and pupillary diameter (measured photographically) were recorded daily at 8:30 a.m. and 11:00 a.m.

Subjective measures, Multiple subjective effect measures were recorded daily. At 8:30 a.m. patients completed a 60-item symptom-rating scale developed in our laboratory which is a sensitive measure of opiate withdrawal effects; this reported on their experiences during the preceding 23-24 hours (effects of the preceding day's methadone). At 11:00 a.m. patients completed three true/false scales of the Addiction Research Center Inventory (Haertzen 1974): the Morphine-Benzedrine Group scale (MBG,. 49 items), a version of the Weak Opiate Withdrawal scale (WOWs, 35 items), and the Chronic Opiate scale (ChrO, 26 items); these reported on their immediate experiences. At 6:00 p.m. patients completed the Profile of Mood States (POMS), a 65-item mood-rating scale providing scores on multiple mood dimensions; this reported on their mood throughout that day.

Performance measures. Each patient's psychomotor performance was assessed daily at 8:30 a.m. and 11:00 a.m. using a commercially available Saccadic Fixator and Sequence Rotator (Wayne Engineering). In a standing position patients faced a circular panel of lights and associated pushbuttons; throughout a one-minute trial single lights in the array were illuminated in a random order and remained illuminated until the subject pressed the associated pushbutton, at which time another light position in the array was illuminated. Performance score was a count of the number of lights extinguished per one-minute trial.

RESULTS

Five of the six participants successfully reduced their methadone intake to zero in this self-administration paradigm. Thus, the effects of methadone pretreatment upon methadone self-administration were assessed relative to a changing control condition. To characterize the trend of self-regulated detoxification over control days a linear regression line was fit to the amounts of methadone self-administered on control days during the pretreatment period, and the data from pretreatment days were expressed as deviations from the trend of control days.

Figure 1 presents group mean data summarizing the effects of methadone pretreatment upon methadone self-administration and upon subjective, physiological, and behavioral measures. Subjective report measures tended to show trends over the course of the experiment; therefore,' linear regressions were fit to these trends and data are presented as deviations from the control regression. Physiological variables and psychomotor performance were measured twice daily, and these data are expressed in Figure 1 as within-day difference scores; measures taken one-half hour prior to pretreatment were subtracted from those taken two hours following pretreatment.

A one-way analysis of variance for repeated measures revealed significant pretreatment effects for total symptom score ($p<0.005$), ARCI MBG scale ($p<0.01$), and pupil diameter ($p<0.005$); a borderline, though nonsignificant, trend was found for methadone self-administration ($p<0.10$). The p-values shown in Figure 1 indicate the results of this analysis of variance. Further statistical analyses were performed by means of pair-wise t-tests for correlated samples (one-tailed).

Examination of individual subject data revealed that for six out of six subjects mean methadone self-administration in the 30-mg pretreatment condition was somewhat below mean self-administration in both the control and the placebo conditions. Pairwise t-tests for the group data revealed that subjects self-administered significantly less methadone in the 30-mg pretreatment condition than in the control condition ($p<0.05$) or in the placebo condition ($p<0.05$). Overall, following 30-mg pretreatment, average methadone self-administration was reduced by 4.7 mg below the level predicted by the control day regression line.

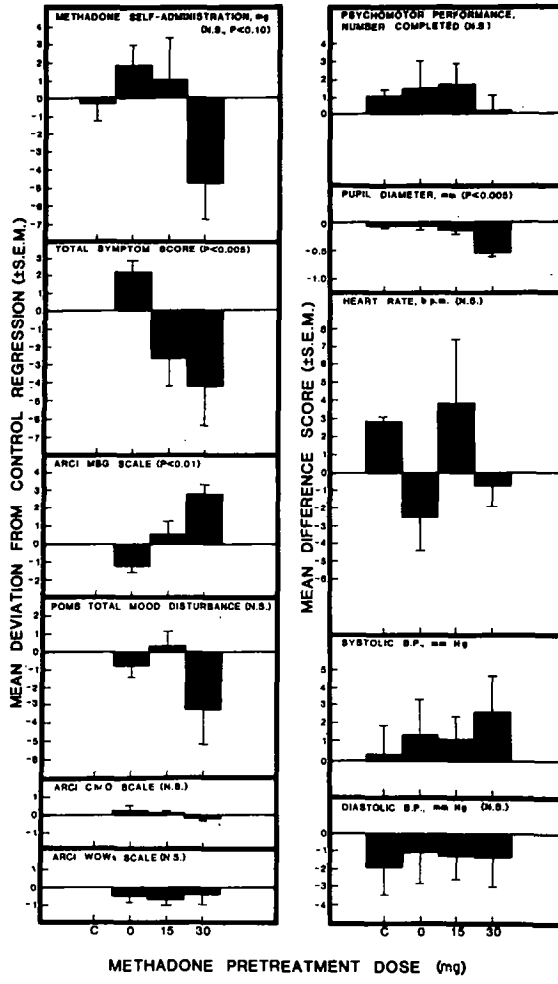
Pairwise t-tests revealed that the reductions in total symptom score relative to the placebo condition were significant for both the 15-mg and the 30-mg pretreatment conditions ($p<0.005$, in both cases). Scores on the ARCI MBG scale were significantly elevated in the 30-mg pretreatment condition both relative to the placebo condition ($p<0.005$) and relative to the 15-mg pretreatment condition ($p<0.05$). The other self-report measures -- the Total Mood Disturbance score of the Profile of Mood States, the ARCI Chronic Opiate scale, and the ARCI Weak Opiate Withdrawal scale -- showed no significant effects of methadone pretreatment.

Pupil diameter was the only physiological measure to be significantly influenced by methadone pretreatment. Pupil diameters were significantly constricted in the 30-mg pretreatment condition compared to the control condition ($p<0.005$) and to the placebo condition ($p<0.01$). Psychomotor performance was not influenced by methadone pretreatment.

DISCUSSION

Six inpatient subjects on methadone maintenance were exposed to a self-regulated methadone detoxification procedure. This procedure

FIGURE 1



Effects of methadone pretreatment. X-axis: Methadone pretreatment dose; Y-axis: Mean deviation from control regression (left panels) and mean difference between pre- and post-treatment measures (right panels). The vertical brackets indicate the standard errors of the means.

included progressively increasing fixed-ratio schedules of methadone reinforcement with occasional methadone pretreatments. Five of the six subjects successfully reduced their methadone intake to zero. Pretreatment with 15 mg methadone reduced the total symptom score of the PSQ (a measure of subjective discomfort) but affected no other measures. Pretreatment with 30 mg methadone reduced methadone self-administration, the total symptom score of the PSQ, and pupil diameter, while increasing the ARCI MBG score (a purported measure of subjective euphoria). No pretreatment dose of methadone significantly modified heart rate, blood pressure, or psychomotor performance. No pretreatment dose significantly modified scores on the POMS, ARCI ChrO, or ARCI WOWs scales.

One purpose of the present study was to assess the utility of this detoxification self-administration paradigm for evaluating the effects of adjunct medications upon the methadone detoxification process. The present data clearly support the utility of this human drug self-administration procedure for conducting such studies. Although all of the relevant data are not presented here, this study has found that the typical signs and symptoms of opioid withdrawal occur during this process of gradual self-regulated methadone detoxification. Further, it has shown that these signs and symptoms can be attenuated by pharmacological pretreatments. In particular, these data show that methadone-tolerant subjects undergoing detoxification remain sensitive to the acute effects of supplemental methadone.

Perhaps the most unique feature of the present study is its inclusion of the behavior of methadone self-administration as a dependent variable and its demonstration that this behavior is sensitive to pharmacological treatments. Thus, this study has demonstrated that pharmacological pretreatments can affect not only the signs and symptoms of methadone withdrawal but can also influence the probability of opioid self-administration by detoxifying addicts.

Overall, we feel that this procedure appears to be a promising and useful technique, not only for the study of the signs and symptoms of gradual opioid withdrawal but for the assessment of pharmacologioal treatment influences upon methadone self-administration and withdrawal. The procedure would appear to hold promise as a potentially useful baseline with which to examine the effects of various adjunct medications other than methadone (e.g., sedative-hypnotics, minor tranquilizers, clonidine) which are frequently used or proposed as adjuncts to methadone detoxification.

REFERENCES

Haertzen, C.A. An Overview of Addiction Research Center Inventory Scales (ARCI): An Appendix and Manual of Scales. DHEW Publication No. (ADM) 74-92. National Institute on Drug Abuse. Washington, D. C.: U.S. Government Printing Office, 1974.

Jaffe, J.H. Drug addiction and drug abuse. In: Gilman, A.G., Goodman, L.S., and Gilman, A., eds. The Pharmacological Basis of Therapeutics, Sixth Edition. New York: Macmillan Publishing Co., Inc., 1980. pp. 535-584.

Martin, W.R., Jasinski, D.R., Haertzen, C.A., Kay, D.C., Jones, B.E., Mansky, P.A., and Carpenter, R.W. Methadone - A reevaluation. Arch Gen Psychiatry, 28:286-295, 1973.

Razani, J., Chisholm, D., Glasser, M., and Kappeler, T. Self-regulated methadone detoxification of heroin addicts. Arch Gen Psychiatry, 32:909-911, 1975.

Senay, E.C., Dorus, W., Goldberg, F., and Thornton, W. Withdrawal from methadone maintenance. Arch Gen Psychiatry, 34:361-367, 1977.

Washton, A.M., and Resnick, R.B. Clonidine versus methadone for opiate detoxification. Lancet, 2:1297, 1980.

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Comparison of Three Outpatient Methadone Detoxification Procedures

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In studies of outpatient opioid detoxification the parameter which has no doubt received most attention is the pharmacological one of the speed or schedule of dosage reduction, with detoxifications ranging in duration from seven days (Silsby and Tennant 1974) to 30 weeks (Senay et al. 1977). Response to detoxification may also be influenced by psychological variables related to degree of patients' knowledge of and participation in the dose-reduction process (Razani et al. 1975).

The present study compared three detoxification procedures which involved comparable-dose reduction periods but which differed in the amount of information available to patients and the degree of self-control which patients could exert over the dose-reduction schedule. In particular, blind, informed, and self-regulated detoxification procedures were compared. All detoxifications were conducted on an outpatient basis and involved a 6-week dose-reduction period scheduled within the context of a 90-day (13 week) detoxification program. Procedures were compared on several variables considered important indicators of success: (1) success at dose reduction; (2) retention in treatment; (3) patient symptomatology; (4) illicit drug use; and (5) follow-up status.

METHODS

Participants. Participants were 60 male opioid addicts who applied to this clinic for outpatient methadone detoxification. Average age was 28.4 years; average number of years since first opioid addiction was 8.3 years; 58 percent were black, and 42 percent were white; at the time of entering this study, 23 percent were enrolled in methadone maintenance treatment and the remaining 77 percent were addicted to illicit opioids (i.e., "street addicts").

Procedure. Volunteers provided written informed consent and enrolled in a 90-day detoxification program. They were informed that they might or might not be given information about their

dose level and that they might or might not be given self-control over their methadone intake. Volunteers were not told the details of the detoxification procedures or dose-reduction schedules to be studied.

The program consisted of a three- to four-week baseline period during which patients were maintained on a stable dose, followed by a six-week active detoxification phase. During the first few days of the baseline period all patients were stabilized at 30 mg methadone p.o. daily. At the end of the baseline period patients were stratified according to whether they entered the program from methadone maintenance or as street addicts, and each group was independently randomly assigned among three treatment conditions: (1) blind, clinic-controlled detoxification (N=20); (2) informed, clinic-controlled detoxification (N=21); or (3) self-regulated detoxification (N=19). In all three conditions patients visited the clinic seven days per week and received liquid methadone under nurses' observation in a standard 60 cc volume.

Patients in the blind and informed conditions received pharmacologically identical detoxifications; they differed only in terms of whether the patients were informed of the dosage schedule. Patients in the blind condition were given no information concerning the start, course, or end of the dose-reduction period. Patients in the informed condition were informed each day during the dose-reduction period of the dose they were receiving; they were not informed in advance of what the schedule of dose reductions would be. For patients in both of these groups methadone dosage was reduced by 5 mg per week in alternating 2 mg and 3 mg decrements. Patients in the self-regulated condition were given almost total dose self-control, with minimal clinic restrictions. On day 1 of the dose-reduction period they were informed that their previous day's dose had been 30 mg and that henceforth they would be free to choose whatever dose they wished each day within the range of 0 to 45 mg (i.e., up to 150 percent of their stabilization dose); they were told that they should have their detoxification completed within six weeks and that any patients failing to do so would receive a rapid clinic-controlled detoxification to complete the process during the remainder of the 90-day period.

At each daily clinic visit patients completed a 59-item symptom self-report rating scale (Physical Status Questionnaire or PSQ) describing the symptoms they had experienced during the preceding 24 hours. Under staff observation patients provided twice-weekly urine samples which were analyzed for evidence of methadone, opioids, quinine, barbiturates, amphetamines, and a variety of miscellaneous sedatives, major tranquilizers, and antidepressants; half of these urine samples were analyzed for evidence of benzodiazepines.

Approximately two weeks after a patient's last clinic visit an effort was made to contact the patient in the community and he was requested to make a follow-up clinic visit for which $20 compensa-

tion was provided. Patients were interviewed about their drug use at this time and a urine sample for laboratory analysis was collected.

RESULTS

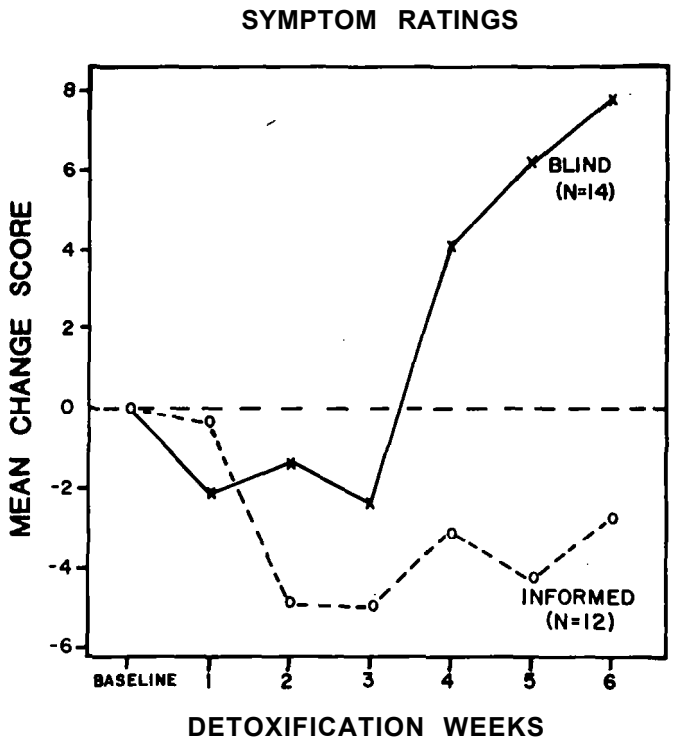
Outcomes were assessed and compared in five dimensions: (1) dose reduction; (2) retention in treatment; (3) symptom self-reports; (4) urinalysis evidence of supplemental drug use; and (5) short-term follow-up status.

Dose Reduction. The three treatment procedures were compared with respect to the minimum methadone dose which patients received during the six-week dose-reduction period. The two clinic-controlled detoxification procedures (Blind and Informed) were equally effective in achieving methadone dose reduction and they were substantially more effective than the Self-Regulated procedure. In the Blind group 13 patients (65.0 percent) achieved a methadone dose of 5 mg or less, and in the Informed group 15 patients (71.4 percent) did so; only five patients (26.3 percent) in the Self-Regulated group achieved a methadone dose of 5 mg or less. These proportions were compared using a z-test for independent proportions (with the Blind and Informed procedures collapsed into a single group) and the difference between the clinic-controlled and the Self-Regulated procedures was found to be statistically significant ($p<0.003$, two-tailed). The ineffectiveness of the Self-Regulated procedure is further indicated by the fact that five patients (26.3 percent) always self-selected methadone doses in excess of their 30-mg stabilization dose.

Retention in Treatment. The Blind and Informed conditions were compared via *t*-test with respect to the mean number of days of treatment participation prior to drop-out. Patients in the Blind condition remained in treatment for an average of 8.3 days longer (69.8 vs. 61.5 days). This difference was of borderline statistical significance, with $p = 0.07$ (two-tailed). Patients in the Self-Regulated condition had an average treatment duration of 74.1 days, but this group was not included in statistical comparisons since these patients tended not to detoxify during the self-regulation period.

Symptom Self-Reports. Total symptom scores on the daily symptom questionnaire during the six-week dose-reduction period were examined in relationship to symptom scores during the last Baseline week of stabilization at 30 mg. Since patients in the Self-Regulated condition tended not to detoxify, emphasis was on comparison of the Blind and Informed groups. These two groups tended to show different patterns of symptomatology in response to pharmacologically identical detoxifications, as illustrated in Figure 1. The figure shows the average total symptom change score for each group during the six dose-reduction weeks relative to each patient's symptom level during the final baseline week of stabilization at 30 mg. Only patients who remained in the study

FIGURE 1



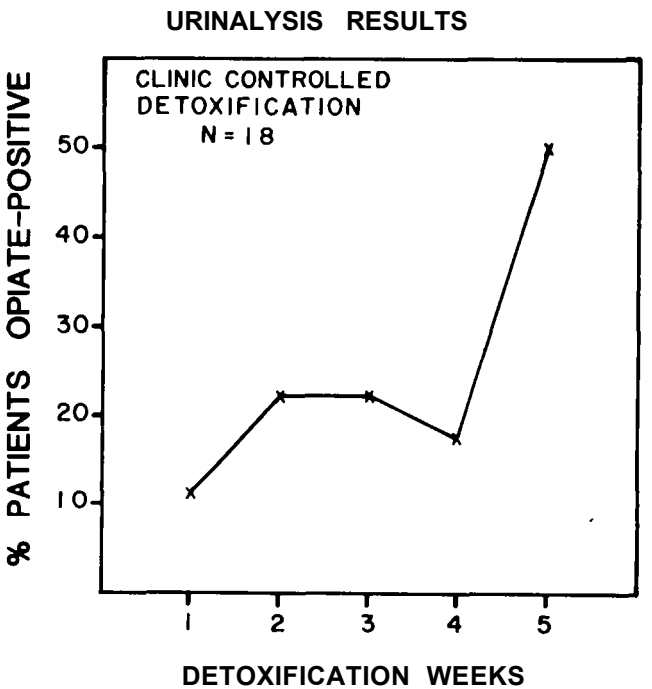
Mean symptom rating scores, as change from baseline.

into the sixth week of detoxification are included in this analysis. Symptoms tended to increase among patients in the Blind condition and tended to decrease among patients in the Informed condition. Linear regression lines were fit to the average data in Figure 1, and subsequent comparison of the correlation coefficients showed these trends to be significantly different ($p<0.02$, two-tailed). In addition, linear-regression trend lines were fit to the daily symptom data of each of these individual subjects, and these correlation coefficients were averaged using Fisher's z' transformation. The Blind group showed a statistically significant positive mean correlation ($r = +0.33$, $p<0.05$), and the Informed group showed a nonsignificant negative mean correlation ($r = -0.02$); these two mean correlations were not, however, statistically significantly different from one another.

Urinalysis Results. Only patients whose three final urine samples of the Baseline period were free of morphine, quinine and other opioids (excluding methadone) were considered appropriate for

inclusion in this analysis. This criterion eliminated 41.7 percent of the total sample who showed evidence of supplemental illicit opioid use shortly prior to their methadone dose reduction even beginning. Because of the small sample sizes remaining no significant differences between groups could be detected. However, the patterns of urinalysis results over weeks of detoxification warrant description. The Self-Regulated group showed no trend in their pattern of drug supplementation, which is compatible with their general failure to detoxify. The two clinic-controlled groups both showed similar patterns (Fig. 2); the probability of

FIGURE 2



Percent of patients providing opiate-positive urine samples as a function of weeks in detoxification.

a dirty urine remained relatively steady at approximately 20 percent for the first four weeks of detoxification and then increased to 50 percent in week 5 (when methadone dose fell below 10 mg).

Follow up. Short-term follow-up data were obtained on 55 patients (91.7 percent). Tweylve of these were free of opioids (including methadone) and quinine; this is 20.0 percent of the entire study population (21.8 percent of those contacted in follow-up). The interval from last active methadone dose until follow-up was

typically two to three weeks, but was occasionally as much as two and one-half months. There were no differences between the treatment groups in follow-up status. The number of patients opioid-free at follow-up was four, three, and five for the Blind, Informed, and Self-Regulated groups, respectively.

DISCUSSION

The primary point to be emphasized in this comparative evaluation of outpatient methadone-detoxification procedures is the relative ineffectiveness of the self-regulated procedure in contrast to the clinic-controlled procedures in achieving substantial reduction of methadone dosage. While it may be the case that self-regulated detoxification procedures are effective for selected groups of patients, the present data indicate that their application with unselected groups will be largely ineffective. In contrast, both clinic-controlled detoxification procedures were quite effective in achieving substantial dose reduction.

It should be noted also that the Blind and Informed conditions appear to differ in the duration of their retention of patients in treatment participation. In certain clinical settings a longer duration of treatment retention might be desirable. For example, in clinics which wish to maintain patients at zero methadone dose for several days in order to enter in narcotic antagonist treatment the present data suggest that a blind detoxification procedure might be most appropriate.

The present data suggest that the patterns of symptomatology by blind and informed detoxification procedures may differ. In particular, it appears that patients in the Blind procedure tended to show patterns of increasing symptom complaints as methadone dose reduction progressed, whereas patients in the Informed condition did not. Thus, knowledge of the dose-reduction schedule may serve to dampen the symptom complaints associated with detoxification. Alternatively, these data might be viewed as suggesting that much of the symptomatology reported by detoxifying patients results from anxiety and uncertainty concerning pharmacological status. In either case the present data suggest that informed detoxification procedures may result in improved levels of subjective comfort for detoxifying patients.

While no differences between treatment groups in the overall rates of illicit drug supplementation have been observed, interesting patterns of relapse to illicit drug use have been observed in the two clinic-controlled detoxification groups. Throughout the first four weeks of dose reduction the probability of illicit opioid supplementation remained at a relatively steady level and then increased abruptly in week 5 when methadone levels fell below 10 mg. This relationship is quite similar to what we have observed in residential laboratory studies of methadone self-administration in detoxifying patients (Bigelow et al. 1981). Thus it appears that illicit opioid supplementation is not a graded function of

decreasing methadone dosage but may instead be selectively associated with the terminal portions of the detoxification process.

Finally, it should be emphasized that in terms of clinical outcome at follow-up none of these detoxification procedures differed significantly. This is not intended to be a pessimistic comment but rather is intended to emphasize that procedural differences in the detoxification process may influence outcomes which are measured during that process while being unrelated to the problem of relapse after the detoxification process is completed. Independently of long-term outcome there are certainly a number of outcome variables which are of concern to clinicians during the detoxification process itself; patient symptomatology, illicit drug use, reduction of methadone dependence, and retention in treatment are among these.

REFERENCES

Bigelow, G.E., Stitzer, M.L., Griffiths, R.R., and Liebson, I. Human methadone detoxification: Opioid self-administration behavior, cigarette smoking, and withdrawal signs and symptoms as a function of progressive dose reductions. Fed Proc, 40:296, 1981

Razani, J., Chisholm, D., Glasser, M., and Kappeler, T. Self-regulated methadone detoxification of heroin addicts. Arch Gen Psychiatry, 32:909-911, 1975.

Senay, E.C., Dorus, W., Goldberg, F., and Thornton, W. Withdrawal from methadone maintenance. Arch Gen Psychiatry, 34:361-367, 1977.

Silsby, H., and Tennant, F.S. Short-term, ambulatory detoxification of opiate addicts using methadone. Int J Addict, 9:167-170, 1974.

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Propoxyphene Napsylate Maintenance Treatment of Narcotic Dependence: Use of a Non-Methadone Model

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ABSTRACT

One hundred seventy-eight (178) heroin addicts entered propoxyphene napsylate (PN) maintenance. Patients attended a general medical clinic two times each week and took home a three- to four-day supply of PN which was usually taken in doses of 300 to 400 mg three to four times per day. Over a 21-month period, the subjects entered and re-entered PN treatment 166 times (1.5 times per patient) and remained a mean of 10.6 weeks per treatment. A comparison with a group of methadone maintenance patients indicated similar performance in employment and heroin use. The ability to take PN, attend a clinic less often than daily, and discontinue and re-enter treatment on a discretionary basis is preferred treatment approach for same narcotic addicts.

INTRODUCTION

In 1973 the relatively weak agonist, propoxyphene napsylate (PN), was introduce for narcotic treatment.[1] Since this time studies have demonstrated that PN is more effective than placebo but less effective then methadone in reducing narcotic withdrawal symptoms.[2,3] A double-blind comparison of methadone and PN maintenance treatment of heroin addicts revealed that, although methadone retained subjects in treatment longer, many addicts safely and effectively maintained with PN.[4,5] Despite the findings, PN is still the treatment agent preferred over methadone, clonidine, and naltrexone by some narcotic addicts who attended our facilities. In 1979, we began using PN for maintenance treatment of opiate addicts by use of a non-methadone model. Patients attend the clinic only two times per week and take medication home rather than attend daily as with methadone. Reported here is our experience with 178 patients.

METHODS

In January, 1979, the project was initiated by informing all patients in short-term, out-patient detoxification treatment that PN maintenance was available as an alternative to methadone maintenance. Criteria for admission were as follows:

1. History of compulsive opiate use:
2. One or more relapses following short-term detoxification in our facilities;
3. Voluntary desire of patient to be on PN maintenance.

Patients attended the clinic twice per week. One dose of 200 to 400 mg of PN was given during each clinic visit, and a three- or four-day supply of PN was given to take home. Patients were instructed to take the medication two to four times per day in intermittent doses.

All patients were instructed that they could discontinue or drop out of the treatment at any time and be subsequently re-admitted whenever they desired. They were informed they could remain for any length of time they desired and that they could transfer to methadone maintenance or other treatment at any time. A urine analysis was collected monthly to screen for abusable drugs.

Patients were treated in three general medical clinics located in Eastern Los Angeles County. These clinics did not have a methadone program on premises. One room in the clinic was assigned for program use where patients could be counseled, medication dispensed, and records maintained. In two clinics attending, staff were: physician, nurse practitioner, licensed vocational nurse and psychologist. In the third clinic, the staff did not have a psychologist. Patients paid a regular medical clinic visit fee each time they attended, clinic. During this period, methadone maintenance fees were equal or less.

During the week of March 20, 1981, patients who were in PN maintenance treatment at this time completed a questionnaire which inquired about their perceptions and satisfaction with PN maintenance using a non-methadone model. Also during this week, each patient gave a urine test and a breath-alcohol test and

underwent examination for needle marks. These patients were compared with 149 methadone maintenance patients in two clinics in Eastern Los Angeles who, during the same week, completed the same questionnaire and had the same tests.

RESULTS

Table One shows characteristics of the entire group of 178 patients. Persons who entered PN maintenance were chronic heroin users with a mean total use of 10.7 years. They had attempted a mean of 3.2 previous treatments.

This group engaged in 266 Separate treatment episodes which averaged 10.6 weeks each (Table Two). The mean maintenance dosage was 1100 mg daily; and patients usually took this in three to four separate, divided doses of 300 to 400 mg each. Approximately 25% of urine speciments collected month from patients contained morphine.

The 44 PN patients who were compared to 149 methadone patients appeared to be quite similar (Table Three). Mean age, employment status, total years of heroin use, and the percent who showed morphine in urine, alcohol in breath or fresh needle marks on an arm were not statistically different. A higher percent of PN patients, however, stated that they could discontinue maintenance medication and not experience withdrawal sickness.

The major reasons given by patients for choosing PN over methadone were that methadone was too addictive and PN worked better (Table Four). The majority of PN patients reported that treatment helped themreduce street drug consumption and avoid arrests.

DISCUSSION

Patients who selected PN maintenance were generally long-experienced, heroin addicts who perceived PN to be less addicting and more effective than methadone. Many (43.2%) Stated that they liked to carry PN with them rather than take maintenance medication in a single daily dose. A likely explanation for this may be related to the plasma half-life of maintenance medication. Although the PN plasma half-life

is longer than that for heroin, it is shorter than that for methadone- In tolerant persons, the plasma half-life of methadone averages about 24 hours.[6] PN is absorbed more slowly than propoxyphene hydrochloride and has a plasma half-life of 6 to 12 hours.[7] Patients reported in this study that they usually had to carry PN with them and take 300 to 400 mg three to four times per day. This schedule is compatible with the plasma half-life of PN, and the ability to take it in multiple, rather than a singledose, in a 24-hour period probably explains why many addicts perceive it to be more effective than methadone.

Those addicts who maintained well on PN appeared little different from a comparison group of methadone patients on indicators of employment heroin use. Similar findings were also found in a double-blind maintenance comparison of PN and methadone. Maintenance periods were short in this study (mean: 10.6 weeks), and most addicts relapsed after voluntary termination and required readmissions to treatment. PN is not apparently a potent enough agonist drug to retain many addicts for long periods. Approximately 41% of subjects stated they could skip a day of PN without withdrawal sickness. Almost 21% indicated they could totally stop PN without sickness compared to less than 1% of methadone patients. The ability to enter and discontinue maintenance treatment on voluntary discretion is apparently an attribute of significant enough value that many addicts reject methadone in favor of PN.

TABLE ONE
DEMOGRAPHIC AND DRUG-USE
CHARACTERISTICS OF PN MAINTENANCE PATIENTS
N = 178

	No.	
Males	125	(70.2%)
Females	53	(29.8%)
White	75	(42.2%)
Hispanic	99	(55.6%)
Black	2	(1.1%)
Asian	2	(1.1%)
Employed	98	(55.1%)
Married	73	(41.0%)

Education Range (years)	6 - 16
Mean Education (years)	11.5
Parole/Probation	39 (21.9%)
Age Range (years)	19 - 51
Mean Age (years)	30.7
Total Heroin Use Range (years)	.4 - 30
Mean Heroin Use (years)	10.7
Daily Heroin Use Range Before Admission (days)	1 - 720
Mean Daily Heroin Use Before Admission (days)	75.1
Number of Heroin Injections Per Day	0 - 12
Mean Number of Heroin Injections Per my	2.7
Number Previous Heroin Treatments (range)	1 - 15
Mean Number Previous Heroin treatments	3.2

TABLE TWO
PERFORMANCE ON PN MAINTENANCE
N = 178

	No.
Number of Separate Treatment Episodes	266
Mean Number of Episodes Per Patient	1.5
Weeks in Each Treatment Episodes (range)	1 - 108
Mean Number of Weeks in Each Episode	10.6
Daily Dosage Range (MGS)	600 - 1600
Mean Daily Dosage (MGS)	1100
Mean Number Self-Reported Ingestions Per Day	3.7
Number of Urine Specimens Collected	427
Number Urine Specimens Which Contained Morphine	109 (25.6%)

TABLE THREE
COMPARISON OF PN AND METHADONE MAINTENANCE
PATIENTS IN TREATMENT ON MARCH 20, 1981

	PN N=44	METH N=149	STAT SIG
Mean Age (years)	32.1	32.5	NS
Employed	27 (61.4%)	80 (53.7%)	NS
Mean Total Heroin Use (years)	9.9	10.9	NS
Length of Time on Maintenance (mos.)	11.3	20.6	P<.05
Can skip Day of Medication Without Sickness	18 (40.9%)	20 (13.4%)	P<.001
Can Totally Stop Medication Without Withdrawal Sickness	9 (20.5%)	1 (.7%)	P<.001
No. of Urines That Contain Morphine	6 (13.6%)	24 (15.8%)	NS
No. of Breath tests That show Alcohol	0 (0%)	2 (1.3%)	NS
No. With Fresh Needle Marks	1 (2.3%)	6 (4.0%)	NS

TABLE FOUR
SELF-REPORT ATTRIBUTES OF PN
N = 44

Reason(s) For Choosing PN Rather Than Methadone

Methadone too addictive	31 (70.5%)
Methadone disagress with me	11 (25.0%)
PN works better	27 (61.4%)
I like to carry PN with me	19 (43.2%)
With methadone, I have to attend clinic daily	9 (20.5%)
PN helped to reduce use of street drugs	43 (97.8%)
Arrested less when I take PN	31 (70.5%)

REFERENCES

1. Tennant, FS Jr: Treatment of Heroin Addicts with Propoxyphene Napsylate. Presented Before the Committee on Problems of Drug Dependence of the National Academy of Sciences. Chapell Hill, No. Carolina, May 23, 1973.

2. Tennant, F Jr; Russell, BA; Casas, SK; et al: Heroin Detoxification: A Comparison of Propoxyphene and Methadone. JAMA 232: 1019-1022, 1975.

3. Tennant, FS Jr; Russell, BA; Tate, J.; et al: Comparative Evaluation of Propoxyphene Napsylate. Intern J Addictions 12:565-574, 1977.

4. Wood, GE; Mintz, J; Tennant, FS Jr.: et al: Lack of Toxicity of High Dose Propoxphene Napsylate When Used for Maintenance Treatment of Addiction. Clin Toxicol 16:473-478, 1980.

5. Woody, GE; Mintz, J; Tennant, FS Jr.; et al: Usefulness of Propoxyphene Napsylate Maintenance Treatment of Narcotic Addiction; Arch Gen Psychiat (In Press).

6. Inturrusi, CE; Verebely, K: The Levels of Methadone in the Plasma in Methadone Maintenance. Clin Pharm Ther 13:633-637, 1972.

7. Wolen, RL; Gruber, CM; Kiplinger, GF; et al: Concentration of Propoxyphone in Human Plasma Following Repeated oral Doses. Toxicol Apple Pharmocol 19: 493-497, 1971.

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Clinical Comparison of Propoxyphene Napsylate and Methadone in the Treatment of Opiate Dependence

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SUMMARY

In this double-blind comparison of propoxyphene napsylate (PN) 800 mg in two divided doses versus methadone 20 mg, methadone 10 mg or placebo methadone, it was found that PN: 1) did not alleviate withdrawal symptoms in patients previously maintained on methadone 20 mg; 2) produced a slightly over-medicated effect in the detoxified group of exmethadone patients; and 3) compared favorably to methadone 10 mg in suppressing withdrawal symptoms without producing evidence of overmedication in those patients previously stabilized on a methadone maintenance dose of 10 mg.

Since PN cannot be studied at doses higher than 800 mg per day if undesirable side effects are to be avoided, it is concluded that PN can be of value only in the treatment of mildly addicted patients requiring 10 mg of methadone or less per day.

INTRODUCTION

Early clinical investigations by Tennant suggested that PN could be of value in the treatment of opiate dependent persons (Tennant et al. 1974; Tennant et al. 1975). His findings indicated that PN acted in a manner similar to methadone by suppressing withdrawal symptoms and eliminating the craving for heroin. Pilot studies by Inaba et al. (1974) proposed that PN be viewed as a promising therapeutic tool and possible alternative to methadone. However, high doses of PN were required to suppress-abstinence symptoms; Disturbing side effects such as nausea, dysphoria, restlessness, hallucinations and seizure-like activity were noted especially when these high doses of PN (up to 1600 mg) were given in one single dose (Tennant 1973).

Dependence studies by Fraser and Isbell in the early 1960's demonstrated that propoxyphene produced mild morphine-like activity that only partially suppressed abstinence symptoms (Fraser and Isbell 1960). They concluded that the addiction liability of propoxyphene was substantially less than that of codeine. More recently, Jasinski

reported that the maximum doses of PN used to treat heroin addicts (1200 mg/day) produce a degree of morphine-like activity equal to that produced by 20 to 25 mg/day of subcutaneously given morphine or 10 mg/day of oral methadone (Jasinski et al. 1977).

Double-blind comparisons between PN and methadone in narcotic detoxification (Tennant et al. 1975) and maintenance (Woody et al. 1980) revealed that methadone suppressed abstinence significantly better than PN. These findings are substantiated by the work of Jasinski who found that mild abstinence was still present in addicted patients during a PN maintenance regime of 1200 mg/day (Jasinski et al. 1977).

preliminary work at the Wood VA Medical Center indicated that single doses of PN should not exceed 600 mg to avoid undesirable side effects. However, when PN was given in divided doses (800 mg/day in two equal doses), no significant adverse reactions were noted. These findings are consistent with the work of Woody et al. (1980), who found no clear evidence of serious toxicity when PN was used for maintenance in divided doses.

These previous investigations indicate that although PN appears to be generally less effective than methadone, there may be indications for its use in the treatment of certain narcotic-dependent persons. The need for further exploration was clearly evident. The study presented here was conducted in a double-blind manner among established heroin addicts on controlled levels of methadone maintenance to determine the pharmacological response of PN 800 mg divided in two equal doses as compared to methadone 20 mg, methadone 10 mg or placebo methadone.

METHOD

Adult male inpatients with a history of opiate addiction were studied at the Drug Treatment Ward of the Wood Veterans Administration Medical Center after informed written consents were obtained. A history of at least two years of recent continuous heroin use with established evidence of current dependence on methadone was required. Only those patients placed on a methadone detoxification schedule or those who recently completed detoxification with methadone were selected to participate in the study.

All patients received a history and physical examination including laboratory tests. Individuals with a history of seizure, heart, liver or kidney diseases were excluded. In addition, the subjects were required to have expressed a desire to detoxify from methadone and were judged physically and psychologically suitable for detoxification by the principal investigator.

During the study, assessments of objective as well as subjective signs of either withdrawal or overmedication, as listed in table 1, were performed by the nurse observer. The rating of each response was arbitrarily assigned the following scores: 0 = absent; 1 = mild; 2 = moderate; 3 = severe. In other words, a higher score indicates greater withdrawal or overmedication. Scores for a

patient were obtained daily by averaging his withdrawal and overmedication scores separately. Comparisons of treatment efficacy were based on the mean values. Random urine surveillance for drugs of abuse was performed three times weekly. Electrocardiograms and vital signs were monitored at regular intervals. Electroencephalograms were recorded before and after the study periods. No other narcotic analgesics were given although prestudy major or minor tranquilizers were continued without change during the study.

TABLE 1

Signs and Symptoms Used to Assess Response to Treatment

Withdrawal: anorexia, nausea, vomiting, abdominal cramps, diarrhea, aches/pains, rhinorrhea, sneezing, yawning, lacrimation, perspiration, goose flesh, chilliness/flushing, agitation, anxiety, irritability, restlessness, depression, tremors, fatigue, weakness, insomnia.

Overmedication: lightheadedness, ataxia, dizziness, nodding, drowsiness, euphoria, intoxication, sedation, speech impediment, constipation.

Three groups of patients were studied. Before the study, the patients were on daily maintenance doses of either methadone 20 mg (Group A), methadone 10 mg (Group B), or were recently detoxified from methadone (Group C). During the seven-day study period, Group A received either PN 800 mg or methadone 20 mg; Group B received either PN 800 mg or methadone 10 mg; Group C received either PN 800 mg or placebo methadone. Medication assignments in each group were randomized and the study was double-blind. All medication was dispensed twice daily in identically appearing capsules with appropriate substitution of active drug or placebo. Bach capsule contained either PN 400 mg, methadone 10 or 20 mg or placebo. The methadone was administered once daily in the morning and a placebo capsule was given in the evening to those patients randomly assigned to the methadone treatment groups. The daily dose of PN 800 mg was divided in two equal doses for those patients assigned to the PN treatment groups.

A total of 30 adult male inpatients were studied whose ages ranged from 22 to 55 years (mean of 33 years). Seventeen (57%) were black, ten (33%) were white and three (10%) were Spanish American. Symptomatology of withdrawal and overmedication was assessed preceding the study and daily for seven days.

Group A - Methadone 20 mg vs Propoxyphene Napsylate 800 mg

Ten patients were stabilized on methadone 20 mg daily prior to the study. Six of these patients received PN and four continued to receive methadone 20 mg. The mean withdrawal scores on Day 0 were 0.39 ± 0.07 (S.E.) in PN patients and 0.26 ± 0.06 in methadone

patients. However, there was no significant difference in the initial status between the two groups of patients. As shown in table 2, during the seven-day treatment with PN the mean withdrawal score increased significantly. Withdrawal in this PN group became more noticeable on days 3, 4, 5, 6 and 7. On the other hand, the seven-day treatment with methadone reduced the mean withdrawal score. Hence, the average of the daily mean withdrawal score for the seven-day period was significantly greater in patients receiving PN (0.54 ± 0.09) than in patients receiving 20 mg methadone (0.18 ± 0.03) ($P<0.001$).

Symptomatology of overmedication was not observed in these patients. There was no significant difference between the two treatments (table 3).

Group B - Methadone 10 mg vs Propoxyphene Napsylate 800 mg

Ten patients were stabilized on methadone 10 mg daily prior to the study. Five of these patients received PN and five continued to receive methadone 10 mg daily. On Day 0, there was no statistical difference in the mean withdrawal scores between PN (0.45 ± 0.07) and methadone (0.64 ± 0.11) patients. Significant reduction in mean withdrawal scores was observed with both PN and methadone treatments (table 2). The average of the daily mean withdrawal scores for the seven-day period in PN and methadone patients was 0.24 ± 0.04 and 0.36 ± 0.07, respectively.

Symptomatolgoy of overmedication was negligible in these patients, and no statistically significant changes were observed with either treatment (table 3).

Group C - Placebo Methadone vs Propoxyphene Napsylate 800 mg

The 10 patients in this. group were completely detoxified from methadone just prior to the study. Five of these patients received PN and five received placebo methadone. There was no significant difference in the 0-day withdrawal scores between PN (0.60 ± 0.09) and placebo (0.77 ± 0.11) patients. Both treatments were effective in significantly reducing the mean withdrawal scores (table 2). The average daily mean withdrawal scores for the treatment period were significantly lower in PN patients (0.37 ± 0.05) than in placebo methadone patients (0.56 ± 0.07).

In patients receiving PN, overmedication scores increased significantly from a mean of 0 on Day 0 to a mean of 0.34 ± 0.07 for the seven-day period (table 3). The overmedication scores were significantly higher in PN patients than in placebo methadone patients on days 2, 4, 5, 6 and 7. No change in overmedication score was observed in patients receiving placebo.

Another way of analyzing the results of the above three groups was the use of linear regression. Linear regression analysis of the withdrawal and overmedication scores showed that symptom change can be attributed to treatment in the following three groups: for

withdrawal, Group A receiving propoxyphene napsylate (86%), and for overmedication, Group A receiving methadone 20 mg (55%) and Group C receiving propoxyphene napsylate (67%).

Although the mean headache scores decreased in all three treatment groups, the changes were not statistically significant. There were no clinically significant changes in vital signs, electroencephalograms or laboratory examinations of urine and blood among the entire study population.

Fourteen out of 90 (15.6%) urine samples taken during the seven-day study periods were positive for opiates among the 30 patients. There was no statistical difference in the number of opiate-positive urines between the PN, methadone or placebo methadone patient groups.

EKG changes were noted on two patients on PN at the end of the seven-day treatment. One patient (Group A) showed flattening of T-waves in V_4 and V_6. Another patient (Group A) exhibited sinus tachycardia and nonspecific S-T and T changes. After a seven-day treatment with placebo methadone, one patient also showed sinus tachycardia and nonspecific S-T and T changes. There were no significant changes in EKG with methadone-treated patients.

DISCUSSION

The efficacy of PN 800 mg to control withdrawal symptomatology in methadone tolerant patients was compared in a double-blind manner to methadone 20 mg, methadone 10 mg and placebo methadone.

It was interesting to note that withdrawal scores before administering study medications were lowest in those patients stabilized on methadone 20 mg and highest in the detoxified group of exmethadone patients.

When PN was compared to methadone 20 mg, the PN-treated patients exhibited significantly more withdrawal symptomatology. On the other hand, when PN was compared to methadone 10 mg, both the PN and the methadone treatments were equally effective in subduing withdrawal symptomatology. The comparison of PN versus placebo methadone in recently detoxified exmethadone patients indicated that PN was more effective in controlling withdrawal than placebo methadone.

Cur results show that PN 800 mg produced a degree of morphine-like activity equal to that produced by methadone 10 mg thus indicating that methadone is 80 times more potent than PN on a mg-for-mg basis. The use of PN for purposes of substitution or withdrawal from opiates would therefore require levels of drug administration in excess of the maximum approved amounts—nearly two times the approved total daily dose and four times the approved single dose.

Based on these findings, it is concluded that patients mildly addicted to narcotics requiring methadone treatment of 10 mg or less daily will find PN adequate to control drug-seeking behavior or to satisfactorily attentuate narcotic deprivation.

TABLE 2

Mean Withdrawal Scores (± S.E.) with Propoxyphene Napsylate (PN), Methadone (MD) and Placebo Treatment

	GROUP A		GROUP B		GROUP C	
Day	PN	MD 20	PN	MD 10	PN	Placebo
0	.39 ± .07	.26 ± .06	.45 ± .07	.64 ± .11	.60 ± .09	.77 ± .11
1	.31 ± .07	.23 ± .06	.34 ± .08	.44 ± .09	.33 ± .05	.52 ± .10
2	.44 ± .09	.40 ± .07	.19 ± .07	.34 ± .08	.31 ± .05	.58 ± .08*
3	.57 ± .09	.03 ± .02*	.16 ± .04	.30 ± .07	.44 ± .08	.63 ± .07
4	.57 ± .10	.13 ± .04*	.36 ± .07	.37 ± .07	.39 ± .07	.64 ± .08*
5	.59 ± .10	.10 ± .03*	.15 ± .04	.38 ± .07*	.42 ± .07	.54 ± .08
6	.61 ± .09	.18 ± .04*	.27 ± .06	.42 ± .07	.39 ± .06	.49 ± .06
7	.72 ± .12	.11 ± .04*	.22 ± .05	.36 ± .06	.28 ± .06	.50 ± .32*

* $P<0.05$ Difference between PN and MD 20 mg or MD 10 mg or placebo

TABLE 3

Mean Overmedication Score (± S.E.) with Propoxyphene Napsylate (PN), Methadone (MD) and Placebo Treatment

	GROUP A		GROUP B		GROUP C	
Day	PN	MD 20	PN	MD 10	PN	Placebo
0	.05 ± .05	0 ± 0	.08 ± .04	.08 ± .04	0 ± 0	.12 ± .07
1	.06 ± .03	0 ± 0	.06 ± .04	.02 ± .02	.28 ± .09	.16 ± .06
2	.07 ± .04	.02 ± .02	.10 ± .04	.06 ± .03	.28 ± .08	.04 ± .03*
3	.10 ± .07	.05 ± .03	.12 ± .06	.06 ± .03	.26 ± .07	.16 ± .06
4	.10 ± .06	.02 ± .02	.16 ± .06	.02 ± .02	.46 ± .08	.12 ± .04*
5	.12 ± .07	.04 ± .03	.08 ± .06	.12 ± .04	.36 ± .08	.14 ± .06*
6	.05 ± .03	.04 ± .03	.08 ± .06	.08 ± .03	.38 ± .09	.14 ± .06*
7	.08 ± .07	.19 ± .07	.08 ± .06	0 ± 0	.46 ± .10	.14 ± .06*

* $P<0.05$ Difference between PN and placebo

REFERENCES

1. Fraser, H.F., and Isbell, H. Pharmacology and addiction liability of d1 and d-propoxyphene. Bulletin on Narcotics XII: 9-14, 1960.

2. Inaba, D.S., Gay, G.R., Whitehead, M.D., and Newmeyer, J.A. The use of propoxyphene napsylate in the treatment of heroin and methadone addiction. West J Med 121:106-111, 1974.

3. Jasinski, D.R., Pevnick, J.S., Clark, S.C., and Griffith, J.D. Therapeutic usefulness of propoxyphene napsylate in narcotic addiction. Arch Gen Psychiat 34:227-233, 1977.

4. Tennant, F.S., Jr. Treatment of heroin addicts with propoxyphene napsylate. Proceedings of the Committee on problems of Drug Dependence 614-619, 1973.

5. Tennant, F.S., Jr., Russell, B.A., McMarns, A., and Cassas, M. Propoxyphene napsylate treatment of heroin and methadone dependence: one year's experience. J Psyched Drugs 6:201-211, 1974.

6. Tennant, F.S., Jr., Russell, B.A., Casas, S.K., and Bleich, R.N. Heroin detoxification. A comparison of propoxyphene and methadone. JAMA 232:1019-1022, 1975.

7. Woody, G.E., Mintz, J., Tennant, F.S., Jr., O'Brien, C.P., and McLellan, A.T. Usefulness of propoxyphene napsylate for maintenance treatment of narcotic addiction. In: Harris, L.S., ed. Problems of Drug Dependence, 1979: National Institute on Drug Abuse Research Monograph 27. DHEW pub. No. (ADM) 80-901. Washington, D.C.: Supt. of Docs., U.S. Govt. print. Off., 1980. pp. 240-246.

8. Woody, G.E., McLellan, A.T., O'Brien, C.P., Tennant F.S., Jr., and Mintz, J. Lack of toxicity of high dose propoxyphene napsylate when used for maintenance treatment of addiction. Clin Toxicol 16:473-478, 1980.

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Opiate Detoxification Using Lofexidine

Arnold M. Washton, Ph.D., Richard B. Resnick, M.D., Joseph F. Perzel, Psy.D., and John Garwood, M.D.

We have found clonidine to be useful in easing the pain and discomfort of opiate withdrawal in outpatients attempting to detoxify from heroin or methadone[1-3]. However, clonidine's potent sedative and hypotensive effects have limited its clinical usefulness with outpatients[2,3]. A nonopiate anti-withdrawal agent with greater specificity and fewer side effects might be safer and more effective for outpatient detoxification.

We now report preliminary findings with lofexidine (Merrell-Dow Pharmaceuticals), a structural analogue of clonidine that my have milder sedative and hypotensive effects[4,5]. Lofexidine has been shown to suppress withdrawal signs in morphine-dependent rats[6] but no previous studies have explored its efficacy in opiate addicted humans.

METHODS

Our subjects were fifteen methadone-dependent male outpatient volunteers who showed no evidence of medical or psychiatric illness and gave informed consent to the study which involved an abrupt switch from methadone to lofexidine. On day 1 subjects received their usual methadone dose (10-25 mg) and began a self-administered lofexidine dose regimen of 0.1 mg two or three times daily. On day 2, methadone was abruptly discontinued with subjects receiving a matched placebo methadone solution and the lofexidine dosage was increased to 0.1 mg four times daily. Subsequently, the lofexidine dose was increased as needed to no more than 0.4 mg four times daily according to symptoms and side effects. All subjects were told that the detoxification procedure would take 11 days and that naltrexone could be started on day 11 (10 days post methadone) provided that they used no illicit opiates during the study as confirmed by the absence of a precipitated withdrawal reaction to intravenous naloxone challenge (2.0 mg) on day 11. Subjects who did use illicit opiates during the first 10 days post methadone were allowed to continue on lofexidine and the naloxone challenge was postponed to the

first opportunity where it posed minimal risk of precipitating a withdrawal reaction (i.e., to at least 5 days after the last opiate use) but no later than day 21 of the study. Subjects who passed the naloxone challenge and started naltrexone on days 11-21 were considered successfully detoxified. Those who returned to using opiates and failed to begin naltrexone by day 21 were considered unsuccessful.

RESULTS

Successful detoxification and induction onto naltrexone was accomplished with ten of the fifteen subjects. All patients rated lofexidine as moderately to extremely effective in reducing most of the commonly experienced withdrawal symptoms: insomnia, lethargy, and muscle/bone pain were the most frequent residual complaints. None of the ten subjects reported unacceptable withdrawal symptoms while taking lofexidine. Those who failed to complete the detoxification procedure cited opiate craving rather than withdrawal discomfort as the major reason for returning to opiate use. No one reported oversedation, dizziness, or light-headedness from lofexidine, despite rapid increases in the dose to as much as 1.6 mg per day within the first 5 days. The maximum daily lofexidine dose ranged from 0.6 mg to 1.6 mg across the ten subjects with an average of 1.2 mg. There was no significant lowering of blood pressure even at the maximum lofexidine dose (mean pre-lofexidine BP=115/74 mm. Hg; mean BP at maximum dose=115/76 mm Hg). Dry mouth and mild drowsiness were the most commonly reported side effects. Upon study completion, reductions in the daily lofexidine dose by 0.2 to 0.6 mg per day produced no symptomatic complaints or significant changes in blood pressure.

COMMENT

This open clinical trial provides preliminary evidence of lofexidine's efficacy in reducing opiate withdrawal. The findings are similar to our results with clonidine[1-3] in terms of detoxification success rates and withdrawal symptom relief, but lofexidine seems to be considerably less sedating and hypotensive. Lofexidine may therefore prove to be safer and more clinically useful than clonidine, especially in outpatient detoxification. Our findings suggest that lofexidine might allow opiate-addicted outpatients even greater access to naltrexone or drug free nodalities without hospital admission. Controlled studies are needed to compare lofexidine with clonidine and/or methadone detoxification procedures.

REFERENCES

1. Washton, A.M., Resnick, R.B., Rawson, R.A. Clonidine hydrochloride: a nonopiate treatment for opiate withdrawal, Psychopharm Bull 16:50-52, 1980.

2. Washton, A.M., Resnick, R.B., Rawson, R.A. Clonidine for outpatient opiate detoxification. Lancet I: 1078-1079, 1980.

3. Washton, A.M. Resnick, R.B. Clonidine for opiate detoxification: outpatient clinical trials. Am J Psychiatry 137:1121-1122, 1980.

4. Maner, T., Mehta, J., Johnson, C., et al: Comparative efficacy of two centrally acting imidazoline derivatives, clonidine and lofexidine. Clin Res 28: 33A, 1980.

5. St. John LaCorte, W., Jain, A.K., Ryan, J.R., et al: Comparative efficacy and tolerability of lofexidine and clonidine given alone or concomitantly with hydrochlorothiazide in hypertensive outpatients. Clin Pharmacol Ther 29:259, 1981.

6. Shearman, G.T., Lal, H., Ursillo, R.C. Effectiveness of lofexidine in blocking morphine-withdrawal sighs in the rat. Pharmacol Biochem Behav 12:573-575, 1980.

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Lofexidine Blocks Acute Opiate Withdrawal

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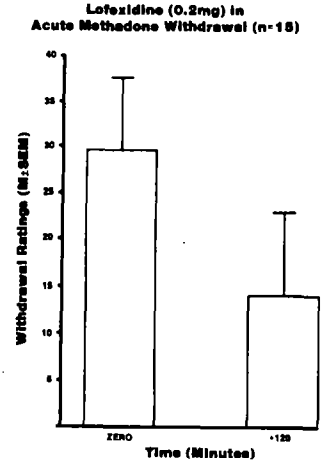
We have described potent antiwithdrawal effects for clonidine, the alpha-2 adrenergic agonist (1-6) which reduces brain noradrenergic activity. On the basis of clonidine's efficacy in human opiate withdrawal (1-6) we have again suggested that the opiate withdrawal syndrome might be better understood from the point of view of final, symptom-generating-events. The neurobiological events that we were particularly interested in were those which follow the discontinuation of chronic opiate administration and results in clinical signs and symptoms (7,8). We have reviewed rodent, primate, and human data which have supported an endorphin-locus coeruleus (LC) disinhibition hypothesis and a norepinephrine (NE) hyperactivity hypothesis for opiate withdrawal (7,8). While other hypotheses are quite viable, we have used this NE hyperactivity hypothesis to explain a large body of preclinical and clinical research and in screening potential antiwithdrawal treatments for clinical use. We tested the efficacy of clonidine in opiate withdrawal not only to demonstrate that clonidine might be a new and important treatment for addicts but also to determine which of the myriad of physiological and affective variables associated with withdrawal would be completely reversed and thereby attributable to specific agonistic effects of low dose clonidine at presynaptic alpha-2 receptors on the LC. The more complete the opiate reversal or opiate substitution by clonidine the more support for the NE hyperactivity hypothesis. After we administered clonidine to methadone addicts who had their methadone abruptly discontinued we recognized that clonidine was effective in reversing the full spectrum of acute withdrawal signs, symptoms and affects (3,4). In addition, clonidine when given chronically continued to suppress (nearly complete) the re-emergence of the withdrawal syndrome and could be safely discontinued without a withdrawal syndrome of its own (5,6). While the efficacy of clonidine offered strong support for the LC disinhibition NE hyperactivity hypothesis on the basis of the known effects of low dose clonidine on the LC and NE activity, it was only one test of the hypothesis. In addition, clonidine by virtue of its hypotensive and sedative effects was a clinical treatment which was ideally suited for rapid opiate detoxification in a hospital setting. More recently, we have suggested that lofexidine, an imidazoline derivative which is a structurally related analogue of clonidine, may be the ideal

non-opiate antiwithdrawal agent for outpatients (9). Lofexidine is a weak antihypertensive agent which has substantial affinity for clonidine binding sites in brain (8) and is believed to have similar anti-NE effects in brain without opiate receptor binding or opiate activity (10-12). We have recent data from 15 male chronic methadone addicts which demonstrate potent antiwithdrawal activity for lofexidine and offer additional support for the NE hyperactivity hypothesis of opiate withdrawal. The patients had been addicted to opiates for at least one year and to methadone for at least 6 months. All patients had previous unsuccessful detoxification attempts. All expressed interest in discontinuing methadone and all gave informed consent to the study, which required abrupt discontinuation of methadone and at least 36 hours with no opiate administration. All had objective 'signs of opiate withdrawal and urine specimens showing only residual methadone. The patients were observed for withdrawal signs and symptoms as reported previously (1-6) every 60 minutes from 8 a.m. while the patients were at bed rest and rated for 19 items associated with withdrawal as severe (3), moderate (2), mild (1) or absent (0). The withdrawal score was added to give a measure of withdrawal severity.

The number of withdrawal signs increased during the pre-lofexidine baseline period. All patients had objective signs as well as symptoms of moderate opiate withdrawal. After lofexidine 3 ug/kg was administered, the withdrawal score was significantly reduced ($p<0.01$) from 29.0 ± 8.3 to 14.1 ± 7.9 at 120 minutes after lofexidine (See Figure 1).

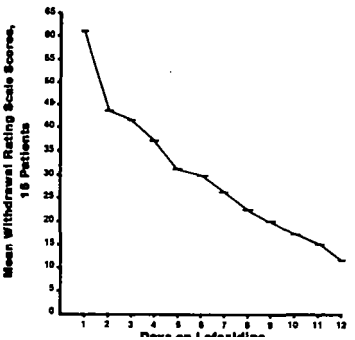
Fig. 1



Systolic and diastolic blood pressure were not significantly decreased and. remained in the normal range. Systolic blood pressure was 118.9 ± 13.8 pre-lofexidine and 111.3 ± 13.5 at 120 minutes. Diastolic blood pressure was 75.0 ± 13.9 pre and 75.4 ± 9.4 post-lofexidine. There were no significant changes in alertness, sedation or mood. Anxiolytic activity and relief from subjective distress was significant. All 15 patients felt that they were in withdrawal or "kicking" prior to lofexidine administration while only 3 of these patients stated that they were

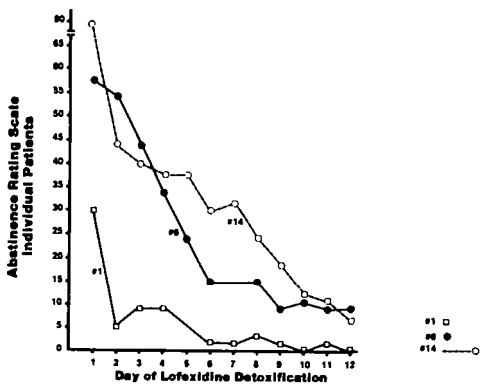
"kicking" at 120 minutes after lofexidine; All elected to remain in the hospital where they were given lofexidine 20 ug/kg/day in divided doses for at least 10 days. All patients were successfully detoxified from chronic methadone addiction in this inpatient study. During the first 5 days of lofexidine administration, there were consistent reductions in. the withdrawal ratings (See Figure 2).

Fig. 2



In addition the antiwithdrawal response was quite variable among individual patients (See Figure 3).

Fig. 3



The only consistent patient complaint was difficulty falling and/or staying asleep.

Opiate interactions with noradrenergic areas such as the locus coeruleus, which are regulated by both alpha-2 adrenergic and opiate receptors, may mediate the effects of exogenous and endogenous opiates which result in clinical signs and symptoms in association with the hyperactivity seen in opiate withdrawal (1-6,9). The effects of clonidine and now

lofexidine in opiate withdrawal support this hypothesis and suggest these medications reverse opiate withdrawal by replacing opiate-mediated inhibition, with alpha-2 adrenergic inhibition of noradrenergic activity. Clonidine, while a potent and effective nonopiate treatment for opiate withdrawal, has a number of properties which limit its usefulness for outpatient detoxification (2,9). Clonidine is sedating and hypotensive in doses necessary to reverse methadone withdrawal. However, with this dose of clonidine, withdrawal symptoms are abruptly terminated during acute withdrawal and continually suppressed during detoxification. Our data with a fixed dose of lofexidine suggest that antiwithdrawal effects can be separated from antihypertensive and sedating effects. However, the lofexidine effect appears incomplete and less potent than that observed for clonidine. Further studies are necessary to confirm the lack of hypotensive and sedating properties of lofexidine reported here. Further studies are also necessary to determine whether higher doses of lofexidine are necessary to produce the marked and near complete antiwithdrawal effects demonstrated for clonidine and whether these doses are also without sedative and hypotensive effects. In addition, the antiwithdrawal efficacy of clonidine and lofexidine should be tested in randomized double-blind studies where identical rating instruments are utilized. However, our demonstration of significant antiwithdrawal efficacy in chronic methadone addicts reported here and elsewhere (10,11) and the report by Dr. Resnick, Washton and co-workers in this volume for the nonopiate medication lofexidine suggest that an additional new treatment may be available for outpatient opiate detoxification and in the transition from opiate dependence to drug-free or naltrexone maintenance (3-5,9,10).

REFERENCES

1. Aghajanian, G.K. Tolerance of locus coeruleus neurones to morphine and suppression of withdrawal response by clonidine. Nature, 276:186-8, 1978.

2. Editorial, Lancet, 2:349-350, 1980.

3. Gold, M.S., Redmond, D.E., Jr., Kleber, H.D. Clonidine in opiate withdrawal. Lancet, 1:929-30, 1978.

4. Gold, M.S., Redmond, D.E., Jr., Kleber, H.D. Clonidine blocks acute opiate-withdrawal symptoms. Lancet, 2:599-601, 1978.

5. Gold, M.S., Pottash, A.L.C., Sweeney, D.R., Kleber, H.D. Opiate withdrawal using clonidine a safe, effective, and rapid nonopiate treatment. Jama, 243:343-346, 1980.

6. Gold, M.S., Pottash, A.L.C., Extein, I., Kleber, H.D. Clonidine in acute opiate withdrawal. N Engl J Med, 302:1421-22, 1980.

7. Gold, M.S., and Kleber, H.D. A rationale for opiate withdrawal symptomatology. Drug Alcohol Depend, 4:419-424, 1979.

8. Gold, MS., Byck, R., Sweeney, D.R., Kleber, H.D. Endorphin-locus coeruleus connection mediates opiate action and withdrawal. Biomedicine, 30:1-4, 1979.

9. Gold, M.S., Pottash, A.L.C., Extein, I., Kleber, H.D. Clonidine and opiate withdrawal. Lancet, 2:1078-79, 1980.

10. Gold, M.S., Pottash, A.L.C., Annitto, W.J., Extein, I., Kleber, H.D. Lofexidine, a clonidine analogue effective in opiate withdrawal. Lancet, 1:992-993, 1981.

11. Gold, M.S., Pottash, A.L.C., Kleber, H.D., Extein, I., Augusthy, K.A., Sweeney, D.R. Clonidine and lofexidine reverse opiate withdrawal. APA Abstract, New Orleans, pg. 156, 1981.

12. Jarrott, B., Louis, W.J., Summers, R.J. Effect of a series of clonidine analogues on clonidine binding in rat cerebral cortex. Biochem Pharmac, 28:141-44, 1979.

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Methodology for Assessing Agents That Suppress Methadone Withdrawal: A Study of Baclofen

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Recent reports that clonidine suppresses opioid withdrawal symptoms (Gold et al., 1980; Washton et al., 1980) and permits a more rapid withdrawal from opioids have rekindled hope that other non-opioid agents might also have value for those purposes.

We describe here (1) the development of an outpatient methodology for assessing agents that might be of value in suppressing methadone withdrawal and (2) some results of a pilot study of the effects of baclofen. Baclofen (Lioresal^{R}) is 4-amino-3(p-chlorophenyl) butyric acid (GABA), yet it does not seem to act via GABA mechanisms (Beart & Johnston, 1973). At present, baclofen is used primarily to reduce spasticity in neuromuscular disorders. It inhibits both monosynaptic extensor and polysynaptic reflexes without inhibiting neuromuscular transmission (Bein, 1972; Pierau & Zimmerman, 1973). In dogs, large doses produced a hypnotic effect (Fehr &C Bein, 1974). The drug inhibits withdrawal jump in opioid dependent mice and naloxone-induced jumping, writhing, salivation and other withdrawal signs in morphine-dependent rats; it does not appear to have a significant abuse potential, and it is not self-administered by baboons in standard self-administration tests (CIBA-GEIGY, unpublished). It does not suppress ethanol withdrawal in rhesus monkeys (Tarika & Winger, 1980).

The two major problems in assessing effects of pharmacological agents on opioid withdrawal syndromes are great variability among patients in terms of drug history and metabolism and the preponderance of physiological withdrawal items on existing rating scales, which require that relatively severe withdrawal be manifest before the items are scored positively. We have addressed these problems by using patients as their own controls in cross-over designs and by developing methods for assessing intensity of very early stages of opioid withdrawal with instruments weighted more toward psychological and subjective than physiological effects.

METHODS AND PROCEDURES

The studies to be described represent distinct stages in the refine-

ment of method. All subjects were volunteers recruited from methadone maintenance programs. Before beginning each study, the protocol was discussed with the subjects who signed informed consents. All studies were double-blind.

Pre-Pilot Work. Twenty-four hours after ingesting their regular dose of methadone, twelve subjects, chosen because they had stated that they often experience withdrawal within 24 hours after the last dose, were given either their regular dose of methadone or a placebo and were then observed for varying lengths of time up to 36 hours after their last regular dose. Subjects completed several self-report assessment forms at 2-hour intervals while observers rated certain behaviors. The assessment measures are described below. The purpose of this stage was to determine which of these measures could discriminate a methadone from a placebo condition during the early stages of withdrawal.

Form I was a nine-point global self-assessment of the subject's feeling with respect to degree of stabilization on methadone. The scale ranged from 1 - "very loaded, can't function" through 5 - "feel O.K., straight," to 9 - "terrible withdrawal sickness." Form II consisted of 38 items and included symptoms taken from the literature on opiate withdrawal, to which were added items obtained during interviews with methadone patients on the kinds of symptoms typically experienced if they missed their usual dose. Items on Form II were scored on a 0 to 3 scale (not at all, slight or a little, moderate, or very much). Form III was an observer rating of behaviors, such as yawning, sweating, tremor, frequently found in withdrawal, as well as the manifest psychological state described by adjectives such as "talkative, relaxed, irritable, happy." Each item was rated on a four-point scale, from 0 (none) to 3 (severe). The Weak Opiate Withdrawal (WOW) Scale (Haertzen, 1974), a battery of 35 true-false statements, was also administered.

This pre-pilot study demonstrated the feasibility of the outpatient study but also indicated that only low levels of withdrawal occur over the 36-hour period following the last dose of methadone. We concluded that a longer period of observation, i.e., at least 40 hours from last dose; would be needed to obtain reliable differences.

Pilot Study. Thirteen male subjects, ages 20 to 55, patients at a methadone clinic in New York City. came to the clinic on Thursday mornings and completed the four instruments described above. Oral temperature and pulse were also recorded.

After ingesting either methadone or placebo (dextromethorphan), in orange juice at approximately 8:30 A.M., subjects and staff went to a nearby motel and remained'there until the following morning. Subjects were under continuous staff observation. The four forms were filled out again at noon, 4 and 8 P.M. and midnight and pulse and temperatures were recorded. Urine specimens were obtained at the end of the session to determine whether any non-prescribed medications had been ingested during the preceding 24 hours, Subjects could drop out of the session by asking to take their "emergency dose" -- the subject's usual dose of methadone or a placebo, depending on what the subject had taken in the morning, prepared in

orange juice. Subjects were paid for their participation and were given a bonus if they completed both the experimental sessions. However, changes in schedules, employment demands and other considerations were such that only 7 of 13 subjects participated in bath conditions of the experiment. Of the remaining 6 subjects, 3 had methadone only and 3 placebo only, making a total of 10 observations for each condition.

Main Study. This study involved 11 male subjects (mean age, 29; range 23 to 40), 4 of whom had participated in some aspect of the pilot study. To further control the pre-study dose, subjects were required to come to the clinic on the Wednesday morning prior to the experimental session on Thursday. On Wednesdays the regular doses of methadone (mean dose, 66.4 ± 23; range 30-100 mg) were reduced by approximately 25% and ingested under direct observation. Because it was dispensed in multiples of 10 mg, precise reductions of 25% were not possible (range of reductions was 17-33%; mean reduction, 25.5%).

On Thursdays at 9 A.M., after a breath alcohol test, recording of temperature, pulse and blood pressure and completion of self-report instruments I and II, the subjects ingested either methadone (their usual dose in mg) or placebo. Methadone was dispensed as an elixir in cherry syrup (10 mg/cc) diluted with 6 oz of Tang solution; the placebo consisted of dextromethorphan in cherry syrup diluted with Tang solution to the same volume. As in the pilot study, an "emergency dose" consisting of the subject's usual dose of methadone or a placebo (depending on which he had ingested in the morning) was prepared and sealed by a research assistant (who did not participate in observations) and held by one of the observers. Subjects were free to discontinue the experiment at any time by asking to take the "emergency dose" and all were free to ingest the dose after the 2 A.M. completion of assessment instruments.

Form I (global self-rating) and Form II (symptom rating) were completed by subjects at 9 A.M., 12 noon, 2, 4, 8 and 10 P.M., 12 midnight, 2 and 8 A.M. Each of two observers filled out an observer checklist (Form III) at each of the times noted above. Subjects remained at the motel until 8 A.M. the following morning, at which time a urine specimen was obtained for subsequent screening for a variety of drugs of abuse. Oral temperature, pulse and blood pressure were recorded at 9:30 A.M., 12 noon, 4 and 10 P.M., and 2 A.M. An electronic sphygmomanometer was used to record blood pressure and pulse.

During the experimental day, the test medication was administered as follows. Immediately after completing the forms at 2, 6 and 10 P.M. subjects ingested two tablets of either baclofen or placebo. There were four experimental conditions: (1) methadone at 9:30 A.M. and placebo at 2, 6 and 10 P.M., (2) placebo at 9:30 A.M. and placebo at 2, 6 and 10 P.M., (3) placebo at 9:30 A.M. and baclofen 10 mg at 2 and 6 P.M. and 20 mg at 10 P.M., (4) placebo at 9:30 A.M. and baclofen 20 mg at 2, 6 and 10 P.M. To control for'the effect of order of administration, subjects were assigned to these conditions in a Latin Square design.

Two different, groups of subjects participated on four consecutive Thursdays in two four-week time periods: June/July and September/ October, 1980.

Results from Pre- and Pilot Studies. The pre-pilot and pilot studies demonstrated that three of the assessment measures (Global self-rating, Symptom rating, and Observer rating) effectively discriminated scores during baseline states (12 noon and 4 P.M.), from scores during expected withdrawal states (8 P.M. and midnight) under the placebo condition at a statistically significant level ($p < 0.05$). As illustrated in Figure 1, the scores on the fourth assessment measure, the Weak Opiate Withdrawal Scale, did not change significantly over the course of the day under the placebo condition; and it was, therefore, not used in the main study.

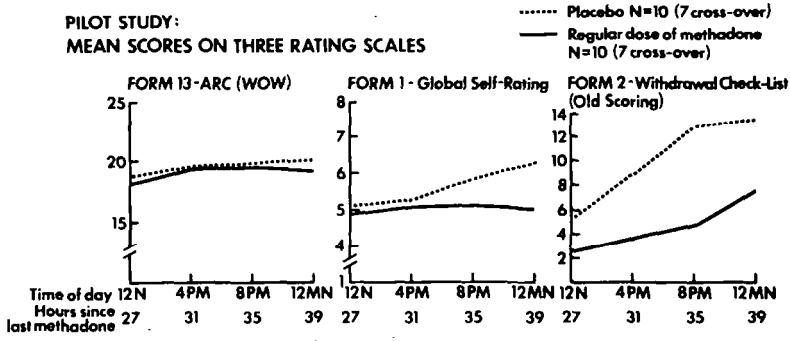

Figure 1

Main Study Results. Ten subjects completed all four conditions, one additional subject was absent for the session on low-dose baclofen.

An item analysis of Form II carried out after completion of the main phase using the placebo and methadone scores permitted us to identify those items which increased substantially during the placebo but not during the methadone condition; In addition, certain items were consistently scored higher during the methadone condition. These, therefore, were scored inversely, i.e., yielding negative scores. In all, 26 items are scored on Form II, five of them inversely, and a negative score indicating methadone effects rather than withdrawal is theoretically possible.

The results of the main study are summarized in Table 1. To obtain the summary scores shown in Table 1, the scores for each form were summed across the 8 P.M., 10 P.M., midnight and 2 A.M. points. The resultant sums were averaged for each treatment.

On Form I (Global self-rating), three subjects showed no change whatever in their scores between methadone and placebo conditions. We believe that including these non-discriminating subjects would inappropriately dilute the results of the other subjects on this form. Using a paired t test comparison of the Form I scores, the other eight subjects showed statistically significant differences (paired t test) between their own placebo and methadone treatments,

and these eight "discriminators" were used in subsequent analysis of Form I data.

Table 1

MEAN (± S.D.) SCORES SUMMED OVER 8 PM, 10 PM, 12 MIDNIGHT AND 2 AM

	METHADONE	PLACEBO	BACLOFEN 60 MG	BACLOFEN 40 MG	F
Form I Global Self-rating	19.1 ± 2.2	25.8 ± 3.0	22.8 ± 3.4	22.5 ± 2.8	7.48**
Form II Symptom Rating	16.5 ± 9.2	66.0 ± 47.8	42.0 ± 23.3	40.4 ± 31.5	8.31** (11 Ss) 5.39** (10 Ss)
Form III Observer Rating	5.4 ± 5.1	18.5 ± 15.0	12.3 ± 9.9	12.0 ± 11.3	6.47** (11Ss) 2.92* (10Ss)

*p = .05

**p = .01

NOTE: For From I, N - 8; for Forms II and III, N - 11 for methadone, placebo and baclofen 60 mg; N - 10 for beclofen 40 mg.

On Form II; all 11 subjects showed differences between their own placebo and methadone conditions (using paired t test) and, therefore, all were used.

The two observers, both blind to the experimental conditions, used Form III to rate all subjects under each test condition; the analysis of the scores for Form III presented in Table I is based on averaging the ratings of both observers.

Subjects had been assigned to treatments by a project monitor using a 4 x 4 Latin square repeated twice. For the Latin-square analysis, the eight who first completed the design were used. Since there was no order effect it appeared appropriate to use all available data in subsequent analysis including that from the extra subjects included in case of drop-out (see footnote 1). A repeated measure ANOVA of the subjects' summed scores was done for all three measures. All F's were statistically significant. On all three measures, the placebo and methadone mean scores were widely separated with the baclofen scores intermediate. It is obvious that there is almost no difference between the two baclofen conditions. A one-tail t test comparing the scores for the 11 subjects who had baclofen (60 mg) and placebo was statistically significant for Form I (p = .0315); and for Form II (p = .0420). Differences on the observer rating were borderline significant (p = .0611).

Changes among the means of the four treatments on Form I across the duration of the experimental day are shown in Figure 2. Despite the reductions in dose the day before the average score on the global self-rating in the morning (Form I) was 5.1 (5 = "feeling O.K., straight"). Under the placebo/placebo conditions, as the day progressed subjects rated themselves as feeling progressively less comfortable, and by 2 A.M. the mean score was 6.875 (7 = "definitely

sick but not enough to bother me much"). Under the methadone condition; there was a relatively prompt and dramatic change in the Form I group mean which continued to drop until 4 P.M. when the score was 4.125 (4 = "feel really good, but not loaded"); the scores progressively increased until 8 A.M.

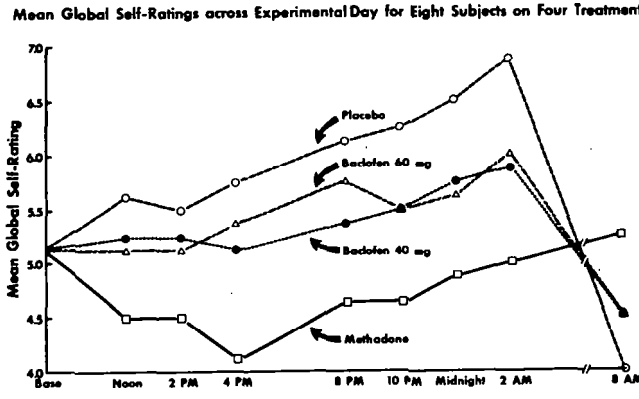

Figure 2

The changes in the reported symptoms (Form II) over the same period produced curves which are remarkably similar to those for Global self-rating shown in Figure 2. There were no significant differences among the four conditions for either blood pressure or oral temperature for any of the time periods.

DISCUSSION

When the Himmelsbach and related scales were developed, two assumptions were generally valid: (1) intervention to terminate the experience would be needed only in special circumstances; (2) patients undergoing withdrawal would exaggerate their distress in order to increase the chances of getting drugs and therefore the overall withdrawal score should give greater weighting to objective physiological signs (sweating, dilated pupils, blood pressure changes, etc.) than to verbally reported subjective changes (anxiety, depression, aches, pains, etc.).

In the present studies, there were few incentives for distorting or exaggerating the degree of distress and minimal penalties for opting to terminate the experience. Subjects seemed to understand what was expected and to take pride in their selection as "good discriminators." Under such circumstances, we felt that subjective reports might be more sensitive indicators of low-level withdrawal than the physiological aberrations which are given greater weight in the more traditional approaches. On the other hand, the decision to limit the period of observation to about 40 hours makes it difficult to know how severe the withdrawal syndrome might have been had it been allowed to run its course over several more days. We wish to emphasize that although the mean dose of methadone was 66 mg/day only relatively mild opioid withdrawal was studied in this experiment. On Form I

(Global self-rating) only two of the 11 Subjects ever rated themselves as "8" (very sick, hard to keep going with other activities") and such ratings occurred only under placebo conditions. Four additional subjects reported a maximum Global score of "7" (definitely sick, but not enough to bother me much") at some point during the study. Three subjects rated themselves almost consistently as "5" ("feeling O.K., straight") across all experimental conditions, although they reported more symptoms during the placebo conditions using Form II.

The low level of withdrawal can also be inferred from the observation that a number of the items on Form II that are usually associated with opioid withdrawal (e.g., nausea, diarrhea, backpains, gooseflesh) were not significantly greater under placebo than methadone conditions for the group as a whole.

The results of this study show that baclofen had a statistically significant suppressant effect on both self- and observer-rated manifestations of early and relatively mild methadone withdrawal with no significant difference between the dose levels (see footnote 1). We cannot account for the observation that, as a group, Subjects rated themselves as experiencing less withdrawal on Forms I and II at 12 noon and 2 P.M., on the days they were scheduled to receive baclofen, but before they actually received it. While these differences are not statistically significant they provoke curiosity. Were subjects able to decode the design with better than chance accuracy using their own internal perceptions as cues? Baclofen, in these subjects and at these doses, seemed remarkably benign. Especially interesting was the absence of sedation, which we had expected to be a problem, and of hypotension, which has proven to be a significant drawback in the use of clonidine.

In conclusion, we found that some signs and symptoms of mild methadone withdrawal were alleviated by baclofen. Whether the aspects of withdrawal alleviated were those associated with drug-seeking behavior is not known.

REFERENCES: Available from senior author upon request.

FOOTNOTE 1: Statisticians at CIBA-GEIGY take the position that only the eight subjects who completed the first two Latin squares of the main study should be used in the data analysis. If the analysis is limited in this way, methadone and placebo conditions are still significantly different from placebo.

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Urine Monitoring of Methadone Maintenance Clients: Does it Prevent Illicit Drug Use?

Barbara E. Havassy, Ph.D., and Sharon M. Hall, Ph.D.

Federal and State of California regulations require that maintenance clients provide urine specimens under observation. All urine specimens are analyzed for the presence of morphine. Urine specimens are also analyzed for the presence of methadone, barbiturates, and amphetamines, but on a less frequent schedule. The urinalyses are used as an objective measure of whether clients are 1) ingesting their methadone dose and 2) using illicit drugs.

The collection and analysis of urine specimens is a costly aspect of maintenance, especially when the staff time to maintain a random system and to observe clients urinating are added to the laboratory costs of drug screens. Furthermore, clients dislike the procedure and often successfully subvert it (Lewis, et al. 1972).

Whether the urine monitoring procedure prevents use of illicit drugs has not been demonstrated. Goldstein and Judson (1974) failed to find significant differences in illicit drug use over a three month period between monitored and unmonitored maintenance clients. The data are only suggestive, however, due to a high attrition rate, the resultant small sample size, marked inter-clinic variability and a short study period.

Equally problematic is the correct identification of drugs present in urine specimens. While accurate identification of commonly abused drugs is technically possible, low degrees of accuracy are found in the actual day-to-day identification of drugs (Gottheil, et al. 1976; Trellis, et al. 1975).

The purpose of the present study was to determine whether the mandated urine monitoring system deters illicit drug use of maintenance clients. The major hypothesis was that monitored subjects would provide more specimens that were free of illicit drugs than unmonitored subjects.

METHOD

Subjects were 431 methadone maintenance clients (271 males and 160

females) recruited from five diverse clinics in northern California. Mean age of the sample was 32 years, mean dose was 50 mg. and the modal time in treatment was 12 months. The demographic and treatment data collected on subjects were: time in treatment, sex, criminal justice status, results of urinalysis for a baseline period of six months prior to study-start, employment status, and ethnic group.

Subjects were recruited at their clinic by research staff and written informed consent was obtained. No clients were recruited for whom the risk of participation was judged to be unacceptable by clinic staff, generally clients who were extreme polydrug abusers or those undergoing involuntary detoxification. (Three of the five clinics did not exclude any clients; one clinic excluded 32 of 138 clients {23%}; another excluded 2 of 113 clients {1.8%}).

Subjects were stratified on the basis of age, sex, parole/probation status and urinalysis results during baseline and randomly assigned to the unmonitored or the monitored condition from within stratified blocks.

The Methadone Monitoring Unit of the Food and Drug Administration's Bureau of Drugs allowed suspension of Federal urine regulations and the California Research Advisory Panel allowed suspension of State urine regulations for the unmonitored group for one year. These subjects did not provide the clinic with any urine specimens for that period. In all other respects, these subjects received standard methadone treatment.

Clinic staff could require unmonitored subjects to leave a urine specimen when it was deemed clinically imperative (discretionary specimens). Each collection of a discretionary specimen was noted.

Monitored subjects continued to adhere to Federal and State urine monitoring requirements.

At four and eight months after the study began, research staff arrived unannounced at the clinics and conducted "surprise" urine tests in which specimens were collected from unmonitored and monitored subjects. No clinic staff knew how many surprise tests there would be, how many days the surprise tests would last, nor at what intervals they would be conducted.

Illicit drug use was measured via analysis of the urine specimens provided. A urine was considered drug-positive if it was positive for morphine, amphetamines, or barbiturates or negative for methadone and/or methadone metabolites.

Urines were analyzed by a commercial laboratory licensed by the, State of California. The laboratory used thin-layer chromatomography (TLC) with confirmation of drug-positive specimens. The laboratory was blind to the purpose of the study and to study conditions.

Six months after study-start a modification of the Client Satisfaction Questionnaire (Larsen, et al, 1976) was administered to both monitored and unmonitored subjects.

RESULTS

At baseline, treatment groups did not differ on the stratifying variables, or on employment status, ethnicity, age, methadone dose, year of first heroin use, year of first continuous heroin use, or year of last continuous use.

Urinalyses

Urine monitoring, as conducted in the five participating clinics, did not significantly affect outcome of the urine tests, We found no statistically significant difference between monitored and unmonitored conditions on the proportion of drug-free specimens.

Two parallel series of chi-square analyses were completed in which the data from all five clinics and all four indicators of illicit drug use (positive morphine; positive barbiturates; positive amphetamines; negative methadone) were combined. In the first series of chi-square tests, we eliminated from the analyses subjects in either, treatment group who refused to provide specimens. In the second series, we counted subjects who refused as having provided drug-positive specimens.

Results are shown in Table 1. When refusals are not counted in the analyses, urine monitoring does produce a slightly greater number of drug-free urines than unmonitored methadone maintenance, but only after eight months (urine test 2), x^2 (1)=3.21, .10>p>.05. This difference does not reach traditionally acceptable levels of significance. The results for four months (urine test 1) are $x^2(1)=0.304$, .70>p>.50. When refusals are counted as drug-positive specimens, differences are further attenated. For urine test 1, $x^2(1)=0.190$, .70>p>.50; for urine test 2, $x^2(1)=1.046$, .30>p>.20. Our overall N was 343 for urine test 1 and 298 for urine test 2. The remainder of the 431 subjects were either no longer in treatment when the surprise tests were conducted or were not available for participation on test days (i.e., in jail, in hospital).

We also examined differences between conditions for each of the four indicators of illicit drug use separately (collapsing data on each individual indicator across the five clinics). There was no association of treatment condition to presence or absence of the indicator.

Discretionary urines. Data on discretionary urines were examined to ascertain whether any unmonitored subjects might have been actually monitored by virtue of multiple discretionary urines. We found discretionary specimens were taken infrequently and only in two of the five clinics.

Recalculating the chi-square tests for just the three clinics that

did not take discretionary specimens did not alter the chi-square values or their associated p levels to any important extent.

Table 1

Outcome of Surprise Urine Tests 1 and 2

		Unmonitored		Monitored	
URINE TEST 1		n	%	n	%
Refusals Not Counted	Drug-free specimen	109	(66)	102	(69)
	Drug-positive specimen	55	(34)	45	(31)
Refusals-Drug Positive	Drug-free specimen	199	(63)	102	(60)
	Drug-positive specimen	65	(37)	67	(40)
URINE TEST 2					
Refusals Not Counted*	Drug-free specimen	93	(68)	94	(78)
	Drug-positive specimen	43	(32)	26	(22)
Refusals-Drug Positive	Drug-free specimen	93	(60)	94	(66)
	Drug-positive specimen	62	(40)	49	(34)

*$p<.10$.

Demographic variables and outcome. The demographic variables were not differentially associated with the two conditions with respect to urine test outcomes.

Experimental Participation and Termination from Treatment

Participation status in the surprise tests (partitioned by subject provided specimen; subject refused to provide specimen; subject terminated treatment; and subject not available) was differentially associated with experimental condition on urine test 1 at $p<.01$ but did not reach significance on urine test 2.

Post hoc analyses on the data partitioned into terminated treatment versus in-treatment indicated that termination from treatment during the study period was differentially associated with experimental condition. By urine test 1, 16% of the monitored subjects had terminated versus 8% of the unmonitored group, $x^2(1)=6.16$, $p<.05$; by test 2, 26% of the monitored subjects had terminated as compared to 18% of the unmonitored subjects, $x^2(1)=3.60$; $p<.10$.

Client Satisfaction with Treatment

Monitored and unmonitored subjects did not differ in overall client satisfaction. When client satisfaction items were partitioned a priori into those having a relationship to the urine-monitoring system and those not, three of the six items judged to be related did discriminate unmonitored and monitored conditions at $p<.05$. In all instances, the unmonitored subjects rated the clinic and their treatment more favorably. None of the items judged to be

unrelated to monitoring discriminated the two groups.

DISCUSSION

Effect of Monitoring on Illicit Drug Use

The major outcome of this study is that no consistent differences between the two groups on illicit drug use emerged, despite our examining the data from several perspectives.

It is important to note that, similar to others, we tested the system as it actually was implemented, not the system as it might be implemented in a laboratory research study (Milby & et al. 1978). While it is possible that improved monitoring systems might achieve better results (Harford & Kleber 1978), the ability of such systems. to do so across a diverse sample of clients remains to be demonstrated.

Termination from Treatment

The higher rate of treatment termination observed in the monitored condition merits further study. We propose two alternative hypotheses regarding the relationship: (1) urine monitoring may increase the subjective "cost" of participation in maintenance, so more clients drop out when monitored than when not; and (2) urine monitoring may be of particular value to clients attempting to taper off methadone and that successful tapers are reflected in termination statistics. We have no data to suport these hypotheses. If this question is to be resolved, further research is needed.

Client Satisfaction with Treatment

While there were no observed differences between treatment groups regarding overall satisfaction with treatment, unmonitored subjects reported a more general satisfaction with some aspects of treatment, and they were more likely to perceive an improvement in their avoidance of illicit drug use. These findings are not surprising, given clients' dislike of the disciplinary consequences of urine monitoring (Lewis et al. 1972, Trellis, et al. 1975).

In conclusion, results. of this study do not indicate that urine monitoring is a strong uniform deterrent to illicit drug use for methadone clients in general or for any particular subgroup of them.

REFERENCES

Goldstein, A., Judson, B.A. Three critical issues in the management of methadone programs. In: Bourne, P., (ed): Addiction New York. Academic Press, 1975, p129-148.

Gottheil, E., Caddy, G.R., Austin, D.L.: Fallibility of urine drug screens in monitoring methadone programs. JAMA 236:1035-1038, 1976.

Harford, R.J., Kleber, H.D.: Comparative validity of random interval and fixed interval urinalysis schedules. Arch Gen Psychiatry 35:356-359, 1978.

Larsen, D., Attkisson, C., Hargreaves, W.: Client Satisfaction Questionnaire, 1976.

Lewis, V.A., Petersen, D.M., Geis, G., Pollack, S.: Ethical and social-psychological aspects of urinalysis to detect heroin use. Brit J Addiction 67:303-307, 1972.

Milby, J., Toro, C., Thornton, S., Rickert, D., Clark, C.: Some urine surveillance effects on drug abusers in psychotherapy. Brit J Addict 143:1-2, 1978.

Trellis, E.S., Smith, F.F., Alston, D.C., Siassi, I.: The pitfalls of urine surveillance: the role of research in evaluation and remedy. Addic Behav 1:83-88, 1975.

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Contingent Reinforcement of Benzodiazepine-Free Urines From Methadone Maintenance Patients

Maxine Stitzer, Ph.D., George Bigelow, Ph.D., and Ira Liebson, M.D.

Supplementation with illicit drugs is commonly observed among patients enrolled in methadone maintenance treatment, and represents continuation of the behavioral problem which brought these individuals into treatment in the first place. Although reduction or elimination of supplemental drug use is invariably seen as a primary goal of treatment, it is somewhat of a paradox that few specific therapeutic techniques are available for dealing with on-going drug use among drug abuse patients. Treatment clinics commonly employ two tactics for dealing with on-going drug use: verbal encouragement to eliminate use and threats of expulsion from the clinic followed by actual expulsion if drug use does not cease. The present paper reports on a specific intervention designed to reduce or eliminate supplemental drug use among methadone maintenance patients. The intervention involves providing alternative reinforcers contingent upon urinalysis-evidence of reduced drug use. The benzodiazepine class of drugs was chosen as a focus for evaluation of this contingent reinforcement intervention both because these drugs appear to be widely abused among methadone patients (Bigelow et al. 1980; Kleber and Gold 1978; Woody et al. 1975) and because an objective and rapid urinalysis test is available for detecting the use of drugs from this class.

METHODS

Ten study participants were selected on the basis of urinalysis evidence of continuing use of benzodiazepine drugs following enrollment in the methadone maintenance clinic. All were male, nine were white and one was black. Table 1 presents demographic characteristics of these patients as well as self-report information obtained from eight of the ten study participants in an unrelated survey study concerning dosages and patterns of benzodiazepine drug use. This self-report information, summarized in Table 1, suggests that these patients by and large used benzodiazepine drugs in an abusive rather than a therapeutic dose range. Furthermore, six of the eight survey participants

TABLE 1

CHARACTERISTICS OF STUDY PARTICIPANTS (N=10)

	Average	Range
Age (years)	28.2	24 - 33
Years of addiction	10.0	5 - 12
Methadone dose (mg)	55.0	30 - 80

SELF-REPORTED BENZODIAZEPINE USE (N=8)

	Median	Inter-quartile Range
Usual daily dose (mg)	72.5	25.0 - 187.5
Highest daily dose (mg)	225.0	60.0 - 482.5

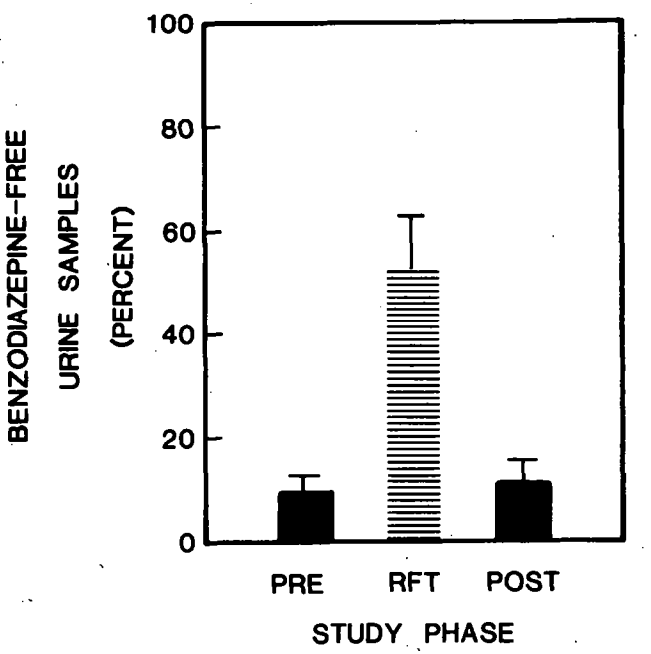
reported taking the daily dose of benzodiazepines all at once generally within an hour of the time they ingested their methadone.

Study participants came to the clinic daily to drink a methadone and cherry syrup solution (Methadose) under nursing supervision and gave urine samples twice weekly on Monday and Friday. Urine samples were tested for benzodiazepines using an on-site EMIT system and were tested for a wide range of other drugs of abuse by TLC analysis provided by an outside laboratory. During pre and post intervention baseline periods of approximately 12 weeks duration, no consequences were attached to results of urinalysis testing. At the start of the contingent reinforcement intervention period, subjects were told that, until further notice, they would be able to obtain a reward for providing benzodiazepine-free urines at the clinic. Subjects were told that this was a voluntary program and that they were free to do as they wished with regard to their extra drug use. During the intervention period, if the urine sample was benzodiazepine-free, subjects could choose one of three incentives offered: 1) two methadone take-home doses; 2) $15 cash payment; 3) two opportunities to regulate the methadone dose received by as much as ± 20 mg. These positive incentives were available twice weekly during the intervention period which generally lasted 12 weeks and were delivered immediately after determination of a benzodiazepine-free urinalysis test result. There were no consequences if the urine sample was positive for benzodiazepines.

RESULTS

Figure 1 shows a dramatic increase in benzodiazepine-free urine samples for the group of subjects during the contingent reinforcement intervention period compared to the pre and post intervention periods. A specific influence of the contingent

FIGURE 1



Percent of urine samples which were free of benzodiazepine drugs is shown for the group of ten study subjects during three study phases: pre intervention baseline (pre), contingent reinforcement intervention (rft) and post intervention baseline (post). Brackets indicate ± 1 S.E.M.

reinforcement intervention is apparent since benzodiazepine negative tests returned to previous low levels when the intervention was withdrawn. The effect on urinalysis test results was significant ($p<0.05$) in a repeated measures analysis of variance. Eight of the ten study participantsreduced their benzodiazepine use during the contingent reinforcement intervention; five remained benzodiazepine-free during the entire 12-week period, while three relapsed to benzodiazepine use during the inter-vent ion.

Figure 2 shows results of urinalysis testing for drugs other than benzodiazepines. No systematic changes in use of drugs from other classes were noted during the period when benzodiazepine use was reduced.

DISCUSSION

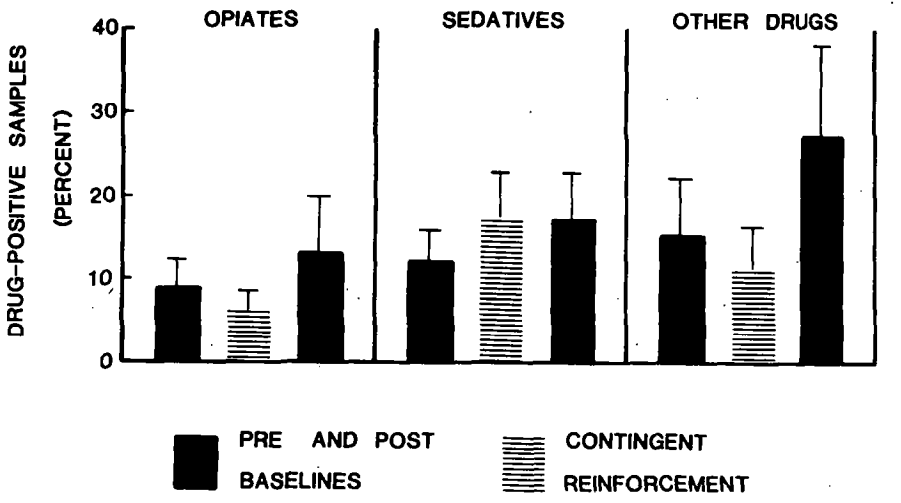
This within-subject evaluation demonstrates that a therapeutic intervention which offers positive incentives for clean urines can have a dramatic impact in reducing supplemental benzodiazepine use as revealed by urinalysis testing. This result was obtained in a group of methadone clinic patients who were, by urinalysis and self-report evidence, chronic abusers of the class of drugs upon which the intervention focused. This study replicates and extends to the benzodiazepine drug class positive results which have been reported for contingent reinforcement procedures when incentives have been offered to heroin supplementers for providing opiate-free urines at the treatment clinic (Hall et al. 1977 1979; Stitzer et al. 1980).

A previous study (Stitzer et al. 1979) showed that reinforcement contingent on refusal of available drugs was effective in reducing requests for benzodiazepine drugs at the clinic dispensary. The present study extends the use of contingent reinforcement procedures for abstinence to drug use which is occurring in the natural environment. The efficacy of these procedures is impressive since reinforcers offered at the clinic must compete with the intrinsic reinforcing efficacy of the drug of abuse. Reinforcement of clean urines appears to be an effective and practical technique when applied in an outpatient methadone maintenance treatment setting. No adverse side-effects of positive incentive procedures were noted in the present study or in previous studies. The results of this study suggest that more widespread application of contingent reinforcement procedures may be warranted for influencing on-going drug use among drug abuse patients enrolled in treatment clinics.

REFERENCES

Bigelow, G., Stitzer, M., Lawrence, C., Krasnegor, N., D'Lugoff, B., and Hawthorne, J. Narcotics addiction treatment: Behavioral methods concurrent with methadone maintenance. Int J Addict, 15:427-437, 1980.

FIGURE 2



Percent of drug-positive samples are shawn for a group of ten study subjects during three study phases. From left to tight within each panel these study phases are pre intervention baseline, contingent reinforcement intervention and post intervention baseline. Opiate positives include morphine, quinine, codeine and demerol; sedative positives include ethchlorvynol, barbiturates, meprobamate and methaqualone; other drug positives include phenothiazines, propoxyphene, phencyclidine and amitriptyline. Brackets indicate ± 1 S.E.M.

Hall, S.M., Cooper, J.L., Burmaster, S., and Polk, A. Contingency contracting as a therapeutic tool with methadone maintenance clients: Six single subject studies. Behav Res Ther, 15:438-441, 1977.

Hall, S.M., Bass, A., Hargreaves, W.A., and Loeb, P. Contingency management and information feedback in outpatient heroin detoxification. Behav Ther, 10:443-451, 1979.

Kleber, H.D., and Gold, M.S. Use of psychotropic drugs in treatment of methadone maintained narcotic addicts. In: Kissin, B., Lowinson, J.H., and Millman, R.B., eds. Recent Developments in Chemotherapy of Narcotic Addiction. Ann NY Acad Sci, 311:81-98, 1978.

Stitzer, M.L., Bigelow, G.E., and Liebson, I. Reducing benzodiazepine self-administration with contingent reinforcement. Addict Behav, 4:245-252, 1979.

Stitzer, M.L., Bigelow, G.E., and Liebson, I. Reducing drug use among methadone maintenance clients: Contingent reinforcement for morphine-free urines. Addict Behav, 5:333-340, 1980.

Woody, G.E., Mintz, J., O'Hare, K., O'Brien, C.P., Greenstein, R.A., and Hargrove, E. Diazepam use by patients in a methadone program - how serious a problem? J Psychedelic Drugs, 7:373-379, 1975.

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Clinical Analgesic Assay of Sublingual Buprenorphine and Intramuscular Morphine

Stanley L. Wallenstein, Robert F. Kaiko, Ada G. Rogers, and Raymond W. Houde

Buprenorphine, a C-ring bridged oripavine, is a strong analgesic derived from thebaine which has demonstrated both narcotic agonist and antagonist activity in man and animals. Its analgesic activity as determined in studies carried out by us(Houde 1979) and others (Heel et al. 1980, Robbie 1979) indicate that intramuscular buprenorphine is 25 to 30 times as potent as intramuscular morphine. As a narcotic antagonist, buprenorphine is estimated to be equal in potency to naloxone on a milligram basis. Sublingual buprenorphine has been employed with sane success in the management of pain due to cancer at The Royal Marsden Hospital in London (Robbie 1979). Individual doses as high as 0.8 mg have been reported to be particularly useful in the management of pain in patients with head and neck and gastrointestinal cancer, and is said to have little constipating effect.

Cur previous study (Houde et al. 1977) of intramucularly administered buprenorphine was carried out in 136 patients (126 with postoperative pain and 8 with chronic cancer pain) as a series of sequentially-related twin crossover assays in doses ranging from 0.1 to 1.6 mg. Only small numbers of patients received the extreme lower and upper doses, and all series were eventually combined in a single estimate of relative potency (ϕ = 28) with rather tight 95% confidence limits for an assay of this type (ϕ = 21 to 35). There was no significant change in the relative potency estimates when the series with the extreme doses were eliminated fran the analysis; nevertheless, the possibility that curvature is present at the high or low doses of the buprenorphine dose-response curve cannot be ruled out, as the test for parallelisn is relatively insensitive in the twin crossover assay. This test is a non-crossover one; and significant effects may merely represent patient group differences.

This present report represents a study in progress of the relative potency of sublingual buprenorphine and intramuscular norphine in patients with postoperative pain and a methodological report of an incomplete block assay designed both to cover a

wide range of doses and to provide sane estimate of the presence or absence of curvature in the dose-effect curves of the drugs under study.

METHODS

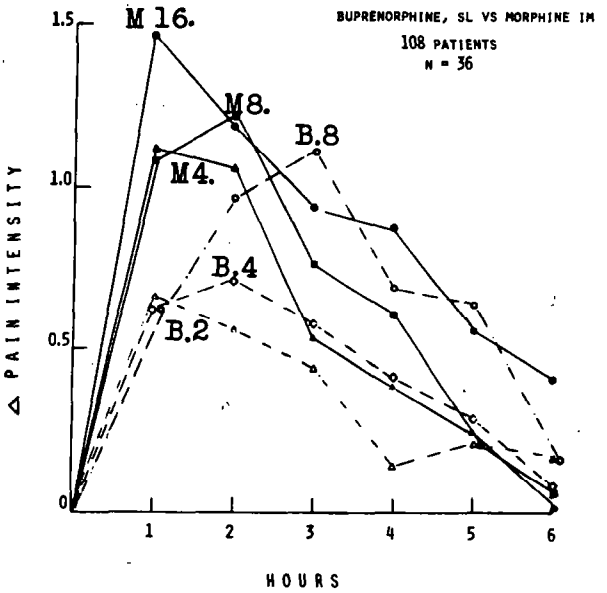
The basic methodology employed in this assay adheres to the principles of clinical study design employed by this group and previously reported (Wallenstein and Houde 1975). Male and female inpatients with postoperative pain were included in the assay if the following conditions were met: The presence of severe or moderate pain; the ability to communicate; age over 18 years; no medical contraindications to narcotic-type drugs; approval of the attending physician or Service to which the patient had been admitted; and the written consent of the patient. patients were seen hourly fran 9 a.m. to 5 p.m. by analgesic nurse observer who recorded the patients' subjective reports of pain intensity and pain relief employing both categorical and visual analogue scales (VAS). Pertinent concomitant signs and symptoms and volunteered side effects are-also recorded. Only one study medication per day was administered and no study drug given within three hours of a prior analgesic. Observations were continued-for either six hours or until pain returned to the premedication level at which time the patient's regular non-study analgesic was administered.

The assay consisted of three equi-log-spaced doses of the standard drug (intramuscular morphine) and of the test drug (sublingual buprenorphine). To maintain double-blind conditions, each patient received both an injection and a sublingual tablet, one of which was a dummy medication and one the active drug as prescribed by the study design. Each patient received only two medications on separate days; a lower dose of one drug and an upper dose of the other, or the middle dose of each drug on a double-blind, randomized basis, but balanced for order. The design is a modification of the sequential twin crossover assay previously employed by us, and has the advantage of covering a wide range of doses without the need for sequential adjustments during the course of the assay. It also has the advantage of providing sane estimate of the curvature of the dose-response slopes of the two drugs. For an ideal assay, the drugs should be evaluated in the same effect range (insignificant drug differences), slope effects should be highly significant with minimal deviations from parallelism and the comparisons made in the straight-line portion of the dose-effect curves of the two drugs (insignificant curvature and deviation in linearity effects).

RESULTS

Of 140 patients started in the assay, 108 have contributed to completed balanced blocks and are included in the relative potency analysis. Patient characteristics of age, sex, race, height and weight were comparable for the three treatment groups, and there were no significant differences in the level of pain at the time of medication for the six doses of study drug.

FIGURE 1



Time-effect curves for 4, 8 and 16 mg of intramus cular morphine (M, solid lines and symbols) and 0.2, 0.4 and 0.8 mg of sublingual buprenorphine (B, broken lines and open symbols).

The time-action characteristics of the two drugs demonstrate a somewhat earlier and more intense peak effect for morphine than for buprenorphine (figure 1). At doses that produced about the same peak intensity (4 mg of morphine, IM and 0.8 mg of buprenorphine, SL), buprenorphine produced a longer lasting analgesic effect. These results are in marked contrast with those we previously obtained with intramuscular buprenorphine, whose time-effect curves were indistinguishable fran morphine.

Statistically valid relative potency estimates (ϕ) were obtained in terms of total relief estimates on both VAS and categorical scales, (table 1). Highly significant slopes with no significant deviations in parallelism or linearity were obtained. The best estimate of relative potency was that sublingual buprenorphine was 15.5 times as potent as intramuscular morphine in terms of total effect. As would be expected fran the shape of the time-effect curves, sublingual buprenorphine is considerably less potent in terms of peak than total effect, and some extrapolation is required to arrive at a relative potency estimate. The best estimate of relative potency in terms of peak action was obtained with the VAS relief scores and indicated buprenorphine to be 9.4 times as potent as morphine.

TABLE 1

Relative potency estimates of intramus cular morphine and subling-ual buprenorphine in terms of peak and total categorial (CAT) and visual analog (VAS) measurements of pain relief.

RELIEF SCORES

	CAT		VAS	
	Peak	Total	Peak	Total
M 4	79	195	2044	5236
M 8	86	236	2258	6189
M 16	81	288		7515
B 0.2	77	197	1908	5178
B 0.4	66	194	1858	5310
B 0.8	77	277	2324	7256

MEAN SQUARES

M - B	6.0**	12	2185*	6600
Slope	1.0	208**	4876**	131950*
Parallelism	1.0	1	0.3	275
Linearity	0.9	22	602	11092
Dev. in Lin.	1.3	13	631	4820
Within Pts.	0.6	13	400	8850
ϕ	—	15.2		
Limits	∞	(7.1, 27.3)	(2.4, 17.9)	(7.0 28.6)

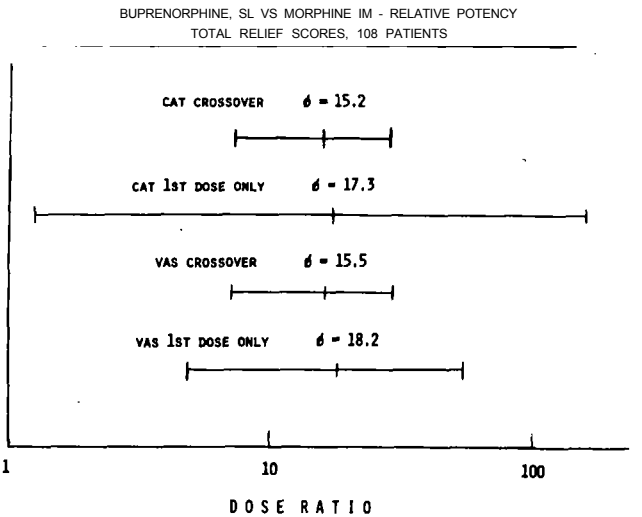
*P<0.05, **P<0.01

Total and peak relief Were also analyzed using only first-data to provide information for a single dose, non-crossover analysis. Valid assays were again obtained in terms of total relief. The results using crossover and non-crossover CAT and VAS data are graphically compared in figure 2. The relative potencies are all similar, indicating no apparent-interaction effect When a second dose was given, but the crossover comparisons were the most efficient providing the narrowest confidence limits.

Patients were not questioned directly about side effects but observed or volunteered side effects were recorded. All patients, including those who failed to complete the crossover assay are included in the analysis of side effects, Which Were observed in 44 percent of the 122 patients who received morphine and 42 percent of the 137 patients Who received buprenorphine. Side effect

occurrence was essentially similar for the two drugs, the most common being sleepiness (47 on M and 54 on B), followed by grogginess (7 on M, 8 on B), lightheadedness (5 on each), nausea (5 on M, 4 on B) and headache (4 on M, 5 on B). More patients were dizzy, sweating and jittery on buprenorphine; and more were warm, stimulated and weak on morphine.

FIGURE 2



Relative potency esimates (ϕ) of sublingual buprenorphine to intramuscular morphine in terms of crossover and first dose only data using CAT and VAS total relief scales with corresponding 95 percent confidence limits.

SUMMARY

A six-point, incomplete block assay of sublingual buprenorphine and intramuscular morphine has been carried out, providing valid relative potency estimates of the two drugs in terms of total relief on both categorical and visual analog scales. Sublingual buprenorphine was about 15.5 times as potent as intramuscular morphine in term of these total relief estimates. Similar

relative potency estimates were obtained using first-dose-only data. There was no evidence of interaction by day in the crossover data, and the crossover study proved more efficient and provided tighter confidence limits. Sublingual buprenorphine produced a lower peak effect than intramuscular morphine. At equivalent peak effects, it produced longer-lasting analgesia. Side effect occurrence was roughly comparable for the two drugs, and no evidence of narcotic antagonist activity was seen after buprenorphine. The six-point assay proved to be effective in defining the dose-effect curves and relative potencies of the two drugs.

REFERENCES

Heel, R.C., Brogden, R.N., Speight, T.M. and Avery, G.S. Buprenorphine: A review of its' pharmacological properties and therapeutic efficacy. Drugs, 17:81-110, 1980.

Houde, R.W. Analgesic effectiveness of the narcotic agonist-antagonists. Brit J clin Pharmacol, 7:297S-308S, 1979.

Houde, R.W., Wallenstein, S.L., Rogers, A., and Kaiko, R.F. Annual report of the Memorial Sloan-Kettering Cancer Center, Analgesic Studies Section. Proceedings of the Thirty-ninth Annual Scientific Meeting of the Committee on Problems of Drug Dependence., pp. 179-180, July, 1977.

Robbie, D.S. A trial of sublingual buprenorphine in cancer pain. Brit J clin Pharmacol, 7:315S-317S, 1979.

Wallenstein, S.L. and Houde, R.W. The clinical evaluation of analgesic effectiveness. In: Ehrenpreis, S. and Neidle, A., eds. Methods in Narcotics Research. New York: Marcel Dekker, Inc., 1975. pp. 127-145.

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Sources of Variation in Morphine Analgesia in Cancer Patients With Chronic Pain

Robert F. Kaiko, Stanley L. Wallenstein, Ada G. Rogers, and Raymond W. Houde

The amount of pain relief has been found to vary greatly among patients receiving identical analgesic treatments. The clinical evaluation of analgesics incorporates various methods in an attempt to control for both known and unknown factors influencing the analgesic response. Such methods as the randomization of treatments, crossover designs, stratification and matching of patients for particular characteristics, and techniques to minimize bias are commonly employed. Large numbers of subjects are often required for analgesic assays in order to provide valid and reproducible results because of the variation fran subject to subject in analgesic response. Identification of sources of variation within any given assay is difficult due to their multiplicity and potential for interaction with one another. However, we do know that, in postoperative pain, the age of the patient and the intensity of the pretreatment pain are significant sources of variation in the response to narcotic analgesics. It has been shown that morphine and pentazocine provide more pain relief in postoperative pain in direct relation to age (Bellville et al. 1971; Kaiko 1980); narcotics provide more relief when postoperative pain is moderate as compared to severe (Gravenstein and Beecher 1957), and when wound pain is steady as compared to sharp (Keats 1956). Less information is available in terms of sources of variation in the relief of chronic pain.

The objective of this retrospective survey w-as to determine the influence of age, race, sex, pretreatment pain intensity, pain character and pain site on the relief of chronic pain due to cancer by graded doses of intramuscular morphine sulfate.

METHODS

Relative analgesic potency assays carried out over a period of approximately twenty years in cancer patients with chronic pain served as the source of data. These assays were double-blind, complete crossover studies in which morphine, 8 and 16 mg, was the standard of comparison in the evaluation of investigational analgesics.

The method of the complete crossover analgesic assay has been previously reported in detail (Houde et al. 1960; Wallenstein and Houde 1975). Briefly, consenting patients had been seen hourly and questioned about the severity of their pain. Pain intensity was categorized as none, slight, moderate and severe. When the patient requested medication for pain which was reported as moderate or severe, a study medication was given. Patients received study medication according to a design randomized for drug, dose and order of administration. Estimates of analgesia, including pain relief, were obtained hourly until pain returned to the premedication level, or up to six hours. Pain relief was categorized as none (0), slight (1), moderate (2), lots (3) and complete (4). Total pain relief (TOTPAR) is the sum of the hourly pain relief scores for the observation period for each study drug administration.

Data were surveyed fran 715 patients receiving 565 8-mg doses and 538 16-mg doses of intramuscular morphine sulfate. Data from patients who failed to complete the crossover were also included. TOTPAR scores were separated into categories according to the patients's age, race and sex and according to the pretreatment pain intensity, pain character and site of pain. Patient and pain characteristic data were complete for 97 percent of the sample.

RESULTS

Mean TOTPAR was 5.95 ± 0.23 (SE) and 8.13 ± 0.27 for the 8- and 16-mg doses, respectively. Subsequent patient- and pain character-related differences will be compared to these scores and to the dose-related difference of 2.2 in terms of TOTPAR. Table 1 shows the TOTPAR scores in relation to categories of patient and pain characteristics following the 8- and 16-mg morphine doses.

The data were arbitrarily divided into four age groups: 18 to 29 year olds, 30 to 49, 50 to 69, and 70 to 89 year olds. The majority of the sample was between 30 and 69 years with about 100 patients less than 30 and about 50 who were 70 years and older. The difference in TOTPAR between the youngest and oldest groups was 4.4 for 8-mg doses and 4.6 for 16-mg doses, as compared to the overall dose-related difference of 2.2 in terms of TOTPAR. Pain relief privided by 8-mg doses in middle-aged groups was comparable to relief provided by 16-mg doses in the youngest group. Relief provided by 8-mg doses in the oldest group was comparable to relief provided by 16-mg doses in the middle-aged groups.

Most patients were white. There were about 125 black patients and relatively few oriental patients. Race-related differences in relief were significant after both doses. While the limited number of oriental patients make their statistical contribution insignificant, it is clear that black patients obtained significantly greater pain relief than white patients after both doses. The difference in TOTPAR between black and white patients was 2.8 for the 8-mg doses and 2.7 for the 16-mg doses, as compared to the overall

TABLE 1. *Total Pain Relief Scores in Relation to Patiaent and Pain Characteristics in Cancer Patients with chronic Pain following Intramuscular Morphine Sulfate.*

CHARACTERISTIC	TOTAL PAIN RELIEF ($\bar{x}$ ± SE, N)					
	8 mg Morphine			16 mg Morphine		
(Overall)	5.95	0.23	565	8.13	0.27	538
Age (yr)						
18 - 29	4.13	0.61	45	5.92	0.71	48
30 - 49	5.95	0.38	205	7.99	0.42	215
50 - 69	6.13	0.35	267	8.46	0.40	254
70 - 89	8.56	1.03	27	10.52	1.57	21
	(F 3.74; df 543; P<0.05)			(F 3.36; df 537; P<0.05)		
Race						
White	5.58	0.23	495	7.75	0.28	466
Black	8.38	0.92	64	10.43	0.84	61
Oriental	10.50	3.22	6	11.80	2.00	10
	(F 9.73; df 564; P<0.01)			(F 6.82; df 536; P<0.01)		
Sex						
Male	5.76	0.36	237	7.65	0.42	213
Female	6.25	0.31	315	8.41	0.35	324
	(t 0.47; df 540; NS)			(t 1.36; df 535; NS)		
Initial Pain						
Severe	5.82	0.26	449	7.72	0.28	447
Moderate	6.65	0.54	108	9.12	0.63	115
	(t 1.43; df 552; NS)			(t 2.17; df 557; P<0.05)		
Pain Character						
Throbbing	3.81	0.65	16	6.00	1.22	13
Radiating and Shooting	4.00	1.58	4	18.00	0	2
Sharp	4.45	0.35	151	7.20	0.45	160
Burning	5.20	1.00	25	6.19	1.57	16
Pulling	6.33	2.32	6	7.67	2.84	6
Soreness	6.34	0.78	59	6.65	0.86	51
Pressing or Tight	6.42	0.69	52	7.45	0.68	67
Dull, Aching and Diffuse	6.82	0.43	187	8.99	0.46	184
Crampy	11.92	0.58	13	11.05	1.77	20
	(F 4.74; df 512; P<O.01)			(F 3.05; df 518; P<0.01)		
Pain Site						
Head	8.30	1.97	10	4.69	1.05	13
Neck	6.11	1.24	19	6.11	1.19	18
Arm	5.24	0.83	49	6.12	0.70	43
Chest	5.24	0.60	72	6.41	0.72	61
Pelvis and Perineum	4.72	0.82	36	7.69	1.05	36
Leg	6.15	0.59	91	7.81	0.59	99
Face	5.80	2.00	5	8.00	4.01	2
Abdanen	7.39	0.73	66	8.83	0.73	82
Back	6.04	0.43	161	9.07	0.52	161
	(F 1.28; df 508; NS)			(F 2.58; df 514; P<0.01)		

dose-related difference of 2.2 in terms of TOTPAR. Pain relief provided by 8-mg doses in black patients was comparable to relief provided by 16-mg doses in white patients.

The ratio of female to male patients was 3 to 2. Sex-related differences were not significant. The trend toward greater pain relief in women is consistent with a lower mean body weight of 60 kg as compared to 65 kg for men in this sample.

Initial pain intensity was reported as severe in 80 percent of cases and as moderate in only 20 percent. Relief was not significantly different in terms of initial pain intensity after the 8-mg doses, but was significantly greater with moderate as compared to severe initial pain after the 16-mg doses of morphine. The difference in TOTPAR after 16-mg doses was 1.4 as compared to the overall dose-related difference of 2.2 in terms of TOTPAR.

The majority of patients reported their pain either as sharp or as dull, aching and diffuse. The categories of pain character are arranged in Table 1 in order of increasing relief for the 8-mg dose. Pain character-related differences in TOTPAR were significant after both doses. The difference in TOTPAR with dull as compared to sharp pain was 2.4 after the 8-mg doses and 1.8 after the 16-mg doses. Pain relief provided by 8-mg doses in dull pain was comparable to relief provided, by 16-mg doses in sharp pain. Most other categories had insufficient data to allow for valid individual comparisons. Nevertheless, an intuitively logical trend of increasing pain relief was observed from throbbing pain through sharp to dull and crampy pain.

Relief was not significantly different in relation to categories of pain site after the 8-mg doses but was significantly different after the 16-mg doses. The categories of pain site are arranged in Table 1 in order of increasing pain relief for the 16-mg doses. After both the 8- and 16-mg doses, relief of abdominal pain was significantly greater than relief of thoracic pain or pain in the am. Other significant pain site-related differences are apparent but were not always consistent in terms of dose.

The independence of the various characteristics were assessed by use of Chi-square analyses and Pearson's coefficient of contingency (Pearson 1901). Some significant, but relatively low degrees of association were observed. There was a relatively greater proportion of black patients in the younger age group as compared to white patients. A greater proportion of black patients than white patients had abdaninal pain as compared to thoracic pain. A greater proportion of patients reporting moderate pretreatment pain than reporting severe pain had dull as compared to sharp pain. Patients with abdominal pain as compared to pain in the arm reported pain as sharp disproportionately more than as dull. Most of these associations would have tended to operate in opposite directions and to have "masked" the influence of the various characteristics, rather than to have "exaggerated" their influence on pain relief.

DISCUSSION

The age-related increase in pain relief is consistent with data reported by Bellville and associates (1971) and by Kaiko (1980) in patients with postoperative pain. The most unexpected observation was the race-related difference in pain relief. While we have observed, but not yet reported, that black patients obtain significantly greater pain relief than white patients with postoperative pain after both intrarmuscular morphine and methadone, we are not aware of any similar reports of racial differences in the analgesic response to narcotics. We were also surprised to find that the difference in relief between the treatment of severe and moderate pain was considerably less than differences in relief associated with differences in other patient and pain characteristics.

The data reported here provides additional evidence of the enormous interindividual variation in the analgesic response to morphine. The clinical use of narcotic analgesics requires careful titration of dose and dosing interval according to an appropriate balance between analgesic and side effects in individual patients. This should be appreciated regardless of what may be considered the standard or "optimal" dose and dosing regimen in patients with particular characteristics.

The data reported here provides a more rational basis for the choice of experimental controls for the clinical evaluation of analgesic drugs in various types of pathological pain models. For example, while investigators using noncrossover designs often stratify patients according to pretreatment pain intensity, stratification according to age, race, sex, pain site or pain character is infrequent (Bell et al. 1976). It is likely that this is due, in part, to limited, and often conflicting,infomation as to what variables are actually associated with significant differences in analgesic response. The use of matched pairs, based on stratification of patients according to any characteristic, is also infrequent in analgesic assays. One reason for this may be the limited availability of qualifying patients. This is the most difficult problem encountered in the conduct of analgesic assays (Dell et al. 1976). Matching patients according to a set of the most significant influencing characteristics would place additional strains on patient availability. Nevertheless, our data in chronic cancer pain indicates that stratification and matching patients according to age, race and selected categories of pain character and pain site may improve study sensitivity to a greater extent than stratification and matching of patients according to sex or even pretreatment pain intensity, in the treatment of moderate to severe pain. Of course, the use of crossover designs, where appropriate, is a most powerful tool for control of most of these variables.

In summary, pain relief after intramuscular morphine is directly related to the age of the patient. Middle-aged patients obtained relief after 8-mg doses of morphine comparable to relief obtained by younger patients after 16-mg doses. Oldest patients obtained relief after 8-mg doses comparable to relief obtained by middle-aged

patients after the 16-mg doses. Black patients receiving 8-mg doses obtained pain relief comparable to relief obtained by white patients receiving 16-mg doses of morphine. Pain relief reported after 16-mg doses was significantly greater in patients With moderate as compared to severe pretreatment pain, whereas there was no significant pretreatment pain intensity-related difference in pain relief after the 8-mg doses. Patients reporting dull pain obtained relief with 8-mg doses comparable to relief obtained by patients with sharp pain after 16-mg doses of morphine. Patients With abdominal pain obtained pain relief With 8-mg doses comparable to relief of pain in the chest or arm after 16-mg doses. The analyses of the degree of independence among the various characteristics indicated that sane significant, but relatively low, degrees of association existed.

In conclusion, our results demonstrate and quantify sources of variation in analgesic response due to particular patient and pain characteristics for which appropriate controls should be considered in the evaluation of analgesics in a population of cancer patients with chronic pain.

REFERENCES

Bell, R.M.S., Ferguson, R.K., Stander, H., and Turek, D. Methodology in clinical analgesic evaluation: a survey in the U.S.A. 38th Annual Scientific Meeting of the Committee on Problems of Drug Dependence, Inc., Proceedings of, 1976. pp. 590-611.

Bellville, J.W., Forrest, W.H., Jr., Miller, E., and Brown, B.W., Jr. Influence of age on pain relief from analgesics. J Am Med Assoc, 217:1835-1841, 1971.

Gravenstein, J.S., and Beecher, H.K. The effect of pre-operative medication with morphine on post--operative analgesia With morphine. J Pharmacol Exp Ther, 119:506-512, 1957.

Houde, R.W., Wallenstein, S.L., and Rogers, A. Clinical pharmacology of analgesics: 1. A method of assaying analgesic effect. Clin Pharmacol Ther, 1:163-174, 1960.

Kaiko, R.F. Age and morphine analgesia in cancer patients with postoperative pain. Clin Pharmacol Ther, 28:823-826, 1980.

Keats, A.S. Post-operative pain: research and treatment. J Chron Dis, 4:72-83, 1956.

Pearson, K. On the correlation of characters not quantitatively measurable. Philos Trans R Soc London, Ser A 195:1-47, 1901.

Wallenstein, S.L., and Houde, R.W. The clinical evaluation of analgesic effectiveness. In: Ehrenpreis, S., and Neidle, A., eds. Methods in Narcotic Research. New York: Marcel Dekker, Inc., 1975. pp. 127-145.

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Physiological and Subjective Effects of Hydromorphone in Postaddict Volunteers

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The present study examined the physiological and subjective effects of intravenous hydromorphone (Dilaudid). The experiment is based on methods for abuse liability testing of opiate-like drugs developed at the USPHS Addiction Research Center (Jasinski 1977) but introduces a number of modifications in these procedures. First, it is a relatively rapid procedure for determining dose-effect relationships. Data collection can typically be completed within 3-4 weeks per subject, conducting three sessions per week for approximately three hours per session. Second, dose-effect relationships are established on a wide variety of standard physiological and subjective measures. We are therefore able to examine the associations between the physiological and subjective effects of the drug. Third, a number of the physiological measures are continuously collected throughout the experimental session on a PDP-8 minicomputer. This has permitted a detailed time course analysis of the drug effect. Finally, drugs are administered intravenously, rather than by the more typical oral or-subcutaneous route. We were therefore able to assess the practicality of intravenous drug administration on a regular basis in subjects with a history of intravenous opiate use.

METHODS

Subjects. The subjects were five males, ranging in age from 28 to 35. All subjects had a history of intravenous opiate use, but were opiate-free at the start of the study. They lived on an eight-bed research unit during the experiment. Subjects were fully informed of the experimental protocol and risks at the start of the study, at which time they signed informed-consent agreements. Subjects were reimbursed for their participation.

Procedure. Sessions were conducted three days per week, usually on Monday, Wednesday and Friday afternoons. A venous catheter was placed in the subject's arm prior to the start of the session. The vein was kept patent by a saline drip, which was removed

approximately one-half hour following the injection. Subjects were seated in an isolated room with the experimenter during sessions of approximately three-hour duration.

There was always a minimum of a half hour between the start of the session and drug administration. Physiological measures stabilized during the first 15 minutes. Baseline data for each session were collected during the next ten-minute period. Five more minutes then elapsed before drug administration. This design ensured that baseline data do not include fluctuations in physiological measures resulting from the presence of the syringe or the injection procedure itself. At the end of this half-hour period, the saline drip was clamped off and the injection was given via the catheter. Data collection continued for two hours following the injection.

Four of the five subjects received 0-, 2-, 4- and 6-mg doses of hydromorphone. One subject only received doses of 0, 2 and 4 mg. Doses were administered under a double-blind procedure in a randomized block design, with subjects receiving each dose at least twice.

The following measures were continuously recorded throughout each session: 1) heart rate, using EKG leads on the chest; 2) skin temperature, using a probe on the finger tip; 3) respiration, using a mercury strain gauge stretched across the abdomen; and 4) blood pressure, using a cuff that automatically inflated and recorded pressure once every minute (Roche Arteriosonde #1216). In addition, a number of measures were intermittently recorded during each session. A pupil photograph was taken approximately 15 minutes prior to, and 5, 15, 30, 60, 90 and 120 minutes following the injection, using a Polaroid camera with 3X magnification. Subjective report forms were also administered approximately 15 minutes prior to the injection and four times following the injection at half-hour intervals. Subjective report forms included: 1) an analogue high scale on which subjects were asked to rate their current degree of “high” from 0 to 100; 2) the short form of the Addiction Research Center’s MBG (Morphine-Ber-edrine Group) scale; and 3) a 32-item adjective checklist, which included the Fraser single-dose opiate questionnaire (Fraser et al. 1961) as well as additional signs and symptoms characteristic of opiate effects. Subjects were instructed to complete all subjective report forms by referring to the way they felt at the present moment.

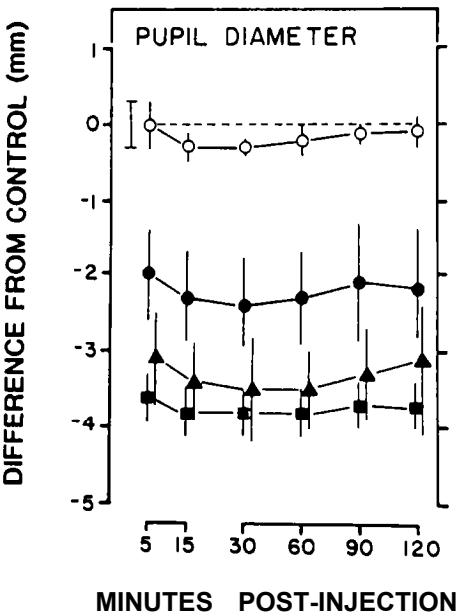
Data analysis. With the exception of skin temperature, physiological data are presented using “difference from control” scores. These were calculated by subtracting postinjection measures from baseline measures for each session. These difference scores were averaged across replications at each dose for each subject and were then summarized across subjects at each dose. Responses to the short form of the MBG and- the full 32-item adjective checklist were also adjusted with respect to predrug data using difference scores. When included in the full checklist, items from the

Fraser single-dose opiate questionnaire were treated as all other items, but when presented separately, scores on the questionnaire were derived using the weighted scoring system introduced by Martin and Fraser (1961). Time course and dose-effect data are presented graphically for the group of subjects.

RESULTS

There were graded changes in most physiological measures as a function of the dose of hydromorphone in the present experiment. Figure 1 summarizes these drug effects on pupil diameter. Following the administration of placebo, pupil diameter remained at baseline levels. A dose of 2 mg of hydromorphone constricted pupils an average of 2.0 to 2.5 mm. Pupil diameter decreased 3.0 to 3.5 mm following 4 mg of hydromorphone and 3.6 to 3.8 mm following 6 mg. Since drug was administered intravenously, there was a very rapid onset of the drug effect at all doses, with maximum pupil constriction occurring within 15 minutes to a half hour following the injection. There was little or no recovery of pupil diameter during the two hour postinjection period.

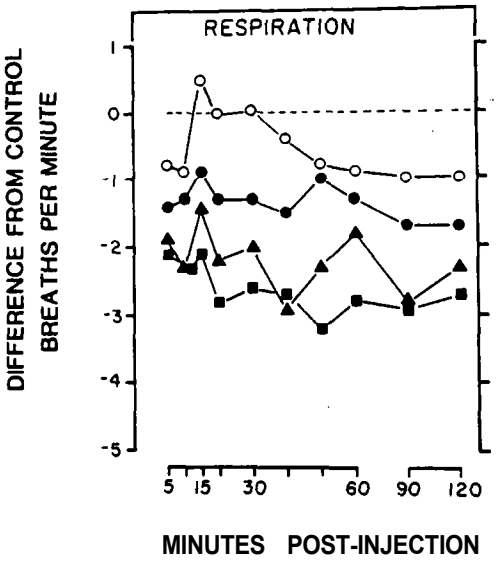
FIGURE 1



The effects of 0 (o), 2(●), 4 (▲) and 6 (■) mg of hydromorphone on pupil diameter as a function of time since injection. Vertical lines indicate ± 1 S.D.

Figure 2 summarizes the dose-dependent effects of hydromorphone on respiration. Control respiration rates tended to decrease slightly during placebo control sessions. Hydromorphone produced additional dose-related decreases in respiration. The high doses of 4 and 6 mg produced an average respiratory depression of three breaths per minute. These decreases persisted throughout the session.

FIGURE 2

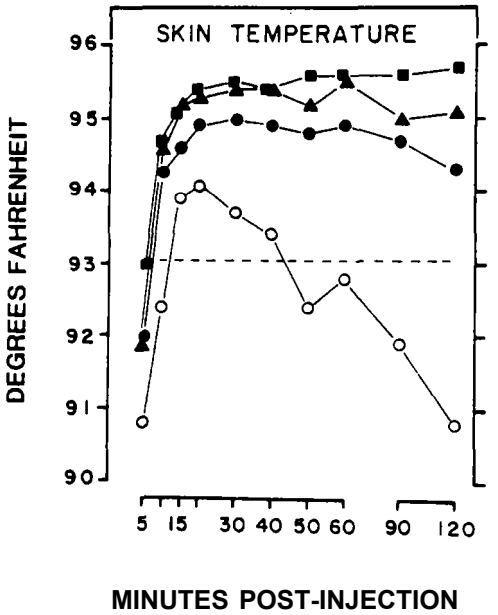


The effects of 0, 2, 4 and 6 mg of hydromorphone on respiration.

As shown in Figure 3, baseline skin temperature averaged 93° F. Following placebo administration, skin temperature increased to a maximum of 94° F 20 minutes following the injection, and then decreased throughout the rest of the session. Hydromorphone produced dose-dependent increases in skin temperature. Skin temperature increased to 95° F following 2 mg of hydromorphone and to 95.5° F following the highest doses. Skin temperature decreased slightly in the final hour of the session following 2 and 4 mg of hydromorphone but remained elevated throughout the experimental session following 6 mg.

Placebo administration produced a slight, very brief increase in systolic blood pressure, which then decreased below baseline levels throughout the rest of the session. All doses of hydromorphone produced a similar initial increase in systolic blood pressure of 12 to 13 mm Hg. Systolic blood pressure gradually

FIGURE 3



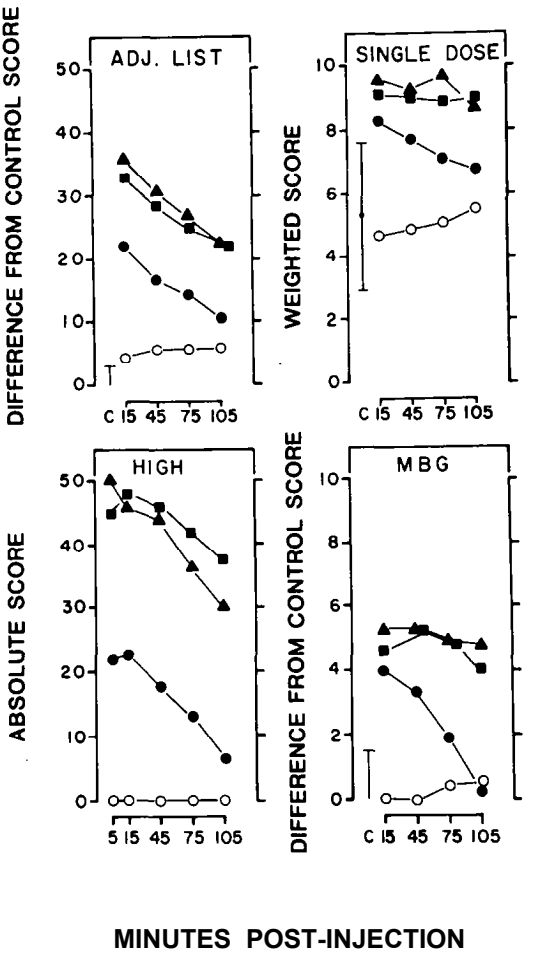
The effects of 0, 2, 4 and 6 mg of hydromorphone on skin temperature.

decreased and returned to placebo levels by the end of the two-hour session following the low doses but remained elevated throughout the two-hour period following the highest dose of drug. Diastolic blood pressure showed less consistent dose-related effects than systolic blood pressure. Following placebo, diastolic pressure remained at baseline levels. Following drug administration, diastolic pressure immediately increased and remained elevated for approximately one hour before returning to placebo levels.

The effects of hydromorphone on heart rate were generally dose-dependent within each subject, although there were substantial individual differences across subjects. In general, the overall effects appeared to be biphasic: first, accelerating heart rate above placebo levels and then decreasing heart rate to or below placebo levels. Subjects differed in the duration of each phase of the effect.

Figure 4 summarizes the effects of hydromorphone on the four subjective report measures. Placebo produced little change from baseline on any of these. There were dose-related increases on all subjective measures following 2 and 4 mg of hydromorphone,

FIGURE 4



The effects of 0, 2, 4 and 6 mg of hydromorphone on several subjective report measures. Brackets indicate ± 1 S.D. for baseline scores.

with little or no further increase following 6 mg. At the low dose of hydromorphone, responses on all measures generally decreased to baseline levels by the end of the two-hour postinjection period. Responses on the analogue high scale and adjective checklist also decreased during the two-hour period following 4 and 6 mg of hydromorphone, although they were still considerably elevated above baseline levels at the end of the session. Scores on the single-dose opiate questionnaire and the MBG scale remained elevated during the entire two-hour session following the 4- and 6-mg doses.

DISCUSSION

The present study determined the effects of several doses of hydromorphone on multiple physiological and subjective measures. Clear dose-effect relationships emerged on all measures. Increasing the dose of hydromorphone generally resulted in an increase in the magnitude of the effect on all measures for doses of 2 and 4 mg, with little further increase in effect at the highest dose. Pupils constricted, respiration decreased and skin temperature increased. These effects are similar to those reported for opiates in other studies.

While hydromorphone produced similar initial effects on all the subjective report measures, there were differences in the time course of the drug effects following the high doses of drug. Following 4 or 6 mg, responses on the adjective checklist and the analogue high scale decreased over time. In contrast, responses on the MBG scale and Fraser single-dose opiate questionnaire remained relatively constant throughout the two-hour postinjection period. This suggests that the adjective checklist and analogue high scale may provide a measure of a transient drug effect commonly associated with intravenous opiate administration and frequently described as the “rush”; whereas, the MBG and single-dose opiate questionnaire may be measuring relatively more stable effects induced by the drug. Thus, there were large changes in some components of subjective effects throughout the two-hour session, although physiological measures such as pupil diameter, skin temperature, and respiration remained stable.

The results of this study demonstrate that the current procedure permits the rapid determination of dose-effect functions for both subjective and physiological measures. Data on a single subject were generally completed in 10 three-hour sessions within a three-week period. Such a restricted time frame makes intravenous drug administration feasible in a postaddict population and also would permit the extension of these procedures to an outpatient setting. Comparisons across drugs or of the effects of various environmental interventions could be quickly and reliably assessed using this procedure.

REFERENCES

Fraser, H.F., Van Horn, G.D., Martin, W.R., Wolbach, A.B., and Isbell, H. Methods for evaluating addiction liability. (A) "Attitude" of opiate addicts toward opiate-like drugs; (B) A short-term "direct" addiction test. J Pharmacol Exp Ther, 133: *371-387,* 1961.

Jasinski, D.R. Assessment of the abuse potentiality of morphine; like drugs (methods used in man). In: Martin, W.R., ed. Handbook of Experimental Pharmacology. Vol. 45. New York: Springer-Verlag, 1977. pp. 197-258.

Martin, W.R., and Fraser, H.F. A comparative study of physiological and subjective effects of heroin and morphine administered intravenously in postaddicts. J Pharmacol Exp Ther, 133:388-399, 1961.

ACKNOWLEDGMENTS

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A Comparison of Some Subjective Effects of Prazepam, Diazepam, and Placebo

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Over the past two decades, the abuse potential of sedative and anxiolytic drugs has become a matter of increasing scientific concern. In particular, distinguished efforts have been made by Jasinski et al. (1977), Bigelow (1976), Griffiths et al. (1976, 1981) and others to assess the subjective effects and reinforcing properties of these substances in man. Paradoxically, despite interest in this area, a recent literature review revealed few studies dealing directly with the abuse potential of anxiolytics, even though they are among the most widely prescribed and easily accessible of psychoactive substances. As part of a survey on college student drug use, Pope et al. (1981) observe in an unreported finding that 13% of students at one major university campus use minor tranquilizers recreationally, while Woody et al. (1975) report that, beginning in 1972, diazepam became one of the most popular street drugs available. Johnston et al. (1980) have also noted the relatively frequent use of tranquilizers among high school students. Bliding (1974) assumes that diazepam's risk of abuse is related to the subjective experience it pro-. duces, which he concludes depends to a large extent on its unusually rapid rate of absorption. Finally, in a behavioral study of human preference for 400 mg of pentobarbital, 200 mg of diazepam and placebo, Griffiths et al. (1981) found that both substances produced similar ratings in magnitude of drug effect and both were preferred to placebo; however, pentobarbital was consistently preferred over diazepam. This study indicates that high doses of diazepam have reinforcing subjective effects which approach those of a highly abusable barbiturate.

In a previous study by our group (Cole et al. 1978), the subjective effects and abuse potential of nefopam, a nonopiate analgesic agent, were examined by comparing the subjective effects experienced by normal recreational users of illegal stimulant drugs, after they had taken 10 mg of amphetamine, 90 mg of nefopam, 300 mg of caffeine, or placebo in a naturalistic setting. Using the Profile of Mood

States - POMS (McNair et al. 1971) and List 116 of the Addiction Research Center Inventory - ARCI (Haertzen 1974), it was possible to discriminate between the effects of the different treatments.

The present study utilized a similar methodology to assess the subjective effects and abuse potential of prazepam, a relatively new benzodiazepine. In this experiment, the subjective effects of 20 mg of prazepam were compared to those of 10 mg of diazepam and placebo. These doses were selected as clinically equivalent high-standard dosage units, although Woody et al. (1975) note anecdotally that the standard recreational dose of diazepam ranges between 30 and 80 mg. Diazepam produces peak blood concentration at 30-90 minutes after ingestion, while the peak blood level of desmethyldiazepam, prazepam's active metabolite, occurs at about six hours.[1] It seems reasonable that a benzodiazepine which produces a slower rise to peak serum level, such as prazepam, may induce less reinforcing subjective effects than diazepam and hence have a lesser propensity for abuse.

SUBJECTS

Twenty-three subjects, 12 males and 11 females, ranging in age from 18 to 28, were included. Subjects were divided into four groups of six subjects each (two groups of males and two of females), except for one group of females which had five subjects. They were recruited by notices posted in various local colleges. Most were students from socio-economically upper middle or upper-class families who were college educated. All participants were casual users of sedative-hypnotics, such as barbiturates, methaqualone, and benzodiazepines and had used one or more of these drugs at least six times in doses above the usual prescribed levels. Subjects were required to complete the Minnesota Multiphasic Personality Inventory - MMPI (Dahlstrom et al. 1972) and undergo a clinical interview. The latter was conducted by a clinical psychologist, who determined previous drug usage, probed for areas of personality dysfunction and for adverse reactions to stress, in addition to reviewing the psychiatric history of the subject and his family of origin. Results from both the MMPI and the clinical interview were used as criteria on which to judge the subjects' suitability for participation. The mean MMPI profile of male and female subjects showed elevations, though below a T-score of, 70, of scales 4 (Pd - Psychopathic deviate) and 9 (Ma - Mania). This pattern is characteristic of a hypomanic and sociopathic personality style that is generally within the range of normal behavior (Dahlstrom et al. 1972).[2] Subjects showed no abnormality during a physical examination, were not dependent on any drug including alcohol, and had had no unusual side effects during their previous drug experiences. A twelve-lead EKG was also used as a screening procedure.

MEASURES

TIhe two major dependent measures were the POMS and the ARCI. The POMS consists of 72 five-point adjective rating items which break down into eight factors designed to measure identifiable subjective mood states, including Elation, Confusion and Fatigue. It has been shown to be-sensitive in discriminating effects of different drugs and it is reliable as a repeated measure over relatively brief

periods of time (Cole et al. 1978).

List 116 of the ARCI is a 102 item inventory which characterizes the subjective effects of a drug compared with those of other well-known drugs of abuse. This version contains seven standard scales in addition to an llitem Amphetamine scale developed by Martin et al. (1971) plus Euphoria and Sedation scales established by Jasinski and his coworkers (1977). The utility of these scales in investigating the subjective effects of various substances is well documented (Martin et al. 1971, Jasinski 1977, Jasinski et al. 1977).

TESTING PROCEDURES

Subjects were run in groups of six, with each group coming in for three five-hour sessions, one week apart. Each subject in fact received all three treatments (20 mg of prazepam, 10 mg of diazepam, and placebo) in random order and double-blind. Thus, each subject served as his or her own control for the experiment. Randomization of treatments ensured that only two subjects in each group were receiving the same drug during each session. Subjects themselves were not aware that they would receive a different treatment at each session, and only knew the possible treatments they could receive.

Subjects were instructed to abstain from drug usage for 48 hours and alcohol for 12 hours prior to each session; they were asked to give a urine sample at the beginning of the session to be screened for illicit drug usage that might interfere with the validity of their ratings. No illicit use was detected. Initial physiological measures were taken, including pulse, temperature, and blood pressure. Pulse determinations were repeated hourly, and blood pressure at the end of the session, for medical monitoring.

Subjects rated their subjective experiences on the two self-rating questionnaires, the POMS and the ARCI. These were administered at baseline (predrug) and hourly for five hours following drug ingestion. They were also asked to rate which drug they thought they and the other subjects received, what they would pay for what they received, and how high they felt during the session.

Groups were run in a living-room-like atmosphere, where subjects were free to play games, talk, read, listen to music, etc. during the times when they were not filling out ratings. Each rating took about twenty-five minutes; thus the subjects had a substantial amount of free time.

DATA ANALYSIS

The F values and corresponding probabilities for main drug effects, time effects, sex effects, and interaction among these variables were obtained by an analysis of covariance, grouped by sex, which adjusted for variations in the subjects' predrug ratings. The baseline scores (predrug) depicted in the figures represent raw means for each scale, while postdrug scale scores have been covaried. No significant differences between the three treatment groups were observed on baseline ratings. Results of this analysis are presented in table I for the ARCI and table II for the POMS. Where main drug

effects, drug-by-time interactions, or trends were observed, an analysis of variance of adjusted mean scores was performed for each separate time point on that measure, and significant results are portrayed below each figure (Figs 1-10). Differences between drug conditions at these time points were analysed using a Newman-Keuls multiple comparison statistic. Results of posthoc drug comparisons are displayed below each figure.

RESULTS AND DISCUSSION

Preliminary findings indicate that it is possible to discriminate between the subjective effects of prazepam, diazepam and placebo at relatively low doses.

An examination of tables I and II reveals a number of significant drug, time and sex effects, as well as interactions. The most consistent pattern of interactions occurs between the drug and time variables, with significant effects being observed on 9 out of 18 scales, indicating that the methodology is able to detect drug-induced mood changes over time.

Significant main drug effects were found only on the ARCI Drunkenness scale (Fig 1), with trends noted on Sedation (Fig 3) and Fatigue (Fig 1) at .07 and .11 alpha levels, respectively. Drug-time interactions in all these scales as well as PCAG (Fig 2), however, demonstrate the drugs' general sedative-like effect over time. On all sedative measures, prazepam and diazepam are distinguishable from placebo at hour one (Figs 1-4), and generally at hours two and three. However, there appeared to be no detectable difference between diazepam and prazepam on any of these scales. By visual inspection of the figures, diazepam appears to reach peak effect at about one hour, while prazepam's rise to peak effects is less steep and seems to induce the strongest changes between two and three hours, suggesting a slower course of action. However, by Newman-Keuls analysis, all significant prazepam-placebo differences are noted first at one hour, though some are also noted at two or, in one case, three hours.

It is important to note that even if the peak blood level of desmethyldiazepam occurred at six hours in our prazepam subjects, the peak subjective effects obviously occur substantially earlier.

A significant drug-by-sex interaction on the POMS Fatigue factor (Figs 5, 6) was noted. Examination of these drug comparisons grouped by sex indicates that the women became more fatigued earlier on diazepam than on prazepam. Men, however, seem to become mildly more fatigued on prazepam than diazepam, and both drugs seem to have a similar time course on this factor in males. Clearly, for all subjects, both prazepam and diazepam increased fatigue by the end of the five-hour study session.

The ARCI LSD scale (Fig 7) and the POMS Confusion factor (Fig 8) both display significant drug effects, with Confusion also exhibiting a drug-by-time interaction. Roth are indices of dysphoric psychological and physical states.[3] Prazepam and diazepam produce more dysphoria than placebo at one hour and at other time points, but again, they are not significantly different from one another.

The ARCI Excitation scale (Fig 9) shows an overall trend attributable to the drugs alone, as well as a drug-time interaction. It is at one hour on this scale that the only significant difference between drugs can be detected, with diazepam causing more excitation than prazepam. The fact that both drugs appear to be equally sedating precludes the possibility that such an effect is dose-related. The Euphoria scale (Fig 10) shows a drug-time interaction, and an effect at the one-hour time point, but no significant drug differences by Newman-Keuls analyses. The diazepam scores showed the greater effect at one hour. These two scales measure states of pleasurable stimulation and their courses are quite similar, suggesting that diazepam may be the more euphoriant of the two drugs, while prazepam induces less excitation.

Subjects' posthoc guesses regarding which treatment they received were not better than chance; however, trends (p=.10) indicate that they were generally able to distinguish both drugs from placebo but not from each other. No significant differences were observed on a 16-cm scale rating highness; the mean rating for prazepam was 3.9 (SE=3.38), 3.7 for diazepam (SD=3.25), and 2.2 for placebo (SD=2.66).

From these results and findings presented earlier, we strongly suspect that thesesubstancesproduce subjectively different states of euphoria but that they are probably not evident at such low doses. The inability of subjects to identify treatments better than chance may be further indication of this contention. By way of contrast, in two studies, one investigating stimulants (Cole et al. 1978) and another examining the subjective effects of 200 and 400 mg of methaqualone (Orzack et al, in preparation), participants were able to identify drug at a rate better than chance, and the highness rating was relatively sensitive to drug-induced mood changes.

It is difficult to generalize about a substance's subjective effects and abuse liability from a single-dose study, particularly with the levels of drugs employed. Thus, the second phase of this preliminary investigation will focus on these drugs at higher doses, which more realistically resemble those used for recreational purposes.

Accurate estimation of abuse liability requires as much methodological precision as possible. Consequently, the areas to be considered in subsequent studies include investigating the ecological validity of the laboratory versus the naturalistic setting, looking at interaction between personality and drug response, and examining group interaction patterns as an index of abuse liability.

References available on request from senior author.

TABLE I: A Summary of Analyses of Covariance of Arci Scores

SCALE	DRUG		TIME		SEX		DRUG-TIME		TIME-SEX		DRUG-SEX	
	F	p	F	p	F	p	F	p	F	p	F	p
Amphetamine	1.36	.27	30.27	<.00*	0.79	.38	1.87	.07	0.56	.69	2.37	.11
Drunkenness	4.00	.03*	21.78	<.00*	1.88	.19	4.22	<.00*	0.14	.97	0.68	.51
Euphoria	1.24	.30	31.97	<.00*	0.15	.70	2.88	<.00*	4.55	<.00*	0.41	.67
Excitement	2.53	.09	2.78	.03*	2.37	.14	1.57	.14	0.58	.68	1.09	.36
LSD	4.12	.02*	7.30	<.00*	0.73	.40	0.78	.62	0.43	.79	0.58	.57
MC	0.01	.99	2.49	.05*	4.71	.04*	2.06	.04*	1.31	.27	1.04	.36
MBG	1.32	.28	19.50	<.00*	0.35	.56	2.29	.02*	1.80	.13	1.46	.24
PCAG	1.63	.21	3.12	.02*	7.37	.01*	2.61	.01*	0.13	.97	0.26	.77
Sedation	2.88	.07	4.09	.01*	6.50	.02*	2.98	<.00*	0.26	.90	0.27	.76

*Denotes significance

FIGURE 1
ARCI DRUNKENNESS: DRUG COMPARISON
Men-Woman Combined

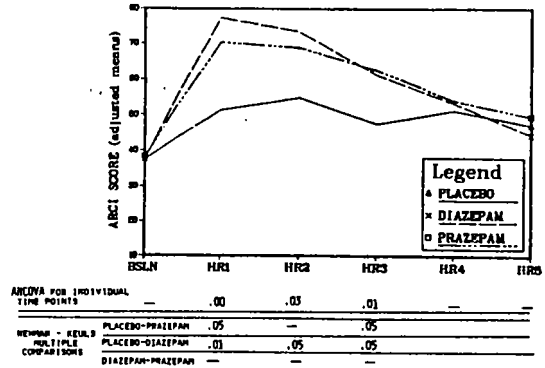
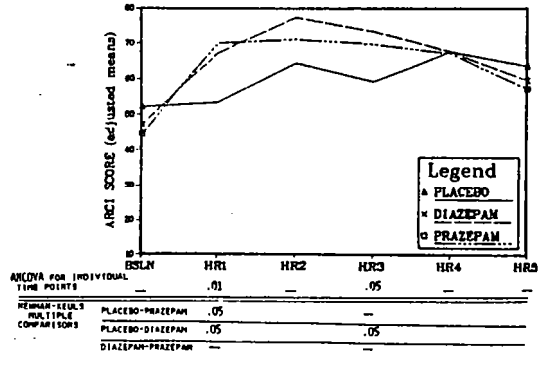


TABLE II: A Summary of Analyses of Covariance of Poms Scores

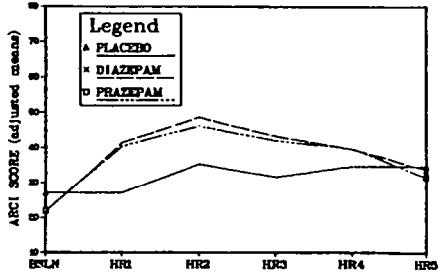
SCALE	DRUG		TIME		SEX		DRUG-TIME		TIME-SEX		DRUG-SEX	
	F	p	F	p	F	p	F	p	F	p	F	p
Anger	00.70	.50	01.30	.27	00.09	.77	00.87	.54	01.84	.12	00.70	.50
Confusion	03.80	.03*	05.91	<.00*	03.59	.07	03.09	<.00*	03.57	.01*	01.27	.29
Depression	00.97	.38	00.59	.67	01.10	.30	01.66	.11	00.21	.93	02.90	.07
Elation	00.29	.75	07.30	<.00*	01.35	.26	05.56	.14	01.09	.36	00.81	.45
Fatigue	02.27	.11	08.93	<.00*	05.67	.03*	02.17	.03*	03.48	.01*	03.26	.05*
Friendliness	00.38	.68	13.96	<.00*	00.23	.64	01.38	.20	01.22	.19	01.07	.35
Tension/Anxiety	01.16	.32	04.67	.00*	02.46	.13	01.32	.23	04.11	<.00*	02.45	.10
Vigor	00.01	.98	05.17	.00*	01.37	.25	01.36	.22	01.10	.36	00.95	.39
THD	00.14	.68	08.60	.00	02.13	.16	02.24	.02	02.05	.09	02.13	.13

*Denotes significance

FIGURE 2
ARCI PCAC: DRUG COMPARISON
Men-Women Combined

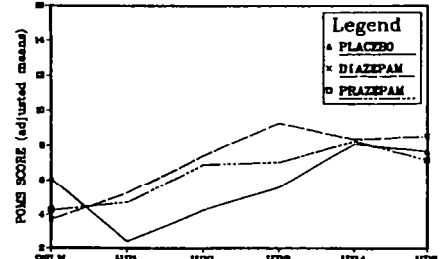


FIGURES 3
ARCI SEDATION: DRUG COMPARISON
Men-Women Combined



ANCOVA FOR INDIVIDUAL TIME POINTS		.02	—	—	—	—
NEWMAN-KEULS MULTIPLE COMPARISONS	PLACEBO-PRAZEPAM	.05	—	—		
	PLACEBO-DIAZEPAM	.05	—	—		
	DIAZEPAM-PRAZEPAM	—	—	—		

FIGURE 4
POMS "FATIGUE": DRUG COMPARISON
Mem-Women Combined



ANCOVA FOR INDIVIDUAL TIME POINTS		—	.01	.06	—	—
NEWMAN-KEULS MULTIPLE COMPARISONS	PLACEBO-PRAZEPAM	.05	.05	—		
	PLACEBO-DIAZEPAM	.01	.05	.05		
	DIAZEPAM-PRAZEPAM	—	—	—		

FIGURES 5
POMS "FATIGUE": DRUG COMPARISON
Men

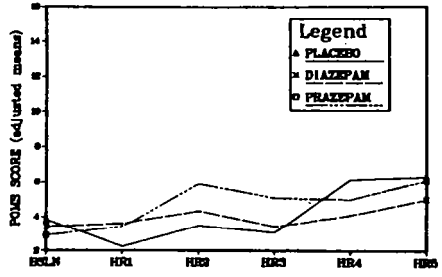


FIGURE 6
POMS "FATIGUE": DRUG COMPARISON
Women

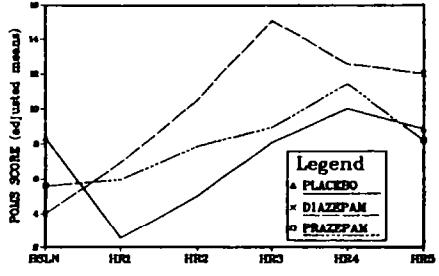


FIGURE 7
ARCI LSD: DRUG COMPARISON
Men-Women Combined

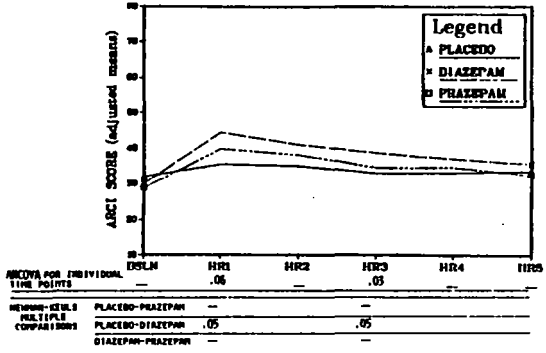


FIGURE 8
POMS 'CONFUSION': DRUG COMPARISON
Men-Women Combined

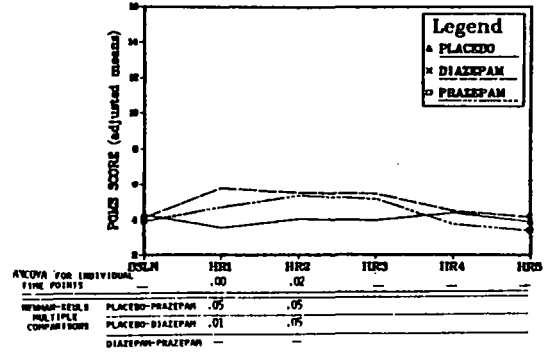


FIGURE 9
ARCI EXCITATION: DRUG COMPARISON
Men-Women Combined

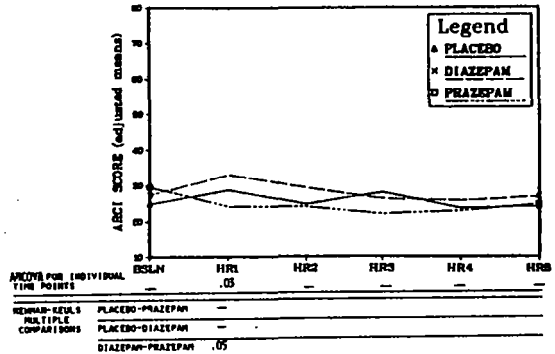
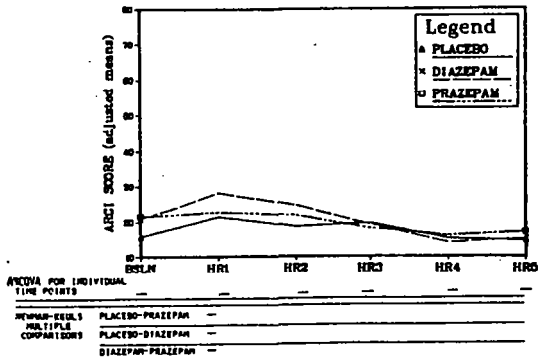


FIGURE 10
ARCI EUPHORIA DRUG COMPARISON
Men-Woman Combined



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Differential Motor and State Functioning in Newborns of Women on Methadone

J. Marcus, S. L. Hans, and R. J. Jeremy

Abstract

Motor and state functioning of 20 infants born to methadone-maintained women and 25 born to controls was assessed at 1 day and 1 month of age using Brazelton Neonatal Behavioral Assessment Scale with Kansas Supplements (NBAS-K). The infants were of mothers who were Black, of low SES, between the ages of 18 and 35 years, and who had good prenatal care. Motor behaviors were scored on 3 NBAS-K items: General Tonus, Motor Maturity, and Tremulousness. State behaviors were scored on 2 items: Alertness and General Irritability. Guttman's Multidimensional Scalogram Analysis (MSA) of individual profiles revealed an orthogonal relationship between motor and state functioning, with motor functioning being a much clearer discriminator between methadone and non-methadone infants than state functioning. With age, both groups generally improved, but non-methadone infants maintained some of their advantage in motor functioning. Both groups showed a variety of behavior patterns during the neonatal period. The results suggest that methadone acts differentially on CNS functioning, with strong effects on neuro-motor functioning.

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The Effects of Perinatal Addiction on Pulmonary Function in the Newborn

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Opiate dependence during pregnancy is overwhelming to the physical condition of the woman, the fetus, and ultimately the newborn infant. The vast majority of addicted women neglect general health care and therefore are predisposed to a host of obstetrical complications during pregnancy. These obstetrical complications as well as other medical complications in pregnant drug dependent women predispose infant to pulmonary illness. (Finnegan, 1980) When the pregnant addicted woman suffers from septicemia, urinary tract infection, amnionitis, chorioamnionitis, premature rupture of the membranes, or septic thrombophlebitis, her infant may be predisposed to pneumonia. Neonatal hypovolemia and shock may occur if the mother develops abruptio placenta, which is a common occurrence in these women, especially if abstinence. is frequent. Maternal withdrawal may occur when the woman cannot obtain the drugs that she needs'to maintain her habit or when she has been involved in a therapeutic detoxification regimen which has been poorly controlled.

With the extremely unstable, intrauterine milieu and exposure of the infant to chronic fetal hypoxia owing to repeated episodes. of withdrawal and overdose, the, infant may be prematurely born. These episodes of maternal withdrawal cause uterine irritability which may progress to the premature onset of labor. The infant who is born early may suffer from respiratory distress syndrome with the possibility of pulmonary hemorrhage as a complication. Additional difficulties which occur because of fetal distress precipitated by repeated episodes of withdrawal and/or overdose may cause the expulsion of meconium in utero, therefore predisposing the neonate to meconium aspiration syndrome.

Pneumothorax, a frequent complication of the aspiration syndrome, may follow. Chronic fetal hypoxia in association with maternal hypertension, venereal disease, preeclampsia, placental insufficiency or the inhibitory effect of heroin upon fetal growth may cause the birth of an infant with intrauterine growth retardation.

Therefore, the infant may have the possibility of developing an aspiration pneumonia, hypoglycemia or hypocalcemia. Hyperviscosity, an occasional complication of growth retardation in the fetus, may be manifested. Both hypoglycemia and hyperviscosity may be associated with respiratory symptomatology (Finnegan, 1980).

Occasionally, the pregnant drug-dependent woman is concerned as to whether she will be treated appropriately with analgesics during labor. Therefore, she may take an increased amount of heroin or other illicit drugs in order to alleviate her labor pains. As a result, respiratory depression immediately postpartum may be encountered in the infants of mothers who use illicit heroin or methadone. Fetal depression may be due either to asphyxia or to narcotic induced depression of the respiratory center (Finnegan, 1980).

Currently, it is fortunate that the majority of pregnant addicted women are treated as high-risk and provided with appropriate prenatal and addictive care which has been shown to eliminate many of the obstetrical and medical complications as well as the subsequent neonatal morbidity (HEW, 1979). Since most of these mothers are maintained on methadone, the major problem that is encountered in over 60 percent of the infants is that of neonatal abstinence. Neonatal narcotic abstinence is described as a generalized disorder characterized by signs and symptoms of central nervous system hyperirritability, gastrointestinal dysfunction, respiratory distress and vague autonomic symptoms which include yawning, sneezing, sweating, stuffy nose, mottling, increased lacrimation, and fever. Infants that are afflicted generally develop tremors which are initially mild and occur only when the infants are disturbed but which progress to the point where they occur spontaneously without any stimulation. High-pitched cry, increased muscle tone, and irritability develop. The infants tend to have increased deep tendon reflexes and a hyperactive moro reflex. The rooting reflex is exaggerated, and the infants are frequently seen sucking their fists or thumbs, yet when feedings are administered, they have extreme difficulty and regurgitate frequently. The feeding difficulty occurs because of an uncoordinated and ineffectual sucking reflex. The infants may develop loose stools and therefore are susceptible to dehydration and electrolyte imbalance (HEW, 1979).

In addition to the above, previous studies have described tachypnea, hypocapnia, and alkalemia secondary to hyperventilation, decreased birthweight, and less than expected incidence of respiratory distress syndrome (RDS) (Glass, et al., 1971; Klain, et al., 1972; Taeusch, et al., 1973; Glass, et al., 1972). Studies of passively addicted newborn animals demonstrated improvement in lung function attributed to induced surfactant synthesis (Taeusch, 1973).

The abstinence-induced tachypnea in these neonates can be a very confusing symptom. The physician must decide whether the tachypnea is simply a result of abstinence or whether it is an initial

symptom of the many conditions previously noted, since these infants are so frequently predisposed to respiratory conditions due to the maternal complications. Clinicians have also been concerned as to the impact of this tachypnea on lung function in these infants during the abstinence syndrome. Therefore, the purpose of the present study was to investigate the relationship between tachypnea, as seen in the neonatal abstinence syndrome and lung function in infants born to opiate-dependent mothers in comparison to normal controls of equivalent age and birth weight.

METHODS

The infants studied were born to opiate-dependent women enrolled in Family Center Program in Philadelphia. The program provides comprehensive obstetrical, medical, addictive and psychosocial care to these women and their children. All infants included in the study were normal except for symptoms of neonatal narcotic abstinence. They were admitted to the intensive-care nursery of our Hospital for observation and assessment of abstinence. During the first 24 hours of life, each newborn was scored by a neonatal abstinence scoring system which we have developed and which has been previously published (HEW, 1979). The infants were scored at birth and once every hour during the first day, and on the second day the infants were scored every two hours. After 48 hours of life, the infants were scored every four hours. As per the protocol of the scoring system, no infant was treated with pharmacologic agents for abstinence if his score was 7 or less. The infants were treated with either paregoric, phenobarbital or diazepam according to a specially devised dosing regimen (HEW, 1979; Finnegan, et al., 1975) which is dependent on a combination of score and infant's weight. The dose was escalated if the Infant maintained a score greater than 7 at a given assessment period and continued that high score for three assessments. Therefore, all infants were treated similarly from the standpoint of assessment as well as pharmacologic treatment.

Sequential pulmonary function measurements were made as soon as possible during the first 24 hours following birth and were repeated at 48 and at 72 hours of age in both study and control infants. Tidal volume was determined by electrical integration of air flow obtained from an infant pneumotachograph calibrated previously with known air flows. The pneumotachograph was attached to an infant rubber mask and applied over the infant's face. The total dead air space of this system was approximately 5 ml. Esophageal pressure was measured using a latex balloon which tested for linear pressure response between $\pm$ 10 CM H_2O. Grass transducers were used to measure air flow and esophageal pressure. These signals were amplified and recorded on a four-channel recorder from which dynamic lung compliance and resistance were calculated by dividing the tidal volume by the change in esophageal pressure, at the time of zero flow, trying to avoid periods of grunting or irregular respiration.

RESULTS

The clinical data of the 18 infants born to opiate-dependent women and the 13 control infants were compared. There was similar distribution of males and females in both groups. Average gestational age for both the study and control infants was 39 weeks. Mean birth weight for the study infants was 2890 grams, and for the controls, it was 3050 grams. Mean one-minute Apgar score for the study infants was 7.8 in contrast to 8.8 for the control infants. This difference was statistically significant but both are in the normal range. At five minutes, mean Apgar score was 9 for the study infants and 9.7 for the controls. Infant morbidity was 50 percent in the study infants and 38 percent in controls.

None of the study or the control infants had hyaline-membrane disease or any other major neonatal complications throughout the study period. Infant morbidity in the study group included intrauterine growth retardation, gonococcal conjunctivitis, asphyxia neonatorum, tiyperbilirubinemia, prematurity, and oral moniliasis. Infant morbidity in the control group included prematurity, hyperbilirubinemia, and postmaturity.

'The mothers of the infants in the study group had used heroin for a mean duration of about 3 1/2 years with a reported mean use of 16 bags per day. The mothers had been maintained on methadone ranging from one week to eight months prior to delivery. The amount of methadone used by these mothers was from 10 to 70 mg/day. Maternal complications occurred in 61 percent of the study group and 30 percent of the control group. The mothers of the study infants had a mean of 4.8 prenatal visits in contrast to the control infants for which it was 7.8 prenatal visits. Fifty percent of the infants in the study group necessitated pharmacologic treatment for abstinence. The agents utilized were phenobarbital in 4, paregoric in 3, and diazepam in 2. Initiation of treatment ranged from 4 hours to 5 days with a mean of 36 hours. Figure 1 shows the lung compliance and lung tidal volume in study infants and control infants. (All the data in the Figures are presented as a mean ± standard error, represented by the vertical bars.) The asterisk indicates that the values are significantly different between infants of drug-dependent mothers and control infants on the first day. On the third day, it is noted that lung compliance and tidal volume were significantly different than on day 1. With regard to inspiratory and expiratory resistance (not shown in Figures), no significant differences were noted for study or control infants, either on day 1 or day 3.

Figure 2 compares respiratory rate and minute volume of the study and control infants. The asterisk indicates that the infants of drug-dependent mothers and control infants are significantly different with regard to respiratory rate on days 1, 2 and 3. With regard to minute volume, the infants of drug-dependent mothers are significantly different than the controls on day 3 and also

significantly different on day 3 in comparison to day 1. As shown in Figures 1 and 2, sequential pulmonary function measurements of the 13 control babies showed no significant variation throughout the first 3 days of life and were in agreement with the literature for normal term infants (Cook, et al., 1955).

Pulmonary function measurements of the 18 infants of drug-dependent mothers were evaluated sequentially. Both lung compliance and tidal volume were significantly increased from day 1 to day 3. Inspiratory and expiratory resistance, as well as respiratory rates varied, but not to a significant degree. Minute volume was increased significantly from day 1 to day 3. Comparison of pulmonary function for infants of drug-dependent mothers with that of control infants has shown that tidal volume and lung compliance were decreased significantly on day 1 for infants of drug-dependent mothers. However, respiratory rate was increased significantly. By day 3, pulmonary function of the infants of drug-epen ent mothers had returned to control levels with the exception of respiratory rate and minute ventilation, which were both significantly higher.

DISCUSSION

Neonatal abstinence and the associated tachypnea, characterized by respiratory rates occasionally rising above 100 breaths per minute, have been studied by Glass and colleagues (Glass, et al., 1972). The abstinence-induced tachypnea has been found to be continuous, differing from the occasional bursts of rapid respirations commonly occurring in normal infants during the first few weeks of life. In adults, these findings have also been seen and the etiology thought to be an increased sensitivity of the respiratory center to carbon dioxide (Glass, et al., 1972).

Pulmonary function studied from birth to 24 hours of age in infants of drug-dependent mothers appears to be characterized by transient decrease in lung compliance and tidal volume when compared with normal control infants. By 3 days of age, lung compliance and tidal volume returned to normal control levels in spite of persistent tachypnea. Although tachypnea in infants of drug-dependent mothers has been previously demonstrated and explained as central nervous system hyperirritability (Klain, et al., 1972) the transient alteration in lung function has not been extensively studied.

The relationship between transitory alterations of lung mechanics and persistent tachypnea in infants of drug-dependent mothers suggests uneven ventilation during the early phases of withdrawal. The evidence of uneven ventilation is indirectly supported by the possibility of pulmonary edema and increased capillary permeability demonstrated in human heroin use (Katz, et al., 1972). Non-uniform ventilation concomitant with rapid breathing has been shown to result in a decreased dynamic compliance as exhibited by infants of drug-dependent mothers on day 1 (Woolcock, et al., 1969; Otis, et al., 1956).

If ventilation is uniform, dynamic compliance will remain unaltered in spite of rapid breathing rates such as those observed in the study infants on day 3.

In summary, it has been shown by sequential pulmonary function studies herein described that infants with abstinence-induced tachypnea are transiently affected with regard to pulmonary function. Despite continuous abstinence and tachypnea, though, the infants appear to be able to compensate by the third day of life, at which time pulmonary dynamics return to normal levels.

REFERENCES

Complete references will be supplied by the Author upon request.

AUTHORS

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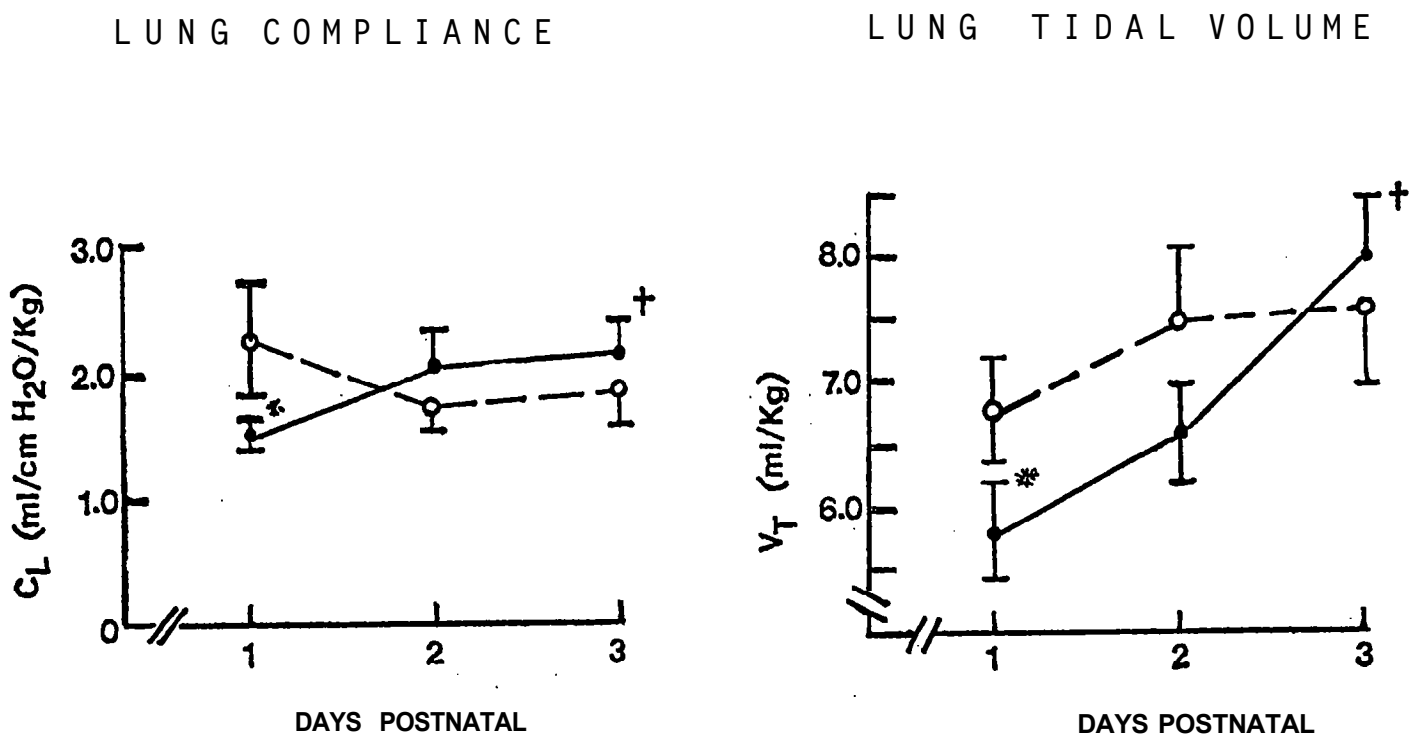
FIGURE 1

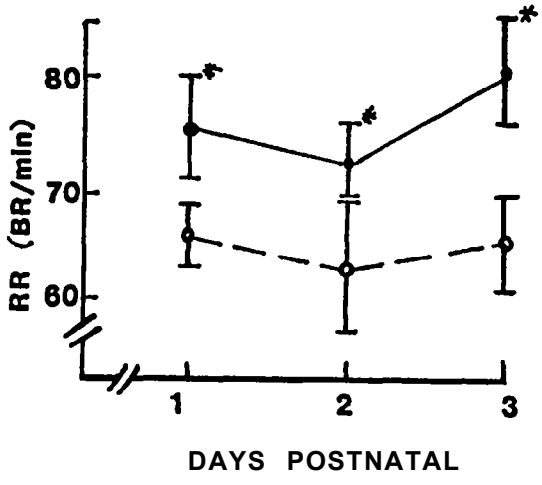


°CONTROL INFANTS (13)

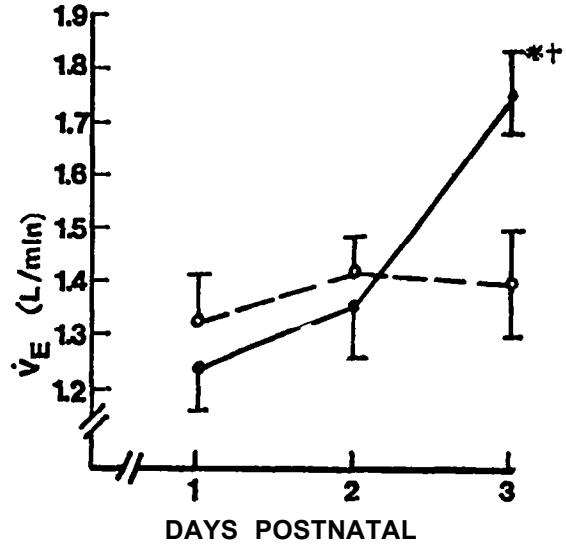
•IDDM (13)

FIGURE 2

RESPIRATORY RATE



MINUTE VOLUME



°CONTROL INFANTS (13)

•IDDM (18)

Patient Self-Adjustment of Methadone Maintenance Dose

Richard B Resnick, M.D., Patricia Butler, R.N., and Arnold M. Washton, Ph.D.

During the course of methadone maintenance treatment, patients often request a change in their daily methadone dose. In most methadone programs the usual procedure for handling such requests is for the patient to first discuss the request with the counselor and then to see the clinic physician who would review the requested dose change and, if approved, transmit orders for the new methadone dose to the dispensing nurse. The purpose of this procedure is to safeguard patients against inappropriate or otherwise contraindicated dose changes. An inordinate mount of staff time appeared to be consumed on this issue, since only in rare instances was there reason to deny requests for a dose change. Also, patients frequently felt frustrated and expressed discontent for the time they often. have to spend waiting to see the physician and for having to relinquish control over an important aspect of their treatment. It is probably the case that the patients themselves best know the dose of methadone they need in order to function optimally. This view is supported by the fact that almost all the requested dose changes were implemented and tended to be rather modest changes of only 5 or 10 mg.

We decided to undertake a trial period during which patients would be allowed to adjust their own methadone dose without having to see their counselor or the clinic physician in hopes that this would both reduce the staff time required to service routine dose changes, without compromising patient well-being, and also reduce the patient's dissatisfaction with the usual procedure.

METHODS

All methadone maintenance patients who were stabilized on at least 20 mg methadone were given the option of adjusting their own methadone dose up or down by 5-mg steps without having to see their counselor or the clinic physician. patients wishing to detoxify below 20 mg were excluded. Requests for dose changes were: (a) implemented on the patient's next visit to the clinic; (b) limited to two changes per week (10 mg per week maximum); and (c) reviewed at a

weekly staff meting. In order to obtain a dose change either larger than 5 mg at a single request, or on the day of the request, prior approval of the clinic physician was required. Requests for dose adjustments were made on a written form on which the patient would circle the word "increase" or decrease", fill in the new dose and circle "yes" or "no" to the statement, "I would like to see the doctor about my request." For patients maintained on LAAM, the Monday and Wednesday or Friday dose could be changed either separately or all at the same time. Signed forms were returned to the dispensing nurse, the new dose entered on the order sheet, signed by the physician and implemented on the patient's next clinic visit: Patients' dose-change activity was reviewed at a weekly interdisciplinary staff meting as a safeguard against potential misuse of the dose-adjustment privilege.

RESULTS

Slightly less than half the patient sample exercised the option of adjusting their own methadone dose and slightly less than half had no dose changes, while a much smaller percentage had the physician implement their dose changes (Table 1).

TABLE 1

UTILIZATION OF DOES-CONTROL OPTIONS

	First 16 wks (N=149)		Second 16 wks (N=157)	
	N	(%)	N	(%)
Used self-adjusted dose change	63	(42%)	74	(47%)[a]
Used physician-adjusted dose change	22	(15%)	17	(11%)[a]
No Dose changes	64	(43%)	77	(49%)

[a]Eleven individuals took both self-adjusted and physician-adjusted dose changes.

The patients who, on sane occasions, used physician-adjusted dose changes rather than self-adjusted changes, did so to obtain the dose change immediately, rather than at the next clinic visit. Only one of these patients asked not to have the option of controlling his own dose. The average methadone maintenance dose for all eligible clinic patients did not change over the 32-week study period (Table 2).

TABLE 2

MEAN METHADONE DOSE AT SUCCESSIVE TIME INTERVALS

At 16 weeks before study (N=149)	54 mg
At start of study (N=149)	60 mg
After 16 weeks of study (N=149)	60 mg
After 32 weeks of study (N=157)	60 mg

Among patients who utilized the dose-control option, the majority took increases in their maintenance dose, with substantially fewer patients taking decreases (Iable 3).

TABLE 3

UTILIZATION AND MAGNITUDE OF SELF-ADJUSTED DOSE CHANGES

	First 16 wks (N=63)		Second 16 wks (N=74)	
	% of Patients	Mean Dose Change	% of Patients	Mean Dose Change
Took increases only	6 %	+10 mg	54%	+13 mg
Took decreases only	21%	-15 mg	31%	-13 mg
Tbok increases & decreases	12%	-.8 mg	15%	+ 9 mg

Net changes in self-adjusted maintenance dose over the 32-week period tended to be small and less than ± 15 mg in nearly all cases. Most patients adjusted their dose by a net of only 5 or 10 mg; the largest overall change for one patient was an increase of 40 mg.

There was some concern that patients might misuse this privilege and seek to elevate their methadone dose to a maximum or to keep themselves in a state of continuous intoxication. The clinical review of dose adjustments made by patients over the 32-week study period indicated that none were contraindicated or clinically inappropriate. In no case was the privilege of self-adjustment of the methadone dose suspended for any patient because of misuse.

COMMENT

Our findings are consistent with an earlier report of Goldstein et al (1975), who also found little change in methadone maintenance dose under patient control and an overwhelming preference for this procedure by patients and staff as compared to the usual physician control of maintenance dose. In that study the patients' motivation to increase their dose was curtailed by not allowing take-home methadone to individuals whose dose was greater than 50 mg. In our study there were no constraints on patients to request a change in their dose.

Thus far, none of our patients have used their dose-control privileges inappropriately. However, continuous monitoring of patient dose-adjustment activity is a necessary feature of the self-adjustment procedure in order to prevent possible misuse and to identify the potential need for clinical interventions other than methadone dose changes that may be indicated and more appropriate. Positive acceptance with the present system by patients and staff have led us to adopt it as an ongoing clinical procedure. These findings

underscore the potential value of having patients povide input into the conduct of their treatment.

REFERENCE

Goldstein, A., Hanstein, R.W. and Horns, W.N. Control of methadone dosage by patients. JAMA, 234 (7): 734-737, 1975.

ACKNOWLEDGEMENTS

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Progress Reports

Biological Evaluation of Compounds for Their Dependence Liability.

V. Drug Testing ‘Program of the Committee on Problems of Drug Dependence, Inc. (1981)

A. E. Jacobson

In my last annual report (1980), I discussed the procedures which were used to evaluate compounds for their dependence liability, the sources of support for the testing, and the work which is done by the involved scientists at the Medical College of Virginia (MCV) and the University of Michigan (UM). I will not try to repeat that data; however. I would like to discuss some of the results from this joint effort. The MCV/UM/NIH/NIDA groups have held 3 meetings this year, at UM during the Interim CPDD meeting in November, at Atlanta during the FASEB meeting in April, and preceding this meeting in San Francisco. Dr. Sorer and, occasionally, Dr. Braude join us as representatives of NIDA. Discussions at these meetings relates to further work which one or both groups should do on compounds of interest. This cooperation has resulted in the preparation of three papers for publication in various journals. There will be a paper on zomepirac, one on an interesting group of homobenzomorphans, and a third, which I will present at this meeting; on some curious 4-methoxy-6-keto-morphinans. The cooperative effort provides, I believe, an extremely valuable resource to the CPDD. Thus, let me mention some of the scientists to whom the Committee owes its thanks: Drs. Harris, Aceto, May, Balster and Dewey, and their co-workers at MCV, and Drs. Woods, Katz, Smith, Medzihradsky, Young, Winger, and Swain and their co-workers, at UM.

Although we examined about the same number of new compounds this year as we did last year, more tests were done on them and each group saw a large increase in the number of compounds which was sent to them, We have, thus, more information on a larger number of compounds than in previous years, and this will become ever larger in the future. The UM group has begun to computerize the obtained data and, one day, it will be more easily retrieved in any number of recombinations. I am happy to report that, in general, the reports are being delivered with great efficiency and the backlog, although variable with the particular assay, is in most instances quite reasonable.

COMPOUNDS RECEIVED UNDER AUSPICES OF CPDD, INC.

In order to provide comparisons with previous data, I have adopted the same time frame as in 1980, calling May 1, 1980 to April 30, 1981 the "evaluation year". During that period of time, 25 compounds were sent to UM for primary screening (SDS), and 29 compounds were sent to MCV. These were new compounds. In that same time period, however, a total of 67 compounds were sent to MCV for various tests, and 81 compounds were sent to UM. It is apparent that further testing is being carried out, beyond SDS, on a considerable number of compounds from former years. Also, many compounds are sent to me for mouse antinociceptive screening and/or receptor affinity experiments, rather than SDS, due to an insufficient supply of compound, or for other reasons. In the 1981 edition of "Problems of Drug Dependence" there will be reports from MCV on 50 compounds, and reports on 45 compounds from UM. This represents a ca. 10 percent increase over the past year.

SOURCES OF NEW COMPOUNDS RECEIVED -

The percentage of compounds received from pharmaceutical industry and other sources was the inverse of that noted in my 1980 report: 20 percent were from U.S. industry, and 24 percent from foreign industry; 16 percent from U.S. universities, 26 percent from foreign universities, 12 percent from NIH, and 2 percent (1 compound) from the DEA. This ratio of 44 percent from industry and 56 percent from universities, et al., is fairly close to the 1:1 ratio noted heretofore. It should be noted that the university sources are not disparate. The U.S. and foreign university compounds are, mostly, from 1 U.S. and 1 foreign university. The industrial sources are considerably more disparate.

TYPES OF COMPOUNDS EXAMINED -

Tables 1 - 8 include most of the compounds released for publication in 1981. I have tried to condense the information given by MCV and UM in their 1981 reports so that the structures of related compounds could be compared. In order to put a sufficient amount of data on these compounds in the tables, many abbreviations were used, and these are listed below.

Table 1 lists the morphine-like structures of interest. I rather doubt whether NIH 9735 is new to the literature; Fishman and Lewenstein refer to it, obliquely, in their 1967 patent. However, it is apparently new to our program. Table 2 considers new types of morphinans. Table 3 shows the effect of a new type of side-chain in the benzomorphans (NIH 9805, 9809). The homobenzomorphans, which I mentioned earlier, are shown in table 4. The considerable amount of new work on phenylmorphans is shown in table 5; and an apparent ketobemidone-type of antagonist is shown in table 6. Table 7 shows the structure of one of the few isoquinoly phenols or pyrindinyl phenols which does not appear to suppress withdrawal in SDS. The miscellaneous compounds examined are listed in table 8. Zomepirac, on which further work was done

this year, is shown. The compound which DEA sent to us, through NIDA, was "China White", alpha-methylfentanyl. It was suspected to have caused deaths among some individuals who thought it was heroin. It is, in fact, considerably more potent than heroin and, as might be expected a priori, was shown to have high PDC in our assays. The two peptides listed in table 8 join the one observed last year in having high estimated PDC. Again, we have not observed any peptide which did not have high PDC, or which had any narcotic antagonist activity.

Detailed information on all of the compounds listed in these tables is given in the MCV - UM annual reports.

ABBREVIATIONS USED IN TABLES

Antinociceptive ED50 values - HP = hot plate assay, SC injection, mice; N = Nilsen assay, sc, mice; PPQ = phenylquinone writhing assay, sc, mice; TF = tall flick assay, sc, mice; TFA = tail-flick antagonism vs. morphine, sc, mice. I = inactive, without a reasonable dose-response relationship, or insufficiently active for statistical analysis.

Receptor binding affinities in rat brain membranes and smooth muscle preparations - RBH = binding affinity, without sodium, to rat brain membranes, in nM (parenthesized number is ratio of +Na/-Na); GPI = electrically stimulated guinea pig ileum EC50 values. E = x10; parenthesized numbers are maximum percent inhibition at EC50; bracketed letters: A = antagonized by naltrexone, NA = not antagonized by naltrexone. No Effect = no inhibition of twitch. VD = electrically stimulated vas deferens EC50 values. Parenthesized numbers and bracketed letters are as listed under GPI.

SDS single dose suppression, rhesus monkeys: NS = no suppression, CS = complete suppression, PS = partial suppression. Parenthesized numbers = dose range studied.

NW = studies in non-withdrawn monkeys: PW = precipitated withdrawal at dose levels indicated in parentheses &/or potency comparison with N (naloxone).

The numbers used in the tables are rounded. For precise values, and details of the procedures, see the Annual Reports of MCV and UM.

AUTHOR

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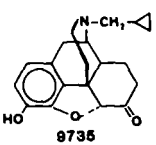
TABLE 1. MORPHINE-LIKE STRUCTURES



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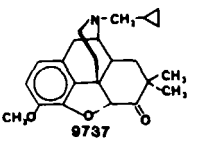

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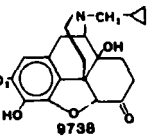

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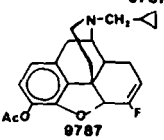

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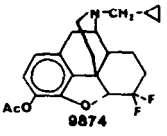
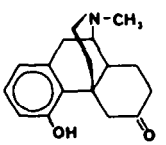


9874

NIH# MCV# UM#	HP, N, PPQ, TF, TFA	RBH	GPI	VD	SDS	MW
9735 4195 1223	I,I,0.01,0.04,0.14	1.2(0.58)	1E-9(54)[A]	NO EFFECT	NS(0.15-0.6)	PW(0.3-1.2)(1980)
DIFFERENCE IN GPI AND VD MAY BE RELATED TO K-COMPONENT OF ACTION. SIMILAR TO NIH 9466 (1979).						
9737 4197 1225	5,12,1,I,I	195(1.2)	9E-8(39)[MA]	4E-8(40)[A]	CS@3(0.75-12)	-
UNUSUAL DIFFERENCE BETWEEN ANTAGONISM IN GPI AND VD.						
9738 4199 1226	4,6.4,I,I(1980)	>20uM	2E-4(98)[MA]	NO EFFECT	-	-
NO OPIATE AGONIST ACTIVITY IN VITRO.						
9787 4206 -	I,I,0.2,I,0.03	-	-	-	NS(0.25-1.0)	PW(0.001-1)[10x#]
DID NOT SUBSTITUTE IN RAT INFUSION (50-200). LONG DURATION OF ANTAGONIST ACTIVITY IN SDS (IRREVERSIBLE?).						
9874 4210 1322	I,20,0.1,I,0.008	4.2(0.5)	3E-9(46)[A]	NO EFFECT	NS(0.003-0.5)	-
MIXED AGONIST-ANTAGONIST WITH NOVEL AGONIST EFFECTS.						

OTHERS - ORIPAVINE (9821). N-secBUTYLNORMORPHINE (9637).

TABLE 2. MORPHINAN-LIKE STRUCTURES



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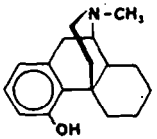

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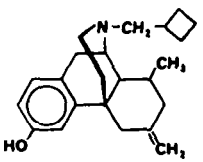
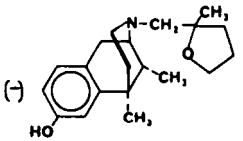


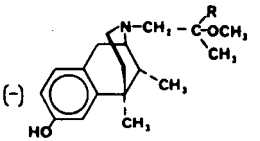
9738

NIH# MCV# UM#	HP, N, PPQ, TF, TFA	RBH	GPI	VD	SDS	MW
9674 - 1200	2,-,-,-,-	150(2.2)	-	-	CS@R(1-4)	
ESTIMATED TO HAVE HIGH PDC.						
9677 - 1201	2,-,-,-,-	55(2.2)	-	-	CS@R(1-4)	
ESTIMATED TO HAVE HIGH PDC.						
9736 4196 1224	I,1,0.02,I,I	1.7(0.8)	1E-5(58)[?]	3E-8(41)[MA]	NS(1-4)	PW(0.125-8)
NON-NARCOTIC COMPONENT OF ACTION (NALTREXONE HAS BIPHASIC ACTION IN GPI). RBH VERY DIFFERENT FROM SMOOTH MUSCLE.						

TABLE 3. BENZOMORPHAN-LIKE STRUCTURES



9804



9805, R = Me
9809, R = H

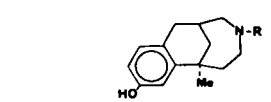
NIH# MCV# UM#	HP, N, PPQ, TF, TFA	RBH	GPI	VD	SDS	NW

9809 4212 1245 I,8,0.06,I,3 18(1.07) 3E-6(70)[*] 4E-8(100)[A] NS(1) PW@0.1(0.03-1)
*=POTENTIATION BY NALTREXONE. HOWEVER, ANTAGONIZED BY NALTREXONE IN VD. POTENT ANTAGONIST IN MONKEY.

9805 4213 1246 0.8,-,I,0.5,I 246(0.8) 4E-10(58)[A] 2E-8(100)[NA] NS(0.2-0.8) ATAXIA(0.4)*
*ATAXIA ANTAGONIZED BY NALOXONE. NO REVERSAL OF WITHDRAWAL (SIMILAR TO EKC, EXCEPT ON RESPIRATION). UNLIKE EKC IN VD. THE CHEMICALLY SIMILAR 9809 (VIDE SUPRA) SUBSTITUTED FOR MORPHINE, COMPLETELY, IN SDS. IT IS A SINGLE STEREOISOMER.

OTHERS - 9624 - 9BETA SUBSTITUTED - CONTINUATION WITH PAS
9625 - 9BETA SUBSTITUTED - CONTINUATION WITH RBH, SMOOTH MUSCLE AND SI.
8439 - N-METHYLENECYCLOPROPYLMETHYL - CONTINUATION WITH SI.
9256 - N-CYCLOPROPYLMETHYL - CONTINUATION WITH SI.
7958 - PENTAZOCINE - LOW DOSE MORPHINE SDS STUDY.

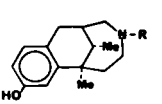
TABLE 4. HOMOBENZOMORPHANS



9612,d
9613,d
9614,l
R:Me

9901,d
9899,d
9900,l
R:CPM

9895,d
9896,l
R:ALLYL



9898, d, R:ALLYL
9902, d, R:CPM

NIH# MCV# UM#	HP, N, PPQ, TF, TFA	RBH	GPI	VD	SDS	NW

9612 4167 1267 0.4,-,0.5,8,20 3580(1.5) NO EFFECT NO EFFECT NS(4.5-18) -
RACEMATE - IN VIVO EFFECTS UNRELATED TO NARCOTIC RECEPTOR. RAT INFUSION SDS - NS(50,200)
PCP-LIKE.

9613 4168 1268 2,-,0.9,8,1 3170(3.2) NO EFFECT LITTLE EFFECT NS PW(2.5-10)
(+)-ENANTIOMER. RAT INFUSION SDS - NS(100,200). EFFECTS UNLIKELY VIA CLASSICAL NARCOTIC MECHANISMS.
PCP-LIKE.

9614 4169 1269 2,13,0.5,I,6 3760(1.3) 2E-6(82)[*] NO EFFECT NS PW(3-12)
(-)-ENANTIOMER. *=NALTREXONE POTENTIATES INHIBITION IN GPI. RAT INFUSION SDS - NS(100,200).
PAS - DEFINITE DEPENDENCE, TOLERANCE - INTERMEDIATE TO HIGH. SI - MINIMAL MAINTENANCE (1/3 CLOSE TO CODEINE).

9901 4250 1277 I,I,3,I,7 5840(1.2) NO EFFECT SLIGHT EFFECT NS(0.3-3) ATAXIA
RACEMATE. ATYPICAL NARCOTIC. PCP-LIKE AT HIGHER DOSES.

9899 4237 - I,I,5,2,I - - - PS,ATAXIA(0.06-1)
(+)-ENANTIOMER.

9900 4238 - I,I,0.2,I,I - - - NS,ATAXIA(1.25-10)
(-)-ENANTIOMER.

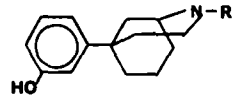
9895 4235 - I,I,0.6,I,1 - - - NS(0.025-2)
(+)-ENANTIOMER. ANESTHETIZED MONKEYS AT 2; NALOXONE - NO EFFECT.

9896 4236 - I,I,8,I,7 - - - NS,ATAXIA(0.125-2)
(-)ENANTIOMER.

9898 4249 1280 I,I,0.8,I,1.1 3120(1.1) SLIGHT EFFECT NO EFFECT ATAXIA ATAXIA
RACEMATE. ATAXIA NOT REVERSED BY NALOXONE. STRONG BEHAVIORAL EFFECT.

9902 4251 1281 I,I,8,I,I 3610(1.1) LITTLE EFFECT NO EFFECT ATAXIA ATAXIA
PCP-LIKE AT HIGH DOSES

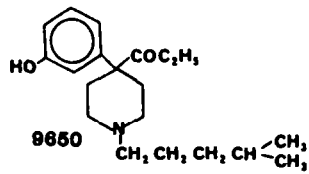
TABLE 5. PHENYLMORPHANS



8508, l, R=Me **9884, l, R=Pr** **9886, l, R=Am**
8509, d, R=Me **9885, l, R=Bu** **9894, d, R=Hex**

NIH# MCV# UM#	HP, N, PPQ, TF, TFA	RBH	GPI	VD	SDS	MW
8508 4231 - (-)-ENANTIOMER	2,-,0.9,6,0.3	-	-	-	NS(0.31-5)	PW(1/80xN)
8509 4232 - (+)-ENANTIOMER.	0.4,-,0.5,5,I	-	-	-	CS(2-8)	
9884 4241 1273 (-)-ENANTIOMER.	I,I,I,I,0.9 DOMINANT ANTAGONIST EFFECT.	418-(0.5)	6E-4(39)[A]	SLIGHT EFFECT	NS(1)	PW(1/170xN)
9885 4242 1274 (-)-ENANTIOMER.	I,I,I,I,I	1800(0.4)	3E-5(84)[A]	NO EFFECT	NS(5)	PW(1/100xN)
9886 4233 - (-)-ENANTIOMER.	I,I,I,I,1.2	-	-	-	NS(0.15-2.5)	PW(1/50xN)
9894 4247 1276 (+)-ENANTIOMER.	I,-,1.7,I,14 VERY POTENT PURE ANTAGONIST IN VITRO AND IN MONKEY.	119(0.4)	3E-5[NA]	NO EFFECT	NS(5.6)	PW(1/30xN)

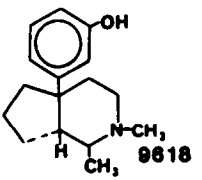
TABLE 6. PETHIDINE-LIKE AND KETOBEMIDONE-LIKE STRUCTURES



NIH# MCV# UM#	HP, N, PPQ, TF, TFA	RBH	GPI	VD	SDS	MW
9650 4190 1198	3,-,0.5,1,I NARCOTIC ANTAGONIST IN VIVO, LESS POTENT THAN NALORPHINE.	-	-	-	NS(2.5-5)	PW(2.5-5)

OTHERS - 9540, 9617, 9521, 9585, 8863 - HIGH ESTIMATED PDC.
9741, 9541, 9585 - RELATIVELY LITTLE EFFECT IN VIVO.

TABLE 7. ISOQUINOLYL PHENOLS AND PYRINDINYL PHENOLS

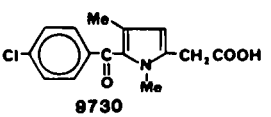


9618

NIH# MCV# UM#	HP, N, PPQ, TF, TFA	RBH	GPI	VD	SDS	NW
9618 4170 -	4,-,2,40,I	-	-	-	NS(6-32)	

OTHERS - 9342, 9576, 9616, 9824, 9825, 9839, 9840 - HIGH ESTIMATED PDC

TABLE 8. MISCELLANEOUS COMPOUNDS



9730

NIH# MCV# UM#	HP, N, PPQ, TF, TFA	RBH	GPI	VD	SDS	NW
9730 4192 1217	I,I,2,I,I	NO EFFECT	3E-5(45)[A]	7E-5(59)[NA]	NS	

ZOMEPIRAC SHOWED ITS ANALGESIC EFFECT ONLY IN PPQ. IT SUPPRESSED TWITCH IN GPI, BUT WITH LOW POTENCY, AND THIS WAS ANTAGONIZED BY NALTREXONE (NON-MORPHINE-LIKE COMPOUNDS HAVE BEEN NOTED TO ACT SIMILARLY IN GPI). ZOMEPIRAC ALSO SUPPRESSED TWITCH IN VD, AGAIN WITH LOW POTENCY, AND THIS WAS NOT ANTAGONIZED BY NALTREXONE.

OLDER COMPOUNDS - 8833, 8835 - THE LATTER HAD MORPHINE-LIKE ANTINOCICEPTIVE ACTIVITY (HP) AND DID NOT MAINTAIN IN SI.

OTHERS - CHINA WHITE (9961), PCP (9580), LEVONANTRADOL (9596), NABILONE (9872), OXAZEPAM (9826), FLURAZEPAM (9827).

ALSO - 2 PEPTIDES (9791 AND 9724) - REASONABLY POTENT IN VIVO AS ANTINOCICEPTIVES. HIGH ESTIMATED PDC. 9810 - RELATIVELY INACTIVE; 9873 - ACTIVE IN VIVO, HIGH ESTIMATED PDC.

Dependence Studies of New Compounds in the Rhesus Monkey, Rat, and Mouse (1981)

M. D. Aceto, L. S. Harris, and E. L. May

All the test drugs were supplied by Dr. Arthur Jacobson, Medicinal Chemistry Section, NIAMDD, under the auspices of the Committee on Problems of Drug Dependence, Inc. Morphine was supplied by Dr. Robert Willette, NIDA. The chemical structures of the test compounds excluding pentazocine were unknown to us when they were originally submitted.

For the most part, the procedures described by Seevers and his colleagues (1936, 1963) and Deneau (1956) regarding the facilities and training of the monkeys were used and a brief description follows. The monkeys were injected with 3 mg/kg/sc of morphine sulfate every 6 hours for at least 90 days before being used. This dose schedule was reported by Seevers and Deneau (1963) to produce maximal physical dependence. In addition, in order to determine whether or not clonidine and pentazocine would substitute for morphine in monkeys dependent on a lower dose of morphine, ten monkeys of 2 groups were made dependent

This study was supported by a contract (#271-77-3404) from the National Institute on Drug Abuse, Dr. Heinz Sorer, Contract Officer. Technical assistance was provided by F. Tom Grove, R. F. Jones, and S. M. Tucker; Medical College of Virginia, Department of Pharmacology, Virginia Commonwealth University, Richmond, Virginia 23298

using 1.5 mg/kg every 6 hours., Modified procedures for the precipitated withdrawal (PPt-W) and single dose suppression (SDS) tests were reported by Aceto and co-workers (1977 and 1978). The PPt-W test was initiated by the injection of a test drug 2½ hours after an injection of morphine and the animals were observed for signs of withdrawal. The SDS test was started approximately 15 hours after the last dose of morphine at which time the animals were showing withdrawal signs. The test compound was injected and the animals were observed for the suppression of abstinence signs. The onset and duration of action of the test drug were noted. In both tests, a vehicle control and an appropriate positive, control [naloxone 0.05 mg/kg or morphine sulfate 3.0 (mg/kg)] along with 3 different treatments (doses) of a test compound were randomly allocated to the 5 monkeys of a group. Occasionally 4 monkeys comprised a group and 2 doses of test compound were studied. Usually, 3 or 4 groups per compound were used. All drugs were given subcutaneously in a volume of 1 ml/kg and the vehicle used is indicated for each compound. The observer was "blind" with regard to the treatment given. A minimum 2-week washout and recuperation period between tests was allowed. In the primary physical dependence (PPD) test, the animals of a group received the drug every 6 hours for 30-50 days. They were placed in abrupt withdrawal and challenged with naloxone periodically, and were observed for signs of physical dependence. All potency estimates are approximations only.

The rat-infusion method was reported by Teiger (1974) and certain modifications are indicated below. Semi-restrained male, Sprague-Dawley rats were medicated by continuous infusion through indwelling, intraperitoneal cannula for 6 days with the drugs. Rats were anesthetized and each was fitted with a specially prepared cannula which was passed subcutaneously from the nape of the neck to the lateral side of the lower abdomen and then inserted in the. peritoneal'cavity. The cannula was anchored at both ends with silk sutures and attached to a flow-through; swivel mechanism which allowed the animal to move about in the cage and eat and drink normally. The swivel was connected to a syringe which was attached to a syringe pump. The animals received 7 to 10 mls of solution every 24 hours.

In the substitution for morphine (SM) test, the animals first received morphine (50 mg/kg/24 hrs on the first day, 100 mg/kg/24 hr on‘the second day, and 200 mg/kg/24 hr from days 3-6). Then, a test drug was substituted for 2 days. The morphine controls received an infusion of water. The animals were observed for changes in body weight and for behavioral-withdrawal signs for ½ hour at 6, 24, 48, 72 and/or 96 hours after stopping the infusion of morphine.

In the primary physical dependence (PPD) study, the animals received test compound for 6 days and then were placed in abrupt withdrawal and observed as above.

Table 1
Comparative Data-ED_{50} mg/kg/sc (95% C.L.) of Selected Standards in 3 Mouse Agonist-Antagonist Tests

Drug	Tail-Flick Test	Tail-Flick Antagonism Test	Phenylquinone Test
Pentazocine	15% at 10.0	18 (12.4-26)	1.65 (1.0-2.5)
Cyclazocine	17% at 1.0[a]	0.03 (0.12-.78	0.011 (0.0046-03)
Nalorphine .HCL	None at 10.0	2.6 (O.-69-9.75)	0.6 (0.25-1.44)
Naloxone .HCL	None at 10.0	0.035 (010-0.93)	No Activity
Naltrexone .HCL	None at 10.0	0.007 (0.002-0.02)	No activity
Morphine Sulfate	5.8 (5.7-5.9)	-----	0.23 (0.20-0.25)

[a]Mice were ataxic at 3.0 and 10.0 mg/kg but no further increase in-reaction time was seen.

Three mouse tests were used in our laboratory at the Medical College of Virginia to provide a preliminary estimate of the, potency and profile of activity of each test compound. The tests were the tail-flick agonist (TF) and the morphine antagonist (TF vs M) tests and the phenylquinone (PPQ) test (Dewey et al., 1970; Dewey and Harris, 1971). Reference-standard data for these-tests are shown in table 1. In addition, Dr. Jacobson supplemented these data and estimated starting doses which were based on results obtained from the mouse hot plate (HP) (Eddy and Leimbach, 1953; Jacobson and May, 1965; Atwell and Jacobson, 1978) and Nilsen (N) (Perrine et al., 1972) tests from his laboratory. Reference data for these tests are shown in table 2.

Table 2

Comparative Data (ED_{50} mg/kg/sc) [95% S.E.] from the Hot Plate and Nilsen Test

Compound	Hot Plate Test Subcutaneous Oral	Nilsen Test Subcutaneous Oral
Morphine Sulfate	0398(0.83-1.1) 6.3(4.7-8.3)	1.3(1.0-1.7) 8.3(6.0-11.4)
Codeine Phosphate	6.8(4.5-10.2) 13.5(9.7-18.7)	7.4(4.9-11.0) 14.7(9.2-23.3)
Levorphanol Tartrate	0.2(0.1-0.3) -	0.2(0.16-0.3) 2.5(1.7-3.7)
Meperidine .HCL	5.3(4.0-7.1) -	- -
(-)-Metazocine.HBr	0.6(0.5-0.9) 10.6(8.0-14.1)	0.5(0.3-0.7) 26.0(21.0-33.0)
Dihydromorphinone .HCL	0.19(0.15-0.25) 0.9(0.7-1.2)	0.2(0.15-0.3) 1.8(1.5-2.1)
Nalorphine .HCL	9.9(5.7-17.1) -	23.0(16.2-32.7) -
Cyclazocine	1.5(1.1-2.1) -	0.1(0.07-0.16) -
Pentazocine	9.3(6.7-12.8) -	6.5(4.4-8.8) -
Chlorpromazine .HCL	1.1(0.9-1.5) -	-

Naloxone .HCL and Naltrexone HCL No dose response

Phenobarbital, Amobarbital, Valium, Oxazepam, Flurazepam, Mepromate and Mescaline are inactive on the hot plate test.

TABLE III

SUMMARY OF TESTS REPORTED

COMPOUND #			CHEMICAL CLASS	MOUSE					RAT		MONKEY		
MCV	NIH	UM		TF,	TFvsM,	PPQ,	HP,	N	SM,	PPD	SDS	PPt-W	PPD
4102	9342	1124	A Phenyldeca-hydroisoquinoline	+	+	+	+	-	-	-	-	-	-
4145	9540	1169	A 4-Phenylpiperi-dine	+	+	+	+	-	-	-	+	-	-
4155	9549	1151	Clonidine-See MCV 4183	+	+	+	+	-	-	-	+ (special)	-	-
4157	9576A	1242	An Octahydropyrin-dine	+	+	+	+	+	-	-	-	-	+
4158	9580A	---	Phencyclidine	+	+	+	+	+	-	-	-	-	+
4167	9612	1267	A Homobenzomorphan	+	+	+	+	-	+	-	-	-	-
4168	9913	1268	A Homobenzomorphan	+	+	+	+	-	+	-	-	-	-
4169	9614	1269	A Homobenzomorphan	+	+	+	+	-	+	-	-	-	-
4170	9618	---	An Octahydropyrin-dine	+	+	+	+	-	-	-	-	-	-
4172	9616	---	An Octahydropyrin-dine	+	+	+	+	-	-	-	+	-	-

TABLE III (Cont'd)

COMPOUND #			CHEMICAL CLASS	MOUSE					RAT		MONKEY		
MCV	NIH	UM		TF,	TFvsM,	PPQ,	HP,	N	SM,	PPD	SDS	PPt-W	PPD
4173	9617	---	A 4-Phenylpiperidine	+	+	+	+	-	-	-	+	-	-
4176	9625A	---	A 3-Benzaracine	+	+	+	+	-	-	-	-	-	+
4183	9571	1151	Clonidine-See MCV 4155										
4187	9724	1212	A (small) peptide	+	+	+	+	-	-	-	-	-	-
4190	9650	1198	A Ketobemidone	+	+	+	+	-	-	-	+	-	-
4192	9730	1217	Zomepirac	+	+	+	+	+	-	+	+	-	-
4196	9736	1224	A Morphinan	+	+	+	+	+	-	-	+	+	-
4197	9737	1225	A Epoxymorphinan	+	+	+	+	+	-	-	+	-	-
4206	8834A	972	A Tetrahydronaphthalene	+	+	+	+	+	-	-	+	-	-
4208	9787	---	An Epoxymorphinan	+	+	+	+	+	+	-	+	+	-
4210	9791	1238	A (small) peptide	+	+	+	+	+	-	+	+	-	-
4212	9804	1245	A Benzomorphan	+	+	+	+	+	-	-	-	-	-

TABLE III (Cont'd)

COMPOUND #			CHEMICAL CLASS	MOUSE					RAT		MONKEY		
MCV	NIH	UM		TF,	TFvsM,	PPQ,	HP,	N	SM,	PPD	SDS	PPt-W	PPD
4213.	9805	1246	A Benzomorphan	+	+	+	+	-	-	-	-	-	-
4217	9809	---	A Benzomorphan	+	+	+	+	-	-	-	+	-	-
4218	9810	---	A Phenyldihydroindole	+	+	+	+	-	-	-	+	-	-
4219	9821	1252	Oripavine	+	+	+	+	-	-	-	+	-	-
4220	9824	1253	A Phenyldecahydroisoquinoline	+	+	+	+	-	-	-	+	-	-
4221	9825	1254	A Phenyldecahydroisoquinoline	+	+	+	+	-	-	-	-	-	-
4222	9826	---	Oxazepam	+	+	+	+	-	-	-	+	-	-
4223	9827	---	Flurazepam	+	+	+	+	-	-	-	+	-	-
4225	9839	1259	An Octahydropyrindine	+	+	+	+	-	-	-	-	-	-
4226	9840	1260	An Octahydropyrindine	+	+	+	+	-	-	-	-	-	-
4227	9832	1261	An Endoethenomorphine	+	+	+	+	-	-	-	+	-	-

TABLE III (Cont'd)

COMPOUND #			CHEMICAL CLASS	MOUSE					RAT		MONKEY		
MCV	NIH	UM		TF,	TFvsM,	PPQ,	HP,	N	SM,	PPD	SDS	PPt-W	PPD
4228	9872	1266	Nabilone	+	+	+	+	-	-	-	+	-	-
4229	9873	---	A Phenylmorpholine	+	+	+	+	-	-	-	+	-	-
4230	9874	1322	An Epoxymorphinan	+	+	+	+	+	-	-	+	-	-
4231	8508A	809	A Phenylmorphan	+	+	+	+	-	-	-	+	+	-
4232	8509A	810	A Phenylmorphan	+	+	+	+	-	-	-	+	-	-
4233	9886	---	A Phenylmorphan	+	+	+	+	+	-	-	+	+	-
4235	9895	---	A 4-Benzazonine	+	+	+	+	+	-	-	+	-	-
4236	9896	---	A 4-Benzazonine	+	+	+	+	+	-	-	+	-	-
4237	9899	---	A 4-Benzazonine	+	+	+	+	+	-	-	-	-	-
4238	9900	---	A 4-Benzazdnine	+	+	+	+	+	-	-	+	-	-
4241	9884	1273	A Phenylmorphan	+	+	+	+	-	-	-	-	-	-
4242	9885	1274	A Phenylmorphan	+	+	+	+	+	-	-	-	-	-
4247	9894	1276	A Phenylmorphan	+	+	+	+	-	-	-	-	-	-
4249	9898	1280	A Benzazonine	+	+	+	+	+	-	-	-	-	-

TABLE III (Cont'd)

COMPOUND #			CHEMICAL CLASS	MOUSE					RAT		MONKEY		
MCV	NIH	UM		TF,	TFvsM,	PPQ,	HP,	N	SM,	PPD	SDS	PPt-W	PPD
4250	9901	1277	A 4-Benzazonine	+	+	+	+	+	-	-	-	-	-
4251	9902	1281	A 4-Benzazonine	+	+	+	+	+	-	-	-	-	-
4268	7958	381	Pentazocine	-	-	-	+	+	-	-	+ (special)	-	-
4287	9961	1324	4-Anilinopiperidine	+	+	+	+	-	-	-	+	-	-

References

Aceto, M.D., Flora, R.E. and Harris, L.S. The effects of naloxone and nalorphine during the development of morphine dependence in rhesus monkeys. Pharmacol, 15:1-9, 1977.

Aceto, M.D., Flora, R.E. and Harris, L.S.
Caffeine elicited withdrawal signs in morphine-dependent rhesus monkeys. Eur J Pharmacol, 50:203-207, 1978.

Atwell, L., and Jacobson, A.E. The search for less harmful analgesics. Lab Animal, 7:42-47, 1978.

Deneau, G.A. An analysis of factors influencing the development of physical dependence to narcotic analgesics in the rhesus monkey with methods for predicting physical dependence liability in man. Doctoral Dissertation, University of Michigan, 1956.

Dewey, W.L., Harris, L.S., Howes, J.F., and Nuite, J.A. The effects of various neurohumoral modulators on the activity of morphine and the narcotic antagonists in the tail-flick and phenylquinone tests. J Pharmacol Exp Ther, 175:435-442, 1970.

Dewey, W.L. and Harris, L.S. Antinociceptive activity of the narcotic antagonists analogues and antagonistic activity of narcotic analgesics in rodents. J Pharmacol Exp Ther, 179:652-659, 1971.

Dewey, W.L. and Patrick, G.A. Narcotic antagonists in the rat infusion technique. Proc. from the 37th annual meeting, Committee on Problems of Drug Dependence, NRS-NAS, U.S.A. 64-73, 1975.

Jacobson, A.E., and May, E.L. Structures related to morphine, XXI, 2'-Substituted benzomorphans. J Med Chem, 8:563-566, 1965.

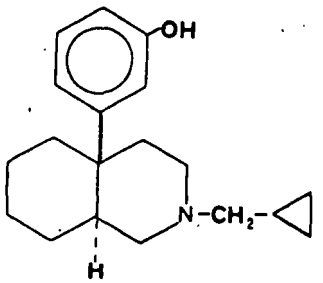
Perrine, T.D., Atwell, L., Tice, I.B., Jacobson, A.E., and May, E.L. Analgesic activity as determined by the Nilsen method. J. Pharm Sci, 61:86-88, 1972.

Seevers, M.H. Opiate addiction in the monkey. I. Methods of study. J Pharmacol Exp Ther 56:147-156, 1936.

Seevers, M.H., and Deneau, G.A. Physiological aspects of. tolerance and physical dependence. In: Root, W.S. and Hofman, F.G., eds. Physiological Pharmacology, Vol. I. New York: Academic Press, 1963. pp. 565-670.

Teiger, D.G. Induction of physical dependence on morphine, codeine, and meperidine in the rat by continuous infusion, J Pharmacol Exp Ther, 190:408-415, 1974.

MCV 4102-NIH 9342-UM 1124. (-)-m-[2-(Cyclopropyl-methyl)-1,2,3,4,4a,5,6,7,8,8aα-decahydro-4aß-isoquinol-yl]phenol succinic acid salt.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF-7.3 (2.8 - 18.6)

2) TF vs M-16% at 1.0, 43% at 10.0 and 22% at 30.0

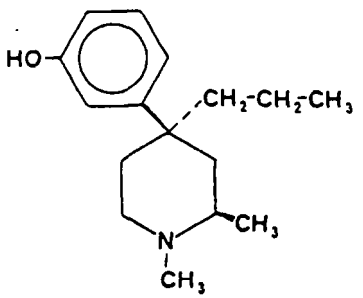
3) PPQ-2.0 (1.0 - 3.9)

4) HP-4.4 (2.9 - 6.6)

MONKEY DATA (SDS)	# ANIMALS Doses (mg/kg/sc)	3 / 1.0 , 3 / 2.0 , 3 / 4.0 , Vehicle-H_2O

MCV 4102 substituted completely for morphine. At the lowest dose, drowsiness was noted in 1/3 animals. Ataxia, salivation, body sagging, ptosis and drowsiness were noted at the 2 higher doses. Its potency is about that of morphine.

MCV 4145-NIH 9540-UM 1169. trans-3-(1,2-Dimethyl-4-propyl-4-piperidinyl)phenol hydrobromide.



MOUSE DATA-ED_{50} (95% C.L.)- (mg/kg/sc)

1) TF-1.1 (0.5 - 2.3)

2) Tf vs M-Inactive at 0.5, 1.0, and 3.0

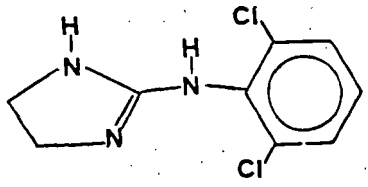
3) PPQ-0.4 (0.2 - 0.9)

4) HP-0.81 (0.62 - 1.06)

MONKEY DATA (SDS)	#ANIMALS Doses mg/kg;sc)	4 / 0.4, 4 / 0.8 , 4 / 1.6 , Vehicle-H_2O

MCV 4145 substituted briefly for morphine. Some drowsiness was noted at all doses tested. The drug is 2-4 times as potent as morphine.

MCV 4155, 4183-NIH 9549, 9571-UM 1151. 2-(2,6-Dichloroanilino)-2-imidazoline (Clonidine) hydrochloride.



MOUSE DATA-ED_{50} (95% C.L.)

1) TF-1.23 (0.23-6.65)

2) TF vs M-Inactive at 0.3
1.0 and 30.0

3) PPQ-0.005 (0.001-0.02)

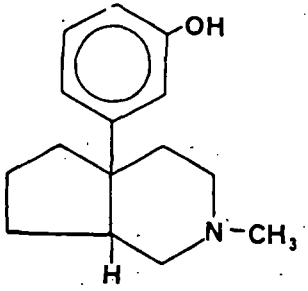
4) HP-1.0 (0.7-1.5)

MONKEY DATA #ANIMALS 2 , 2 , 2 ,
Doese (mg/kg/sc) 0.0625 0.25 0.1
Vehicle-H_2O

1) Special "Lower dose" morphine-dependent monkeys SDS study (1.5 mg/kg/q 6 hours).

MCV 4155 substituted partially for morphine. The drug also produced drowsiness and eyelid ptosis. It does not appear that these lower dose morphine-dependent animals react differently from. he animals dependent on 3.0 mg/kg q 6 hours. Partial substitution does not necessarily indicate that the drug has morphine-like'effects.

MCV 4157-NIH 9576A-UM 1242. (-)-cis-(octahydro-2-methyl-1H-2-pyrindin-4a-yl)phenol, (Z)-2-butenedioic: acid salt.



MOUSE DATA-ED_{50} (95% C.L.)

1) TF-10.4 (3.3-33.2)

2) TF vs M-60.5 (12.8-286.8)

3) PPQ-0.6 (0.3-1.9)

4) HP-2.4 (1.6-3.7)

5) N-2.3 (1.7-3.0)

MONKEY DATA
(PPD)
Four rhesus monkeys that had not received any drug for at least 2 months were given MCV 4157 dissolved in H_2O every four hours, unless indicated otherwise.

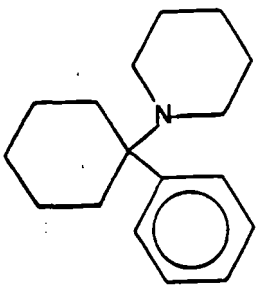
Day	Dose mg/kg/sc/times/day	Comments
1	4.0	The principal drug effects noted during this study were scratching, restlessness
2	8.0	

Day	Dose	Comments
3	16.0	and staring. Convulsions were
4	32.0	observed on days 5, 6, 8, 12,
5	48.0	14, and 26. Infrequently seen
	Skipped 6 p.m.	signs were tremors, wet dog
	35.0 (2xd)	shakes and fighting.
6	35.0	
7	37.0 35.0 (1xd)	
8	35.0 (3xd)	
9-14	35.0	
15	PPt-W	Precipitated withdrawal
	0.05 mg/kg naloxone	signs noted were: 4/4
	8:35 a.m.	drowsy, 2/4 wet dogs and
		restlessness; 1/4 fight-
		ing, avoids contact,
		yawning, and tremors
15 - noon	30.0	
16	30.0	
17 - 22	32.0	
22 8:30 a.m.	PPt-W	Precipitated withdrawal
	5.0 mg/kg naloxone	signs noted were:
		4/4 wet dogs; 3/4 rest-
		less, retching vocalized
		when abdomens palpated,
		rigid abdominal
		muscles, and drowsy; 2/4
		lying on side or
		abdomens; 1/4 fighting,
		avoid contacts, and
		coughing.
22 - noon	33.0	
23-30	32.0	
31 Abrupt Withdrawal	- Abrupt withdrawal signs noted were: Twelve hours after last injection 3/4 vocalized when abdomens pal- pated and vocalized; 1/4 wet dogs. Eighteen hours after last injec- tion peak withdrawal 3/4 vocalized when abdomens palpated; restless and rigid abdomens; 2/4 vocalized; 1/4 fighting, avoids contact, tremors and retching. Thirty- six hours after the last injec- tion 2/4 vocalized when abdomens palpated.	

Conclusion

MCV 4157 produced opiate-like signs of physical dependence after naloxone challenge and during abrupt withdrawal. Convulsions were frequently observed in the dose range of 32.0-48.0 mg/kg. The drug probably has an intermediate to high physical dependence liability.

MCV 4158-NIH 9580A. 1-(Phenylcyclohexyl)piperidine hydrochloride (Phencyclidine).



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF-Inactive at 1.0, 3.0 and 10.0

2) TF vs M-0.3 (0.1-1.0)

3) PPQ-1.4 (0.5-4.1)

4) HP-Inactive, convulsion at 10.0

5) N-See HP

MONKEY DATA

PPD (second study - See 1980 Report for First Study).

Five monkeys received MCV 4158, 6 x d subcutaneously as indicated below. The animals had not received any drugs for at least 2 months. The drug was dissolved in H_2O and the animals were observed for behavioral signs 15-30 minutes after drug for 15 minutes.

Day	Dose mg/kg/sc (6 x day) 6 and 9 a.m., noon, 3 and 6 p.m. and midnight	Comments and Signs
1	0.1	Dose-related side effects ranging from wet-dog shakes and tremors, ataxia and slowing at the lower doses to severe ataxia, incoordination falling and an inability to pick themselves up. The onset was rapid; the effects peaked in 1/2 hour and had abated by 1 to 1 1/2 hours.
2	0.2	
3-9	0.3-0.45	
9.14	0.45-0.6	

Day	Dose	
15		PPt-Withdrawal - At 8:45 a.m., after a 5.0 mg/kg naloxone challenge, 5/5 wet dog shakes, 1/5 restlessness and 1/5 avoids contact were the only signs noted.
16-22	0.6	
23-		Abrupt Withdrawal The principal signs noted during the 24 hr. abrupt withdrawal period were fighting, avoids contact, restless, tremors, wet-dogs shakes.
24-30 - 0.6-0.7		
3 1		Abrupt Withdrawal The principal signs noted were: 1/5 fighting, 2/5 avoids contact, 4/5 restlessness, 5/5 tremors. This cluster of symptoms started at 2 hours and peaked at 6 hours. All the animals developed diarrhea 10 hours into withdrawal and it was still evident in 2/5 the following morning. At this time staring was also noted. Myoclonic jerks were noted 15 hours into withdrawal.
32-39	0.7	
40		PPt-W - Received a total of 10 mg/kg/sc of naloxone within 1 hour.

Withdrawal signs noted were: 1/5 fighting, 2/5 restless, 5/5 drowsy, 3/5 tremors, 5/5 wet-dog shakes, 1/5 vocalizes when abdomen palpated, 3/5 rigid abdominal muscles, 2/5 stretching and rubbing.

41-44	0.75	
45	Abrupt Withdrawal -	The principal sign noted during the first 5 hours was tremor. Other signs noted were 1/5 lying on side or abdomen (at 5 hours only), fighting, avoids contact, restless, wet-dog shakes. Few signs were seen after 24 hours.

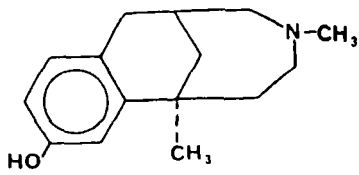
Conclusions

MCV 4158 produced signs indicating the development of some degree of physical dependence. The syndrome may be characterized by the signs fighting,, tremor, restlessness, and wet-dog shakes, Since some of these signs are also seen while the animals are on lower doses of MCV 4158 and since the last abrupt-withdrawal reaction was noticeably weaker than the first, it is difficult to make firmer conclusions.

The results noted with precipiated withdrawal suggest that naloxone at very high doses may produce a mild withdrawal reaction.

Approximately one month after the study was terminated, one of the animals delivered an apparently healthy baby that appeared to be doing well at 4 months.

MCV 4167-NIH 9612-UM 1267. (±)-9-Hydroxy-4,7-dimethyl-C-homobenzomorphan hydrobromide.



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-1. 6.4 (3.9-10.5)
2. 15.5 (7.4-32.2)

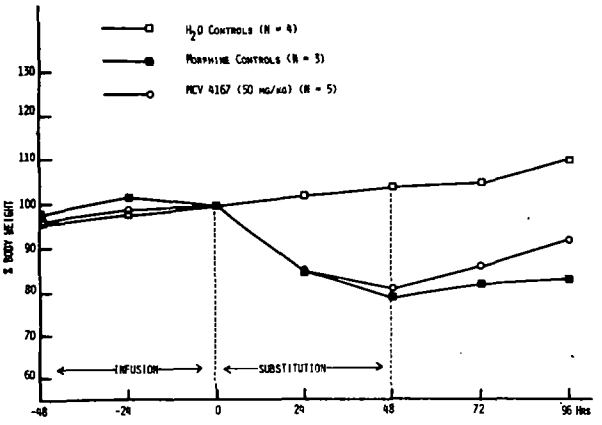
2) TF vs M-1. 19.8 (10.5-37.2)
2. 24.9 (10.8-57.4)

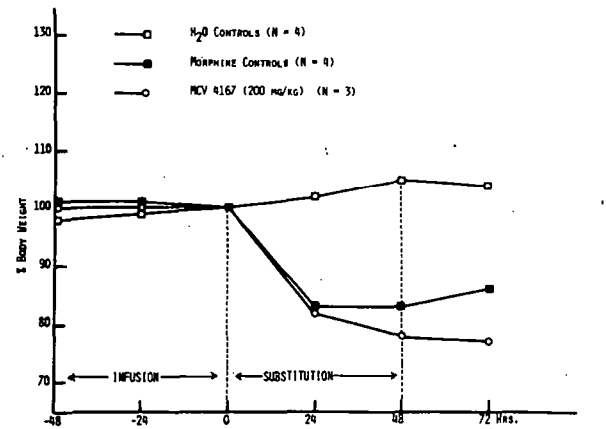
3) PPQ-0.5 (0.2-1.3)

4) HP-1. 0.4 (0.25-0.6)
2. 0.49 (0.36-0.65)

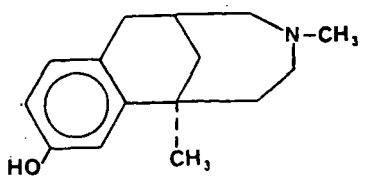
Rat Infusion (SM)

MCV 4167 did not substitute for morphine at doses of 50 and 200 mg/kg/24 hours. The-animals receiving MCV 4167 lost nearly as much weight as the morphine infusion - water substitution group as shown in the figures. In addition, no significant differences were calculated between these two groups regarding withdrawal signs.





MCV 4168-NIH 9613-UM1268. (+)-9-hydroxy-4,7-dimethyl-C-homobenzomorphan hydrobromide.



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-1. 8.2 (3.1-21.8)
2. 6.7 (2.5-18.4)

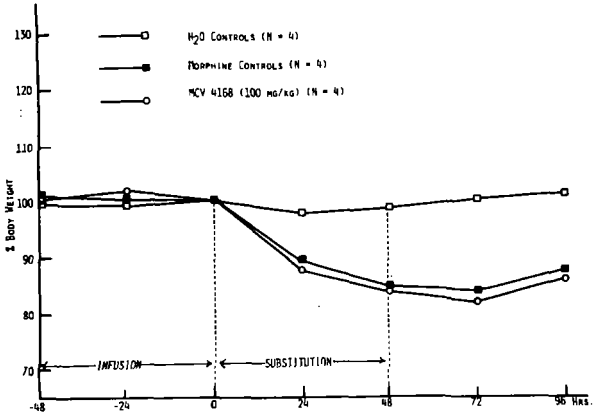
2) TF vs M-1. Inactive at 3.0, 6.0, 10.0, and 30.0
2. Inactive at 3.0, 3.0, 10.0, and 30.0

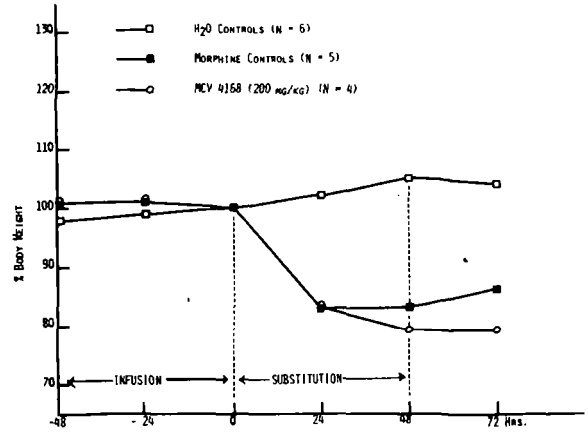
3) PPQ-1. 0.3 (0.1-1.0)
2. 0.9 (0.4-2.2)

4) HP-1. 2.6 (2.1-3.4)
2. 2.4 (1.4-4.0)

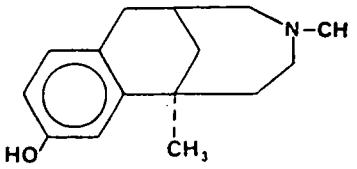
Rat Infusion (SM)

We conclude that MCV 4168 did not substitute for morphine at doses of 100 and 200 mg/kg/24 hours. As shown in the figures, the animals receiving MCV 4168 lost nearly as much weight as the morphine infusion - water substitution group. No significant differences in withdrawal signs were calculated at 6, 24, 48 and 72 hours between these two groups.





MCV 4169-NIH 9614-UM 1269 (-)-9-Hydroxy-4,7-dimethyl-C-homobenzomorphan hydrobromide.



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

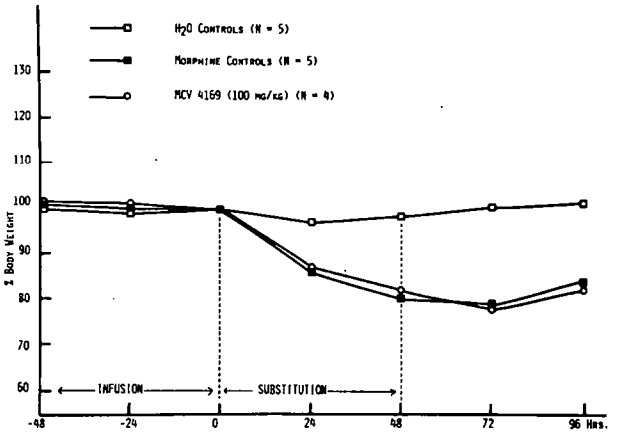
1) TF-1. Inactive at 3.0, 6.0, 10.0, and 30.0
2. Inactive at 3.0, 10.0, and 30.0

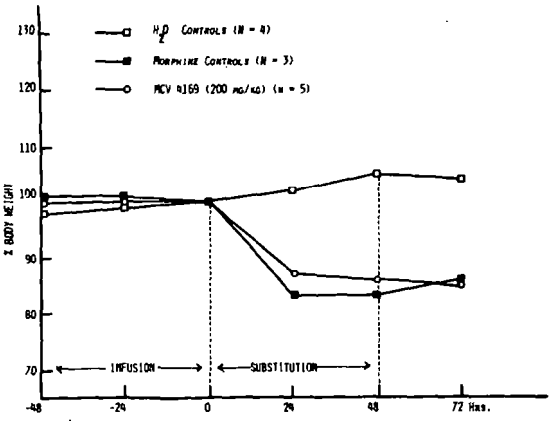
2) TF vs M-1. 13.4 (5.7-31.3)
2. 5.5 (1.2-25.9)

3) PPQ-1. 0.5 (0.2-1.7)
2. 0.4 (0.1-1.3)

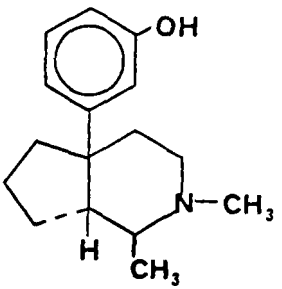
Rat Infusion (SM)

MCV 4169 did not substitute for morphine at doses of 100 and 200 mg/kg/24 hours. As shown in the figures, the animals receiving this compound lost nearly as much weight as the morphine infusion - water substitution group. Significant differences for withdrawal signs were not calculated between morphine controls and the MCV 4169-dosed rats.





MCV 4170-NIH 9618. cis-3-Octahydro-1ß,2-dimethyl-4aH-2-pyrindin-4a-yl)phenol, (Z)-2-butenedioic acid salt.



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

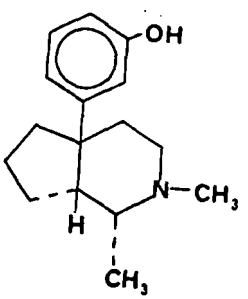
1) TF-39.7 (13.6-115.9)

2) TF vs M-13% at 10.0, 29% at 30.0 and 36% at 100.0

3) PPQ-2.2 (1.0-5.1)

4) HP-4.1 (3.0-5.7)

MCV 4172-NIH 9616. cis-3-(Octahydro-1α,2-dimethyl-4H-2-pyrindin-4a-yl)phenol, (Z)-2-butenedioic acid salt.



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-13.1 (4.3-40.3)

2) TF vs M-None at 3.0, 10.0 and 30.0

3) PPQ-1.4 (0.4-2.3)

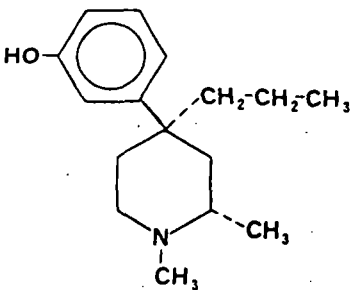
4) HP-1.8 (1.5-2.2)

MCV 4172-NIH 9616.

MONKEY DATA (SDS)	# ANIMALS Doses (mg/kg/sc)	3 , 2.5	3 , 5.0	3 , 10.0	Vehicle- H_2O

At the highest dose, MCV 4172 substituted completely and briefly for morphine. Its potency is estimated as 1/3 that of morphine.

MCV 4173-NIH 9617. cis-2-(1,2-Dimethyl-4-propyl-4-piperidinyl) phenol, (Z)-2-butenedioic acid salt.



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-Inactive at 1.0, 10.0 and 30.0

2) TF vs M-13.3 (3.6-49.6)

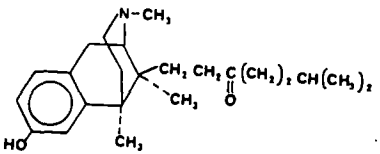
3) PPQ-1.8 (0.7-4.6)

4) HP-4.4 (3.5-5.4)

MONKEY DATA (SDS)	#ANIMALS Doses (mg/kg/sc)	3 , 2.0	3 , 4.0	3 , 8.0	Vehicle- H_2O

A dose-related reduction in withdrawal signs was noted. The drug substituted completely for morphine at the highest dose. The onset of action is prompt and the duration appears to be approximately 3 hours. It is about 1/3 as potent as morphine.

MCV 4176-NIH 9625A. 1-[(2-alpha,6-alpha,11S)-(±)-1-(1,2,3,4,5,6-Hexahydro-8-hydroxy-3,6,11-trimethyl-2,6-methano-3-benzazocin-11-yl)]-6-methyl-3-hepatanone methanesulfonate.



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-Inactive at 3.0, 10.0, and 30.0

2) TF vs M-14.8 (3.7-58.6)

3) PPQ-0.002 (0.0003-0.01)

4) HP-1.1 (0.8-1.3)

MONKEY DATA
(PPD)

Five monkeys that had not received any drug for at least 2 months were medicated with MCV 4176 as indicated below. The drug was dissolved in H_2O and given every 6 hours unless othemise noted.

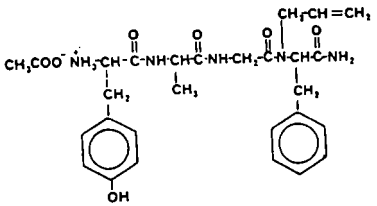
Day	Dose mg/kg/sc (times/day)	Comments
1	1.0	
2	2.0	During the first 4 days, scratching, fighting,
3	4.0	avoiding contact, and
4	8.0	restlessness were noted.
5	8.0 (1 x d) and 6.0 (3 x d)	When the dose was raised to 8.0, all the
6	6.0 (3 x d)	animals stopped eating
7	5.0	and had jaw sag, were
8	6.0	slow and salivated.
9	7.0	The dose was lowered.
10-12	8.0	On the sixth day, one
13-14	9.0	monkey became unconscious and was removed from study. By day 12, one monkey was bleeding from the site of injection and on day 13 all bled from sites of injection.
15	10.0	
16 8:30 a.m.	PPt-W 2.0 mg/kg naloxone	4/4 drowsy; 3/4 wet dogs, restlessness; 2/4 retching; 1/4 coughing, fighting, crawling.
16	5.0 (2 x d)	On day 16, 2 monkeys
17 Stopped Study		became unconscious after injection and one had an ulcer on its back.

Conclusion

MCV 4176 may have an opiate-like dependence liability but because the drug caused bleeding at the site of injection which progressed to ulcers in one monkey, and due to the severe drug effects, the study was terminated.

MCV 4187-NIH 9724-UM 1212. L-Tyrosyl-D-alanylglycyl-L-N-α-allylphenylalanine amide acetate.

MCV 4187NIH 9724-UM 1212.



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

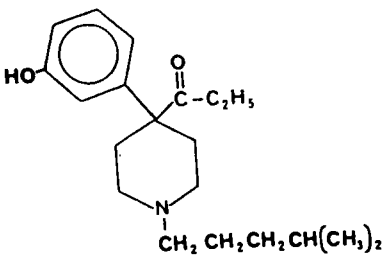
1) TF-4.5 (2.3-8.7)

2) TF vs M-24% at 0.01; 11% at 0.1; 11% at 1.0 and 0% at 5.0

3) PPQ-0.2 (0.05-0.6)

4) HP-1.9 (1.4-2.6)

MCV 4190-NIH 9650-UM 1198. N-4-Methylpentylnorketobemidone hydrobromide.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF-1.0 (0.3-3.9)

2) TF vs M-Inactive at 1.0 and 30.0

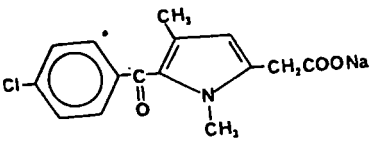
3) PPQ-0.45 (0.3-0.8)

4) HP-3.2 (2.3-4.4)

MONKEY DATA (SDS)	#ANIMALS				
	Doses (mg/kg/sc)	3, 2.5	3, 5.0	3, 10.0,	Vehicle-H_2O

MCV 4190 did not substitute for morphine in the dose range tested. Severe tremors were noted in one animal receiving the highest dose. Tremors were also noted in one animal at the lowest dose and in two at the intermediate dose.

MCV 4192-NIH 9730-UM 1217. Sodium 5-(4-Chlorobenzoyl)-1, 4-dimethyl-1H-pyrrole-2-acetate (Zomepirac).



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg.sc)

1) TF-Inactive at 1.0, 10.0 and 30.0

2) TF vs M-Inactive at 0.1 and 10.0

3) PPQ-1.8 (0.6-5.7)

4) HP-Inactive

5) N-No dose-response, 2/8 at 50.0

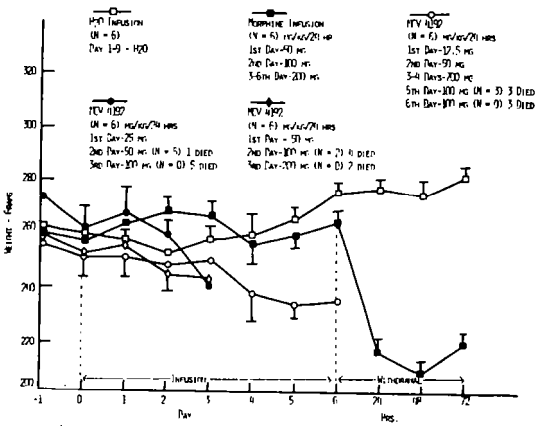
MCV 4192-NIH 9730-UM 1217.

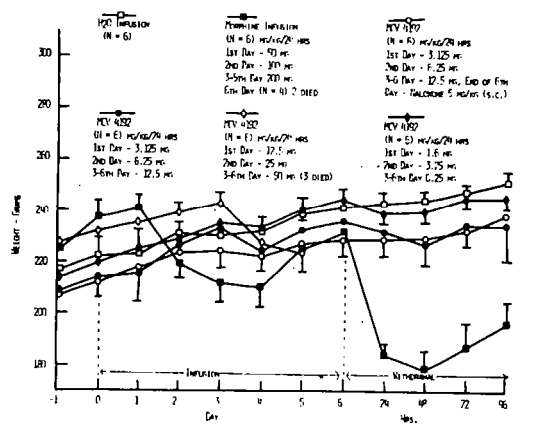
MONKEY DATA (SDS)	# ANIMALS Doses (mg/kg/sc)	3, 2.5	3, 5.0	3, 10.0	Vehicle- H_2O

MCV 4192 did not substitute for morphine in the dose range tested. Body tremors were noted at the highest dose.

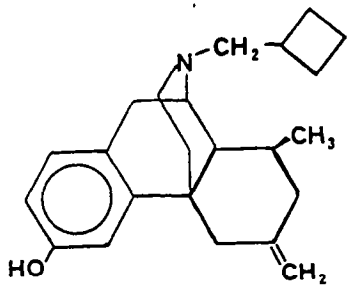
Rat Infusion (PPD)

At two dose schedules, MCV 4192 did not produce physical dependence (See Figures). The drug is toxic at doses of 50 mg/kg/24 hours or higher. A naloxone challenge did not precipitate withdrawal sians in the animals receiving the lowest dose schedule. No behavioral withdrawal signs or weight loss (See Figures) were noted.





MCV 4196-NIH 9736-UM 1224. N-Cyclobutylmethyl-3-hydroxy-6-methylene-8ß-methylmorphinan.



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-8% at 0.1; 48% at 1.0; 12% at 10.0 and 8% at 30.0

2) TF vs M-0% at 0.01; 48% at 0.1; 44% at 1.0, 54% at 10.0 and 61% at 30.0

3) PPQ-0.02 (0.002-0.18)

4) HP-Inactive

5) N-1.3 (0.73-2.4)

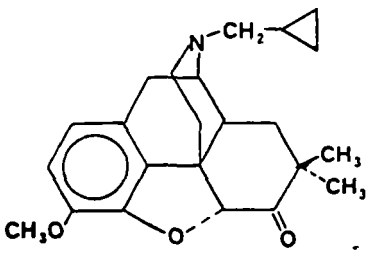
MONKEY DATA #ANIMALS 3 , 2 , 3 , Vehicle-lactic
A (SDS) Doses(mg/kg/sc) 1.0 2.0 4.0
acid + H_2O (cloudy solution).

The drug did not substitute for morphine. Salivation was noted in one monkey receiving the high -and low doses. Jaw sag and eyelid ptosis were also noted at the 2 higher doses.

#ANIMALS 1 , 1 , 2 ,
B. PPt-W Doses (mg/kg/sc) 0.125 0.25 0.5
3 , 2 , 1 -Vehicle-See
2.0 4.0 8.0 SDS Study above.

The drug precipitated withdrawal signs at all doses tested. Onset of action was rapid and duration of action was longer than for naloxone. Jaw sag and salivation were seen. The animal receiving the highest dose had a pale face.

MCV 4197-NIH 9737-UM 1225. 17-Cyclopropylmethyl-7,7-dimethyl-3-methoxy-4,5α-epoxymorphinan-6-one.



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-Inactive at 0.1, 1.0, 10.0 and 130.0

MCV 4197-NIH 9737-UM 1225.

2) TF vs M-1.3 (0.2-7.7)

3) PPQ-1.1 (0.2-6.2)

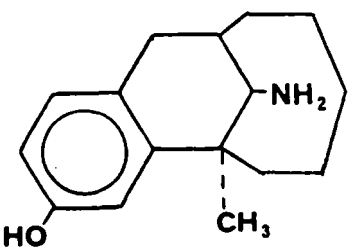
4) HP-5.2 (3.5-7.8)

5) N-11.5 (7.2-18.4)

MONKEY DATA (SDS)	#ANIMALS Doses (mg/kg/sc)	3 , 3 , 3 , 1 , 1 0.75 1.5 3.0 6.0 12.0 Vehicle-lactic acid and H_2O

At the 3 higher doses, MCV 4197 substituted completely and briefly for morphine. Its potency is like that of morphine.

MCV 4206-NIH-8834A-UM 972. (-)-13ß-Amino-5,6,7,8,9,10,11, 12-octahydro-5 α-methyl-5,11-methanobenzocyclodecen-3-ol hydrobromide.



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-2.6 (0.8-8.1)

2) TF vs M-16% at 1.0, 18% at 10.0 and 61% at 30.0

3) PPQ-0.3 (0.07-1.0)

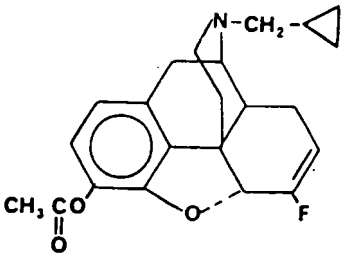
4) HP-0.7 (0.5-0.9)

5) N-0.9 (0.7-1.1)

MONKEY DATA (SDS)	#ANIMALS Doses (mg/kg/sc)	2 , 2 , 2 , 1.25 2.5 5.0 , Vehicle-H_2O

MCV 4206 did not substitute for morphine. The drug exacerbated withdrawal. Two monkeys at the 2 higher doses were given morphine after 2 hours to terminate severe withdrawal. At 12 noon, they still showed signs of withdrawal. Drug supply was exhausted.

MCV 4208-NIH 9787. 17-Cyclopropylmethyl-6,7-didehydro-4, 5α-epoxy-6-fluoro-3-acetoxymorphinan.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF-17% at 0.1, 23% at 1.0 and 4% at 30.0

2) TF vs M- 0.03 (0.01-0.06)

3) PPQ-0.24 (0.03-2.1)

4) HP-No dose response

5) N-No dose response

MONKEY DATA

#ANIMALS	2 ,	2 ,	2 ,
Doses (mg/kg/sc)	0.25	0.5	1.0 , Vehicle-H_2O

1) SDS - The drug exacerbated withdrawal. The onset of action was rapid; it had a long duration of action. All the monkeys receiving the drug in the first group were given morphine 90 minutes after drug to terminate severe withdrawal. In the second group tested, all the monkeys receiving MCV 4208 still vocalized after abdominal palpation even though they had received the noon time injections of morphine. This drug may produce an insurmountable or irreversible antagonism.

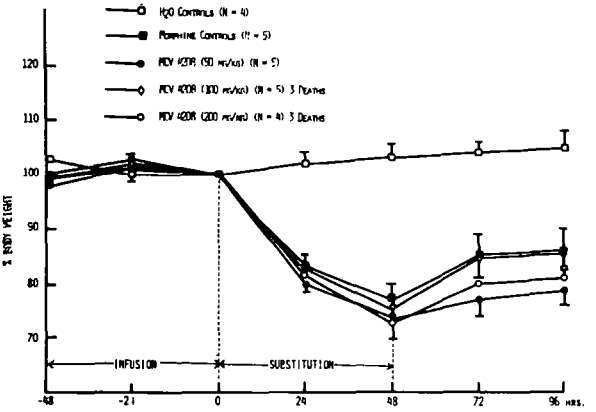
2) PPt-W -

2 ,	2 ,	3 ,	1 ,	2 ,	1 ,	1 ,	Vehicle-
0.001	0.004	0.015	0.06	0.25	0.5	1.0	H_2O

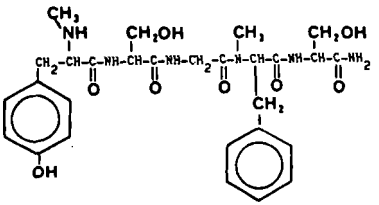
MCV 4208 precipitated withdrawal signs at all the doses tested. The drug acted promptly and its duration of action was at least 2½ hours. The duration of action of naloxone is about 90 minutes. This drug is approximately 10 x more potent than naloxone. Severe tremors were noted at the highest dose and at the 0.25 dose. The incidence of tremor was greater in all the animals receiving doses of 0.004 or higher.

Rat Infusion (SM)

At 50.0, 100.0 or 200.0 mg/kg/24 hr. MCV 4208 did not substitute for morphine in morphine-dependent rats. The drug was lethal at the intermediate and high doses (See Figure). The drug did not suppress behavioral withdrawal signs.



MCV 4210-NIH 9791-UM 1238. N-Methyl-L-tyrosyl-D-seryl-glycyl-N-methyl-L-phenylalanyl-D-serinamide monoacetate.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF-3.5 (1.1-11.3)

2) TF vs M-Inactive at 1.0, 10.0 and 30.0

3) PPQ-0.1 (0.05-0.3)

4) HP-1.4 (1.1-1.8)

5) N-1.5 (1.1-2.1)

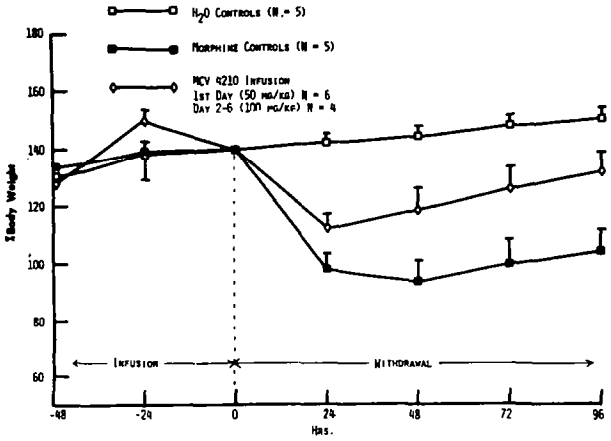
MONKEY DATA (SDS)

# ANIMALS	1	2	3	4
Doses (mg/kg/sc)	4.0	8.0	16.0	32.0
	3	2	Vehicle-H_2O	
	48.0	64.0		

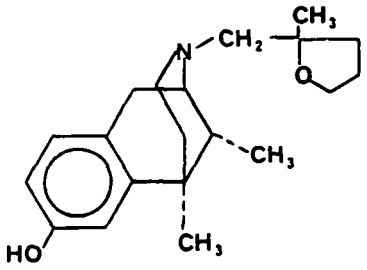
At the highest dose, the drug may have substituted completely for morphine. More animals should be studied at this dose. The drug effectively suppressed retching at all doses.

RAT DATA

Rat Infusion - (PPD) MCV 4210 produced primary physical dependence of the opiate type. The animals lost weight (See Figure) and showed typical withdrawal signs when the infusion was stopped. The drug was lethal to 2 of 6 animals. It is about as potent as morphine.



MCV 4212-NIH 9804-UM 1245. (-)-(1R,5R,9R,2"S)-5,9-Dimethyl-2'-hydroxy-2-(2-methyltetrahydrofurfuryl)-6,7-benzomorphan, L-tartrate.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF-Inactive at 1.0 and Text

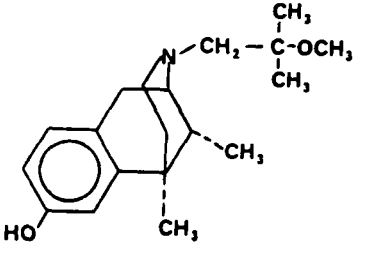
2) TF vs M-3.1 (1.2-8.0)

3) PPQ-0.06 (0.01-0.28)

4) HP-Inactive (toxic at 20.0)

5) N-7.7 (5.6-10.5)

MCV 4213-NIH 9805-UM 1246. (-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(2-methoxyisobutyl)-6,7-benzomorphan.



MOUSE DATA-ED_{50} (95% C.L.)- (mg/kg/sc)

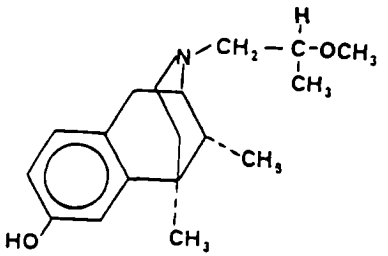
1) TF-0.5 (0.06-3.6)

2) TF vs M-Inactive at 1.0 and 30.0

3) PPQ- Inactive at 1.0 and 30.0

4) HP-0.8 (0.6-1.1)

MCV 4217-NIH 9809. (-)-(1R,5R,9R,2"S)-5,9-Dimethyl-2'-hydroxy-2-(2-methoxypropyl)-6,7-benzomorphan hydrobromide.



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-0.008 (0.003-0.02)

2) TF vs M-Inactive at 0.01, 0.1 and 1.0

3) PPQ-0.008 (0.002-0.02)

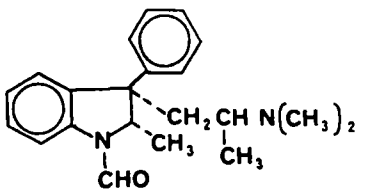
4) HP-0.008 (0.006-0.01)

MONKEY DATA (SDS)	#ANIMALS	1	2	3
	Doses (mg/kg/sc)	0.016	0.008	0.004

3	3	2	1
0.002	0.001	0.00025	0.00006

At doses of 0.001 or less, this drug substituted partially for morphine. In 2/3 monkeys at 0.002 and 1/3 at 0.004, the drug substituted completely for morphine. At doses of 0.004 or higher, substitution was also seen but other agonist side effects such as jaw and body sag, slowing and tremors developed. Severe ataxia was also noted at highest dose. In a preliminary study after receiving a dose of 0.04 mg/kg, the animal lost its righting reflex. A dose of 0.05 mg/kg ip of naloxone appeared to ameliorate this situation. The animal was able to sit and looked much more normal. The drug is about 1000 x as potent as morphine.

MCV 4218-NIH 9810. 2,3-Dihydro-2-methyl-3-[2-(dimethylamino)-propyl]-3-phenyl-1H-indol-1-carboxaldehyde methanesulfonate.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF-Inactive at 1.0, 10.0 and 30.0

2) TF vs M-Inactive at 1.0, 10.0 and 30.0

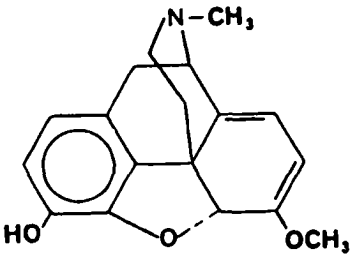
3) PPQ-15.4 (2.5-94.2)

4) HP-Inactive

MONKEY DATA (SDS)	#ANIMALS	2	2	2	Vehicle-
	Doses (mg/kg/sc)	5.0	10.0	20	H_2O

The drug did not substitute for morphine at doses of 5.0, 10.0 and 20.0 mg/kg. At the highest dose, severe tremors were noted in one animal.

MCV 4219-NIH 9821-UM 1252. Oripavine hydrochloride.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF-3.0 (1.4-6.6), Toxic at 10.0

2) TF vs M-(Inactive at 1.0 and 10.0; Toxic at 10.0

3) PPQ-1.7 (0.8-3.3)

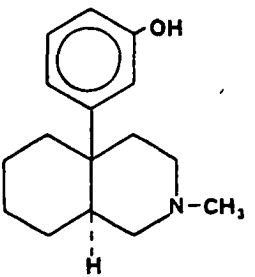
4) HP-1.5 (1.1-2.0)

MONKEY DATA (SDS)	#ANIMALS Doses (mg/kg/sc)	2, 0.5	2, 1.0	2, 2.0	Vehicle-H_2O

In a preliminary study the animal developed severe tremors after receiving a cumulative dose of 5.6 mg/kg in 45 min. (0.8, 1.6 and 3.2 at 15 min. intervals). The animal was-given pentobarbital (60 mg) and morphine (1.5 mg/kg) ip. to terminate these severe tremors.

The drug did not substitute for morphine 'at any of the doses tested.

MCV 4220-NIH 9824-UM 1253. (-)-trans-[(2-Methyl)-1,2,3,4, 4a,5,6,7,8,8aα-decahydro-4aß-isoquinolyl]phenol hydrobromide.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

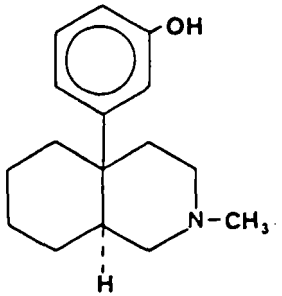
1) TF-10.7 (3.7-31.1)

2) TF vs M-Inactive at 1.0 and 30.0

3) PPQ-1.2 (0.4-3.4)

4) HP-2.1 (1.6-2.8)

MCV 4221-NIH 9825-UM 1254. (+)-trans-[2-(Methyl)-1,2,3,4,4a,5,6,7,8,8aα-decahydro-4aß-isoquinolyl]phenol hydrobromide.



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

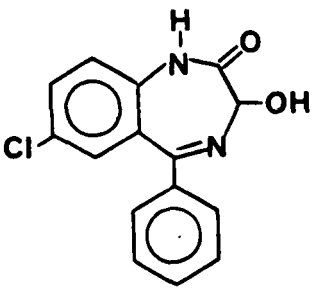
1) TF-0.6 (0.15-2.4)

2) TF vs M-Inactive. at 1.0 and 3.0

3) PPQ-0.3 (0.1-0.7)

4) HP-0.5 (0.4-0.7)

MCV 4222-NIH 9826. 7-Chloro-1,3-dihydro-3-hydroxy-5-phenyl-2H-1,4-benzodiazepin-2-one (Oxazepam).



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF-Inactive at 1.0 and 30.0

2) TF vs M- 22% at 1.0, 29% at 10.0

3) PPQ-1.2 (0.3-5.5)

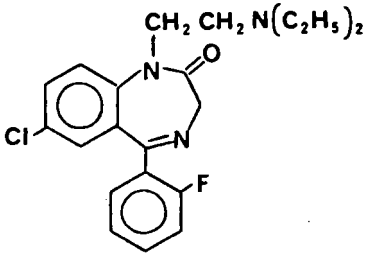
4) HP-No dose-response

MONKEY DATA (SDS)	# ANIMALS Doses (mg/kg/sc)	2 , 15.0	2 , 30.0	2 , 60.0

Suspended in 1/2% carboxymethylcellulose aqueous solution.

MCV 4222 did not substitute for morphine in the dose range tested. The drug appeared to suppress retching at all doses. Drug supply was exhausted.

MCV 4223-NIH 9829. 7-Chloro-1-[2-(diethylamino)ethyl]-5-(o-fluorophenyl)-1,3-dihydro-2H-1,4-benrodiazepin-2-one dihydrochloride (Flurazepam).



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF-Inactive at 1.0 and 30.0

2) TF vs M-Inactive at 1.0 and 30.0

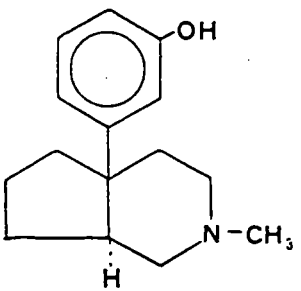
3) PPQ-15.7 (10.5-23.6)

4) HP-Inactive

MONKEY DATA (SDS)	#ANIMALS Doses (mg/kg/sc)	4, 3.75	4, 7.5	4, 15.0	Vehicle-H_2O

MCV 4223 substituted partially for morphine at the highest dose. A reduction in the number of withdrawal signs designated: vocalizes when adbomen palpated, lying on side or abdomen, and retching was evident. In addition, the drug produced ataxia which was still obvious in all animals, 9 hours after receiving drug. Drowsiness and relaxed abdominal muscles were also noted. Partial substitution does not necessarily imply that a drug has morphine-like dependence properties.

MCV 4225-NIH 9839-UM 1259. (-)-trans-3-(Octahydro-2-methyl-1H-2-pyrindin-4a-yl)phenol (Z)-2-butanedioate.



MOSUE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

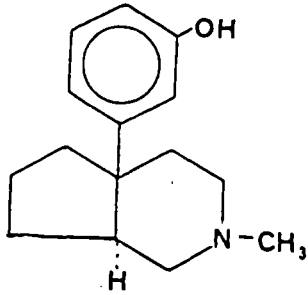
1) TF-2.9 (1.0-8.3)

2) TF vs M-Inactive at 1.0 and 30.0

3) PPQ-3.1 (0.9-10.0)

4) HP-8.1 (5.8-11.3)

MCV 4226-NIH 9840-UM 1260. (+)-trans-3-(Octahydro-2-methyl-1H-2-pyrindin-4a-yl)phenol (Z)-2-butanedioate.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

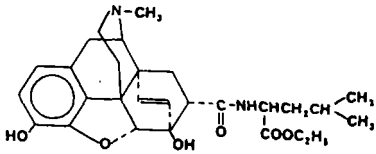
1) TF-0.9 (0.4-2.0)

2) TF vs M-Inactive at 1.0 and 30.0

3) PPQ-0.4 (0.1-1.0)

4) HP-1.1 (0.8-1.3)

MCV 4227-NIH 9832-UM 1261. N-(6,14-Endoetheno-7,8-dihydro-morphine-7α-carbonyl)-L-leucine ethyl ester hydrochloride.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF-3.1 (1.0-9.3)

2) TF vs M-Inactive at 1.0

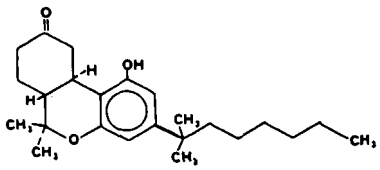
3) PPQ-0.9 (0.3-2.5)

4) HP-0.8 (0.6-1.0)

MONKEY DATA (SDS)	#ANIMALS	2 ,	3 ,	3 ,
	Doses (mg/kg/sc)	4.0	8.0	16.0 ,
		Vehicle-H_2O		

MCV 4227 substituted completely, but briefly in 2 of 2 monkeys at the highest dose, and in 1 of 3 monkeys at the. intermediate dose. Its potency is about 1/5 that of morphine.

MCV 4228-NIH 9872-UM 1266. (±)-trans-3-(1,1-Dimethyl heptyl)-6,6aß,7,8,10,10aα-hexahydro-1-hydroxy-6,6-dimethyl-9H-dibenzo[b,d]pyran-9-one (Nabilone).



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF-Inactive at 1.0 and 30.0

2) TF vs M-1.5 (0.3-8.1)

3) PPQ-2.5 (0.9-6.7)

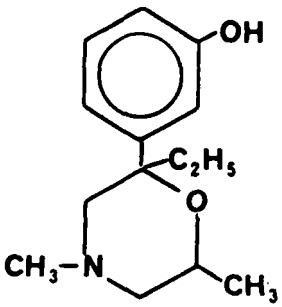
4) HP-3.6 (2.5-5.2)

MCV 4228-NIH 9872-UM 1266.

MONKEY DATA (SDS)	#ANIMALS					
	Doses (mg/kg/sc)	1 , 0.025	1 , 0.05	1 , 0.075		
1 , 0.15	1 , 0.5	1 , 1.0	1 2.0	Vehicle-H_2O-alcohol and Tween 80		

The drug did not substitute for morphine. It did suppress the withdrawal signs retching and vomiting at doses of 0.15 or higher. The drug had strong depressant properties and a long duration of action. Slowing was observed at all doses but one namely, 0.075 mg/kg. Monkeys receiving 2.0, 1.0 and 0.5 mg/kg appeared ill for about 2 weeks. In addition, monkeys receiving 0.05 and 0.025 mg/kg did not appear to recover completely for nearly 9 hours after drug in spite of the fact that they had received the noon injection of morphine.

MCV 4229-NIH 9873. 3-(2-Ethyl-4,6-dimethyl-2-morpholinyl) phenol.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF-4.9 (1.4-17.4)

2) TF vs M-Inactive at 1.0 and 30.0

3) PPQ-7.9 (0.4-1.8)

4) HP-2.1 (1.6-2.8)

MONKEY DATA (SDS)	#ANIMALS				
	Doses (mg/kg/sc)	2 , 0.19	2 , 0.75	3 , 1.5	1 , 3.0

Vehicle-H_2O

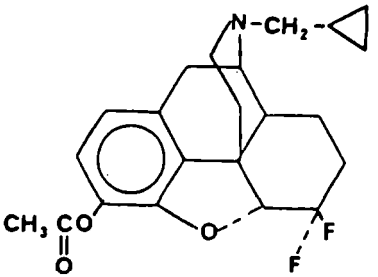
At the 2 higher doses, this compound substituted completely and briefly for morphine. The onset of action was prompt and the duration was approximately 1½ hrs. The duration of action of morphine is at least 2½ hrs. It is equipotent with morphine.

MCV 4230-NIH 9874-UM 1322. 17-Cyclopropylmethyl-4,5α-epoxy-6,-6-difluoro-3-acetoxymorphinan.

MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF-Inactive at 1.0 and 30.0

2) TF vs M-0.0008 (0.0002-0.003)



3) PPQ-0.1 (0.02-0.9)

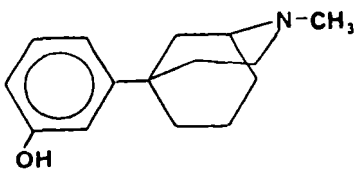
4) HP-No dose-response

5) N-19.8 (12.9-30.2)

MONKEY DATA #ANIMALS 3 , 3 , 2 ,
A. (SDS) Dose (mg/kg/sc) 0.003 0.0125 0.5
Vehicle-HCl + H_2O

The drug did not substitute for morphine. At the 2 higher doses, tremors were noted in all the animals. One monkey receiving the intermediate dose retched frequently. The drug may exacerbate withdrawal.

MCV 4231-NIH 8508A-UM 809. (-)-5-(m-Hydroxyphenyl)2-methylmorphan hydrochloride.



MOSUE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF-6.1 (1.9-19.4)

2) TF vs M-Inactive at 1.0 and 30.0

3) PPQ-0.9 (0.4-2.0)

4) HP-1.5 (1.2-1.5)

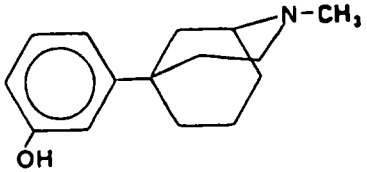
MONKEY DATA #ANIMALS 2 , 2 , 2 , Vehicle-H_2O
(SDS) Doses (mg/kg/sc) 0.31 1.25 5.0

MCV 4231 did not substitute for morphine: One monkey receiving the highest dose was given morphine after 35 min to relieve repeated retching. The drug seemed to exacerbate withdrawal.

B. (PPt-W) - 1 , 3 , 2 , Vehicle-H_2O
0.5 4.0 8.0

This drug precipitated withdrawal in morphine-addicted monkeys. Naloxone appears to be approximately 80 times more potent; however, MCV 4231 has a longer duration of action than naloxone. It was still active 2½ hrs after its administration. The duration of action of naloxone is approximately 90 minutes.

MCV 4232-NIH 8509A-UM 810. (+)-5-(m-Hydroxyphenyl)-2-methylmorohan hydrochloride.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF-4.8 (1.5-15.5)

2) TF vs M-0% at 1.0; 18% at 30.0

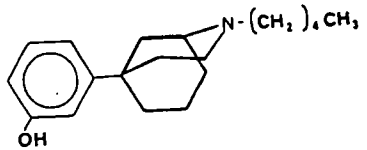
3) PPQ-0.5 (0.3-0.9)

4) HP-0.35 (0.28-0.45)

MONKEY DATA (SDS)	#ANIMALS	3 ,	3 ,	4 ,	Vehicle-
	Doses (mg/kg/sc)	2.0	4.0	8.0	H_2O

MCV 4232 substituted completely for morphine in 3/4 animals at the highest dose and in all 3 at the next lower dose. The drug acts promptly and has a duration of action of about 90 min. Morphine's duration of action is at least 2½ hrs. The potency is estimated to be 1/2-1/3 that of morphine.

MCV 4233-NIH 9886. (-)-5-(m-Hydroxyphenyl)-2- n-pentylmorphan hydrochloride.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF-0% at 1.0 and 28% at 30.0

2) TF vs M-1.2 (0.6-2.5)

3) PPQ-14% at 1.0 and 20% at 30.0

4) HP-Inactive to 50.0

5) N-Inactive to 50.0

MONKEY DATA	#ANIMALS	3 ,	3 ,	1 ,
A. (SDS)	Dose (mg/kg/sc)	0.156	0.625	2.5

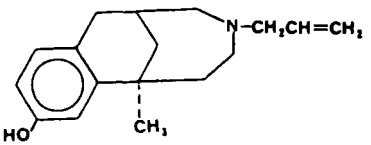
Vehicle-H_2O

The drug did not substitute for morphine. One monkey at the highest dose and another two at the intermediate dose were given morphine to suppress repeated retching. Severe tremors were also noted at the highest dose.

B. (PPt-W) - 2/0.156, 2/0.625, 2/2.5,

This compound promptly precipitated withdrawal in a dose-related manner. The drug is approximately 1/50th as active as the reference standard naloxone and its duration of action is about 2 1/2 hrs. whereas that of naloxone is about 1 1/2 hrs.

MCV 4235-NIH 9895. (+)-4-Allyl-1-methyl-1O-hydroxy-2,3,4,5,6, 7-hexahydro-1,6-methano-1H-4-benzazonine.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF-23% at 1.0 and 22% at 30.0

2) TF vs M-13% at 1.0, 42% at 10.0 and 46% at 30.0

3) PPQ-0.6 (0.3-1.0)

4) HP-6/10 convulsed at 1.0 md/kg

5) N-Inactive to 5.0, convulsions at 5.0

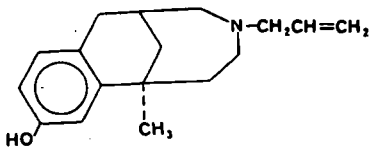
MONKEY DATA (SDS) #ANIMALS 2, 2, 2, 2, 2, 1, 1, 1,

Doses (mg/kg/SC) 0.006 0.0125 0.025 0.1 0.2 0.5 2.0

Vehicle-H_2O

At the 2.0 mg/kg dose, the animal appeared anesthetized, within 10 min. Naloxone at 0.025 mg/kg had no effect. After 90 min, the animal was able to move and 2 hours later could sit. The 0.5 mg/kg dose also produced anesthesia within 10 min and this animal was able to sit in 90 minutes. The drug caused ataxia and slowing at 0.2 and 0.1 mg/kg, produced some abdominal relaxation and appeared to suppress vocalization accompanying abdominal palpation for the first 1/2 hr. Suppression of retching and vomiting was evident at all doses tested for 30-90 minutes. The drug does not substitute completely for morphine.

MCV 4236-NIH 9896. (-)-4-Allyl-1-methyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1H-4-benzazonine.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF-Inactive at 0.3, 1.0, 3.0, 10.0 and 30.0

2) TF vs M-6.7 (3.2-13.7)

3) PPQ-4.3 (1.4-13.1)

4) HP-Insuff. activity at 50.0
Convulsions at 50.0

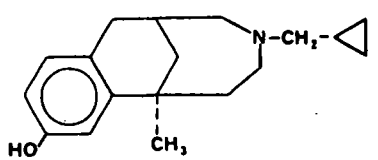
5) N-Inactive at 5.0

MONKEY DATA (SDS)	#ANIMALS	2	3	3
	Doses(mg/kg/sc)	0.125	0.5	2.0

Vehicle-dil HCl + H_2O

In the dose range 0.125 - 2.0 mg/kg, this compound does not substitute for morphine. Ataxia was noted at the highest dose.

MCV 4237-NIH 9899. (+)-1-Methyl-4-cyclopropylmethyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1H-4-benzazonine.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF vs M-0% at 1.0, 3.0, 10.0 and 30.0

2) TF-1.5 (0.5-4.2)

3) PPQ-4.7 (1.9-11.0)

4) HP-Insufficient activity convulsions at 20.0

5) N-Inactive at 5.0

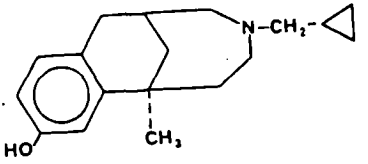
MONKEY DATA (SDS)	#ANIMALS	3	2	3
	Doses (mg/kg/sc)	0.06	0.25	1.0

Vehicle-dil HCl + H_2O

The drug substituted partially for morphine at all doses. Severe ataxia, slowing, incoordination, and staring were noted at the highest dose. In the preliminary study, in one monkey

given 1.0 mg/kg the following signs were noted: ataxia, catalepsy, lying'on side, unable to walk. The animal was able to move about after 1 hour. Partial substitution does not necessarily imply that the drug has morphine-like activity.

MCV 4238-NIH 9900. (-)-1-Methyl-4-cyclopropylmethyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1H-4-benzazonine.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF-25% at 1.0, 0% at 30.0

2) TF vs M-0% at 1.0, 17% at 10.0 and 29% at 30.0

3) PPQ-0.02 (0.007-0.08)

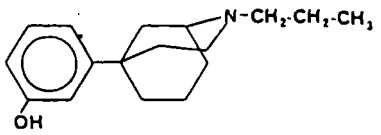
4) HP-Insufficient activity at 50.0

5) N-Insufficient activity at 50.0

MONKEY DATA (SOS)	#ANIMALS				
Vehicle-HCl + H_2O	Doses (mg/kg/sc)	2	4	4	1
		1.25	2.5	5.0	10.0

In the dose range tested, MCV 4238 did not substitute for morphine. Convulsions were noted at the highest dose which were terminated by the injection of 60 mg/ip of pentobarbital. In addition, ataxia, sagging, slowing and relaxed abdominal muscles were seen at 5.0 mg/kg. Relaxed abdominal muscles and ataxia were also seen at the 2.5 mg/kg dose.

MCV 4241-NIH 9884-UM 1273. (-)-5-(m-Hydroxyphenyl)-2-*n*-propylmorphan hydrochloride.



MOUSE DATA-ED_{50} (95% C.L.) (mg/kg/sc)

1) TF-Inactive at 1.0 and 30.0

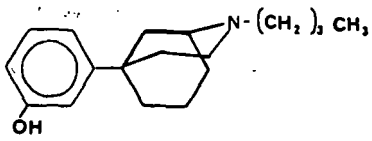
2) TF vs M-0.9 (5.4-15.4)

3) PPQ-0% at 1.0 31% at 10.0 and 39% at 30.0

4) HP-Inactive - 6/10 dead at 100.0

5) N-Inactive

MCV 4242-NIH 9885-UM 1274. (-)-2-n-Butyl-5-(m-hydroxyphenyl) morphan hydrochloride.



MOUSE DATA- ED_{50} (95% C.L.) -

1) TF-Inactive at 1.0 and 10.0

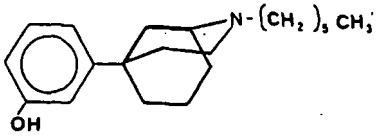
2) TF vs M-31% at 0.1, 44% at 0.3, 21% at 1.0 and 22% at 30.0

3) PPQ-Inactive at 1.0and 30.0

4) HP-Incompletely active and Convulsions at 50.0

5) N-Inactive

MCV 4247-NIH 9894-UM 1276. (+)-2-n-Hexyl-5-(m-hydroxyphenyl) morphan hydrochloride.



MOUSE DATA-ED_{50} (95% C.L.)-

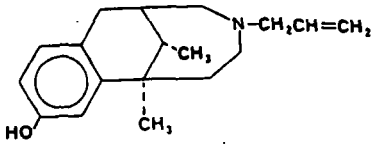
1) TF-12% at 1.0 and 30.0

2) TF vs M-14.2 (6.1-32.9)

3) PPQ-1.7 (0.5-5.3)

4) HP-Inactive at 50.0 - Convulsions

MCV 4249-NIH 9898-UM 1280. 1,12α-Dimethyl-4-allyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1H-4-benzazonine.



MOUSE DATA-ED_{50} (95% C.L.) -

1) TF-0% at 1.0 and 24% at 30.0

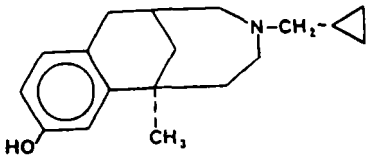
2) TF vs M-15% at 1.0, 16% at 10.0, 41% at 30.0

3) PPQ-0.1 (0.01-1.10)

4) HP-Insufficient activity - Convulsions at 5.0

5) N-Inactive at 5.0

MCV 4250-NIH 9901-UM 1277. (±)-1-Methyl-4-cyclopropylmethyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1H-4-benzazonine.



MOUSE DATA -ED_{50} (95% C.L.) - (mg/kg/sc)

1) TF-Inactive at 1.0 and 30.0

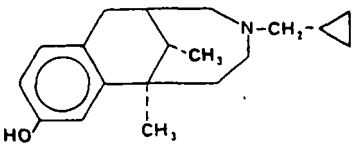
2) TF vs M-7.3 (3.2-16.5)

3) PPQ-3.0 (1.0-9.3)

4) HP-Insufficient activity at 50.0 - Convulsions

5) N-Inactive at 50.0

MCV 4251-NIH 9902-UM 1281. 1,12α-Dimethyl-4-cyclopropylmethyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1H-4-benzazonine.



MOUSE DATA-ED_{50} (95% C.L.) - (mg/kg/sc)

1) TF-Inactive at 1.0, 10.0 and 30.0

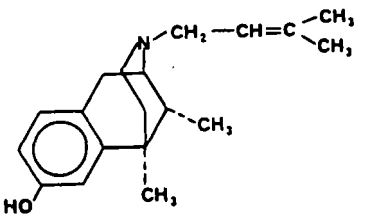
2) TF vs M-10% at 1.0, 12% at 10.0 and 22% at 30.0

3) PPQ-3.5 (1.2-10.1)

4) HP-No dose response

5) N-Inactive at 50.0

MCV 4268-NIH 7958-UM 381. (±)-2'-Hydroxy-5,9α-dimethyl-2-(3,3-dimethyla'llyl)-6,7-benzomorphan (pentazocine ampuls).



MOUSE DATA-ED_{50} (95% C.L.) - (mg/kg/sc)

1) TF-

2) TF vs M-

3) PPQ-

4) HP-g.3 (6.7-12.8)

5) N-6.5 (4.4-8.8)

MCV 4268-NIH 7958-UM 381.

MONKEY DATA (SDS)	#ANIMALS Doses (mg/kg/sc)	1, 2.5	2, 5.0	2, 10.0	Vehicle-H_2O

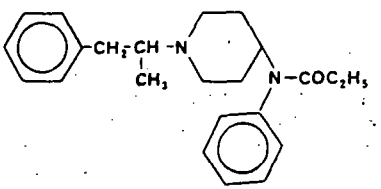
At the highest dose, both monkeys had relaxed abdomens, did not vocalize when their abdomens were palpated and did not retch or vomit. However, one of these monkeys developed severe tremors and convulsions. Sixty mg of pentobarbital was given ip to control these convulsions. Penfazocine substitutes partially for morphine: Partial substitution does not necessarily indicate that the drug has morphine-like properties.

(SOS) Lower dose addicted monkeys

1, 2.5	2, 5.0	1, 10.0	2, 20.0	Vehicle H_2O

In order to determine whether or not MCV 4268 would substitute for morphine in monkeys addicted to a lower dose of morphine namely, 1.5 mg/kg/sc, we initiated this study. At the highest dose, the monkey promptly developed convulsions and was treated with 24 mg pentobarbital ip. At 10.0 mg/kg, one animal also developed convulsions and was treated with pentobarbital. Severe tremors were noted in the second monkey at this dose. However, this animal did not vocalize-when its abdomen was palpated and the abdominal muscles were relaxed'for approximately 1½ hours after injection. In addition, other withdrawal signs such as retching and vomiting were not observed. Thus, the drug substituted partially for morphine.

MCV 4287-NIH 9961-UM 1324. 1-(1-Methyl-2-phenylethyl)-4-(N-propanilido)piperidine hydrochloride



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-0.002 (0.00007-0.004)

2) TF vs. M-INactive at.0.01, 0.03 and 0.1

3) PPQ-0.0016 (0.0010-0.0027)

4) HP-0.006 (0.004-0.009)

MONKEY DATA (SDS) Vehicle-H_2O	#ANIMALS Doses (mg/kg/sc)	1, 0.0025	3, 0.005	3, 0.01

At the highest dose, the compound substituted completely and briefly for morphine. It had a quick onset and short duration of action (<90 min.). The drug is about 300 x more potent than morphine.

1981 Annual Report: Evaluation of New Compounds for Opioid Activity

James H. Woods, Jonathan L. Katz, Fedor Medzihradsky, Charles B. Smith, Alice M. Young, and Gail D. Winger

The evaluation of new compounds by the programs at the University of Michigan and the Medical College of Virginia is coordinated by Dr. Arthur E. Jacobson, Medicinal Chemistry Section, NIAMDD, National Institutes of Health, Bethesda, MD. The drugs, which come originally from pharmaceutical companies, universities, and government laboratories, are submitted to Dr. Jacobson, who performs the MOUSE ANALGESIA tests. Values obtained in these tests for some representative opioid drugs are given in Table 1.

At the UM and MCV laboratories, drug samples arrive from Dr. Jacobson with only the following information: (1) an identifying NIH number, (2) molecular weight, (3) solubility information and (4) a recommended starting dose. Only after the evaluation is canplete and the report submitted back to Dr. Jacobson are the chemical structure and the mouse-analgesia data released to the evaluating laboratory.

The single dose suppression test (SDS) determines the ability of a drug to suppress the signs of withdrawal in monkeys which have been made dependent by the chronic administration of morphine (3 mg/kg every six hours). Compounds suspected of having morphine-antagonist properties are tested for their ability to precipitate the withdrawal syndrome in nonwithdrawn (NW) morphine-dependent monkeys. Nondependent monkeys (Normals) are used to determine whether the acute effects of the test drug are reversible by nalorphine or naloxone. In a primary dependence study (PDS), non-dependent monkeys receive the test. drug every six hours for 30 days to determine whether withdrawal signs will appear when the animals are challenged with an antagonist or when drug administration is discontinued.

Details of these techniques have been presented in the ANNUAL REPORT to the Committee in 1963 (Minutes of the 25th Meeting) by

TABLE I

MOUSE ANALGESIA. Before submission to The University of Michigan, all compounds are evaluated for analgesic activity by Dr. Arthur E. Jacobson. Shown below are comparative data (ED 50 mg/kg) (95% Confidence Interval) from Hot Plate[a-c] and Nilsen[d] assays. umol/kg

Compound NIH #	HOT PLATE (sc, mg/kg) / (sc, umol/kg)	HOT PLATE (oral, mg/kg) / (oral, umol/kg)	NILSEN (sc, mg/kg) / (sc, umol/kg)	NILSEN (oral, mg/kg) / (oral, umol/kg)
Morphine sulfate NIH 0001, 9929	0.98 (0.83-1.1) / 2.9 (2.5-3.3)	6.3 (4.7-8.3) / 18.9 (14.1-24.9)	1.3 (1.0-1.7) / 3.9 (3.0-5.1)	8.3 (6.0-11.4) / 24.9 (18.0-34.1)
Codeine phosphate NIH 0002	6.8 (4.5-10.2) / 17.1 (11.3-25.7)	13.5 (9.7-18.7) / 34.0 (24.4-47.1)	7.4 (4.9-11.0) / 18.6 (12.3-27.7)	14.7 (9.2-23.3) / 37.0 (23.2-58.7)
Levorphanol tartrate NIH 4590	0.2 (0.1-0.3) / 0.5 (0.2-0.7)	- / -	0.2 (0.16-0.3) / 0.5 (0.4-0.7)	2.5 (1.7-3.7) / 6.2 (4.2-9.1)
Meperidine.HCl NIH 5221	5.3 (4.0-7.1) / 18.7 (14.1-25.0)	- / -	- / -	- / -
(-)-Metazocine.HBr NIH 7569	0.6 (0.5-0.9) / 1.9 (1.4-2.8)	10.6 (8.0-14.1) / 34.1 (25.7-45.3)	0.5 (0.3-0.7) / 1.6 (1.0-2.3)	26.0 (21.0-33.0) / 83.6 (67.5-106.1)

TABLE I continued

Dihydromorphinone.HCl NIH 0123	0.19 (0.15-0.25) 0.6 (0.5-0.8	0.9 (0.7-1.2) 2.8 (2.2-3.7)	0.2 (0.15-0.3) 0.6 (0.5-0.9)	1.8 (1.5-2.1) 5.6 (4.7-6.5)
Nalorphine.HCl NIH 2105	9.9 (5.7-17.1) 28.4 (16.4-49.1)	- -	23.0 (16.2-32.7) 66.1 (46.6-94.0)	- -
Cyclazocine NIH 7981	1.5 (1.1-2.1) 5.5 (4.1-7.7)	- -	0.1 (0.07-0.16) 0.4 (0.3-0.6)	- -
Pentazocine NIH 7958	9.3 (6.7-12.8) 32.6 (23.5-44.9)	- -	6.5 (4.4-8.8) 22.8 (15.4-30.9)	- -
Naltrexone.HCl NIH 8503	No dose response			
Naloxone.HCl NIH 7890	No dose response			

No antinociceptive activity in hot plate assay: Phenobarbital, amobarbital, diazepam, meprobamate, mescaline, oxazepam, flurazepam.

Chlorpromazine.HCl	1.1 (0.9-1.5) 3.2 (2.4-4.2)

a) Eddy and Leimbach (1953); b) Jacobson and May (1965); c) Atwell and Jacobson (1978); d) Perrine, Atwell, Tice, Jacobson and May (1972).

Deneau and Seevers (1963) and by Villarreal (1973).

SELF-ADMINISTRATION BY MONKEYS

Tests of self-administration determine the ability of the drug to maintain responding in monkeys trained to self-inject codeine. Each of at least three monkeys was studied with saline as a negative control and a number of doses of the test compound until a maximum rate of responding was obtained or until, in the absence of evidence of a reinforcing effect, directly observable changes in behavior were produced by the compuond.

The schedule of intravenous drug delivery was a fixed-ratio 30; when a light above a lever was illuminated, the 30th response produced a five-second intravenous drug injection accompanied by another light that was illuminated during drug delivery. After each injection, a ten-minute timeout condition was in effect during which responses had no scheduled consequence and neither light was illuminated. Each of the two daily sessions consisted of 13 injections or 130 minutes, whichever occurred first. Other details of the procedure and initial findings with a variety of narcotics are given in previous reports (Woods, 1977; 1988).

Doses of the drugs are typically described in terms of moles/kg/injection (inj), to facilitate direct comparisons among drugs. Duplicate observations of codeine (7.5×10^{-5} mol/kg/inj; 0.32 mg/kg/inj) and of saline were obtained for each monkey. A saline substitution was conducted before and after the series of observations on a test drug; the control rates of codeine-reinforced responding were obtained by, a random sampling of two sessions interpolated between the drug-substitution sessions. These data are represented in the following graphs with individual symbols for each of the monkeys; each symbol is the mean of duplicate observations for a given dose in each monkey. There are two additional types of averaged data presented. The closed circles indicate the averaged data for observations on the subset of monkeys used to study each drug under each of the experimental conditions. The open circles indicate the codeine and saline rates of responding of 20 monkeys studied under the same conditions. The brackets indicate ± 3 standard errors of the codeine mean, and + 3 standard errors of the saline mean for the group of 20 monkeys. In all cases, the rates of responding given are those calculated during only the fixed-ratio portion of each session.

DISPLACEMENT OFDI- OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

Details of the binding assay were described in the 1978 ANNUAL REPORT (Swain et al., 1978). Briefly, aliquots of a membrane preparation from rat cerebrum were incubated with ^{3}H-etorphine in the absence and presence of 150 mM NaCl, and in the presence of different concentrations of the drug under investigation. Stereospecific, i.e., opioid-receptor related, binding of etorphine was determined and the potency of the drug in inhibiting binding of etorphine was obtained from log-probit plots of the

TABLE II

Values for the EC 50 (M) of representative compounds in displacing ^{3}H-etorphine from membrane preparations of rat cerebrum.

DRUG	EC 50		
	+NaCl	-NaCl	+Na/-Na
Naltrexone	2.0×10^{-9}	7.9×10^{-9}	0.25
Naloxone	9.1×20^{-9}	3.2×10^{-8}	0.29
Nalorphine	2.0×10^{-8}	5.1×10^{-8}	0.39
Cyclazocine	3.6×10^{-9}	6.4×10^{-9}	0.56
Levallorphan	5.5×10^{-9}	7.0×10^{-9}	0.79
Dextrorphan	1.8×10^{-5}	1.4×10^{-5}	1.32
Levorphanol	2.1×10^{-8}	1.5×10^{-8}	1.39
Codeine	3.5×10^{-5}	1.8×10^{-5}	1.95
l-Pentazocine	1.7×10^{-7}	8.5×10^{-8}	2.04
d-Pentazocine	6.2×10^{-6}	8.7×10^{-6}	0.71
Morphine	1.4×10^{-7}	6.0×10^{-8}	2.36

NOTE: Binding data for a number of other compounds are included in the 1978 ANNUAL REPORT.

data. Values obtained with this method for some representative opioid drugs are given in Table II.

INHIBITION OF TWITCH OF ELECTRICALLY-STIMUKLATED GUINEA-PIG ILEAL AND MOUSE VAS DEFERENS PREPARATIONS

submitted drugs are evaluated on two smooth muscle preparations, the details of which were described in the 1978 ANNUAL REPORT (Swain et al., 1978). Shown in the following pages are the EC 50's for the tested drug alone, for the drug in the presence of naltrexone (a pure opioid antagonist which is more effective against so-called "mu" agonists than against so-called "kappa" agonists), and for the drug in the presence of UM 979 (an antagonist which appears to be more effective against "Kappa" than against "mu" drugs) (Smith, 1978). The maximum depression of the electrically-induced twitch in each of the preparations is also indicated. The concentrations of both naltrexone and UM 979 always used in tests of antagonism are for the guinea-pig ileum, $10^{-}7$ M, and for the mouse vas deferens, 10^{-8} M.

SUMMARY OF TESTS-PERFORMED

The Compounds which were evaluated at The University of Michigan during the past year and the individual tests which were performed are shown in Table III. Also shown are dates of Annual Reports in which results are reported of earlier tests on those compounds conducted at Michigan.

TABLE III

SUMMARY OF TESTS PERFORMED

COMPOUND NUMBER			CHEMICAL CLASS AND/OR							
UM	NIH	MCV	GENERIC NAME	SDS	NW	N	SA	GPI	MVD	BIND	PDS
747	8439		Benzomorphan	1970	-	-	+	-	-	-	1970
952			Buprenorphine	+	1974	-	1977	1978	1978	1978	1975
961	8833		Benzylcyclohexanol	-	+	-	-	-	-	-	1975
972	8834		Benzocyclodecenol	1974	1976	-	-	-	-	-	1974
973	8835		Pyrroloindolizine	1976	-	-	+	-	-	-	1975
983	8863	4068	4-amino-piperidine	1975	-	1975	+	-	-	-	-
1076	9112		Phenylpiperdine	1976	1977	-	+	-	-	-	-
1103	9256		Benzomorphan	1977	-	-	+	-	-	-	-
1124	9342		Phenylisoquinoline	1977	-	+	+	-	-	-	1977
1160	9521		Phenylpiperdine	+	-	+	+	-	-	-	-
1169	9540		Phenylpiperdine	+	-	-	+	+	+	+	-
1170	9541	4146	Phenylpiperdine	1979	-	-	+	1979	1979	1979	-
1195	9637		Morphine	1980	-	-	+	1980	1980	1980	-
1200	9674		Morphinan	+	-	-	-	-	-	-	-
1201	9677		Morphinan	+	-	-	-	-	-	-	-
1212	9724	4187	Tetrapeptide	+	-	-	-	+	+	+	-
1217	9730	4192	Zomepirac	-	-	-	+	+	+	+	-
1218	9585		Ketobemidone	1980	-	-	-	+	+	+	-
1221	9741		Ketobemidone	1980	-	-	-	+	+	+	-
1223	9735	4195	Morphinone	-	-	-	-	+	+	+	-

TABLE III Continued

SUMMARY OF TESTS PERFROMED

COMPOUND NUMBER			CHEMICAL CLASS AND/OR								
UM	NIH	MCV	GENERIC NAME	SDS	NW	N	SA	CPI	MVD	BIND	PDS
1224	9736		Morphinan	-	-	-	-	+	+	+	-
1225	9737		Morphinan-6-one	-	-	-	-	+	+	+	-
1226	9738	4199	2-Nitronaltrexone	-	-	-	-	+	+	+	-
1237	9789		Ketobemidone	1980	-	-	-	+	+	1980	-
1238	9791	4210	Tetrapeptide	-	-	-	-	+	+	+	-
1243			Mianserin	+	-	+	-	+	+	+	-
1245	9804	4212	Benzomorphan	+	+	-	-	+	+	+	-
1246	9805	4213	Benzomorphan	+	-	+	+	+	+	+	-
1252	9821	4219	Oripavine	-	-	-	-	+	+	+	-
1253	9824	4220	Phenylisoquinoline	+	-	-	-	+	+	+	-
1254	9825	4221	Phenylisoquinoline	+	-	-	-	+	+	+	-
1258	9624	4175	Benzomorphan	-	-	-	1980	+	+	+	-
1259	9839	4225	Phenylpyrindine	+	-	-	-	+	+	+	-
1260	9840	4226	Phenylpyrindine	+	-	-	-	+	+	+	-
1261	9832A	4227	Endoethanomorphine	-	-	-	-	+	+	+	-
1262 (106)	4591		Dextrorphan	+(1955)	-	-	-	-	-	-	-
1263			Ketamine	+	-	-	-	-	-	-	-
1264	9580	4158	Phencyclidine	+	-	-	-	-	-	-	-
1265	9596	4161	Levonantradol	+	-	-	+	-	-	-	+
1266	9872	4228	Nabilone	+	-	-	+	-	-	-	+
1267	9612	4167	Homobenzomorphan	-	-	-	-	+	+	+	-

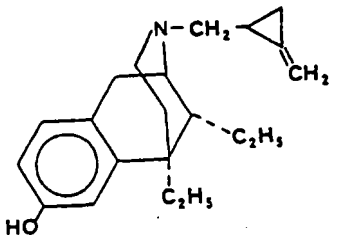
TABLE III Continued

SUMMARY OF TESTS PERFORMED

COMPOUND NUMBER			CHEMICAL CLASS AND/OR								
UM	NIH	MCV	GENERIC NAME	SDS	NW	N	SA	GPI	MVD	BIND	PDS
1268	9613	4168	Homobenzomorphan	-	-	-	-	+	+	+	-
1269	9614	4169	Homobenzomorphan	-	-	-	+	+	+	+	-
1270			Δ^9-tetrahydrocannabinol	+	-	+	+	-	-	-	-
1273	9884	4241	Phenylmorphan	+	+	-	-	+	+	+	-
1274	9885	4242	Phenylmorphan	+	+	-	-	+	+	+	-
1276	9894	4247	Phenylmorphan	+	+	-	-	+	+	+	-
1277	9901	4250	Homobenzomorphan	+	+	-	-	+	+	+	-
1280	9898	4249	Homobenzomorphan	+	+	-	-	+	+	+	-
1281	9902	4251	Homobenzomorphan	+	-	-	-	+	+	+	-
1322	9874	4230	Oxymorphinan	-	-	-	-	+	+	+	-
1324	9961	4287	Phenethylpiperidine	-	-	-	-	+	+	+	-

SDS = Single-dose suppression of withdrawal signs in morphine-dependant monkeys
NW = Attempted precipitation of withdrawal in non-withdrawn, morphine-dependant monkeys
N = Attempted reversal by nalorphine end naloxone of effects in nondependent monkeys
SA = Teat of reinforcing properties in monkeys which normally self-administer codeine
GPI = Suppression of twitch in electrically driven guinea-pig ileum preparation
MVD = Suppression of twitch in electrically driven mouse vas deferens preparation
BIND = Stereospeciflc displacement of ^{3}H-etorphine in membrane preparation from rat cerebrum
PDS = Primary dependence study In monkeys

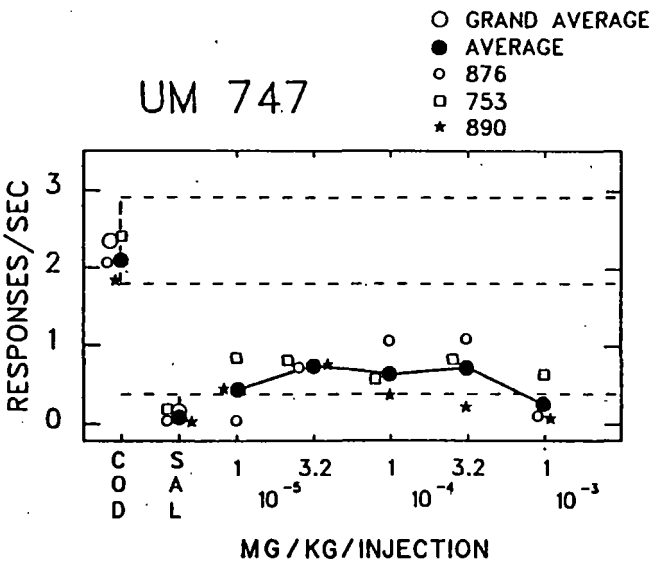
UM 747 NIH 8439



MOUSE ANALGESIA, ED50 (mg/kg)
Hot plate: 0.07 (0.05 - 0.09)
Nilsen:

(-)-5,9α-Diethyl-2'-hydroxy-2-methylenecyclopropylmethyl-6,7-benzomorphan hydrochloride

DRUG SELF-ADMINISTRATION IN RHESUS MONKEYS

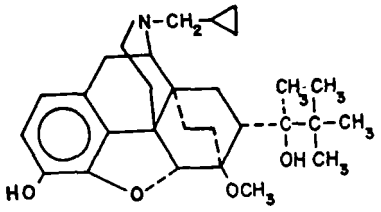


UM 747 maintained, at one or more doses, average rates of responding in each monkey slightly above those maintained by saline.

COMMENT

UM 747 is a unique opiate because it produces naloxone-reversible increases in the turnover of dopamine and norepinephrine in mouse brain but does not increase locomotor activity in the mouse (Smith and Sheldon, 1973).

UM 952 NIH 8805 BUPRENORPHINE



MOUSE ANALGESIA ED 50 (mg/kg)
Hot plate: 0.04 (0.03-0.04)
Nilsen: 0.04 (0.03-0.06)

N-Cyclopropylmethyl-7'α-[1-(S)-hydrOxy-1,2,2-trimethyl-propyl]-6,14-endoethano,6,7,8,14-tetrahydxonororipavine

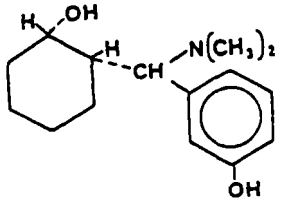
OBSERVATIONS IN MORPHINE DEPENDENT RHESUS MONKEYS

Doses studied: 0.001 to 0.3 MG/KG, s.c.
SDS: Buprenorphine exacerbated withdrawal signs at doses of 0.17 and greater.

SUMMARY

Buprenorphine has been reported to suppress signs of withdrawal in morphine dependent dogs as well as precipitate withdrawal in nonwithdrawn subjects (Martin et al., 1976). No evidence of suppression of withdrawal was obtained in these experiments.

UM 961 NIH 8833



MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: 15.6 (11.4 - 20.4)
Nilsen: No dose response

(-)-cis-2-(Dimethylamino-m-hydroxybenzyl)cyclohexanol hydrochloride

OBSERVATIONS IN MORPHINE DEPENDENT RHESUS MONKEYS

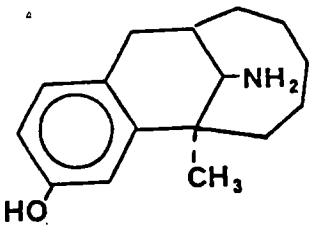
Doses studied: 0.31 to 5.0 mg/kg, s.c.

NW: UM 961 precipitated withdrawal with a potency of about one thirtieth of naloxone. Additionally it produced ataxia and decreased responsivity to external stimuli. The drug had a long duration of action.

SUMMARY

UM 961 represents a novel structure for a narcotic antagonist. Its actions should be studied more fully in other preparations.

UM 972 NIH 8834 WY 16225



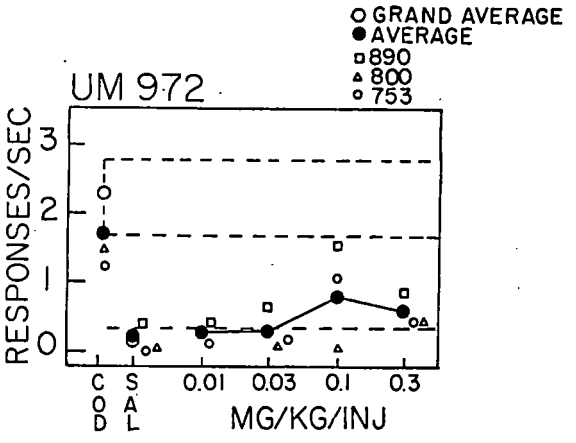
MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: 0.7 (0.5 - 0.9)
Nilsen: 0.9 (0.7 - 1.1)

1-13-Amino-5,6,7,8,9,10,11,12-octahydro-5-inethyl-5,11-methano-benzocylodecen-3ol hydrobromide

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

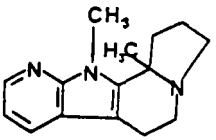
	+Na	-Na	+Na/-Na
BC 50 (M)	5.4×10^{-8}	6.6×10^{-8}	0.81

DRUG SELF-ADMINISTRATION IN RHESUS MONKEYS



In two of three monkeys UM 972 (0.1 to 0.3 mg/kg/inj) maintained responding (self-administration) at rates between codeine and saline levels. For a third monkey, responding was maintained marginally above saline levels only at 0.3 mg/kg/inj.

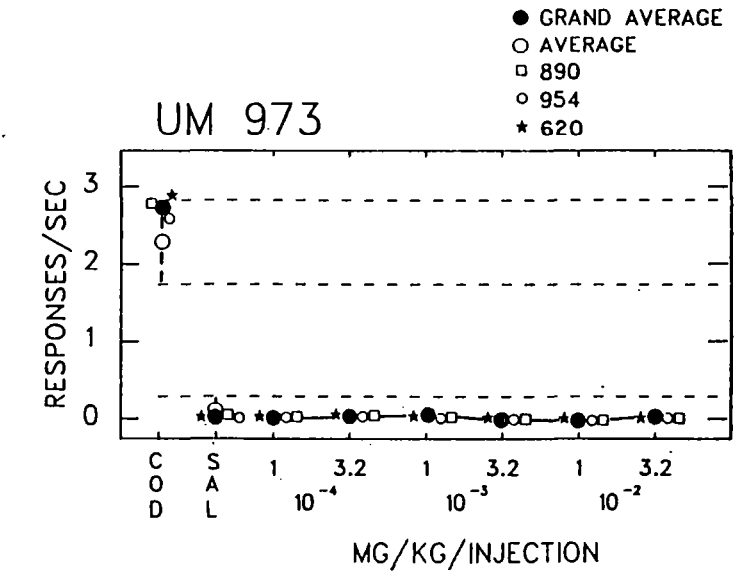
UM 973 NIH 8835



MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: 1.3 (1.1 - 1.7)
Nilsen:

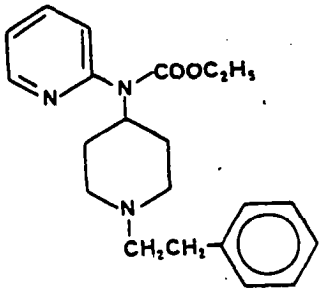
2,3,5,6,11,11b-Hexahydro-11,11b-dimethyl-1H-pyrido[3',2':4,5]pyrrolo[3,2- g] indolizine dihydrochloride

DRUG SELF-ADMINISTRATION IN RHESUS MONKEYS



UM 973 failed to maintain responding (drug self-administration) at levels above saline over the tested range of doses (0.0001 to 0.032 mg/kg/inj).

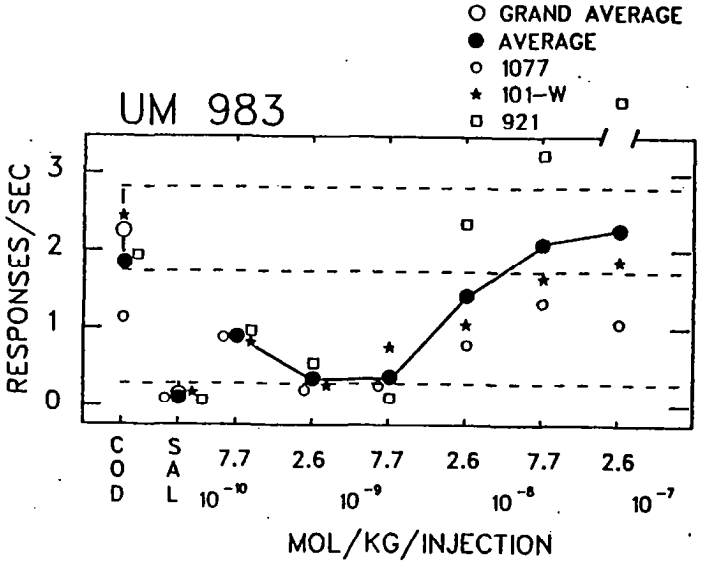
UM 983 NIH 8863



MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: 0.92 (0.74 - 1.2)
Nilsen:

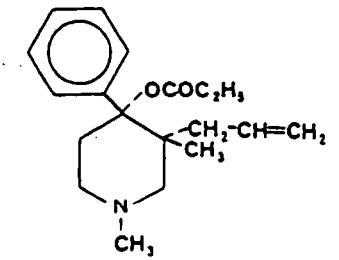
N-(α-Pyridyl),N-(1-ß-phenylethyl-4-piperidyl)-ethylcarbamate hydrochloride

DRUG SELF-ADMINISTRATION IN RHESUS MONKEYS



The three highest doses tested maintained average rates of responding similar to those maintained by codeine. For one monkey, 7.7 x 10^{-8} and 2.6 x 10^{-7} mol/kg/inj (0.032 and 0.1 mg/kg/inj) doses maintained rates over 3 responses/second. Doses of 2.6 or 7.7 x 10^{-9} mol/kg/inj (0.0001 or 0.0032 mg/kg/inj) maintained rates no higher than those maintained by saline; the lowest dose (7.7 x 10^{-10} mol/kg/inj 0.00032 mg/kg/inj) maintained rates higher than saline for all three monkeys.

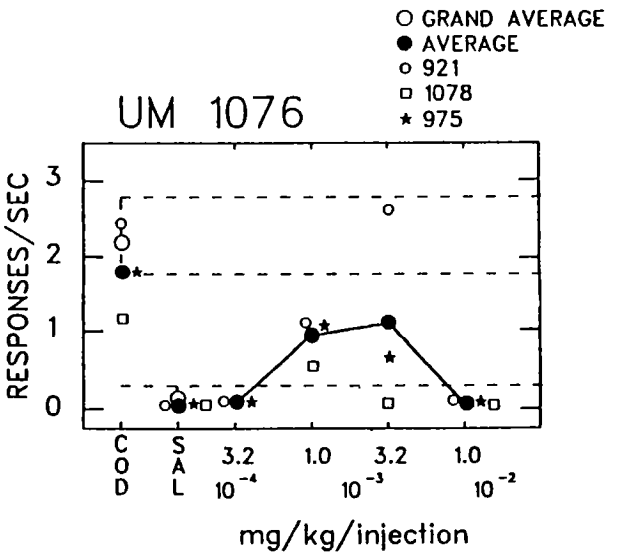
UM 1076 NIH 9112



MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: 0.01 (0.0096 - 0.017)
Nilsen:

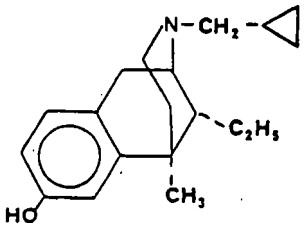
d1-3-Allyl-1,3-dimethyl-4-phenyl-
4-propionoxypiperidine hydrochloride

DRUG SELF-ADMINISTRATION IN RHESUS MONKEYS



UM 1076 maintained responding (self-administration) at one or more doses in each monkey; average rates maintained by UM 1076 were slightly less than those maintained by codeine. UM 1076 maintained maximal rates of responding at 1.0 x 10^{-3} mg/kg/inj in two monkeys and maintained much higher maximal response rates at 3.2 x 10^{-3} mg/kg/injection in the third monkey. The lowest and highest injection dose of UM 1076 maintained rates no higher than those maintained by saline.

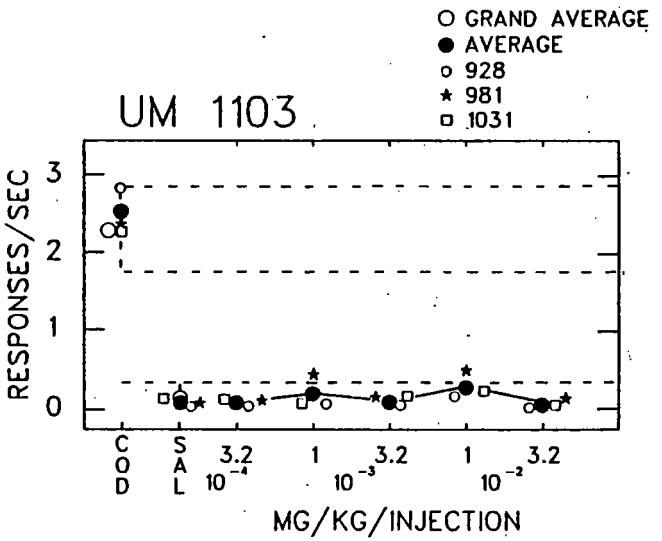
UM 1103 NIH 9256



MOUSE ANALGESIC, ED 50 (mg/kg)
Hot plate: Inactive
Nilsen: Inactive

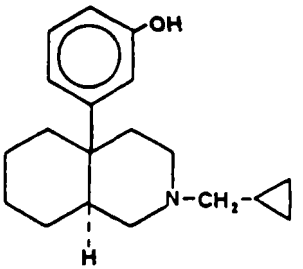
2-Cyclopropylmethyl-9α-ethyl-2'-hydroxy-5-methyl-6,7-benzomorphan

DRUG SELF-ADMINISTRATION IN RHESUS MONKEYS



UM 1103 did not maintain responding (self-administration) over the tested range of doses (0.00032 to 0.032 mg/kg/inj).

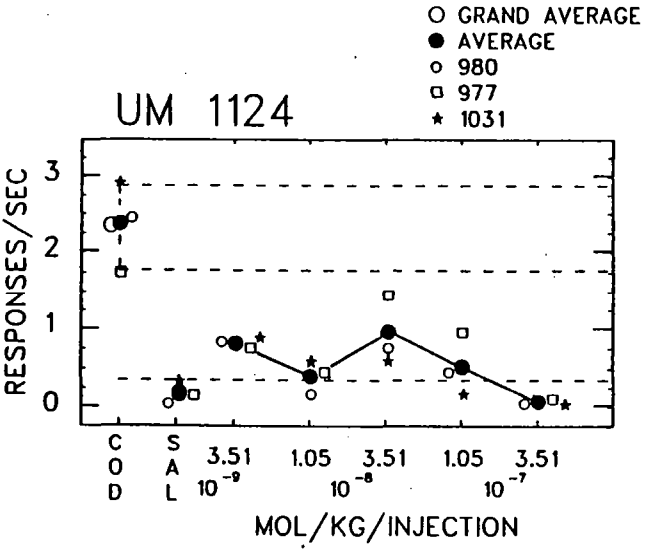
UM 1124 NIH 9342 MCV 4102



MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: 4.4 (2.9 - 6.6)
Nilsen:

(-)-m-[2-(Cyclopropylmethyl)-1,2,3,4,4a,5,6,7,8,8a-decahydro-4a-isoquinolyl] phenol succinic acid salt

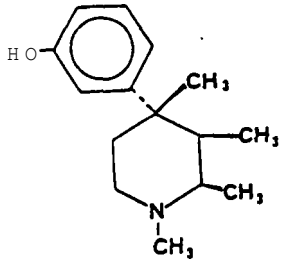
DRUG SELF-ADMINISTRATION IN RHESUS MONKEYS



UM 1124 maintained rates of responding (self-administration) slightly above saline over the ranqe of 3.5×10^{-9} to 1.05×10^{-7} mol/kg/inj. UM 1124 did not maintain rates of responding equivalent to those maintained by codeine.

For comparison see compound UM 1112 (Swain et al. 1978; Woods et al. 1979).

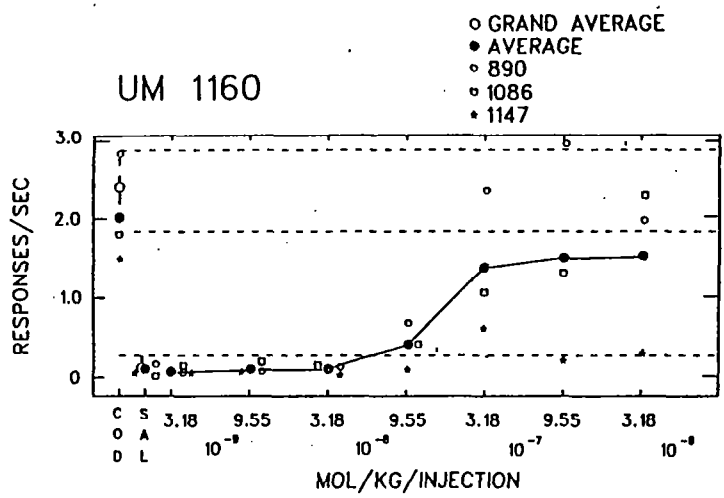
UM 1160 NIH 9521



MOUSE ANALGESIC, ED 50 (mg/kg)
Hot plate: 2.9 (2.2 - 3.8)
Nilsen:

3 alpha-(1,2 beta,3 beta,4-Tetramethyl-
4-piperidinyl)phenol hydrobromide

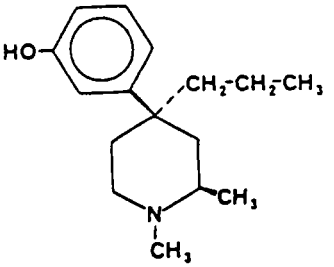
DRUG SELF-ADMINISTRATION IN RHESUS MONKEYS



We reported in 1978 that UM 1160 was a short-acting, less potent morphine-like drug in the morphine-withdrawn rhesus monkey. In addition, it produced some signs of possible disorientation and muscle incoordination at doses that completely suppressed withdrawal. UM 1160 maintained responding (self-administration) at one or more doses in each monkey; on average, at rates slightly less than those maintained by codeine. The maximal rates maintained, however,

differed among subjects. For two monkeys, UM 1160 doses of 9.55×10^{-7} or 3.18×10^{-6} mol/kg/inj (0.32 or 1.0 mg/kg/inj) maintained ,response rates slightly hi her than those maintained by codeine. At 3.18×10^{-6} mol/kg/inj (1.0 mg/kg/inj) the total dose of UM 1160 was equal to that which produced muscle incoordination in the morphine-withdrawn monkey. For these two subjects, the three highest doses of UM 1160 maintained response rates above those maintained by saline; lower injection doses maintained rates no different from those maintained by saline. For the third monkey, UM 1160, 3.18×10^{-7}mol/kg/inj (0.10 mg/kg/inj), maintained rates slightly above those maintained by saline: lower and higher doses maintained rates no different from those maintained by saline. Higher doses were not tested because the drug supply was depleted. It appears that the direct, observed effects mentioned above did not interfere with the capacity of UM 1160 to maintain responding.

UM 1169 NIH 9540 MCV 4145



MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: 0.81 (0.62 - 1.1)
Nilsen:

trans-3-(1,2-Dimethyl-4-propyl-4-piperidinyl) phenol hydrobromide

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+ Na	- Na	+Na/-Na
EC 50 (M)	3.3×10^{-7}	1.4×10^{-7}	2.29

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN GUINEA-PIG ILEUM

	EC 50 (M)	MAXIMUM RESPONSE (%)
Drug alone	1.9×10^{-7}	100
After naltrexone	unchanged	unchanged
After UM 979	unchanged	unchanged

UM 1169, unlike morphine, produced a complete inhibition of the twitch in this preparation. Additionally, it further inhibited the twitch after a maximally effective concentration of morphine. At concentrations from 10^{-5} M to 3 x 10^{-4} M, the drug produced a forceful, sustained contracture equivalent to 50% of that produced by carbachol.

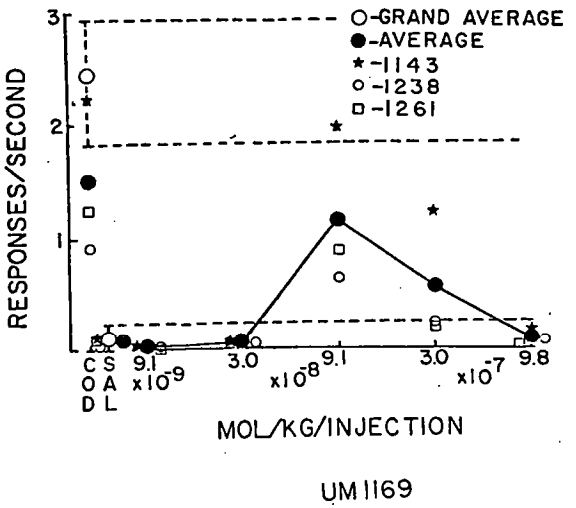
INHIBITION OF TWITCH OF ELCETRICALLY-DRIVEN MOUSE VAS DEFERENS

	EC 50 (M)	Maximum Response (%)
Drug alone	8.4 x 10^{-7}	57

UM 1169 was different from morphine in that it did not completely inhibit the twitch of this preparation. At concentrations from 10^{-5} to 3 x 10^{-4} M the drug enhanced the twitch. Neither naltrexone nor UM 979 altered the responses to UM 1169.

Doses studied: 0.4 to 3.2 mg/kg, s.c.
SDS : UM 1169 had morphine-like agonist actions and was about three times as potent as morphine.

DRUG SELF-ADMINISTRATION IN RHESUS MONKEYS

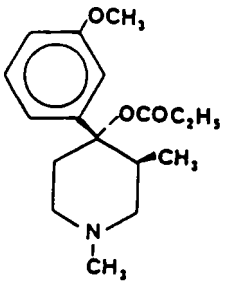


UM 1169 maintained responding (self-administration) at levels approximating those maintained by codeine and with about ten times the potency of codeine.

SUMMARY

The in vivo and in vitro action of this drug clearly differ fran each other. UM 1169 is more potent than morphine in the dependent monkey but less potent in the displacement of ^{3}H-etorphine and in both smooth muscle preparations. The sodium ratio for displacement of ^{3}H-etorphine is consistent with a morphine-like action. However, although UM 1169 suppresses the twitch in both smooth muscle preparations, its actions differ from morphine in that in neither preparation are the effects of UN 1169 antagonized by naltrexone or UM 979.

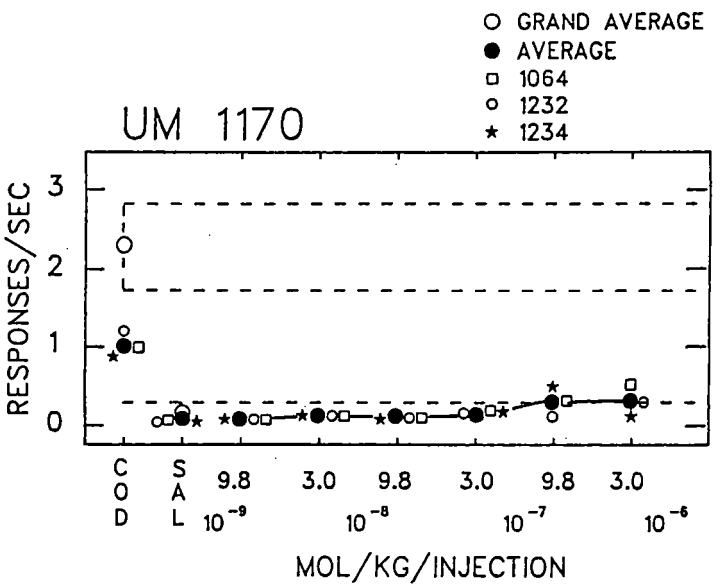
UM 1170 NIH 9541



MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: 21.8 (14.6 - 32.7)
Nilsen:

4ß-(m-Methoxyphenyl)1,3-dimethyl-4 α-piperidinol propionate hydrochloride

DRUG SELF-ADMINISTRATION IN RHESUS MONKEYS



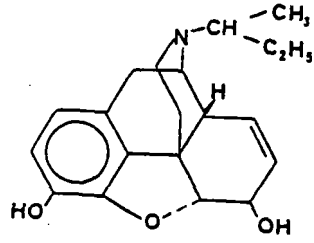
UM 1170 did not maintain responding (self-administration) over a range of doses from 9.8 x 10^{-9} to 3.0 x 10^{-6} mol/kg/inj.

SUMMARY

UM 1170 is interesting in several respects. First, like meperidine, UM 1170 has virtually no activity in displacing tritiated etorphine from its binding site, however, it has typical morphine-like agonist actions in the morphine-dependent rhesus monkey (Swain et al., 1979). Second, the drug has actions upon both smooth muscle preparations which are unlike morphine (Swain et al., 1979). Finally, the drug is one of two compounds that have been identified (see UM 1167 in woods et al. 1981) that act as morphine-like agonists in the dependent monkey but do not maintain responding in the drug self-administration procedure.

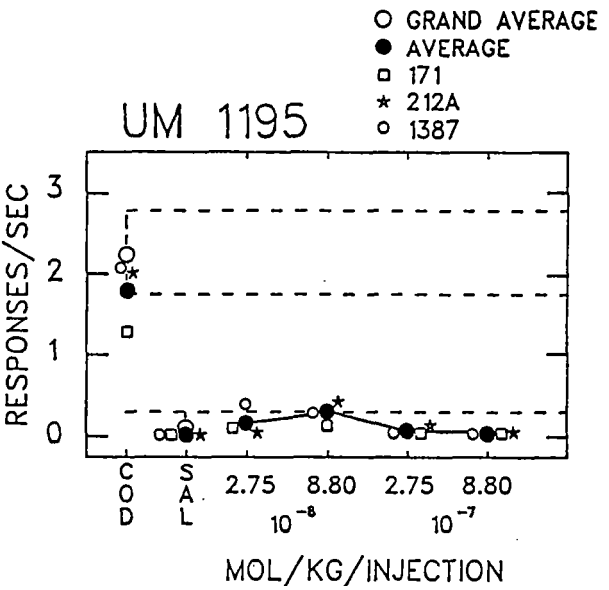
A previous report (Swain et al., 1979) of responding maintained by UM 1170 comparable to that maintained, by codeine was in error.

UM 1195 NIH 9637



MOUSE ANALGESIA, ED 50 (mg/kg)
Hot Plate: 15.0 (11.3 - 19.8)
Nilsen:

s-N-sec-Butylnormorphine hydrochloride

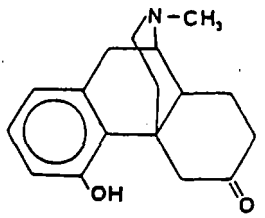


UM 1195 did not maintain responding (self-administration) comparable to codeine at any dose studied. At one dose, 8.8 x 10^{-8} mol/kg/inj (0.032 mg/kg), rates were maintained marginally above saline levels (15% of the codeine maintained response rate).

SUMMARY

On the basis of results reported previously (Woods et al. 1981) in the binding and guinea-pig ileum assays, UM 1195 had some low potency morphine-like agonist actions. In the dependent monkey and mouse vas deferens, however, the drug appeared to be non-narcotic. It also appears unlike morphine in self-administration.

UM 1200 NIH 9674



MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: 1.6 (1.2 - 2.1)
Nilsen:

(-)-4-Hydroxy-N-methylmorphinan-6-one hydrobromide

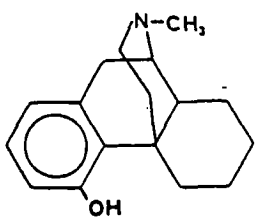
DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC 50 (M)	1.2×10^{-7}	5.5×10^{-8}	2.20

OBSERVATIONS IN MORPHINE DEPENDENT RHESUS MONKEYS

Doses studied: 1.0 to 4.0 mg/kg, s.c.
SDS: UM 1200 had morphine-like agonist actions and was slightly more potent than morphine. Its duration of action was longer than that of morphine.

UM 1201 NIH 9677



MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: 1.6 (1.2 - 2.3)
Nilsen:

(-)-4-Hydroxy-N-methylmorphinan hydrochloride

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC 50 (M)	5.1 x 10-	1.5 x 10^{-7}	3.42

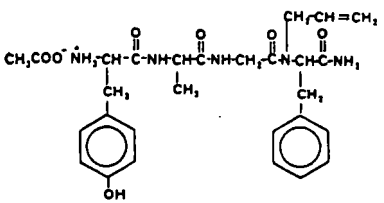
OBSERVATIONS IN MORPHINE DEPENDENT RHESUS MONKEYS

Doses studied: 1.0 to 4.0 mg/kg, s.c.
SDS: UM 1201 had morphine-like agonist actions with a potency similar to that of morphine. Its duration of action was shorter than that of UM 1200.

SUMMARY

The change in the hydroxy from 'the phenolic 3-position (levorphanol) to the I-position (UM 1201) decreased potency in the analgesic assay by a factor of eight, however, its potency in the dependent monkey was only decreased by a factor of four. A recent study of displacement of ^{3}H-naltrexone has shown slightly larger changes in EC 50 with the same change in position of the hydroxy substituent (Simon et al., 1981).

UM 1212 NM 9724 MCV 4187



MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: 1.9 (1.4 - 2.6)
Nilsen:

L-Tyrosyl-D-alanylglycyl-L-N -α-allyl-phenylalanine amide acetate

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC 50 (M)	1.2 X 10^{-8}	6.7 x 10^{-9}	1.74

The slope of the concentration-displacement curve was markedly lower than most compounds previously studied.

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN GUINEA-PIG ILEUM

	EC 50 (M)	Maximum Response (%)
Drug alone	9.5×10^{-10}	45.7
Afternaltrexone	2.1×10^{-7}	unchanged
After UM 979	2.7×10^{-8}	30.1

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN MOUSE VAS DEFERENS

	EC 50 (M)	Maximum Response
Drug alone	4.0×10^{-9}	98.4
After naltrexone	1.1×10^{-7}	unchanged
After UM 979	9.9×10^{-9}	unchanged

OBSERVATIONS IN MORPHINE DEPENDENT RHESUS MONKEYS

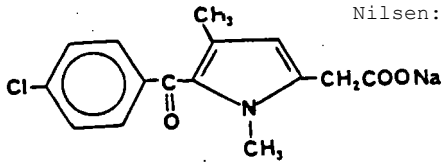
Doses studied: 1.0 to 16.0 mg/kg, s.c.
SDS: UM 1212 had morphine-like agonist actions but with a short duration of action and about one-fifth of the potency of morphine.

SUMMARY

This drug is morphine-like in all preparations. The in vitro potency of UM 1212 did not predict the in vivo potency.

UM 1217 NIH 9730 MCV 4192 ZOMEPIRAC

MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: Inactive up to 100 mg/kg
Nilsen: No Dose



Sodium 5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrole-2-acetate

DISPLACEMENT OF STEREOSOECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na
EC 50 (M)	$>2 \times 10^{-5}$	$>2 \times 10^{-5}$

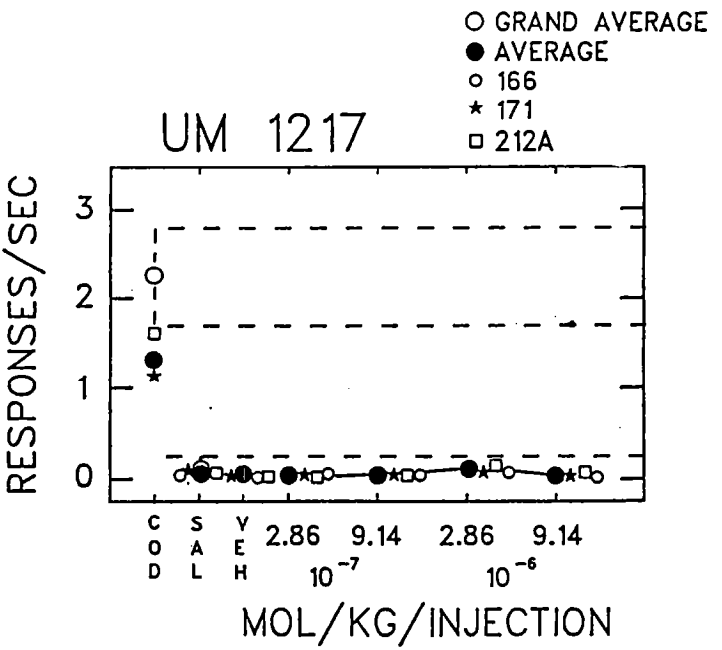
INHIBITION OF ELECTRICALLY-DRIVEN GUINEA-PIG ILEUM

	EC 50 (M)	Maximum Response (%)
Drug alone	3.4×10^{-5}	44.8
After naltrexone	9.9×10^{-5}	unchanged

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN MOUSE VAS DEFERENS

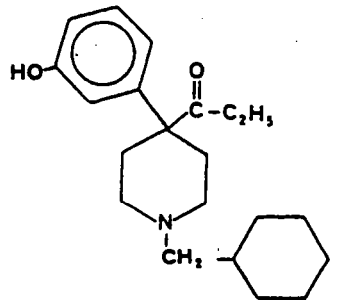
	EC 50 (M)	Maximum Response (%)
Drug alone	7.8×10^{-5}	59.3
After naltrexone	unchanged	unchanged
After UM 979	unchanged	unchanged

SELF-ADMINISTRATION IN RHESUS MONKEYS



No dose studied maintained responding above vehicle levels. The highest dose was administered in a vehicle consisting of 95% ethanol (33%), propylene glycol (19%) and water (48%).

UM 1218 NIH 9585



MOUSE ANALGESIA, ED 50 (mg/kg)
Hot Plate: No dose response
Nilsen:

N-Cyclohexylmethylnorketobemidone
hydrobromide

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC 50 (M)	1.7×10^{-6}	1.5×10^{-6}	1.10

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN GUINEA-PIG ILEUM

Concentrations lower than 10^{-5} M did not alter the magnitude of the twitch. From 10^{-5} M to 10^{-4} M UM 1218 increased baseline tension. Neither naltrexone nor UM 979 altered this response.

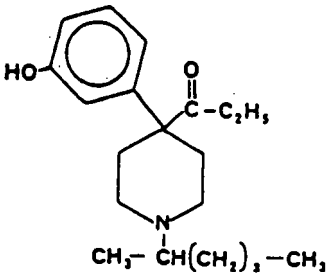
INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN MOUSE VAS DEFERENS

Concentrations from 10^{-6} M to 3×10^{-5} M increased the twitch without increasing baseline tension indicating that the drug did not directly contract the vas deferens.

SUMMARY

See UM 1237.

UM 1221 NIH 9741



MOUSE ANALGESIA, ED 50 (mg/kg)
riot plate: No dose response
Nilsen:

N-2-Hexylnorketobemidone hydrobromide

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC 50 (M)	1.5×10^{-6}	1.8×10^{-6}	0.84

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN GUINEA-PIG ILEUM

UM 1221 was inactive to a concentration of 3×10^{-6} M. At concentrations of 10^{-5} M and higher a sustained increase in baseline tension was obtained that was not altered by naltrexone or UM 979.

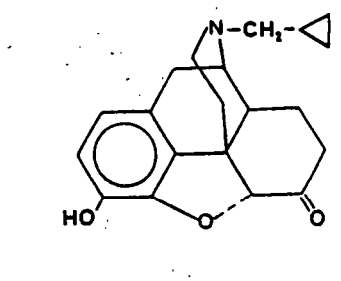
INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN MOUSE VAS DEFERENS

UM 1221 increased the magnitude of the twitch at concentrations of 10^{-9} M and higher. This response was not affected by either naltrexone or UM 979.

SUMMARY

See UM 1237

UM 1223 NIH 9735 Mcv 4195



MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: Inactive up to 50 mg/kg

N-Cyclopropylmethyl-7,8-dihydronormorphinone

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC 50 (M)	7.2×10^{-10}	1.2×10^{-9}	0.58

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN GUINEA-PIG ILEUM

	EC 50 (M)	Maximum Response (%)
Drug alone	1.4×10^{-9}	53.8
After naltrexone	6.5×10^{-8}	unchanged
After UM 979	7.6×10^{-8}	unchanged

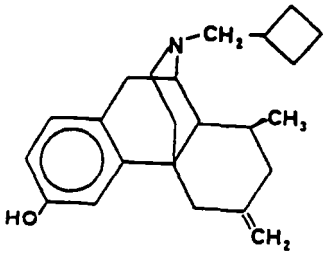
INHIBITON OF TWITCH OF ELECTRICALLY-DRIVEN MOUSE VAS DEFERENS

UM 1223 was inactive with an occasional increase in magnitude of the twitch at 3×10^{-4} and 10^{-4} M.

SUMMARY

UM 1223 is very potent in the binding assay and has a low sodium ratio. It is morphine-like upon the ileum but ten times more potent. However, it is inactive upon the vas deferens.

UM 1224 NIH 9736 MCV 4196



MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: Insufficient activity
Nilsen: 1.3 (0.73 - 2.4)

N-Cyclobutylmethyl-3-hydroxy-6-methylene-8ß-methylmorphinan

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC 50 (M)	1.4×10^{-9}	1.7×10^{-9}	0.80

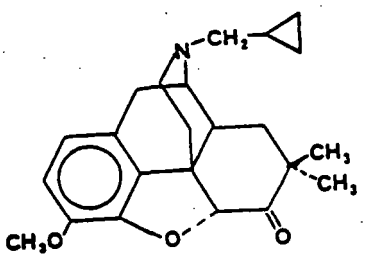
INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN GUINEA-PIG ILEUM

	EC 50 (M)	Maximum response (%)
Drug Alone	1.0×10^{-5}	57.6
After naltrexone	Biphasic dose-response curve with EC 50 for the first phase:	
	5.1×10^{-9}	33.4
	second-phase:	
	8.5×10^{-6}	58.9
After UM 979	1.1×10^{-5}	unchanged

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN MOUSE VAS DEFERENS

	EC 50 (M)	Maximum Response (%)
Drug alone	2.8×10^{-8}	41.4
After naltrexone	3.4×10^{-8}	unchanged
After UM 979	3.0×10^{-8}	unchanged

UM 1225 NIH 9737 MCV 4197



MOUSE ANALGESIA, ED 50 (mg/kg)
Hot Plate: 5.2 (3.5 - 7.8)
Nilsen: 11.5 (7.2 - 18.4)

17-Cyclopropylmethyl-7,7-dimethyl-3-methoxy-4,5α-epoxymorphinan-6-one

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC 50 (M)	2.4×10^{-7}	2.0×10^{-7}	1.24

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN GUINEA-PIG ILEUM

	EC 50 (M)	Maximum Response (%)
Drug alone,	9.5×10^{-6}	38.9
After naltrexone	8.0×10^{-6}	58.3
After UM 979	8.4×10^{-6}	57.3

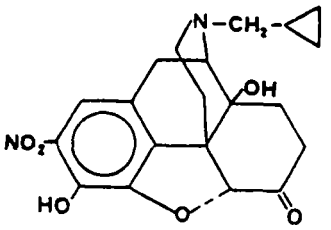
UM 1225 alone produced increases in baseline tension at 3×10^{-5} M and 10^{-4} M.

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN MOUSE VAS DEFERENS

	EC 50 (M)	Maximum Respinse (%)
Drug alone	4.1×10^{-8}	39.7
After naltrexone	1.8×10^{-7}	unchanged
After UM 979	6.6×10^{-8}	unchanged

Small increases in twitch magnitude above maximal inhibitory response occurred with UM 1225 at 10^{-5} M and 3×10^{-5} M. At 10^{-4} M there was an initial complete suppression of twitch followed by a gradual recovery to a force 2.9 times baseline level.

UM 1226 NIH 9738 MCV 4199



MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: 3.7 (2.3 - 5.7)
Nilsen: 5.8 (4.1 - 8.4)

2-Nitronaltrexone

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na
EC 50 (M)	$> 2 \times 10^{-5}$	$> 2 \times 10^{-5}$

INHIBITION OF TWITCH OF ELECTRICALLT-DRIVEN GUINEA-PIG ILEUM

	EC 50 (M)	Maximum Response (%)
Drug alone	1.6×10^{-4}	97.9
After naltrexone	6.0×10^{-5}	unchanged
After UM 979	4.0×10^{-5}	unchanged

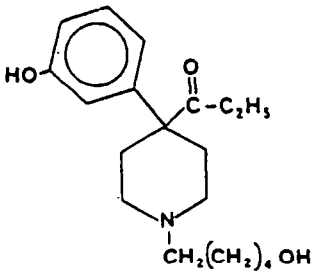
INHIBITION OF ELECTRICALLY-DRIVEN MOUSE VAS DEFERENS

UM 1226 did not inhibit the twitch up to a concentration of 3×10^{-6} M above which the magnitude of the twitch was increased. Neither naltrexone nor UM 979 altered the response to UM 1226.

SUMMARY

The 2-nitro substitution on the phenyl ring markedly decreases potency in displacing etorphine and thus inhibits antagonist activity (See Aceto et al., 1981).

UM 1237 NIH 9789



MOUSE ANALGESIA ED 50 (mg/kg)
Hot plate: Incompletely active at 100 mg/kg
Nilsen:

5-Hydroxypentylnorketobemidone
hydrobromide

INHIBITION OF TWITCH ELECTRICALLY-DRIVEN GUINEA-PIG ILEUM

	EC 50 (M)	Maximum Response (%)
Drug alone	2.6×10^{-5}	36.9
After naltrexone	2.5×10^{-5}	Unchanged
After UM 979	3.0×10^{-5}	unchanged

Concentrations of 10^{-4} M and 3×10^{-4} M increased baseline tension.

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN MOUSE VAS DEFERENS

	EC 50 (M)	Maximum Response (%)
Drug alone	5.1×10^{-9}	51.3
After naltrexone	1.6×10^{-8}	36.4
After UM 979	1.4×10^{-8}	42.2

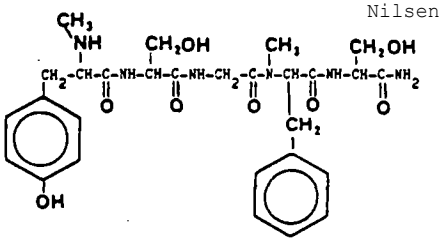
At higher concentrations (10^{-6} to 3×10^{-4} M), the compound enhanced the twitch; neither antagonist altered this response.

SUMMARY

UM 1237, like UM 1218 and UM 1221, has *in vitro* actions like the quasi-withdrawal inducing agents, UM 1037 and UM 1046 (valentino et al., 1981), however at the doses tested, these canpounds failed to show any *in vivo* actions (Woods et al., 1981).

UM 1238 NIH 9791 MCV 4210

MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: 1.4 (1.1 - 1.8)
Nilsen: 1.5 (1.1 - 2.1)



N-Methyl-L-tyrosyl-D-serylglycyl-N-methyl-
L-phenylalanyl-D-serinamide monoacetate

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC 50 (M)	2.5 x 10-7	1.3 x 10-7	1.87

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN GUINEA-PIG ILEUM

	EC 50 (M)	Maximum Response (%)
Drug alone	6.1×10^{-8}	55.9
After naltrexone	2.3×10^{-6}	unchanged
After UM 979	4.1×10^{-7}	Unchanged

Both antagonists increased the slope of the concentration-effect curve.

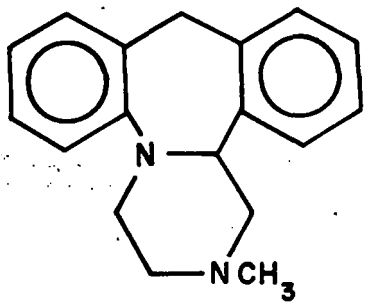
INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN MOUSE VAS DEFERENS

	EC 50 (M)	Maximum Response (%)
Drug alone	$7.2. \times 10^{-8}$	97.4
After naltrexone	1.3×10^{-6}	Unchanged
After UM 979	1.6×10^{-7}	unchanged

SUMMARY

UM 1238 is morphine-like in all three preparations.

UM 1243 MIANSERIN



1,2,3,4,10,146-Hexahydro-2-methyldibenzo{c,t}pyrazino{l,2a}azapine

DISPLACEMENT OF TWITCH OF ELECTRICALLY-DRIVEN GUINEA-PIG ILEUM

	+Na	-Na	+Na/-Na
EC 50 (M)	$>2.0 \times 10^{-5}$	$>2.0 \times 10^{-5}$	——

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN GUINEA-PIG ILEUM

	EC 50 (M)	Maximum response (%)
Drug alone	1.8×10^{-6}	91.8
After naltrexone	1.8×10^{-5}	unchanged
After UM 979	4.8 x 10-5	unchanged

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN MOUSE VAS DEFERENS

	EC 50 (M)	Maximum response (%)
Drug alone	1.1×10^{-8}	60.2
After naltrexone	5.9×10^{-9}	37.4
After UM 979	2.1×10^{-8}	unchanged

Concentrations of 3×10^{-6} M and higher produced marked increases in the magnitude of the twitch but did not alter the baseline tension.

OBSERVATIONS IN MORPHINE-DEPENDENT AND NON-DEPENDENT RHESUS MONKEYS

Doses studied: 5.0 to 20.0 mg/kg, s.c.

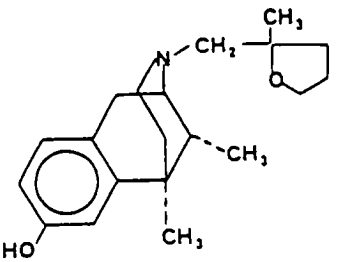
SDS: UM 1243 neither suppressed nor exacerbated withdrawal signs across the dose range studied. At the highest

dose there were signs of sedation.
Nondependent subjects: Effects of 20.0 mg/kg included sedation and dozing, slight ataxia and increased respiratory rate. None of these effects was reversed by naloxone (2.0 mg/kg, i.v.).

SUMMARY

UM 1243 is an example of a drug which appears to be morphine-like upon the guinea-pig ileum but is devoid of opiate activity in all of the other preparations.

UM 1245 NIH 9804 MCV 4212



MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: Inactive
Toxic at 20 mg/kg
Nilsen : 7.7 (5.6 - 10.5)

(-)-(1R,5R,9R,2"S)-(5,9-Dimethyl-2'-hydroxy-2-(2-methyltetrahydrofurfuryl)-6,7-benzamorphan) L-tartrate

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na / -Na
EC 50 (M)	1.9×10^{-8}	1.8×10^{-8}	1.07

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN GUINEA-PIG ILEUM

	EC 50 (M)	Maximum Response (%)
Drug alone	2.5×10^{-6}	69.8
After naltrexone	5.1×10^{-7}	86.4
After UM 979	7.5×10^{-7}	82.6

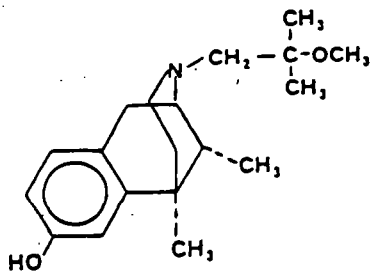
INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN MOUSE VAS DEFERENS

	EC 50 (M)	Maximum response (%)
Drug alone	4.3×10^{-8}	100
After naltrexone	1.4×10^{-6}	unchanged
After UM 979	7.8×10^{-8}	unchanged

OBSERVATIONS IN MORPHINE-DEPENDENT RHESUS MONKEYS

Doses studied: 0.03 to 1.0 mg/kg, s.c.
NW: UM 1245 precipitated narcotic withdrawal signs promptly with a potency about one-tenth that of naloxone in the morphine-dependent monkey.

UM 1246 NIH 9805 MCV 4213



MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: 0.83 (0.62 - 1.1)
Nilsen:

(-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(2-methoxyisobutyl)-6,7,benzomorphan

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	- Na	+Na/-Na
EC 50 (M)	2.0×10^{-7}	2.5×10^{-7}	0.79

INHIBITION OF THE TWITCH OF ELECTRICALLY-DRIVEN GUINEA-PIG ILEUM

	EC 50 (M)	Maximum Response (%)
Drug alone	4.1×10^{-10}	58.3
After naltrexone	2.4×10^{-7}	unchanged
After UM 979	3.2×10^{-7}	unchanged

INHIBITION OF TWITCH OF ELCTRICALLY-DRIVEN MOUSE VAS DEFERENS

	EC 50 (m)	Maximum Response
Drug alone	2.3×10^{-8}	100
After naltrexone	3.7×10^{-8}	unchanged
After UM 979	5.2×10^{-8}	unchanged

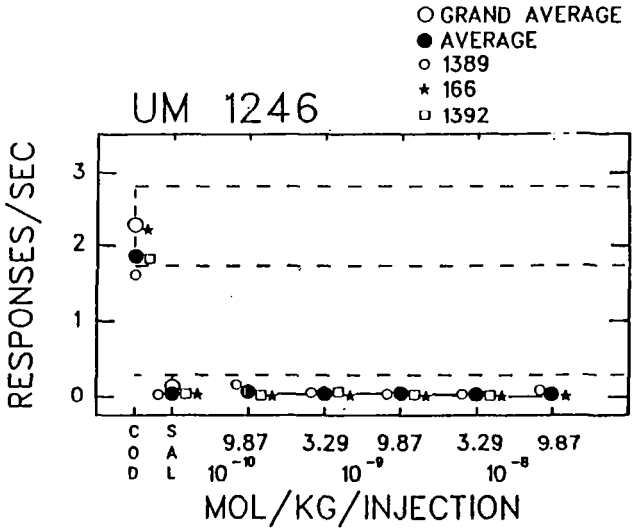
OBSERVATIONS IN MORPHINE DEPENDENT AND NON-DEPENDENT RHESUS MONKEYS

Doses studied: 0.2 to 0.8 mg/kg, s.c.

SDS: UM 1246 (0.2 - 0.8 mg/kg, s.c.) failed to suppress the withdrawal signs in morphine-dependent rhesus monkeys though the compound produced marked signs of motor incoordination and sedation. The compound is similar to ethylketazocine in this regard.

Nondependent subjects: UM 1246 (0.4 mg/kg, s.c.) produced ataxia, pupil dilation, decreased responsivity to external stimuli, ptosis, dozing, and increased respiratory rate. All effects except those on respiration were antagonized by 1.7 mg/kg naloxone. Additionally these effects, except those on respiration, are similar to those produced by ethylketazocine.

DRUG SELF-ADMINISTRATION IN RHESUS MONKEYS

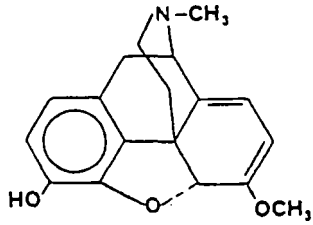


UM 1246 did not maintain responding (self-administration across a range of doses from 9.87 x 10^{-10} to 9.87 x 10^{-7} mol/kg/inj (0.03 to 30 µg/kg/inj).

SUMMARY

UM 1246 is an atypical narcotic agonist; it appears to be unlike morphine in that it fails to suppress narcotic withdrawal signs in the dependent monkey, it does, not maintain responding in the self-administration procedure, and it has an intermediate sodium response ratio. Its direct CNS effects in normal monkeys, however, are reversed by the narcotic antagonist naloxone. These findings are typically associated with ethylketazocine-like compounds in these preparations. On the guinea-pig ileum, UM 1246 is very potent, and it is markedly antagonized by both naltrexone and UM 979. In contrast, on the mouse vas deferens UM 1246 is an agonist which is as potent as, and equally efficacious to morphine. However, neither antagonist reverses the effects of UM 1246 upon this preparation. Thus, UM 1246 does not appear to be either morphine- or ethylketazocine-like in its actions on the mouse vas deferens. In conclusion, UM 1246 appears to be a narcotic with an important spectrum of agonist actions warranting further study.

UM 1252 NIH 9821 MCV 4219 ORIPAVINE



MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: 1.5 (1.1 - 2.0)
Nilsen:

Oripavine hydrochloride

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+ Na	- Na	+Na/-Na
EC 50 (M)	8.0×10^{-7}	4.3×10^{-7}	1.88

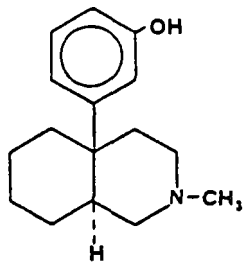
INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN GUINEA-PIG ILEUM

	EC 50 (M)	Maximum Response (%)
Drug alone	5.3×10^{-7}	52.0
After naltrexone	$> 3 \times 10^{-4}$	
After UM 979	1.7×10^{-5}	unchanged

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN MOUSE VAS DEFERENS

	EC 50 (M)	Maximum Response (%)
Drug alone	3.5×10^{-6}	88.7
After naltrexone	5.4×10^{-5}	unchanged
After UM 979	2.7×10^{-6}	unchanged

UM 1253 NIH 9824 MCV 4220



MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: 2.1 (1.6 - 2.8)
Nilsen:

(-)-trans-3-(Octahydro-2-methyl-4a(2H)-isoquinoline)phenol hydrobromomide

DISPLACEMENT OF STEREOSPECIFIC 3H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC 50 (M)	1.4×10^{-7}	7.6×10^{-8}	1.84

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN GUINEA-PIG ILEUM

	EC 50 (M)	Maximum Response (%)
Drug alone	6.3×10^{-7}	78.6
After naltrexone	1.6×10^{-5}	unchanged
After UM 979	7.4×10^{-6}	unchanged

Both antagonists increased the slope of the concentration-effect curve.

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN MOUSE VAS DEFERENS

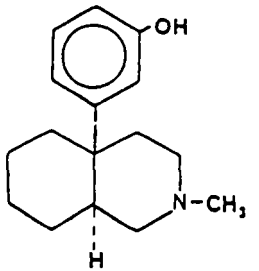
	EC 50 (M)	Maximum Response (%)
Drug alone	2.3×10^{-5}	92.6
After naltrexone	4.8×10^{-5}	unchanged
After UM 979	9.7×10^{-5}	unchanged

UM 979 increased the slope of the concentration-effect curve.

OBSERVATIONS IN MORPHINE-DEPENDENT RHESUS MONKEYS

Doses tested: 1.0 to 8.0 mg/kg, s.c.
SDS: UM 1253 had morphine-like agonist actions and was approximately equal in potency to morphine.

UM 1254 NIH 9825 MCV 4221



MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: 0.53 (0.42 - 0.67)
Nilsen:

(+)-trans-3-(Octahydro-2-methyl-4a(2H)-isoquinoline)phenol hydrobromide

DISPLACEMENT OF STEREOSPECIFIC 3H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC 50 (M)	2.8×10^{-8}	1.4×10^{-8}	1.94

INHIBITION OF TWITCH ELECTRICALLY-DRIVEN GUINEA-PIG ILEUM

	EC 50 (M)	Maximum Response (%)
Drug alone	2.2×10^{-7}	72.2
After naltrexone	1.2×10^{-5}	unchanged
After UM 979	3.7×10^{-6}	unchanged

Both antagonists increased the slops of the concentration-effect curve

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN MOUSE VAS DEFERENS

	EC 50 (M)	Maximum Response (%)
Drug alone	9.3×10^{-7}	95.1
After naltrexone	2.0×10^{-6}	unchanged
After UM 979	3.9×10^{-4}	unchanged

OBSERVATIONS IN MORPHINE-DEPENDENT RHESUS MONKEYS

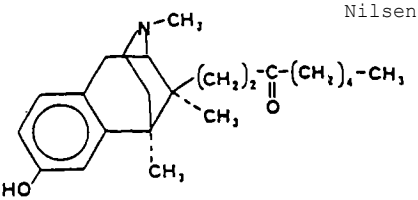
Doses tested: 0.15 to 0.6 mg/kg,s.c.
SDS: UM 1254 had morphine-like agonist actions and was greater than 5 times as potent.

SUMMARY

UM 1254 and UM 1253 are a pair of stereoisomers that show potency differences but share qualitatively similar actions. For a comparison with the stereoisomeric cis pair see Aceto et al. (1981).

UM 1258 NIH 9624 MCV 4175

MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: 2.4 (1.7 - 3.3)
Nilsen:



dl-1-[(2 α,6α,11S)-1-(1,2,3,4,5,6-Hexahydro-8-hydroxy-3,6,11-trimethyl-2,6-methano-3-benzazocin-11-yl)]-3-octanone methanesulfonate

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC 50 (M)	3.3×10^{-9}	3.1×10^{-9}	1.07

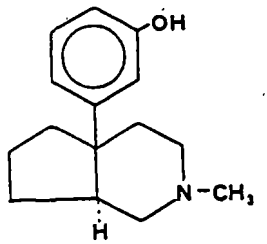
INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN GUINEA-PIG ILEUM

UM 1258 (10^{-9} to 10^{-4} M) failed to inhibit the twitch sufficiently to obtain an EC 50; the slight inhibition obtained at high concentrations was not changed by naltrexone or UM 979.

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN MOUSE VAS DEFERENS

	EC 50 (M)	Maximum Response (%)
Drug alone	1.8×10^{-8}	50.3
After naltrexone	8.5×10^{-9}	unchanged
After UM 979	2.2×10^{-8}	unchanged

UM 1259 NIH 9839 MCV 4225



MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: 8.1 (5.8 - 11.3)
Nilsen:

(-)-trans-3-(0ctahydro-2-methyl-lH-2-pyrindin-4a-yl) phenol (Z)-2-butanedioate

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC 50 (M)	2.8×10^{-7}	2.2×10^{-7}	1.28

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN GUINEA-PIG ILEUM

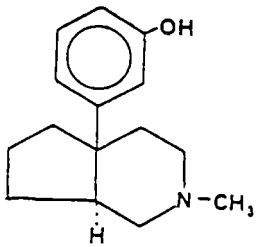
	EC 50 (M)	Maximum Response (%)
Drug alone	1.1×10^{-7}	33.8
After naltrexone	insurmountable	antagonism
After UM 979	insurmountable	antagonism

Concentrations of UM 1259 above 10^{-6} M in the presence of either antagonist increased the magnitude of the twitch without affecting baseline.

	EC 50 (M)	Maximum Response (%)
Drug alone	2.2×10^{-7}	62.8
After naltrexone	4.6×10^{-6}	unchanged
After UM 979	1.1×10^{-6}	unchanged

Doses tested: 2.0 to 8.0 mg/kg, s.c.
SDS: UM 1259 had morphine-like agonist actions and was about one-half as potent as morphine.

UM 1260 NIH 9840 MCV 4226



MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: 1.1 (0.83 - 1.3)
Nilsen:

(t)-trans-3-(Octahydro-2-methyl-1H-2-pyrindin-4a-yl)phenol (Z)-2-butanedioate

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	- Na	+Na/-Na
EC 50 (M)	8.8×10^{-8}	3.6×10^{-8}	2.43

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN GUINEA-PIG ILEUM

	EC 50 (M)	Maximum Response (%)
Drug alone	2.8×10^{-7}	58.1
After naltrexone	4.8×10^{-6}	unchanged
After UM 979	1.2×10^{-6}	unchanged

Both antagonists increased the slope of the concentration effect curve.

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN MOUSE VAS DEFERENS

	EC 50 (M)	Maximum Response (%)
Drug alone		98.2
After naltrexone		unchanged
After UM 979		unchanged

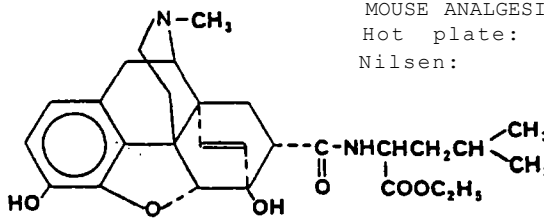
OBSERVATIONS IN MORPHINE-DEPENDENT RHESUS MONKEYS

Doses tested: 0.3 to 1.2 mg/kg, s.c.
SDS: UM 1260 had morphine-like agonist actions and was about 5 times more potent than morphine.

SUMMARY

UM 1260 and UM 1259 are a pair of stereoisomers that show qualitatively similar actions with correlated potency differences in binding and'behavioral effects. For a comparison with the stereoisomeric cis pair see Aceto et al. (1981) and also Woods et al. (1981).

UM 1261 NIH 9832 MCV 4227



MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: (0.59 - 1.0)
Nilsen:

N-(6,14-Endoetheno-7,8-dihydromorphine- 7^{α} -carbonyl)-
L-leucine ethyl ester hydrochloride

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	- Na
EC 50 (M)	2 to 3 x 10^{-9}	1 to 2 x 10^{-9}

Heterogeneous log probit plots makes it impossible to give exact EC 50 values.

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN GUINEA-PIG ILEUM

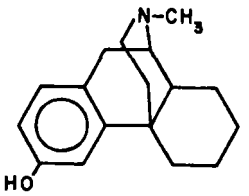
	EC 50 (m)	Maximum Response (%)
Drug alone	4.0 x 10^{-9}	60.2
After naltrexone	1.7 x 10^{-7}	unchanged
After UM 979	9.1 x 10^{-9}	unchanged

Naltrexone slightly increased the slope of the concentration-effect curve.

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN MOUSE VAS DEFERENS

	EC 50 (M)	Maximum Response (%)
Drug alone	2.8 x 10^{-8}	95.3
After naltrexone	1.4 x 10^{-7}	unchanged
After UM 979	4.4 x 10^{-8}	unchanged

UM 106
UM 1262 NIH 4591 DEXTRORPHAN



d-3-Hydroxy-N-methyl-morphinan tartrate

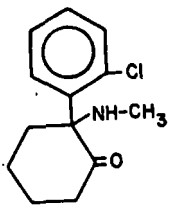
DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC 50 (M)	1.8×10^{-5}	1.4×10^{-5}	1.32

OBSERVATIONS IN MORPHINE-DEPENDENT RHESUS MONKEYS

Doses tested: 3.0 to 10.0 mg/kg, s.c.
SDS: Dextrorphan neither suppressed nor exacerbated withdrawal signs in the monkey but produced marked ataxia and decreased responsivity to external stimulation. See UM 1264.

UM 1263 KETAMINE



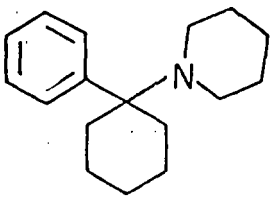
dl-2-(o-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride

OBSERVATIONS IN MORPHINE-DEPENDENT RHESUS MONKEYS

Doses tested: 1.0 to 5.6 mg/kg, s.c.
SDS: Retamine neither suppresssed nor exacerbated withdrawal signs in the monkey but produced marked ataxia with decreased responsivity to stimulation from observers. See UM 1264.

UM 1264 NIH 9580 MCV 4158 PHENCYCLIDINE

MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate:
Nilsen:

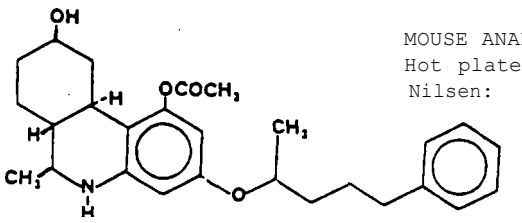


1-(1-Phenyclohexyl) piperidine
hydrochloride

OBSERVATIONS IN MORPHINE-DEPENDENT RHESUS MONKEYS

Doses tested: 0.1 to 0.56 mg/kg, s.c.
SDS: Phencyclidine neither suppressed nor. exacerbated withdrawal signs in the monkey but produced marked ataxia and decreased responsivity to stimulation from observers. Phencyclidine was about ten times more potent than ketamine and thirty times more potent than dextrorphan in producing these effects.

UM 1265 NIH 9596 MCV 4161 LEVONANTRADOL



MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: 0.15 (0.13 - 0.19)
Nilsen:

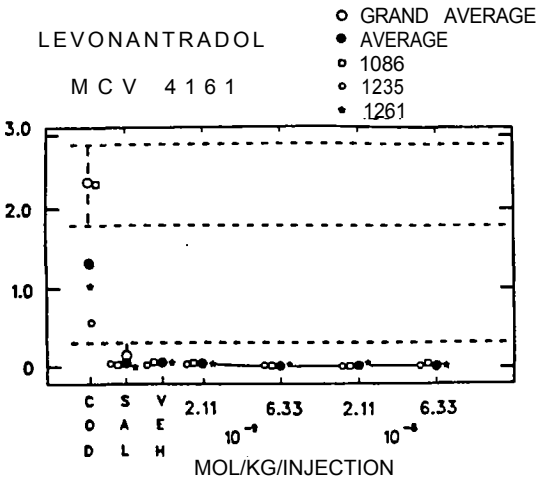
(-)-trans-5,6,6aß,7,8,9,10aα-Octahydro-1-acetoxy-9ß-hydroxy-6ß-methyl-3-(5-phenyl-2-pentyloxy)phenanthridine hydrochloride

OBSERVATIONS IN MORPHNE-DEPENDENT RHESUS MONKEYS

Doses tested: 0.03 to 0.56 mg/kg, s.c.

SDS: Levonantradol produced neither overall suppression nor exacerbation of withdrawal signs in the monkey although there was relaxation of the abdominal musculature that is typically contracted during morphine withdrawal. Other effects included ataxia, ptosis and pupil dilation. At doses of 0.3 and 0.56 mg/kg, onset of action was definite by one hour following injection. Levonantradol was approximately twice as potent as UM 1266 (nabilone) and about ten times as potent as UM 1270 (Δ^9-tetrahydrocannabinol).

DRUG SELF-ADMINISTRATION IN RHESUS MONKEYS



Across the range of doses studied, levonantradol did not maintain responding (self-administration).

PRIMARY DEPENDENCE STUDY

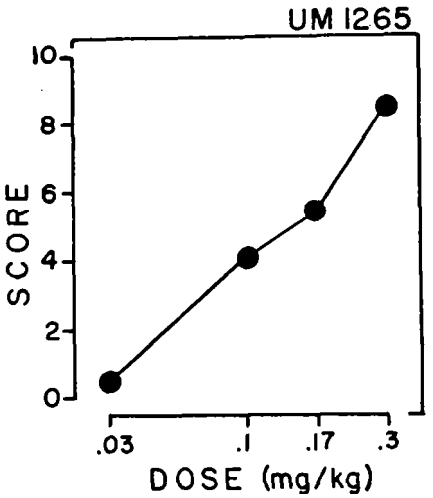
Animals. Rhesus monkeys numbered 279, 347, and 392 were used. Throughout the study their weights changed less than five percent of their predrug values and none of the monkeys showed any apparent ill-effects from the drug.

Dosage schedule. The drug was suspended in a mixture of emulphor, ethanol (95%) and distilled water, and administered subcutaneously every six hours. The starting dose was 0.17 mg/kg/6 hr and was incremented as follows:

Day	Dose (mg/kg/6 hr)
1	0.17
4	0.3
6	0.56
9	1.0
10	1.7
15	3.8
17	5.6
19	10.0

On day 14 the subjects were tested for precipitation of withdrawal signs with nalorphine and were tested with naloxone on days 16 and 21. On the thirtieth day the drug administrations were discontinued. Additionally subjects were tested on days 20 through 30 for cross tolerance to morphine, UM 1072, Δ^{9}-THC, and UM 1266 (nabilone).

Acute effects. Administration of UM 1265 caused marked effects characterized by ptosis, dozing, pupil dilation, ataxia and a reduced responsivity to stimulation from observers and cagemates. Each of these signs was given a score of 0, 1 or 2 depending on whether the sign was absent, present, or present to a marked degree, respectively. A composite score for drug effect then ranged from zero to ten. As can be seen in the figure, over a one log unit range of doses, effects ranged from near zero to 10. The ED 50 for these effects was appoximately 0.13 mg/kg.

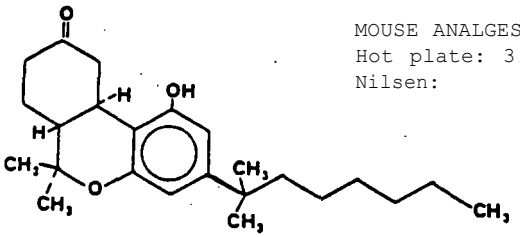


Chronic effects. Upon repeated administration of UM 1265 effects decreased. Initially, some of the effects could be recaptured with dosage increments (up to 1.7 mg/kg), however, once tolerance developed to effects of 1.7 mg/kg, further increases in dose had virtually no effects at all. Doses as high as 100.0 mg/kg had virtually no effect in subjects receiving 10.0 mg/kg/6 hrs. Additionally in those subjects, normally effective doses of Δ^9-THC and UM 1266 were without effect. In contrast there was minimal, if any, cross tolerance to the effects of morphine and UM 1072. Some tolerance to effects of UM 1265 lasted 6 weeks after the discontinuation of drug treatment.

Dependence. Neither nalorphine nor naloxone administration precipitated clear withdrawal signs in these subjects. Upon abrupt discontinuation of UM 1265 there was some irritability due to handling of the subjects and sane latency above normal to eat food at daily feeding time. Marked signs similar to those of narcotic withdrawal were not observed.

Summary. Chronic administration of UM 1265 produced a marked degree of tolerance to its effects such that doses about 1000 times the original ED 50 had no ef feet. Additionally cross-tolerance was conferred to Δ^9-THC and UM 1266, but not to morphine or UM 1072. Moreover, neither the administration of narcotic antagonists nor discontinuation of the drug resulted in any clear signs of withdrawal.

UM 1266 NIH 9872 MCV 4228 NABILONE



MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: 3.6 (2.5 - 5.2)
Nilsen:

dl-trans-3-(1-1-Dimethylheptyl)-6,6aß,7,8,10,10a α-hexahydro-1-hydroxy-6,6-dimethyl-9H-dibenzo[b,d]pyran-9-one

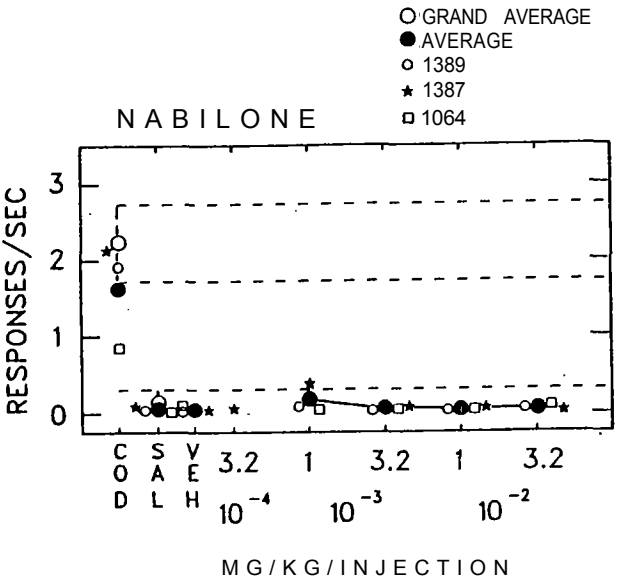
OBSERVATIONS IN MORPHINE-DEPENDENT RHESUS MONKEYS

Doses studied: 0.01 to 1.0 mg/kg, s.c.

SDS: Nabilone produced neither overall suppression nor exacerbation of withdrawal signs in the monkey although there was occasional relaxation of the abdominal musculature that is contracted during morphine withdrawal. Other effects included pupil dilation, ptosis, ataxia and some decreased responsivity to stimulation from observers. At doses of 0.3 and 1.0 mg/kg the onset of action occurred at 3 hrs.

SELF-ADMINISTRATION IN RHESUS MONKEYS

SELF-ADMINISTRATION IN RHESUS MONKEYS



Across the range of doses studied (3.2×10^{-4} to 3.2×10^{-2} ms/kg/inj), nabilone did not maintain responding (self-administration).

PRIMARY DEPENDENCE ESTUDY

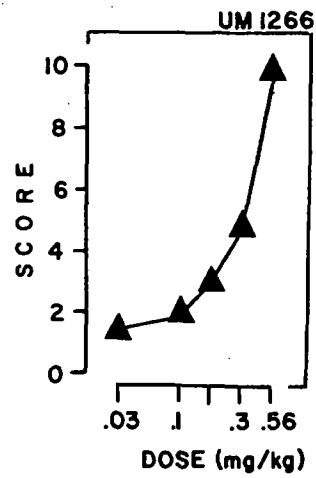
Animals. Rhesus monkeys numbered 115-A and 334 were used. Initially both monkeys lost weight (115-A to a greater extent than 334) but gained all (334), or most (115-A) of it back by the end of the study. Both monkeys also developed abscesses at injection sites and additionally developed scrotal edema. The abscesses and edema may have been due to the vehicle.

Dosage schedule. The drug was suspended in a mixture of Tween 80, alcohol (95%), and distilled water, and administered subcutaneously. At higher doses little or no water was used in the vehicle. The starting dose was 0.3 mg/kg every 12 hrs since the drug has a slow onset and long duration of action. on the third day, and thereafter, injections were given every 6 hrs. The increments in dosage were as follows:

Day	Dose (mg/kg)
1	0.3 (every 12 hrs)
3	0.3 (every 6 hrs)
5	0.53 (every 6 hrs)
6	1.0 (every 6 hrs)
13	1.7 (every 6 hrs)
16	3.0 (every 6 hrs)
17	5.6 (every 6 hrs)
18	10.0 (every 6 hrs)
20	17.0 (every 6 hrs)
21	30.0 (every 6 hrs)

On days 15 and 22 the subjects were tested for precipitation of withdrawal with naloxone administration. On the thirtieth day drug administrations were discontinued. Additionally on days 24 through 30 subjects were tested for cross tolerance to morphine, UM 1072, Δ^9-THC and UM 1265 (levonantradol).

Acute effects. Administration of UM 1266 caused marked effects characterized by ptosis, dozing, pupil dilation, ataxia and a reduced responsivity to stimulation from observers and cagemates. Each of these five signs was scored as either 0, 1, or 2 depending on whether the sign was absent, present, or present to a marked degree, respectively. A composite score for drug effect than ranged from zero to ten. As can be seen in the figure, the dose-effect curve was steep and varied from near zero-to 10 within about a single log unit range of doses. The ED 50 for these effects was approximately 0.24 mg/kg.

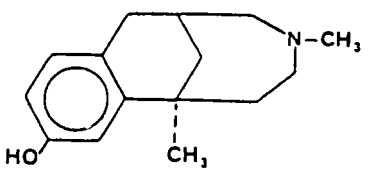


Chronic effects. Upon repeated administration of UM 1266 effects decreased. Initially sane effects could be recaptured by 1/4 log unit increments in dose, however, beyond a dose of 1.7 mg/kg (day 13) further dose increments had no effects on the scored signs. Although these signs were absent, the subjects did not look canpletely normal. They had a general appearance of malaise and were often observed to be lying prostrate on the cage floor. Usually when lying prostrate they could be aroused by the observer. Doses as high as 170 mg/kg of UM 1266 had virtually no effect in monkeys receiving 30 mg/kg/6 hrs. Additionally in those subjects, normally effective doses of Δ^9-THC and UM 1265 were without effect. In contrast there was minimal, if any, cross tolerance to morphine and UM 1072.

Dependence. With administration of naloxone there was no indication of precipitation of any withdrawal signs; neither was there indication of withdrawal signs upon discontinuation of UM 1266. Subjects spent most of the time huddled on their perch and there was some hindlimb rigidity and some perinasal redness. Effects on posture and movement may have been due to the scrotal edema that developed.

Summary. Chronic administration of UM 1266 produced a marked degree of tolerance such that doses about 1000 times an effective dose in normal subjects were without effect. Additionally cross-tolerance was conferred to effects of Δ^9-THC and UM 1265, but not to morphine or UM 1072. Finally, neither the administration of naloxone nor discontinuation of drug treatment resulted in clear signs of withdrawal.

UM 1267 NIH 9612 MCV 4167



MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: 0.49 (0.36 - 0.65)
Nilsen:

dl-9-Hydroxy-4,7-dimethyl-C-hanobenzanorphan hydrobromide

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC 50 (M)	5.4×10^{-6}	3.6×10^{-6}	1.51

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN GUINEA-PIG ILEUM

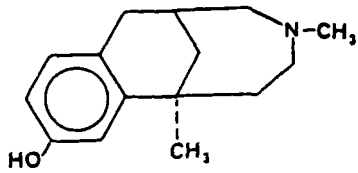
UM 1267 did not inhibit the twitch of this preparation. At a concentration of 10^{-9} M it increased the magnitude of the twitch and at concentrations of 3×10^{-5} M and higher it increased baseline tension.

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN MOUSE VAS DEFERENS

	EC 50 (M)	Maximum Response (%)
Drug alone	6.1×10^{-7}	68.7
After naltrexone	6.8×10^{-9}	unchanged
After UM 979	4.0×10^{-8}	decreased

Concentrations of UN 1267 alone greater than 3×10^{-5} M produced increases in baseline tension.

UM 1268 NIH 9613 MCV 4168



MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: 2.4 (1.4 - 4.3)
Nilsen:

(+)-9-Hydroxy-4,7-dimethyl-C-hanobenzomorphan hydrobromide

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC 50 (M)	9.7×10^{-6}	3.2×10^{-6}	3.05

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN GUINEA-PIG ILEUM

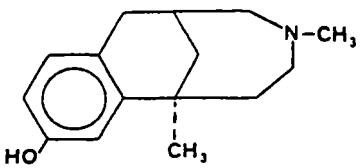
UM 1268 did not inhibit the twitch of this preparation. At concentraton of 3 x 10^{-9} M and greater the magnitude of the twitch was increased. At concentrations of 10^{-5} M and higher the baseline tension was increased. Neither naltrexone nor UM 979 had any effect on the response to UM 1268.

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN MOUSE VAS DEFERENS

	EC 50 (M)	Maximum Response (%)
Drug alone	2.7 x 10^{-7}	34.4
After naltrexone	3.0 x 10^{-5}	unchanged
After UM 979	1.2 x 10^{-6}	unchanged

Concentrations of UM 1268 alone greater than 10^{-4} M produced increases in the magnitude of the twitch as well as increases in baseline tension.

UM 1269 NIH 9614 MCV 4169



MOUSE ANALGESIA, ED 50 (mg,kg)
Hot plate: 2.5 (1.9 - 3.3)
Nilsen: 13.0 (9.6 - 17.7)

(-)-9-Hydroxy-4,7-dimethyl-C-homobenzomorphan hydrobromide

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC 50 (M)	4.8 x 10^{-6}	3.8 x 10^{-6}	1.27

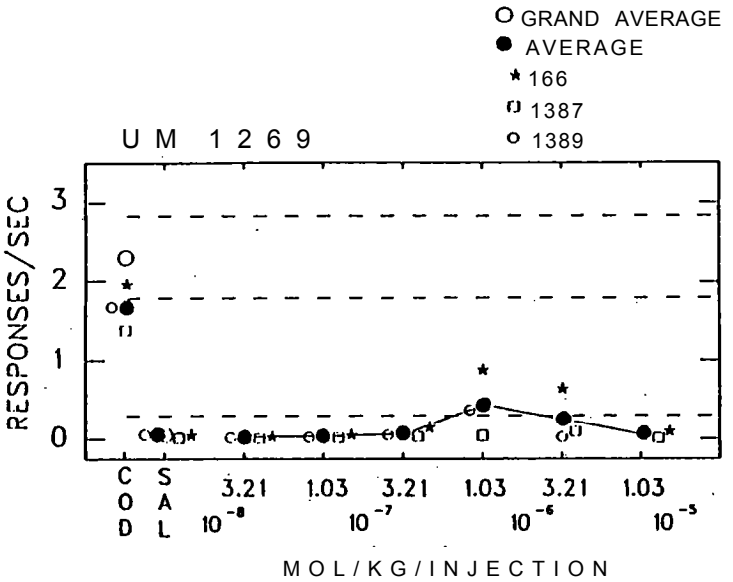
INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN GUINEA-PIG ILEUM

	EC 50 (M)	Maximum response (%)
Drug alone	2.5 x 10^{-6}	82.0
After naltrexone	2.5 x 10^{-7}	unchanged
After UM 979	unchanged	unchanged

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN MOUSE VAS DEFERENS

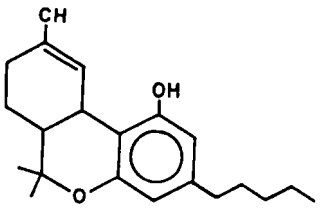
Over a range of concentrations from 10^{-9} M to 3 x 10^{-4} M, UM 1269 did not inhibit the twitch of this preparation. At 10^{-6} M, UM 1269 failed to reverse the inhibitory effect of morphine (10^{-9} M to 3 x 10^{-4} M).

DRUG SELF-ADMINISTRATION IN RHESUS MONKEYS



Responding was maintained at rates only marginally above saline and at only one dose (0.3 mg/kg/inj). The maximal percentage of the codeine-maintained response rate at that dose was 26. Following the administration of 20 mg/kg, i.v., subjects were sedated, occasionally dozed, and showed marked ataxia. Naloxone (0.32 mg/kg) failed to reverse these effects of UM 1269.

UM 1270 Δ^{9}-TETRAHYDROCANNABINOL



Δ^{9}-Tetrahydrocannabinol

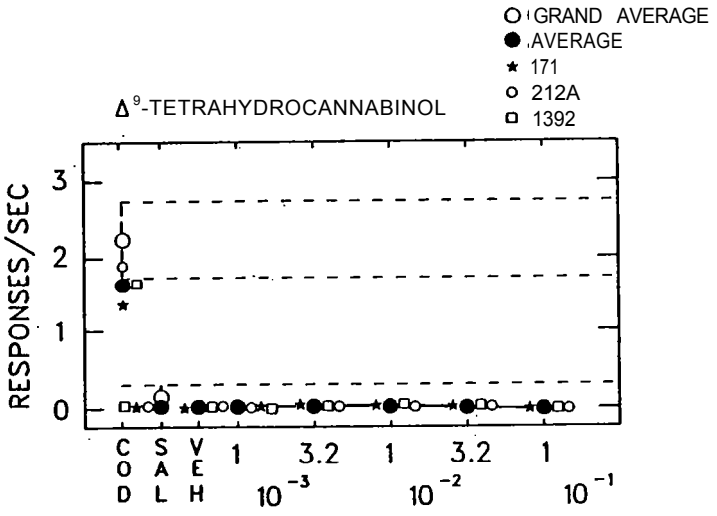
OBSERVATIONS IN MORPHINE-DEPENDENT AND NON-DEPENDENT RHESUS MONKEYS

Doses studied: 0.1 to 3.0 mg/kg, s.c.

SDS: Δ^{9}-Tetrahydrocannabinol neither suppressed nor exacerbated withdrawal signs in the rhesus monkey. Other effects included ataxia, ptosis, pupil dilation, dozing and decreased responsivity to stimulation from observers. At 3.0 mg/kg the onset of effect occurred by one hour after injection.

Nondependent subjects: Effects in normal subjects included: ataxia, pupil dilation, ptosis, dozing and decreased responsivity to stimulation from observers and ca emates. Compared to UM 1265 (levonantradol), Δ^{9}-THC was one-tenth as potent in producing these effects. The above effects were not reversed by naloxone (1.7 mg/kg, i.m.).

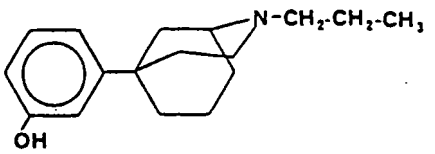
SELF-ADMINISTRATION IN RHESUS MONKEYS



Across the range of doses studied (1 x 10^{-3} to 1 x 10^{-1} mg/kg/inj, Δ^9-tetrahydrocannabinol did not maintain responding (self-administration).

UM 1273 NIH 9884 MCV 4241

MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: Incompletely active and toxic at 100 mg/kg
Nilsen: Inactive



(-)-5-(m -Hydroxyphenyl)-2-n-propylmorphan hydrochloride

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC 50 (M)	2.0×10^{-6}	4.2×10^{-6}	0.48

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN GUINEA-PIG ILEUM

	EC 50 (M)	Maximum Response (%)
Drug alone	6.3×10^{-4}	68.7

Both naltrexone and UM 979 produced an unsurmountable antagonism of the effects of UM 1273 up to a concentration of 10^{-4} M at which point a decrease in the amplitude of the twitch occurred which was accompanied by spontaneous contractions of the ileum.

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN MOUSE VAS DEFERENS

UM 1273 produced a slight (less than 10%) decrease in twitch starting at a concentration of 10^{-7} M. At 3×10^{-6} M and higher concentrations there was an increase in magnitude of the twitch without a change in baseline tension. These responses to UDM 1273 were not altered by naltrexone or UM 979.

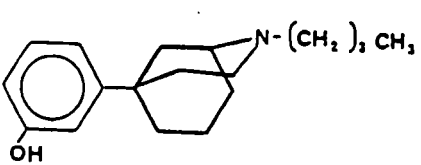
OBSERVATIONS IN MORPHINE-DEPENDENT RHESUS MONKEYS

Doses tested: 1.0 to 3.0 mq/kg, s.c.
NW: UM 1273 precipitated withdrawal with 0.006 times the potency of naloxone.

SUMMARY

See UM 1276.

UM 1274 NIH 9885 MCV 4242



MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: Incompletely active and convulsive at 50 mg/kg
Nilsen: Inactive

(-)-2-n-Butyl-5-(m-hydroxyphenyl)morphan hydrochloride

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC 50 (M)	6.3×10^{-7}	1.8×10^{-6}	0.35

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN GUINEA-PIG ILEUM

	EC 50 (M)	Maximum Response (%)
Drug alone	3.3×10^{-5}	83.7
After naltrexone	5.7×10^{-4}	unchanged
After UM 979	9.9×10^{-4}	unchanged

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN MOUSE VAS DEFERENS

UM 1274 did not inhibit the twitch of this preparation. At 10^{-5} M there was an increase in the magnitude of the twitch which was not altered by either naltrexone or UM 979.

OBSERVATIONS IN MORPHINE-DEPENDENT AND NON-DEPENDENT RHESUS MONKEYS

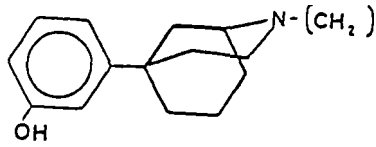
Doses studied: 1.0 to 5.6 mg/kg, s.c.
NW: UM 1274 precipitated withdrawal with one-hundredth the potency of naloxone.

SUMMARY

See UM 1276

UM 1276 NIH 9894 MCV 4247

MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: Incanpletely active and convulsive at 50 mg/kg
Nilsen:



(+)-2-n-Hexyl-5-(m-hydroxyphenyl)morphan hydrochloride

DISPLACEMENT OF SPEREOSPECIFIC ^{3}H-ETORPHINE BIHDING

	+Na	-Na	+Na/-Na
EC 50 (M)	5.1×10^{-8}	1.2×10^{-7}	0.43

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN GUINEA-PIG ILEUM

	EC 50 (M)	Maximum Response (%)
Drug alone	2.5×10^{-5}	100.0
After naltrexone	unchanged	unchanged
After UM 979	unchanged	unchanged

The complete inhibition of the twitch of this preparation with UM 1276 occcurred at a very high concentration (10^{-4} M) and did not appear to be mediated by narcoticmsns.

INHIBITION OF TWITCH ELECTRICALLY-DRIVEN MOUSE VAS DEFERENS

UM 1276 produced a slight (less than 10%) inhibition of the twitch of this preparation at 3×10^{-9} M. At concentrations of 10^{-6} M and greater the magnitude of the twitch was increased.

OBSERVATIONS OF MORPHINE-DEPENDENT RHESUS MONKEYS

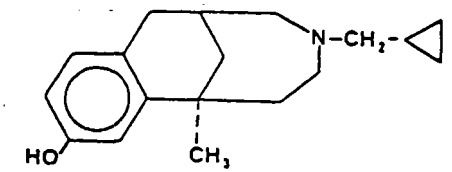
Doses studied: 0.3 to 5.6 mg/kg, s.c.
NW: UM 1276 precipiated withdrawal with one-thirtieth the potency of naloxone.

SUMMARY

UM 1273, UM 1274, and UM 1276 represent a novel set of phenylmorphan narcotic antagonists capable of precipitating withdrawal in the morphine-dependent monkey. As the alkyl chain length is increased from three to seven carbons, antagonist potency increases as does affinity for the narcotic receptor. Each drug had low sodium ratio. Each compound also inhibited the twitch of the guinea-pig ileum. Increases in alkyl chain length were correlated with decreases in the ability of the antagonists, naltrexone and UM 979, to antagonize the actions of the phenylmorphans. The absence of narcotic agonist activity in the mouse vas deferens is an interesting feature of their spectrum of actions.

UM 1277 NIH 9901 MCV 4250

MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: Insufficient activity and convulsive at 50 mg/kg
Nilsen: Inactive at 50 mg/kg



dl-1-Methyl-4-cyclopropylmethyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methane-1H-4-benzazonine

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC 50 (M)	6.9×10^{-6}	5.9×10^{-6}	1.19

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN GUINEA-PIG ILEUM

At concentrations of 10^{-9} M to 3×10^{-5} M UM 1277 was inactive. At 10^{-4} M, UM 1277 increased the magnitude of the twitch.

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN MOUSE VAS DEFERENS

At 3×10^{-8} M, UM 1277 produced a slight (less than 10%) inhibition of the twitch. At 3×10^{-5} M, there was a large increase in the magnitude of the twitch. These effects were not altered by either naltrexone or UM 979.

OBSERVATIONS OF MORPHINE-DEPENDENT AND NON-DEPENDENT RHESUS MONKEYS

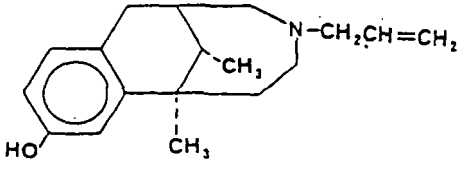
Doses studied: 0.3 to 3.0 mg/kg, s.c.
SDS: UM 1277 neither suppressed nor exacerbated withdrawal Signs. In addition the drug produced severe ataxia.
Nondependent subjects: Doses of either 1.0 or 1.7 mg/kg produced ataxia, pupil dilation, and decreased responsivity to observers and cagemates. These effects appeared to be partly antagonized by naloxone (1.7 mg/kg, s.c.

SUMMARY

See UM 1281.

UM 1280 NIH 9898 MCV 4249

MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: Insufficient activity; convulsions at 5.0 mg/kg
Nilsen: Inactive at 5.0 mg/kg



1,12α-Dimethyl-4-allyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1H-4-benzazonine

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC 50 (M)	3.4×10^{-6}	3.1×10^{-6}	1.09

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN GUINEA-PIG ILEUM

At concentrations between 3×10^{-6} M and 3×10^{-5} M, UM 1280 produced a small (less than 10%) inhibition of the twitch that was completely antagonized by either naltrexone or UM 979. At concentrations above 3×10^{-5} M, UM 1280 increased the amplitude of the twitch.

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN MOUSE VAS DEFERENS

UM 1280 did not inhibit the twitch at any concentration studied. At 10^{-6} M and greater, UM 1280 increased the amplitude of the twitch. Neither naltrexone nor UM 979 altered the response to UM 1280.

OBSERVATIONS IN MORPHINE-DEPENDENT AND NON-DEPENDENT RHESUS MONKEYS

Doses studied: 0.1 to 1.0 mg/kg, s.c.

SDS: UN 1280 neither suppressed nor exacerbated withdrawal signs in the monkey. Other effects included ataxia, pupil dilation and decreased responsivity to stimulation from observers.

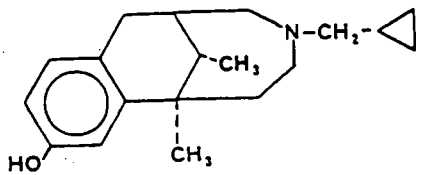
Nondependent subjects: UM 1280 produced ataxia, pupil dilation and decreased responsivity to external stimuli. These signs were not reversed by 1.7 mg/kg naloxone, s.c.

SUMMARY

See UM 1281.

UM 1281 NIH 9902 MCV 4251

MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: No dose response
Nilsen: Inactive at 50 mg/kg



1,12$^{\alpha}$-Dimthyl-4-cyclopropyl,mthyl hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1H-4-benzanine

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC 50 (M)	3.8×10^{-6}	3.6×10^{-6}	1.05

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN GUIEA-PIG ILEUM

UM 1281 was inactive up to a concentration of 3 x 10^{-6} M where it produced a small (less than 5%) inhibition of the twitch. Both naltrexonee and UM 979 completely blocked this effect. At concentrations of 10^{-5} M and higher the magnitude of the twitch was increased.

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN MOUSE VAS DEFERNS

At no concentration did UM 1281 decrease the magnitude of the twitch. At concentrations of 3 x 10^{-6} M and higher, the magnitude of the twitch was. increased without changes in baseline tension. Neither naltrexone nor UM 979 altered the response to UM 1281.

OBSERVATIONS IN MORPHINE-DEPENDENT AND NON-DEPENDENT RHESUS MONKEYS

Doses studied: 1.0 to 3.0 mg/kg, s.c.

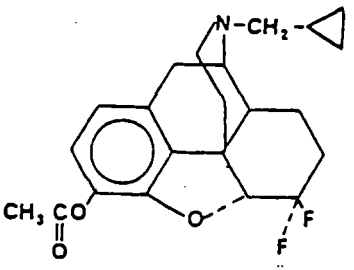
SDS: UM 1281 neither suppressed nor exacerbated withdrawal signs in the monkey but produced other effects including: ataxia, pupil dilation, ptosis, and reduced responsivity to external stimuli.

Nondependent subjects: UM 1281 produced ataxia, pupil dilation, salivation, ptosis, and decreased responsivity to external stimuli. There was a partial reversal of these effects by 1.7 mg/kg s.c., naloxone.

SUMMARY

UM 1277, UM 1280, and UM 1281 are interesting structural analogs of cyclazocine and SKF-10,047 with decreased affinity for the opiate receptor and an elimination of antagonist action.

UM 1322 NIH 9874 MCV 4230



MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: No dose response
Nilsen: 19.8 (12.9 - 30.2)

17-cyclopropylmethyl-4,5α-epoxy-
6,6-difluoro-3-acetoxymorphinan

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC 50 (M)	2.1×10^{-9}	4.2×10^{-9}	0.50

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN GUINEA-PIG ILEUM

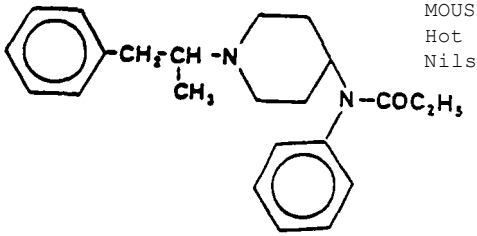
	EC 50 (M)	Maximum Response (%)
Drug alone	2.6×10^{-9}	45.9
After naltrexone	2.2×10^{-7}	unchanged
After UM 979	2.0×10^{-8}	22.9

At concentrations of 3×10^{-5} M and higher, UM 1322 increased the magnitude of the twitch.

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN MOUSE VAS DEFERENS

UM 1322 did not decrease the magnitude of the twitch; at concentrations of 3×10^{-6} M and higher, the magnitude was increased. Neither naltrexone nor UM 979 altered the response to UM 1322.

UM 1324 NIH 9961 MCV 4287 CHINA WHITE



MOUSE ANALGESIA, ED 50 (mg/kg)
Hot plate: 0.006 (0.004 - 0.009)
Nilsen:

1-(-Methyl-2-phenylethyl)-4-(N-propranilido)piperidine hydrochloride

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC 50 (M)	4.2×10^{-8}	2.3×10^{-8}	1.80

UM 1324 was unusual in that the slope of its concentration-displacement curve was lower than most compounds that have been studied. The heterogeneous log probit plot makes it impossible to given exact EC 50 values.

INHIBITION OF TWITCH OF ELECTRICALLY-DRIVEN GUINEA-PIG ILEUM

	EC 50 (M)	Maximum Response (%)
Drug alone (1)	9.0×10^{-12}	61.6
Drug alone (2)	3.1×10^{-7}	89.6 (28% further)
After naltrexone	1.5×10^{-7}	unchanged
After UM 979	6.2×10^{-8}	unchanged

UM 1324 was unusual in that it had two inhibitory effects the first producing a 61.6 percent inhibition of the twitch and the second, at higher concentrations, producing a further 28% inhibition of the twitch. The results with the antagonists suggest that they virtually abolish the inhibitory effects obtained at low concentrations of UM 1324 but leave the effects of higher concentrations unchanged.

INHIBITION OF TWITCH ELECTRICALLY-DRIVEN MOUSE VAS DEFERENS

	EC 50 (M)	Maximum Response (%)
Drug alone	7.5×10^{-10}	100
Drug naltrexone	5.6×10^{-8}	unchanged

After UM 979 2.2×10^{-9} unchanged

Both antagonists decreased the slope of the concentration-effect curve.

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REFERENCES

Aceto, M.D., Harris, L.S., Dewey, W.L., and May, E.L. Annual Report: Dependence studies of new compounds in the rhesus monkey (1980). In: Harris, L.S., ed. Problems of Drug Dependence: 1980. National Institute on Drug Abuse Research Monograph 34. DHHS publication number (ADM)81-1058. Washington, D.C.: Supt. of Documents, U.S. Govt. Print. Off. 1981. pp. 297-326.

Atwell, L. and Jacobson, A.E. The search for less harmful analgesics. Lab. Animal 7, 42-47, 1978.

Deneau, G.A. and Seevers, M.H. Evaluation of new compounds for morphine-like physical dependence capacity. Proceedings of the Twenty-fifth Annual Meeting, Committee on Problems of Drug Dependence, NAS. 1963. Addendum 25.

Eddy, N.B. and Leimbach, D. Synthetic analgesics. II. Diethienyl-butenyl- and diethienylbutylamines. J. Pharmacol. Exp. Ther., 107, 385-393, 1953.

Jacobson, A.E. and May E.L. Structures related to morphine, XXI, 2' substituted benzomorphans. J. Med. Chem., 8, 563-566, 1965.

Martin, W.R., Eades, C.G., Thompson, J.A., Huppler, R.E. and Gilbert, P.E. The effects of morphine- and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. J. Pharmacol. Exp. Ther., 197, 517-532, 1976.

Perrine, T.D., Atwell, L., Tice, I.B., Jacobson, A.E., and May, E.L. Analgesic activity as determined by the Nilsen method. J. Pharm. Sci., 61, 86-88, 1972.

Simon, L.D., Simon, F.R., Mohasci, E., Berger, L., and Simon, E.J. Effect of the position of the phenolic group in morphinans on their affinity for opiate receptor binding. Life Sci., 28, 2769-2772, 1981.

Smith, C.B. Actions of furyl benzomorphan derivatives upon the isolated mouse vas deferens. In: van Ree, J.M. and Terenius, L., eds. Characteristics and Functions of Opiods. Amsterdam: Elsevier, 1978. pp. 237-238.

Smith, C.B. and Sheldon, M.I. Effects of narcotic analgesic drugs on brain noradrenergic mechanisms. In: Kosterlitz, H.W., Collier, H.O.J., and Villarreal, J.E., eds., Agonist and Antagonist Actions of Narcotic Analgesic Drugs. Baltimore: University Park Press, 1973. pp. 164-175.

Swain, H.H., Fly, C.L., Woods, J.H., Snith, C.B. and Medzihradsky, Annual Report, 1978. Proceedings of the Fortieth Annual Meeting, Committee on Problems of Drug Dependence, Inc. 1978. pp. 644-666.

Valentino, R.J., Smith, C.B., and Woods, J.H. Physiological and behavioral approaches to the study of the quasi-morphine withdrawal syndrome. Fed. Proc., 40, 1502-1507.

Villarreal, J.E. The effects of morphine agonists and antagonists on morphine-dependent rhesus monkeys. In: Kosterlitz, H.W., Collier, H.O.J., and Villarreal, J.E., eds. Agonist and Antagonist Actions of Narcotic Analgesic Drugs, Baltimore: University Park Press, 1973. pp. 73-93.

Woods, J.H. Narcotic-reinforced responding: A rapid screening procedure. Proceedings of the Thirty-ninth Annual Meeting, Committee on Problems of Drug Dependence, NAS-NRC, 1977. pp. 420-437.

Woods, J.H. Narcotic-reinforced responding: A rapid evaluation procedure. Drug and Alcohal Dependence, 5, 223-230, 1980.

Woods, J.H., Smith, C.B., Medzihradsky, F., and Swain, H.H. Preclinical testing of new analgesic drugs. In: Beers, R.F. and Bassett, E.G., eds., Mechanisms of Pain and Analgesic Compounds. New York: Raven Press. pp. 429-445.

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Papers Read by Title but not Presented

Use of Contingency Contracts in Specialty Clinics for Cocaine Abuse

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ABSTRACT

Animal research reveals that cocaine is a highly reinforcing drug, and patients &scribe it as "compelling"; the drug maintains vigorous self-administration behavior in animals and humans despite its clear adverse effects. This suggests that the drug is very difficult for experienced users to give up. It further suggests a need for vigorous treatment to produce and maintain abstinence, thus permitting patients to relearn drug-free behaviors which are alternative to continued cocaine use.

This 12-month pilot study aimed to determine 1) whether cocaine abusers would enter and remain in treatment, and 2) whether contingency contracts appear to complement standard clinical treatment in initiating and maintaining abstinence. We established cocaine clinics in Denver and Aspen. Of the first 67 patients admitted into those clinics, 32 (48 percent) elected to utilize contingency contracts. Thirty-one of those completely abstained from cocaine use during the treatment. Of the 35 patients who did not elect to use contingency contracts, no one remained abstinent and in treatment for more than four weeks. The results indicate that cocaine abusers will enter treatment, and that contingency contracting may contribute to a favorable outcome.

INTRODUCTION

This pilot study demonstrates that users of a very popular and highly reinforcing drug can be attracted into treatment, and it suggests that contingency contracts may help these patients to abstain from the drug.

Cocaine abuse has become a significant clinical problem in Colorado. A 1979 Colorado survey estimated that cocaine had been consumed at least once in the previous year by 5.5 percent of the 12-and-older population (Booth, 1979). Seven percent had used cocaine in the Denver metropolitan area, and 26 percent had used

the drug during the previous year in the region of the major ski resorts. Of these Colorado users, over 75 percent reported moderate to severe problems related to their use. CODAP reports that 4.4 percent of 1980 (January-September) admissions to drug abuse programs nationwide were cocaine abusers; as compared to 1.7 percent in 197% Colorado cocaine admissions were 14.0 percent, and in the Denver area they were 18.2 percent (NIDA, 1980). Denver had the highest incidence of cocaine admissions of all cities reporting; Miami was second highest with 12 percent.

Nationally, a trend of increasing cocaine abuse is also evident. In 1975 CODAP reports (Thomas Coughlin, NlDA, personal communication, April 1981 that there were 2,195 patients admitted to treatment for cocaine abuse; in 1980 that figure rose to 11,110 (an increase of 500%). The 1979 national survey on drug abuse (Miller, Cisin, 1979) indicated that 28 percent of young adults had used cocaine at some time in their lives as opposed to approximately 3 percent in 1967. Moreover, about 46 percent now feel that they have an opportunity to use this drug, as opposed to approximately 6 percent in 1967. Thus, exposure to cocaine is quite common--a worrisome trend if the drug is likely to be repeatedly self-administered by those exposed to it.

Cocaine does vigorously reinforce self-administration behavior in animals, with dire consequences for the organism. Deneau et al. (1969) demonstrated that monkeys with unlimited access to cocaine overdosed and died within 30 days. Similarly, Wilson (1970), Pickens and Thompson (1968), Woods and Schuster (1968), and Goldberg and colleagues (1970, 1979a, 1979b, 1976) demonstrated that cocaine potently reinforced self-administration behavior. There is some evidence that certain monkeys which fail to self-administer opioids or amphetamine-like drugs will work for cocaine injections (Young, Woods, 1980).

The potency of cocaine as a reinforcer of self-administration behavior suggests that patients might be unlikely to seek abstinence-directed treatment for cocaine abuse before they suffer severe consequences, and it further suggests that during treatment patients might have difficulty in remaining abstinent. Moreover, medical treatments comparable to methadone maintenance are not available for cocaine abuse; studies of lithium blockade of the cocaine high (Resnick, et al., 1977; Cronson and Flemenbaum, 1978) have not supported the initial optimism with which this treatment was recommended. Although there is some reason to believe that alpha-methylparatyrosine might reduce stimulant self-administration (pickens, et al., 1968), this drug probably is not safe enough for wide clinical use. Therefore, it seems especially important to develop psychological techniques for treating cocaine abuse. But we are unable to find any controlled research assessing the efficacy of psychological interventions for this problem.

The behavior of drug ingestion, like other behaviors, appears to occur more or less often depending upon the events which regularly follow it. The frequency of the behavior is controlled by the

consequences of the behavior (Skinner, 1954). An agreement between a patient and therapist to change drug abuse behavior by having the therapist deliver certain consequences, or "contingencies" upon drug use is termed "contingency contracting". The usefulness of contingency management procedures has been demonstrated for a variety of behavior settings and circumstances, for example, abstinence from smoking (Elliott, and Tighe, 1968; Winett, 1973), drug use (Liebson et al., 1973, 1978; Baldridge et 1974; Stitzer et al., 1977, 1979a, 1979b; Yen, 1974; Hall et al., 1977: Bigelow et at., 1976, 1980) and alcohol use (Miller,-1974, 1975; Cohen et al., 1971; Griffiths, 1978; Bigelow et al., 1975; Hunt and Azain, 1973). These numerous controlled reports have been done in hospitalized research subjects, or in small numbers of patients using, for example, ABA designs. Boudin (1972) and Boudin et al. (1977) also report application of these techniques to a general population of drug users in a substance abuse clinic.

The present pilot study examined the hypotheses that cocaine abusers, despite the reinforcing properties of the drug, could be drawn into treatment and that outpatient contingency contracting could be useful in securing abstinence.

METHODS

We established cocaine clinics in Denver and Aspen. Patients were recruited through news media, professional referrals and educational presentations. Persons over the age of 18 with a DSM III (American Psychiatric Association, 1980) diagnosis of cocaine abuse were eligible for admission. We excluded individuals who consistently were psychotic or who had a previous history of schizophrenia, manic-depressive illness, or chronic organic brain syndrome.

All patients were offered standard clinical treatment and the additional option of using contingency contracts as an adjunct to therapy. Standard treatment was: 1) brief hospitalization if indicated; 2) psychological, and, as indicated, medical evaluation; 3) weekly individual psychotherapy; 4) family and couples therapy as is standard in our clinics; 5) urine collection and analysis; 6) education and consultation; 7) interagency referral; and 8) after care/follow up. Contingency contracts included two basic elements: 1) agreement to participate in a urine monitoring program, and 2) attachment of an aversive contingency to either a cocaine-positive urine report or a failure to produce a scheduled urine sample. Aversive contingencies were derived from patients' own statements of the adverse consequence which they expected to result from continued cocaine use. In order to make that adverse effect a more potent deterrent to drug use, we used the contract to "reschedule" (Kelleher, Goldberg, 1976) the adverse effect to occur at the very next use of cocaine.

The following case report illustrates our method.

Case

A 33-year-old married white male Certified Public Accountant (CPA) injected 3-5g of cocaine daily for 18 months. He had spent about $100,000 on cocaine. His wife threatened divorce if he didn't abstain, and when he entered treatment she was planning to leave him. His independent business was failing because of the patient's inability to concentrate, poor memory, mood fluctuations, and binges with failure to produce promised work, and because of significant debts and embezzelment of company funds. The patient anticipated losing his house, land, and business. His mood was extremely &pressed; affect was blunted. His paranoid thinking persisted beyond each cocaine intoxication. He expressed feelings of guilt, remorse and suicidal ideation. In sum, he stated that the risks of continued cocaine use included career, financial, family, and personal loss.

Although these risks and impairments were obvious to the patient, he still was ambivalent about giving up the drug because he "loved it" and "needed it". He had made several attempts to abstain in order to avoid impending loss, but each time he had resumed using the drug within two weeks.

He now was convinced that he had to abstain and that he needed help to do so. He was sure that continued cocaine use would lead to eventual revocation of his CPA certification. We suggested that he write a letter to the State Board of Accountancy, explaining in the letter that he had been abusing cocaine, that he had entered a stringent outpatient program, but that he had failed to abstain (jeopardizing his professional performance), and that he therefore was surrendering his certification. He deposited this letter with us. In a written contract he directed us to collect frequent, random, observed urine samples for six months; the contract also directed us to mail the letter in the event of a cocaine-positive urinalysis or a failure to appear for a scheduled urine sample.

During a six-month period of abstinence the patient was engaged in regular individual psychotherapy and intermittent couples psychotherapy. He and his wife have negotiated terms for continuing their relationship and for relocating the family and business. Work productivity increased and the bulk of past-due debts were paid, thus avoiding foreclosure on his properties. Psychologically, the patient reports that symptoms of depression and paranoia are "much relieved". He states that he finds no loss associated with discontinued use of cocaine but recognizes numerous beneficial Changes. At the end of his six-month contract, the patient elected to utilize a contract for another six months to ensure "separation" from the drug. It appears that the reinforcement associated with an abstinent life may be exerting more control over his behavior than the reinforcement of cocaine self-administration.

Some patients believed that continued use would lead to arrests or other legal actions; they have written and deposited with us

letters informing the District Attorney or Drug Enforcement Administration of their drug use. Others have determined that jobs were at stake and have written and deposited with us letters informing their employers of cocaine use. Still other patients felt that continued use would lead to loss of income or loss of property; these patients directed us to transfer a large sum of money or a deed for property (deposited with us) to charities in case of resumed drug use. Each punishment was individually determined, based on the patient's assessment of those adverse consequences, unique to him or her, associated with continued use. Each contract was written for a specified period of several months and directed us to apply the adverse contingency if both halves of any divided urine sample (a protection against laboratory error) were cocaine-positive, or if the patient failed to appear for a scheduled urine test.

RESULTS

Our cocaine clinics admitted 67 patients in 12 months. The average age of the patients was 28.8 (R=19-42) years. Seventy-five percent of the patient population was male. Marital status included 42 percent single, 22 percent married, 27 percent divorced, and 9 percent separated. Most patients were employed (72 percent), and the mean educational level was 14.2 years. The group included two Blacks, one Chicano, and 64 non-Hispanic Whites. In general, this sample appeared to be more educated, more Anglo-White, and more affluent than our program's population of opioid users.

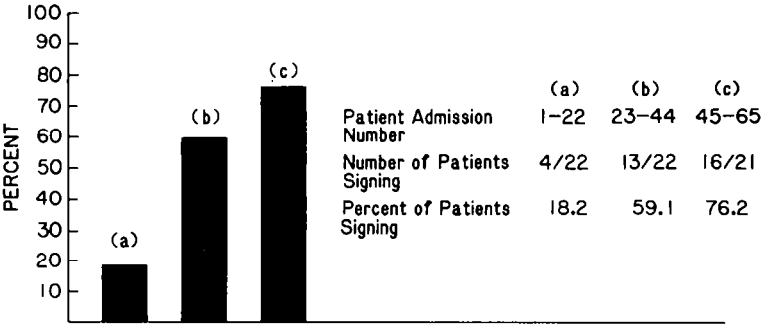
Our patients refer to cocaine with such comments as "I love it", "giving it up would be like losing my best friend", "it grabs me by the balls, and won't let go", and "it is the most compelling experience I have ever had". Such statements suggest the reinforcing ability of the drug, which drives continued self-administration despite the clear adverse effects reported by the patients, including: endangering of successful professional practices, auto accidents during intoxication, significant personal losses, expenditures for the drug up to $180,000 in six months, loss of business and property because of drug expenses, legal involvement, major psychological dysfunction (depression, delusions, hallucinations, and organic confusion), and physical effects including nasal and sinus problems, headaches, tremors, and seizures. Thus, this pilot project demonstrates that seriously dysfunctional patients will enter outpatient specialty clinics for the treatment of cocaine abuse, despite the very attractive qualities of this drug.

Thirty-two of these 67 patients entered contingency contracts with seriously punishing consequences, agreeing that the threat of a potent, immediate punishment would help to counter the drug's reinforcing effects, which compel repeated self-administration. Although 52 percent of our 67 patients refused contracts, Figure 1 illustrates that the percentage of patients signing contracts has increased from 18.2 percent of our first 22 patients to 76.2 percent of our last 21 patients.

FIGURE I

PERCENTAGE OF PATIENTS SIGNING CONTRACTS

(by consecutive admissions)



	(a)	(b)	(c)
Patient Admission Number	1–22	23–44	45–65
Number of Patients Signing	4/22	13/22	16/21
Percent of Patients Signing	18.2	59.1	76.2

Of the 32 patients with contracts, 31 have continued to produce cocaine-free urines, have appeared regularly for urinalysis, have regularly participated in psychotherapy sessions, and have not used cocaine. The 32nd patient did use cocaine, voluntarily told his employer of his drug use (this was the contingency), and immediately entered a residential treatment program. After discharge from the program, that patient signed another contingency contract with us and now remains abstinent in treatment. The profound reduction in cocaine use among this group of daily or almost-daily users suggests a powerful therapeutic effect associated with the contingency contracting procedure.

Patients who chose to use a contract could designate 1) whether to include drugs in addition to cocaine and 2) the duration of the contract period. The mode was three months; however, many of those who originally opted for three months requested extensions of an additional three months. Several patients have contracted to remain abstinent for a year. The duration of the contract and abstinence is typically three to six months.

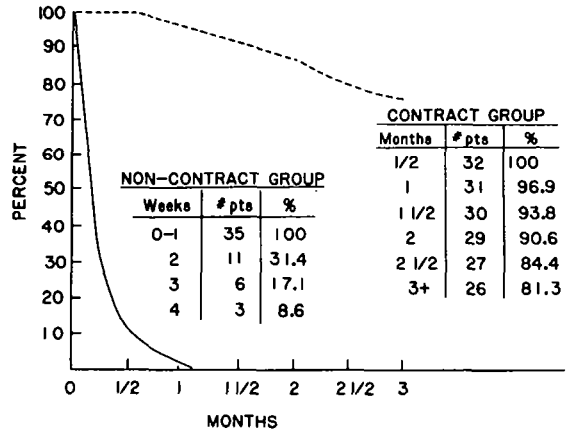
No one in the contract group left treatment prior to a mutual decision to terminate. Approximately 81 percent of the 32 patients who signed contracts remained in treatment and abstinent for three or more months. (See Figure 2.) Although there was only one "failure," two patients signed one- and two-month contracts, and three patients moved for reasons of employment. Of the patients who used contingency contracts as an adjunct to their treatment, five have been discharged by mutual agreement. One of these five patients returned to treatment because he had resumed cocaine use three months following discharge. Follow-up contacts indicate that the other four discharged patients remain abstinent for up to six months after treatment.

Thirty-five patients refused contracts. Twenty-nine of them dropped out of treatment within five visits most of these within one or two visits. Only 8.6 percent of the non-contract patients

remained in treatment and abstinent for four weeks. Of the patients who continued in treatment without a contract, the longest. duration of abstinence was four weeks and the longest duration in treatment was two months.

FIGURE 2

PERCENTAGE OF PATIENTS
REMAINING IN TREATMENT AND ABSTINENT



DISCUSSION

The first goal of this pilot project was to determine whether an outpatient specialty clinic could attract severely dysfunctional cocaine abusers. The project clearly succeeded in this effort.

Our second goal was to make a preliminary, open-design assessment of the apparent efficacy and safety of contingency contracting to secure abstinence in these patients. It appears from these results that among a group of daily or almost-daily cocaine users entering a specialty clinic, over 75 percent may agree to a properly presented contingency contract which provides severely punishing, individualized consequences for further cocaine use. Moreover, it appears that nearly all of those entering such a contract will abstain for a lengthy period of time while they engage in therapy aimed at promoting long-term abstinence. Our results further indicate that those who do not enter such a contract may have a much less favorable prognosis.

The clinical problem as we see it with these patients is to avoid early relapses which frequently result in termination from treatment; with the contracts, patients abstained and remained in treatment long enough for them to redevelop rewarding cocaine-incompatible behaviors which could then sustain choices for continued abstinence. We assisted patients in redeveloping cocaine-incompatible behaviors through counselling to increase contacts

with non-using friends, elimination of paraphernalia and drug stashes, termination of relationships with dealers, changing phone numbers or addresses (as needed) to stop drug-related calls and visits, counselling with spouses, and psychotherapy as needed around related problem areas in the patient's life.

Of course in this uncontrolled pilot project, self-selection may have affected outcome. Conceivably, patients who were more motivated to abstain also were more willing to sign the contingency contracts, resulting in more favorable outcomes among those who entered the contracts. Omly a controlled study with random assignment to contract vs. non-contract treatment groups can definitely settle this point. But there is an indication that self-selection is not the main factor determining the different outcomes in our clinic. We may assume that there were about equal proportions of well- and poorly-motivated patients in the first one-third, second one-third, and third one-third (Figure 1) of our admissions. Many more of our later patients, however, signed contracts, presumably because of our increasing skill at presenting the contracts. If motivation level had been the important determiner of outcome, outcome probably would have been similar in the three subgroups. But in fact, signing the contract seems to have been the important determiner; almost all signers abstained, and outcome in the three subgroups varied with each group's proportion of signers.

Despite the drastic nature of the contingency contracts, the risk/benefit ratio seems to be favorable; only one of the patients has undergone loss or embarrassment as a result of entering a contract, and the medical and psychological health of patients has improved considerably with sustained abstinence. However, controlled research still is needed to demonstrate definitively that the benefits do outweigh the risks in this drastic treatment, which does put patients at risk of loss or embarrassment.

References will be furnished upon request.

ACKNOWLEDEMENT

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A Comparison of Urine Collection Schedules with Different Predictability in a Methadone Clinic

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Urinalysis data are the most valid indicators of patients' actual drug use and as such can provide useful information to the clinician. Marks et al. (1969) and Nightingale et al. (1972) have suggested, that these data can also encourage client's abstinence from illicit drug use and symbolize the clinician's concern about the client's progress. Such data can also provide an important measure of treatment program efficacy. To achieve maximum validity observed urine specimens would have to be collected from every patient daily. That was actually done at many clinics in the early 1970's when methadone maintenance was a relatively new treatment for opiate abuse, but the cost in staff time and laboratory fees was enormous, and most clinics have gone to less rigorous, less costly procedures.

Goldstein and Brown pointed out in 1970 that random urine collection schedules provide the most reasonable alternative to daily collection. Because these schedules are unpredictable, they minimize the possibility that the patient who continues to abuse drugs will be able to avoid detection. Random schedules also allow the clinic staff to decide on the level of certainty of detecting illicit drug use they are willing to accept and set the schedule interval accordingly.

Harford and Kleber presented a dramatic example of the comparative efficacy of fixed and random urinalysis schedules in 1978, when they published a retrospective study of the effects of a switch from a fixed interval schedule to a random interval schedule. They examined urine data collected in a clinic in New Haven, Connecticut, from January 1970 to July 1975, and compared the percentage of morphine positives detected each month for 11 months before the change to a random schedule and for 56 months after. In the first month after the change in schedules the percentage of morphine positives detected rose from 2.4% to 6.8% of all urines analyzed. In the following 55 months the rates dropped dramatically. In only three of those months did the rates equal or exceed the lowest rates detected on the fixed interval schedule. They assumed the rate of opiate use was reduced by increasing the probability of detection

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and the application of clinical sanctions such as revocation of take-home medication privileges and the threat of termination from treatment. Unfortunately, there are two serious weaknesses in the Harford and Kleber study. Their hypothesis that the random schedule accounted for the steep increase in the percentage of morphine-positive urines detected does not explain the high rates which were detected on the fixed-interval schedule six months before the schedule change. Secondly, there was no concurrent control group available for comparison of the efficacy of the two schedules. We have shown that supply interdiction can produce a long-lasting decrease in percentage of detected opiates comparable to the decrease presented by Harford and Kleber (Atkinson, 1981). Without a control group, causal factors other than the schedule and clinical sanctions cannot be ruled out. It was because of these weaknesses that we undertook two prospective studies of a urine schedule change using a control group.

The urine-collection schedule in use at our clinic in Denver was a variation of a random schedule which included "safe periods," periods when the probability of detection of illicit drug use was close to zero. Clients were randomly assigned to one of five urine groups at admission. The groups were randomly assigned each week to give specimens on one weekday. For example, clients in group 1 night be assigned to give on Tuesday, groups 2 and 3 on Monday, group 4 on Thursday, and group 5 on Wednesday. Specimens were collected only once each week from every client, so after a client had given a specimen, he/she was safe from detection until the following week. It seemed likely that the "safe period" would allow clients to use illicit drugs without detection and cause us to underestimate actual drug use among our patients. We decided, therefore, to change all methadone patients to individually randomized schedules in a stepwise procedure which would both ease the administrative difficulties of the change and allow us to monitor the effects of the change.

METHOD

Eligibility for methadone treatment is determined by federal criteria, and no one who was in treatment and required to come to the clinic daily was excluded from the study. Two samples were drawn from among these patients. Clients in one sample were assigned to a new random-schedule group. Clients in the other sample remained on their usual urine schedules and served as a control group. The random schedules had a maximum interval of 11 days and an average of 7 days. Schedules were individualized and specimens were collected seven days per week. Data were gathered for three months before the end of the three-month post-change period were dropped. The final sample sizes were 15 clients in the regular-schedule control group and 18 in the random-schedule group.

Urine specimens from this clinic are analyzed at the Colorado Department of Health laboratory. They are routinely screened for

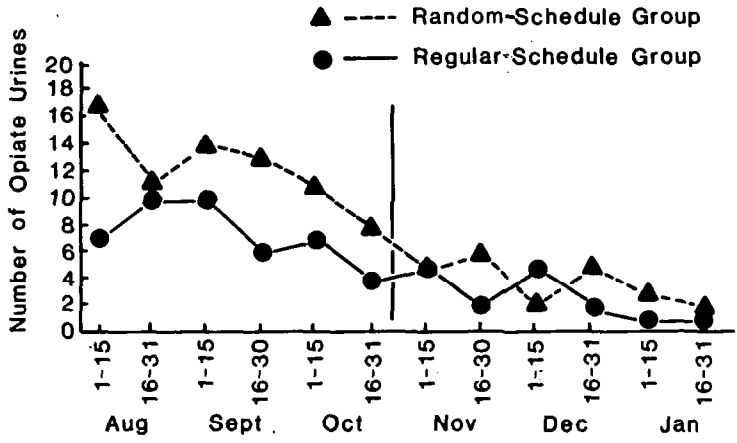
opiates, amphetamine, barbiturates, and cocaine using a combined EMIT (Enzyme Multiple Immunoassay Technique, The CIVA Co.) and thin-layer chromatography procedure developed, at the laboratory (Wislocki, et al. , 1974) and revised in 1979. Turn-around time for urine specimens averages three days.

RESULTS

An average of 225 patients are in treatment at our clinic each month; of these approximately 152 receive methadone. The average dose is *35 mg.* Most clients are in the 20 to 35 age range and 66 percent are males. Approximately 42 percent are Anglo, 23 percent Black, and 32 percent Hispanic. Patients in the random-schedule group had an average age of 32; 22 percent were Black, 33 percent Anglo, and 44 percent were Hispanic. There were eleven males and seven females. The average number of years since first opiate addiction was 9.9, with a range of 2 to 29 years. The average age of the regular schedule control group was 30; 20 percent were Black, 46 percent Anglo, and 33 percent were Hispanic. There were seven males and eight females in this group. The average number of years since first opiate addiction was 9.8, with a range of 2 to 23 years.

It was anticipated that there would be no difference between groups in frequency of opiate-positive urines before the implementation of the random schedules and that there would be an increase in the number of detected opiates in the random-schedule group after the change. The results are shown in Figure 1.

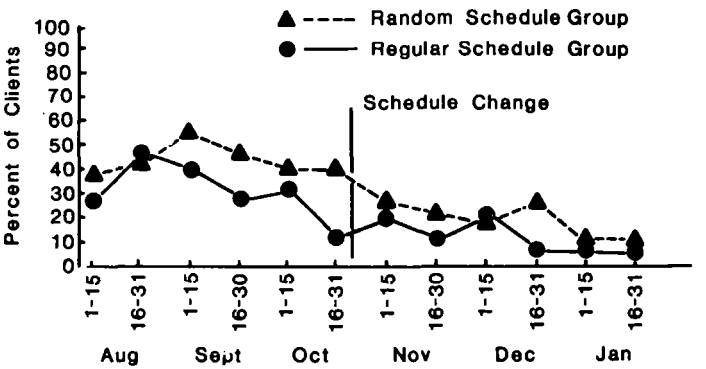
FIGURE 1



Number of opiate urines detected from two groups of clients before and after October 31st, when the random-schedule group was placed on individually randomized schedules.

There was a consistent, but non-significant, difference between groups before the change in schedules with somewhat more opiates detected in specimens from the random-schedule group. The increase noted by Harford and Kleber (1978) in the number of opiates detected with the random schedule failed to occur in our sample. The percentage of clients responsible for opiate urines is shown in Figure 2. Again it can be seen that the random schedule failed to detect opiate use differentially.

FIGURE 2

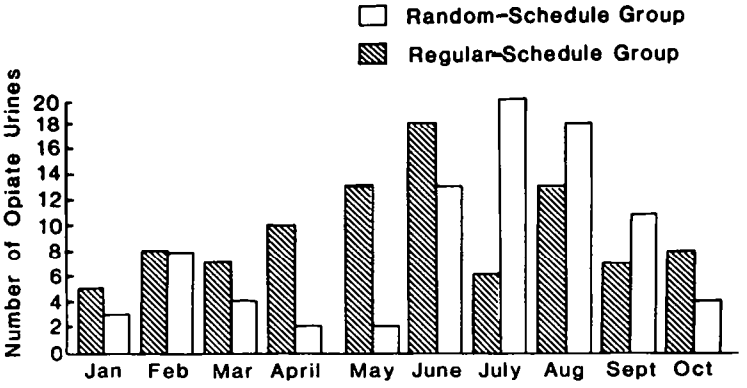


Percentage of clients responsible for opiate-positive urines before and after October 31st, when the random-schedule group was placed on individually randomized schedules.

In a second study beginning in December 1979, clients admitted to the clinic, who qualified for methadone treatment by federal criteria were alternately assigned to the random-schedule group or one of the regular treatment groups. Since all new patients are required to come to the clinic daily, there were no exclusions. A total of 121 clients were admitted, of whom 59 were assigned to the randon-schedule and 62 to the regular-schedule urine groups. Again schedules were individually randomized for each client in the random group and those patients were at risk to give specimens seven days per week. The regular-schedule group continued, as before, to have predictable "safe periods" following urine collection. The two groups were comparable in age, average number of years since first opiate addiction, sex, and ethnic composition.

The number of specimens containing illicit opiates detected from clients on the random and regular schedules from time of admission are shown in Figure 3. Contrary to our expectation, more opiates were detected on the regular schedule in seven of the ten months.

FIGURE 3



Number of opiate-positive urine specimens collected from patients admitted to methadone treatment, January through October, 1980. Clients in the random-schedule group were placed on individually randomized schedules at admission. Clients in the regular-schedule group were placed on semi-random schedules with known "safe periods."

DISCUSSION

The basic assumptions underlying the urine studies cited here is that drug abusers attempt to conceal their drug use in or&r to avoid clinical sanctions, and minimizing predictability of urine collection schedules &creases their ability to avoid detection. It was assumed that patients in the Harford and Kleber study had been avoiding detection by abstaining from drugs for 36 to 48 hours before giving a urine specimen, or employing some other method to avoid detection when the schedule was predictable. When the random schedule was instituted they were no longer able to predict when they would have to give a specimen, and the number of opiate-positive urines detected increased. The number then dropped as the contingencies were enforced, either because patients quit using opiates to avoid the sanctions, or because those who did not were dismissed from treatment, or both. Another possibility, as mentioned above, was that the change in the number of detected opiates was the result of factors not considered in their study.

Based on the above assumptions we assume that the change to a ran-&m schedule at our clinic did not affect the number of dirty urines detected in our clinic because the contingencies were not strong enough to alter patients' behavior; neither the rewards for abstinence, e. g., verbal reinforcement from the counselor and take-home privileges after four months of abstinence and six months of treatment, nor the punishment, delay of take-home privileges, were effective. That is, the number of detected opiates did not change with the institution of a schedule without "safe periods"

because the patients were not bothering to avoid detection in the first place.

The only tangible reinforcement for abstinence in most methadone clinics is the take-home methadone dose. Typically this reinforcement is not available until the patient has been abstinent for months. The patient finds him/herself in a position of choosing between the immediate reinforcement of using an opiate and the long delayed take-home medication privilege. It is not surprising that many habitual drug abusers choose the immediate reinforcement. Clinical sanctions such as reduction of dose and discharge from treatment may have a stronger effect than the take-home privilege reinforcement, but many programs are unable to effectively use these sanctions because of census/funding problems, or treatment philosophy. A comparison of the efficacy of sanctions and *reinforcements* in methadone treatment is an interesting possibility for future research.

Havassy and Hall (1981) suggested that urinalysis is ineffective in reducing opiate abuse among methadone patients. They seem to view urinalysis as a treatment rather than a treatment tool. We believe that urinalysis is a vitally important tool which must be used therapeutically with immediate rewards and sanctions contingent upon the results of the analyses.

REFERENCES

Atkinson, C. A. The effects of law enforcement activity on a population of opiate abusers. Problems of Drug Dependence, 1980. National Institute on Drug Abuse Research Monograph Series 34, 1981.

Goldstein, A. and Brown, B. W. Urine testing schedules in methadone maintenance treatment of heroin addiction. JAMA, 214:311-315, 1970.

Harford, R. J. and Kleber, H. D. Comparative validity of random-interval and fixed-interval urinalysis schedules. Arch. Gen. Psychiatry, 35:356-359, 1978.

Havassy, B. and Hall, S. Efficacy of urine monitoring in methadone maintenance: A treatment trial. Paper presented at the meeting of the Committee on Problems of Drug Dependence, 43rd Annual Scientific Meeting, San Francisco, July, 1981.

Marks, V., Fry, D., Chapple, P. A., and Gray, G. Application of urine analysis to diagnosis and treatment of heroin addiction. Br. Med. J., 2 (5650):153:155, 1969.

Nightingale, S. L., Michaux, W. W., and Platt, P. C. Clinical implications of urine surveillance in a methadone maintenance program. Int. J. Addict., 7(3):403-414, 1972.

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Depression in Pregnant Drug-Dependent Women

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Family Center is a multidisciplinary program which provides comprehensive medical and psychosocial services to pregnant drug-abusing women. Outpatient prenatal care for these high-risk patients is provided, and intensive social and/or psychiatric services are provided for these women on an individual, family, or group basis. Our present patient population is 65 percent black, 35 percent white; their average age is 28.8 years; and 90 percent of the clients receive welfare and/or medical assistance.

It was clinically observed that our clients, particularly heroin addicts, appeared to be depressed on admission for detoxification from opiates and other drugs such as barbiturates and diazepam. Clients transferred from other methadone programs also demonstrated signs and symptoms of depression.

Data were collected in order to be able to evaluate levels of depression existing among pregnant drug-dependent females admitted to our program during 1979 and 1980. The 13-item Beck Depression Inventory (Beck et al., 1974) as well as the Profile of Mood States (POMS), which measures depression, tension, anger, vigor, fatigue, and confusion, were utilized. A violence questionnaire is also routinely administered to Family Center clients in order to measure the presence of possible sexual or physical abuse in the clients" lives. Clients are also routinely evaluated on admission by our program psychiatrist.

SYMPTOMS OF DEPRESSION

De ressive symptomatology includes: 1) a change in mood, involving feelings of sadness, apathy, and/or loneliness; 2) a negative self-concept with feelings of guilt, self-blame, or reproach; 3) a loss of interestin usual activities, including sex, and a general loss of energy; 4) problems with sleeping and/or eating (an increase or decrease in weight may occur); 5) poor concentration; 6) psychomotor retardation or agitation (Rosenfield, 1980).

METHODOLOGY

The Beck and POMS questionnairs were self-administered by all pregnant women admitted to our program during 1979 and 1980. A comparison group of pregnant women, presumably drug-free, who were enrolled as patients in the prenatal clinic of Thomas Jefferson University Hospital in 1981, were used as controls. The Family Center researcher obtained volunteers, explaining the interest in studying the mental attitudes of pregnant women. Anonymity and confidentiality were guaranteed, and written permission was obtained. The Beck Depression Inventory and the Profile of Mood States (McNair, et al., 1971), as well as a questionnaire on violence, were self-administered.

The purpose of this paper is to present information on the prevalence of depression among drug-abusing women and to evaluate the hypothesis that this patient population has a higher rate of depression than that found among the general population and methadone-maintained males. In addition, a number of other variables with respect to the presence or absence of depressive symptomatology were evaluated. The negative effects of depression on parenting and as a factor in continued illicit drug use are discussed, as are differentials with respect to marital status.

RESULTS

Of 84 multiparous women admitted to the Family Center Program in 1979 and 1980, 75 percent reported varying levels of depression as measured by the Beck Depression Inventory. The average Beck score was 9.8 with a standard deviation of 6.6. Using the following scores, patients were divfded into four depression-level groups: 0-4 = none or little; 5-7 = mild; 8-15 = moderate; 16+ = severe. The results were as follows: 19 percent of the women had mild depression; 37 percent were moderately depressed; and 19 percent were severely depressed.

Because of the high correlation observed between Beck and POMS scores (Oehlberg et al., 1980), analysis of depression was focused on the results of Beck scores rather than multiple scoring systems. An analysis of the women was done to see if current placement of children with relatives or in foster care was a factor. There was a significantly* higher incidence of moderate or severe depression among' the drug-busing women whose children were in placement as compared to women whose children lived with them. Placement of children appears to be a factor in depression and/or may be one factor which contributed to the necessity for placing the child. It is difficult, however, to ascertain whether child placement is an antecedent or consequential variable.

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*An Analysis of Variance was performed on the Beck scores resulting in $F = 8.8$ at $df = 82$ and $p. < .01$.

No significant differences were found in depression levels in our population when they were differentiated according to race or marital status. This lack of difference is surprising in light of present knowledge about the prevalence of depression in various marital-status groups, especially the well-documented findings of "marital protection" as found in Gove (1977).

CONTROLS VERSUS FAMILY CENTER CLIENTS

As previously stated, the current investigation includes the gathering of information about depression from a control group of 26 pregnant women with similar socioeconomic status and who reported no current drug use.

Results of a comparison between the control and drug-abusing groups do indeed provide us with evidence of depression differentials. While 50 percent of the controls exhibited Beck scores of 5 or more, 75 percent of the Family Center patients reported feelings of depression resulting in Beck scores of 5 or more.

As reported in the previous section, the average Beck score for the Family Center patients was 9.8 (SD=6.6). The average Beck score of the control group was 6.3 (SD=5.6). Performing an analysis of variance on the scores resulted in a significant difference with $p < .05$ ($F = 5.72$).

It must also be kept in mind that the control group consists of volunteers. The fact that they have volunteered to provide us with information on their emotional well-being may indeed be a bias, the direction of which can not be ascertained.

DISCUSSION

Depression in Drug-Abusing Populations

The 56-percent moderate and severe depression rate found in Family Center Program clients is consistent with the depression rate in a study done by Dorus and Senay (1980) on 432 male and female substance abusers. This study found that on admission 46 percent of the subjects reported moderate or high levels of depression on the Beck while female subjects were significantly more (57 percent) depressed than male subjects as measured by the Beck and Hamilton scales. It was also shown that education level was inversely proportional to Beck-Scale depression levels; i.e., the subgroup with the largest percentage of high depression scores (26 percent) was the least educated. Also, a larger proportion of moderate and high depression scores were found among the younger clients (56 percent) (Dorus and Senay, 1980). Additionally, the group of subjects who had the least occupational skills were the most depressed. Dorus and Senay found that there was an apparent improvement in levels of depression in all groups eight months after admission, but "substantial numbers of subjects remained clinically depressed throughout the study" (Dorus and Senay, 1980).

The high rates of depression found in the Family Center clients and in the Dorus and Senay study of substance abusers were also found in a study of 106 methadone-maintained men in a New Haven drug-treatment program (Weissman et al., 1976). The authors found that about one-third of the men were moderately to severely depressed as assessed on standard rating scales for depression. The authors felt the subjects were clinically depressed and not suffering from withdrawal since they were already stabilized on methadone prior to the interviews.

The high rates of depression found among drug users, particularly in opiate-dependent populations, may represent the "drug effect" since "chronic opioid use results in increased feelings of dysphoria and depression" (Dorus and Senay, 1980). However, our study indicates that loss of children by placement may be a contributing factor in our female substance-abusing population at Family Center Program. The 2:1 sex ratio (female to male) of depression in drug abusers is consistent with the sex ratio of depression found in the population at large in the United States and is "fairly consistent over time" (Weissman and Klerman, 1977). Other countries report a similar preponderance of female depression "with the exception of a number of developing countries such as India, Iran, New Guinea, and Rhodesia" (Weissman and Klerman, 1977). These exceptions may be due to the decreased availability of medical care in third-world countries.

Theories of Female Depression

There are multiple theories extant which attempt to explain the higher prevalence of depression in women which range from the belief that the rates are a reporting artifact to a belief that female endocrinology is a factor in depression.

> The preponderance of women among depressed patients is a real finding rather than an artifact of reporting (Weissman and Klerman, 1977).
>
> Post-partum depressive changes do frequently occur, and there is overwhelming evidence that the longer post-partum period (up to 6 months) carries an excess risk for more serious psychiatric disorders (Weissman and Klerman, 1977).
>
> Married women have higher rates of depression than married men (Gove, 1977).
>
> Reporting artifacts include the evidence that women obtain medical care more frequently than males and therefore are more likely to be diagnosed.
>
> In addition, the marital differentials could be due to a selection process in which depressed/ill females are more likely to marry under the classical sex-role circumstance in which the male is the caretaker. Depressed or

> mentally ill males, not able to assume the "head of household" role, would then marry less frequently.
>
> Married females exhibit less evidence of mental illness than single (never married) females (Gove, 1977).
>
> A psychosociological explanation for the increased prevalence of depression in women is that the disadvantaged status of women "makes it difficult for them to achieve mastery by direct action and self assertion...These inequities lead to legal and economic helplessness, dependency on others, chronically low self-esteem, low aspirations, and ultimately, clinical depression." (Weissman and Klerman, 1977).

The presence of high levels of depression in pregnant, addicted women may be multiply determined by biosocial psychological factors. Addicted women have low levels of self-esteem, high levels of anxiety, as well as depression and fewer social supports than control groups of non-addicted women and addicted men (Reed, 1977). Addicted women show a greater adherence to traditional sex-role ideology than non-addicted women. They share with addicted men traditional ex ectations for sex-based divisions of labor. Reed et al. (1977) found that addicted women expressed feelings of dependency toward men but also expressed the alternative view that women are strong, while men are weak. Addicted women are therefore in a bind, since they are dependent upon the males, whom they mistrust. The drug subculture is male-dominated and, in many cases, the women are abused by their spouses or partners who may also be drug-dependent. Addicted women are also more responsible for their children than male addicts are, which can increase their levels of stress. Another factor which may account for the depression levels of our client population is their high level of unemployment. Employment outside the home seems to have a positive effect on depressed women and helps them to feel more able to cope with the stresses of daily life. It should also be noted that there is a high degree of association between low educational levels and unemployment. For the most part, the Family Center patients are not high-school graduates.

Depression and Parenting

In a 1955 retrospective analysis of clinic records from a child-guidance clinic, there was evidence of maternal depression in one-third of the mothers (Fabian and Donohue, 1956). The authors speculated that the children had been vulnerable to the effects of maternal depression at a-critical juncture in their lives and were evidencing dysfunctional behavior as a response to their mothers' depression.

The high rates of depression found in pregnant women admitted to' our program compounds the difficulty in attaching to an infant who is being treated in the intensive care nursery for neonatal abstinence syndrome (NAS) secondary to maternal drug use. In

addition to the guilt the women feel regarding drug use, some of the women have children in placement and may be in mourning for these children. Due to unresolved mourning, the women may experience difficulty in attaching to a new baby. The attachment process is further complicated by the long course of therapy necessitated by treatment for neonatal abstinence syndrome. A child who is ill from the effects of prescribed methadone or illicit maternal drug use is a subtle or overt rebuke to the mother's sense of herself as a good person. The distressed mothers report: "I know the baby is sick because of what I took and I feel so guilty about it."

Depression, as well as drug-related dysphoria, may cause irritability in the mother in addition to anger toward her infant, a feeling most women have difficulty in acknowledging. Continued maternal depression over time can also have a devastating effect on the mother-child interaction unless there is intervention or dilution of this too intense or too distant relationship by other interested family members or a surrogate parent. Neglect or abuse may also occur in the context of drug use and depression.

In summary, the presence of depression in pregnant drug-abusing women is a significant problem and needs to be addressed as early as possible in the pregnancy so that maternal depression may not distort the quality of attachment in the neonatal period and the long-term parent/child relationship.

REFERENCES

Beck, A., Rial, W., and Richels, K. Short form of depression inventory: Cross-validation. Psych. Reports 34:1184, 1974.

Dorus, W. and Senay, E. Depression, demographic dimensions, and drug abuse. Am. J. Psychiatry 137:6, 1980.

Fabian, A. and Donohue, J.F. Maternal depression: A challenging child guidance problem. Am. J. Orthopsychiatr. 26:400, 1956.

Gove, W.R. Relationship between sex roles, marital status and mental illness. Social Forces 51:34, 1977.

McNair, D., Lorr, M., and Droppleman, L. (eds.) Manual for the Profile of Mood States. San Diego: Educational and Testing Service, 1971.

Oehlberg, S., Regan, D.O., Rudrauff, M.E., and Finnegan, L.P. A preliminary evaluation of parenting, depression, and violence profiles in methadone maintained women. National I PA, Research Monograph Series, problems of drug dependence, 380, 1980.

Reed, B., Colten, M.E., Tucker, B., Binion, V. and Douvan, E. Addicted Women: Family Dynamics, Self-Perceptions and Support Systems. Institute for Social Research at the University of Michigan, 1977.

Rosenfield, S. Sex differences in depression: Do women always have higher rates? J. Health and Social Behav; 21:33, 1980.

Weissman, M., Slobetz, F., Prusoff, B., Mezritz, M. and Howard, P. Clinical depression among narcotic addicts maintained on methadone in the community. Am. J. Psychiatry 133:12, 1976.

Weissman, M. and Klerman, G. Sex differences and the epidemiology of depression. Arch. Gen. Psych. 34: 98, 1977.

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LAAM Instead of Take-Home Methadone

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INTRODUCTION

A public health problem of major concern about methadone maintenance treatment is widespread diversion of take-home methadone doses. LAAM (levo-alpha acetylmethadol) is a long-acting opioid that offers a viable alternative to daily methadone ingestion for many patients (Klett 1978, Ling et al. 1976, Resnick et al. 1976). Supervised administration of LAAM three times per week in the clinic allows maintenance of the opioid-dependent patient without take-home doses.

One approach to curtailing methadone diversion might be to restrict or eliminate take-home methadone and offer LAAM as the only alternative for patients who desire reduced clinic visits. We now report a clinical trial which tested the feasibility of conducting a maintenance treatment program where patients had the choice of either LAAM requiring three clinic visits per week or daily methadone requiring six clinic visits per week.

METHODS

During the eight-month trial period patients admitted for maintenance treatment were given the choice of: (.a) attending the clinic three days per week for LAAM; or, (b) attending six days per week for methadone with one take-home dose. As contrasted with our clinic policy before this eight-month trial and usual policy at other clinics in this geographical area, no additional take-home methadone doses were available during the study period. Patients had the option of switching between maintenance on LAAM and methadone.

RESULTS

No patient declined admission to the program during the study period, despite the restrictions on take-home methadone. Choice of LAAM or methadone for the 19 patients admitted during the study period is shown in Table 1.

TABLE 7

PATIENTS' CHOICE OF LAAM OR METHADONE

	Initial Drug Choice	
	LAAM N=10	Methadone N=9
Continued initial drug choice	5	5
Switched to other drug	4	3
Dropped out	1	1

Patients were almost equally divided in terms of choice of LAAM or methadone treatment. Patients who switched from methadone to LAAM cited conflict between working schedules and daily clinic visits as the major reason for the switch. Three of the four patients who switched from LAAM to methadone did so after receiving only two LAAM doses. When supplemental methadone was made available on alternate days during LAAM induction, all patients choosing LAAM completed induction.

CONCLUSIONS

A. Cur findings demonstrate the feasibility of conducting a maintenance treatment program using LAAM or restricted take-home methadone to curtail methadone diversion.
B. Acceptability of LAAM can be maximized by making supplemental methadone available on alternate days to prevent abstinence symptans during the initial LAAM induction period.
C. Further testing of the present strategy for reducing methadone diversion appears warranted and may have implications for formulating program policies.

REFERENCES

Klett, C.J. The SAODAP cooperative-studies of LAAM: unblinded comparison with methadone. In Petersen, R.C., ed. The International Challenge of Drug Abuse. National Institute on Drug Abuse Research Monograph 19. DHEW Pub. No. (ADM) 78-654. Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., 1978. pp. 271-276.

Ling, W., Charuvastra, V.C., Kaim, S.C., and Klett, C.J. Acetylmethadol and methadone as maintenance treatments for heroin addicts. A Veterans Administration Cooperative Study. Arch Gen Psychiatry, 33:709-720, 1976.

Resnick, R.B., Orlin, L., Geyer, G., Schuyten-Resnick, E., Kestenbaum, R.S. and Freedman, A.M. ℓ--Alpha-acetylmethadol (LAAM): prognostic considerations. Am J Psychiatry, 133:814-819, 1976.

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Methadone-Induced Endorphin Dysfunction in Addicts

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INTRODUCTION

A number of reproducible neuroendocrine responses are influenced by the administration of exogenous opiates, endogenous opioids, and opiate antagonists (eg., Naloxone),and these have been used to understand and assess the endorphin system in the brain. Neuroendocrine functions are influenced by the administration of exogenous opiates, endogenous opioids, and opiate antagonists (Naltrexone) (1,2,3). The acute infusion of the exogenous opiate, mathadone, has been demonstrated to produce a decrease in plasma cortisol levels in man(4). Corticotropin(ACTH) and B-lipotropin/B-endorphin are formed from a larger precursor protein which has been called pro-ACTH/endorphin (5,6). ACTH and B-LPH/B-endorphin are located and stored in the same cells and secretory granules within the pituitary and may be inhibited by opiate administration. These and other data (2,3,4,7) suggest that chronic opiate receptor stimulation by exogenous self-administered opiates may, through a feedback mechanism, cause a decrease in the release and possibly the synthesis and available stores of pro-ACTH/endorphin and therefore decrease ACTH and cortisol response to a provocative stimulus (3).

Chronic exogenous opiate administration might be responsible for both the acute and protracted opiate withdrawal syndrome (8,9) by producing a prolonged decrease in the availability of endorphins or functional integrity of the B-Endorphin system originating from a cell group near the arcuate nucleus of the hypothalamus which sends long axons to midbrain/locus coeruleus and limbic structures (10). However, the hypothesis that opiate administration may decrease endorphins in brain has been difficult to test. We have recently administered the provocative test substance Naltrexone, orally, to assess endorphin reserve and reported that chronic methadone may have anti-endorphin effects (3). This preliminary finding was limited by the fact that Naltrexone is administered orally, it is not available in medical centers as a test substance, and is a less profound stimulus of endorphin, ACTH or Cortisol release than the short-acting intravenous Naloxone. In addition, we did not test both heroin and methadone addicts to determine whether

the reported lack of response was related to methadone or opiate addiction.

We have recent Naloxone-endorphin reserve data from methadone and heroin addicts which support and extend our previous findings on diminished activity. The subjects were 5 male methadone addicts who had been addicted to $\geq$ 40 mg of methadone for 1-8 years, 5 male opiate addicts who had been addicted to heroin for $\geq$ 6 months, and 5 normal, age-matched male opiate-naive volunteers. The addicts had their chronic methadone abruptly discontinued and clonidine suppression of withdrawal signs and symptoms as reported previously (9). All subjects were opiate and clonidine-free and at least 16 days after their last opiate dose for the naloxone test. All subjects were NPO past midnight and were at rest in bed for the placement of an indwelling venous catheter at 800 h. Small samples of blood were taken for the measurement of plasma cortisol in duplicate by radioimmunoassay (3) through the catheter at -30, 0, 15, 30, 45, 60, 75, 105, and 135 minutes after 20 mg of Naloxone was administered intravenously at 930 h.

In our group of 5 methadone addicts Naloxone caused a small and insignificant (paired t test, t=1.64,NS) increase in plasma cortisol levels from a baseline of 19.3 ± 2.5 ug/dl to a peak of 23.1 ± 1.9 ug/dl at 45 minutes after Naloxone administration. Mean Δ cortisol was 3.7 ± 2.3 ug/dl for the group of methadone addicts. In normal controls Naloxone produced the expected rapid and significant increase in cortisol from pretreatment baseline of 15.1 ± 6.0 ug/dl to a peak of 24.8 ± 6.7 at + 45 minutes (paired t test, $t = 4.64$ $p < 0.01$). Mean Δ cortisol for the normal controls was 9.7 ± 2.1 ug/dl. The two groups had significantly ($t=3.9$, $p < 0.01$) different cortisol responses to Naloxone. Mean Δ cortisol for heroin addicts was 7.9 ± 1.8 ug/dl. cortisol response to Naloxone for heroin addicts was not significantly different than normal controls. Methadone addicts had a reduced response when compared to heroin addicts ($t=2.88$, $p < 0.05$). For our group of lofexidine patients reported in this volume, there was no significant increase in cortisol demonstrated with a mean Δ cortisol at 45 minutes after naloxone (20 mg) of 5.1 ug/dl.

While these data rely on the measurement of cortisol, they are not likely to relate to adrenal factors since they are in agreement with previous studies in the literature which have demonstrated decreased ACTH in opiate addicts (7) and suggested that chronic exogenous opiate administration might cause an endorphin system inbalance (3,8,9,11,12,13,14). However, to further evaluate this endorphin hypothesis and the possibility of opiate-induced adrenal dysfunction, we administered 20 mg Naloxone to recently detoxified methadone addicts as described above. Methadone had a markedly impaired ACTH response to naloxone suggesting that chronic exogenous opiate administration had led to an impaired functional reserve of endorphin precursor. ACTH response to naloxone (20 mg) was rapid and significant for normal opiate-naive controls from baseline levels of 15.4 ± 11.1 to a peak of 59.0 ± 28.2 pg/ml at + 45 minutes. The recently detoxified methadone addicts (n=8) did

not demonstrate an ACTH response to naloxone. Baseline levels of 26.2 ± 20.2 ware not significantly different than peak levels of 29.3 ± 21.3 pg/ml at + 45 minutes from the naloxone infusion. Our data are also consistent with animal data which have shown reduced brain B-endorphin immunoactivity in rats addicted to morphine for 3 months or longer (15) and decreased B-endorphin immunoactivity and Naltrexone test response in chronic male opiate addicts (3). Additional larger studies of methadone addicts are necessary to confirm these data and to expand the biological measurements (before and after Naloxone) to endorphin and B-lipotrophin. If these data are confirmed, studies are also necessary to cause an endorphin system dysfunction and to determine whether methadone has more serious antiendorphin effects than other opiates.

We have previously suggested (8,9,11) that opiate withdrawal my result from a sudden lack of exogenous opiates and an inadequate functional endorphin reserve. The effects of opiates on catecholamine neurons have been reported elsewhere (19-23) but have tended to show that opiates can decrease NE activity and turnover (22,24, 25). Studies of the brain's major noradrenergic nucleus, nucleus locus coeruleus (LC), have clearly demonstrated that the prototype opiate, morphine, causes a marked reduction in the normal LC neuronal firing rate (25). These LC neurons are known to respond to a painful stimulus with an increased firing rate and this pain-induced effect can be blocked by morphine (25). These data demonstrated an important opiate-NE interaction and suggested the possibility that some of the effects of opiates might be mediated by opiate-induced decreases in LC activity and NE release (25,26). The discovery of specific opiate receptors in the brain (27,30), the data by Pert, et al (28) and Simon (29) demonstrating very dense opiate receptor a accumulations in the LC and the use of naloxone reversal in electrophysiological studies as means of identifying effects which could be attributable to opiate-receptor stimulation (22,27,31) allowed LC-endorphin, LC-enkephalin and LC-opiate interactions to be expanded and more clearly understood. Investigators using single neuronal recording techniques and microiontophoresis reported that endogenous opiates and exogenous opiates decreased LC firing rates and that this effect was specifically reversed by the opiate antagonist naloxone (22,32). These data suggested that the specific opiate receptors on the LC which might normally utilize endorphins as a natural neurotransmitter inhibit LC firing rate and modulate ascending NE activity (22,32). These data suggested that this LC-opiate interaction was not tonic; that is, endorphins do not tonically inhibit LC activity but rather endorphins are released in response to neural or environmental events. These data suggested to us that a critical endorphin-LC connection might exist and be related to some opiate effects and possibly play a critical role in opiate withdrawal (8,11,12,13,14). Chronic exogenous opiate administration would tonically inhibit the LC and compromise endorphin biosynthesis or functional integrity (8,11,12,13). Acute opiate abstinence might be due to a rebound NE hyperactivity and protracted abstinence due to slow endorphin recovery and incomplete functional inhibition of spontaneous or environmentally produced LC hyperactivity (8). In summary, we

have investigated the opiate-withdrawal syndrome from the clinical point of view. Neural events associated with opiate withdrawal produced behavioral and phenomenological events in man and non-human primates which could be reproduced by phamacological or electrical activation of noradrenergic neuronal system. A NE hyperactivity hypothesis was proposed for opiate-withdrawal-related and naturally occurring panic states. This hypothesis was tested in non-human primates and in man during methadone, heroin and other opiate withdrawal. These data supported the NE hypthesis on the basis of Clonidine and Lofexidine's efficacy and the neuropharmacology of these medications. The data supporting an endorphin-LC connection were preliminarily studied using a naloxone ("endorphin reserve") test paradigm These provocative studies demonstrated impaired cortisol and ACTH responses consistent with an impaired B-Endorphin-ACTH precursor reserve. These data support an important role for endorphin-system dysfunction in acute and protracted abstinence syndrome. Further studies of various anti-NE medications in withdrawal as well as studies of chronic high-dose methadone addiction and endorphin study are necessary. The effect of endorphin capacity and recovery on outcome measures need careful consideration.

The specific opiate antagonists Naltrexone and Naloxone have been reported to cause a marked increase in plasma ACTH and cortisol levels in normal man (2,3), and this response may be a measure of endophin function in vivo (3). These impaired Naloxone response data reported here for recently detoxified addicts suggest that chronic methadone administration decreases the synthesis, storage, and quantity of available pro-ACTH/endorphin and endorphin/endogenous opiate reserve. The data reported here and recent demonstration of an endorphin pathway to the locus coeruleus (10) support the hypothesis that opiate withdrawal results from the failure of endogenous opioid systems to compensate for the loss of exogenous opiate-induced inhibition (8). These data also suggest that prolonged abstinence, post-detoxification depression and other affective symptoms which contribute to relapse may result from a prolonged endorphin derangement (33). These data reporting significant response differences for heroin and methadone addicts may explain the increased withdrawal severity and poor detoxification/outcome studies for methadone. Whether these findings relate only to the potency of methadone vs. heroin or the natural history of heroin addiction ("always in and out of withdrawal") having a sparing effect on endorphin systems remains to be determined.

REFERENCES

1. Gold, M.S., Redmond, D.E. Jr., Donabedian, R.K., The effects of opiate agonists and antagonists on serum prolactin in primates: Possible role for endorphins in prolactin regulation. Endocrinology 105 284-289, 1979.

2. Volavka, J., Cho, D., Mallya, A., and Bauman, J. Naloxone increases ACTH and cortisol levels in man. N Eng J Med 300 1056-1057, 1979.

3. Gold, M.S., Pottash, A.L.C., Kleber, H.D., and Extein, I Antiendorphin effects of methadone. Lancet II 973, 1980.

4. Gold, P.W., Extein, I., Pickar, D., Rebar, R., Ross, R. and (Goodbwin, F.K. Suppression of plasm cortisol in depressed patients by acute intravenous methadone infusion. Am J Psychiatry 137:862-863, 1980.

5. Weber, E., Martin, R. and Voight, K.H. Corticotrophin/B-endorphin precursor: Concomitant storage of its fragments in the secretory granules of anterior pituitary corticotropin/endorphin cells. Life Sci 25:1111-1118, 1979.

6. Gillemin, R., Vargo, R., Rossier, J., Minick, S., Ling, N., Rivier, C., Vale, W. and Bloom, F. Beta-endorphin and adrenocorticotropin are secreted concomitantly by the pituitary gland. Science 1367-1369, 1977.

7. Ho, W.W.K., Wen, H.L., and Fung, K.P. Beta-endorphin-like immunoactivity in the plasma of heroin addicts and normal subjects. Clin. Chim. Acta 75:415-419, 1975.

8. Cold, M.S., Byck, R., Sweeney, D.R., and Kleber H.D. Endorphin locus coeruleus connection mediates opiate action and withdrawal. Biomedicine 30:1-4, 1979.

9. Gold, M.S., Pottash, A.L.C., Sweeney, D.R., and Kleber, H.D., Opiate withdrawal using clonidine: A safe, effective and rapid nonopiate treatment for opiate withdrawal JAMA 243: 343-346, 1980.

10. Bloom, F.D., Rossier, J., Battenberg, E.L., Bayon, A., French; E., Hendricksen, S.J., Siggins, G.R., Segal, D., Browne, R., Ling, N., and Guillmin, R., Beta endorphin: Cellular localization electrophysiological and behavioral effects. Adv Biochem. Psychopharmacol 18:89-109, 1978.

11. Gold, M.S., and Kleber, H.D., A rationale for opiate withdrawal symptomatology. Drug and Alcohol Dependent 4:419-424, 1979.

12. Gold, M.S., Redmond, D.E., Jr., and Kleber, H.D. Clonidine in opiate withdrawal. Lancet, 1:929-930, 1978.

13. Gold, M.S., Redmond, D.E., Jr. and Kleber, H.D. Clonidine blocks acute opiate withdrawal symptoms. Lancet, 2:599-602, 1978.

14. Kleber, H.D., and Gold, M.S. Use of psychotropic drugs in treatment of methadone maintained narcotic addicts. Ann NY Acad Sci 311:81-98, 1978.

15. Ho, W.W.K., Wen, H.L., and Ling, N. Beta-endorphin-like immunoactivity in the plasma of heroin addicts and normal subjects. Neuropharmacology 19:117-120, 1980.

16. Gold, M.S., Pottash, A Carter. The neurobiological implications of clonidine HCL. Ann N.Y. Acad Sci 362:191-202, 1981.

17. Gold, M.S., Pottash, A.L.C., Extein, I., Kleber, H.D., Clonidine in acute opiate withdrawal. New Engl J Med 302:1421-1422, 1980.

18. Gold, M.S., Pottash, A.L.C., Extein, I., Kleber, H.D., Clonidine and opiate withdrawal. Lancet II 1078-1079, 1980.

19. Eidelberg, E. Possible action of opiates upon synapses. Prog. Neuro Biol 6:81-102, 1976.

20. Lal, H. Narcotic dependence, narcotic action and dopamine receptors. Life Sci 17:483-496, 1975.

21. Roberts, D.C.S., Mason, S., Fibiger, H.C. 6-OHDA lesions to the dorsal noradrenergic bundle alters morphine-induced locomotor activity and catalepsy. Eur J Pharmacol 52:209-214 1978.

22. Bird, S.J., Atweh, S.F., Kuhar, M.J. Microiontophoretic study of the effects of opiates on autoradiographically localized opiate receptors. In: Kosterlitz H, (Ed) Opiates and endogenous Opioid Peptides. Amsterdm: Elsevier Press, 199-204, 1976.

23. Fry, J.P., Herz, A., Zieglgansberger, W. A demonstration of naloxone-precipitated opiate withdrawal on single neurones in the morphine-tolerant/dependent rat brain. Br J Pharmacol 68:585-592, 1980.

24. Herz; A., Blasig, J., Papeschi, R. Role of catecholaminergic mechanisms in the expression of the morphine abstinence syndrome in rats. Psychopharmacologia 39:121-143, 1974.

25. Korf, J., Bunney, B.S., Aghajanian, G.K., Noradrenergic neurons: morphine inhibition of spontaneous activity. Eur J Pharmacol 25:165-169, 1974.

26. Basbaum, A.I., Field, H.L., Endogenous pain control mechanisms: Review and hypothesis. Ann Neurol 4:451-462, 1978.

27. Gold, M.S., Byck, R., Endorphins, lithium, and naloxone: Their relationship to pathological and drug-induced manic-euphoric states. In: Petersen R, (Ed) The International Challenge of Drug Abuse. Rockville: NIDA Research Monograph 19:192-209, 1978.

28. Pert, C.B., Kuhar, M.J., Snyder, S.H. Autoradiographic localization of the opiate receptor in rat brain. Life Sci 16: 1849-1954, 1975.

29. Simon, E.J., Opiate receptor binding with 3H-etorphine. Neurosci Res Program Bull 13:43-50, 1975.

30. Pert, C.B., Snyder, S.H. Opiate receptors: Demonstration in nervous tissue. Science 179:1011-1014, 1973.

31. Gold, M.S., Pottash, A.L.C., Extein, I., and Stoll, A. Clinical utility of clonidine in opiate withdrawal NIDA Monograph, 34:95-100, 1981

32. Kuhar, M.J., Opiate receptors: Some anatomical and physiological aspects Ann NY Acad Sci 311:35-48 1978.

33. Hollt, V., Herz, A. Endorphins in addiction. 3rd World Congress of Biological Psychiatry. Vol. 1 p 163, 1981.

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Characteristics of 68 Chronic Phencyclidine Abusers Who Sought Treatment

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ABSTRACT

An analysis of 68 phencyclidine (PCP) users who sought treatment reveals that chronic compulsive, daily use occurs and that intravenous use is relatively common. Twenty-five (36.8%) subjects considered themselves to be addicted to PCP and 19 (27.9%) desired medication to assist withdrawal. Unwanted behaviors under the influence of PCP were common and primarily related to memory loss, or acts which resulted from loss of impulse control.

INTRODUCTION

Compulsive daily use of phencyclidine (PCP) recently has been recognized as a significant clinical problem, but little is known about the characteristics of chronic dependence in humans (1). Behavioral studies with rats and mice suggest amphetamine-like properties; however, PCP appears to have a calming effect with guinea pigs and depressant effects on monkeys (2,3). Subjective effects reported by human beings under the influence of PCP include thought disturbances, heightened sensitivity to stimuli, stimulation, tranquilization, mood elevation and irritability. (4,5). Attention lapses and perceptual distortions often occur under its influence although relatively few users report hallucinations (5,6). PCP is generally considered nonaddicting; however, monkeys will self-administer and appear to develop a post-withdrawal syndrome (3). In this study 68 chronic PCP abusers who sought treatment were surveyed to determine major subjective effects of the drug in humans.

METHODS

Subjects were 68 PCP users who lived in Los Angeles County and who sought treatment specifically for PCP in the years 1979 and 1980. At the time of admission all subjects completed a PCP drug questionnaire which included demographic information, drug use data, type of treatment desired, pharmacologic effects, and unwanted behavior. Subjects were not clinically intoxicated at

the time of admission although almost all subjects admitted to previous use of marijuana, alcohol, and a small number had occasionally used amphetamines, sedatives, and other non-opiate drugs. None, however, considered these other drugs to be a problem which required treatment.

RESULTS

There were 37 (54.4%) males and 31 (45.6%) females (Table One). Ages ranged from 14 to 38 years with a mean of 19.2. Use of PCP ranged from 1 to 13 years with a mean of 3.0 years. A total of 42 (61.8%) used PCP daily, and 14 (20.6%) injected PCP intravenously. Twenty-five (36.8%) considered themselves addicted to PCP. Psychologic counseling was a desired treatment for the majority of subjects (55; 80.9%), although 19 (27.9%) desired medication to withdraw, and 15 (22.1%) desired a substitute maintenance drug (Table Two).

The most commonly reported pharmacologic effectsof PCP were decreased appetite, confused thoughts, loss of memory, "speedy" feeling, euphoria, and insomnia (Table Three). When PCP use was discontinued, the most common symptoms reported were PCP craving, increased appetite, increased need for sleep, depression, and laziness (Table Four). Unwanted behaviors tile under the influence of PCP were reported to be common and included events related to memory loss (e.g., lost money, got lost, etc.) violence (e.g., fights, hurt self or someone else, etc.), or loss of inhibitions (e.g., unwanted sex act, suicide, drug taking, etc.) (Table Five).

DISCUSSION

This study provides self-reported information on characteristics of PCP abusers who desired treatment. Data collected from these subjects could not be collaborated with body-fluid analysis in all cases since most subjects had ceased PCP use just prior to appearing for treatment. Data collected from these subjects, therefore, do not necessarily apply to all PCP users.

Long term, chronic dependence was present in many of these subjects since the mean length of usage was 3.0 years. The majority (42; 61.8%) used PCP daily, and 25 (36.8%) felt they were addicted. Nineteen (27.9%) desired medication to withdraw. These reports, therefore, suggest that physical dependence may occur in humans. Some animal studies indicate that a withdrawal syndrome may occur after chronic PCP administratian (3).

Subjects reported numerous behaviors which have been described in other studies. Memory loss appeared to be particularly prevalent since subjects frequently became lost or misplaced money. Other unwanted behaviors under the influence of PCP were related to violence and loss of inhibitions which resulted in fights, suicide attempts, sex acts, and crime.

PCP has often been considered to be a compound which is primarily hallucinogenic or sedating in humans (1,2). The major effects reported by these subjects, however, were amphetamine-like. A majority stated the drug decreased appetite, increased strength, and produced a "speedy" feeling. When PCP was stopped a post-amphetamine type of syndrome was apparent with the most commonly described symptoms being PCP craving, increased appetite, need for sleep, and depression. Although PCP is known to have various effects on the neurotransmitters, dopamine and norepinephrine, its chronic use in humans is apparently perceived to be more amphetamine-like than hallucinogenic or sedative (7).

TABLE ONE
DEMOGRAPHIC AND DRUG-USE CHARACTERISTICS
N = 68

Age Range (Yrs.)	14 to 38
Mean Age (Yrs.)	19.2
Males	31 (57%)
Females	23 (43%)
white	10 (19%)
Non-White	44 (81%)
Mean Education (Yrs.)	9.7
Range of PCP Use (Yrs.)	1 to 13
Mean PCP Use (Yrs.)	3.0
Number of Daily Users	42 (61.8%)
Number Who Feel Addicted	25 (36.8%)
Number Who Use Other Drugs	63 (92.6%)

TABLE TWO
DESIRED TREATMENTS*
N = 68

TREATMENT DESIRED	
Psychologic Counseling	55 (80.9%)
Residential program	7 (10.3%)
Withdrawal Medication	19 (27.9%)
Substitute Drug for PCP	15 (22.1%)

* Some subjects desired more than one treatment.

TABLE THREE
SELF-REPORTED PHARMACOLOGIC EFFECTS OF PCP
N = 68

EFFECTS	
Decreased Appetite	42 (61.8%)
Confused Thoughts	41 (60.3%)
Loss of Memory	40 (58.8%)

Increased Strength	39	(57.4%)
Feel Speedy	38	(55.9%)
Euphoria	37	(54.4%)
Drowsiness	35	(51.5%)
Bad Trips	30	(44.1%)
Insomnia	28	(41.2%)
Depression	24	(35.3%
Dizziness	23	(33.8%)
Increased Anger	23	(33.8%)
Increased Anxiety	23	(33.8%)
Increased Violence	22	(32.4%)
Increased Sex Drive	20	(29.4%)
Visual Hallucinations	19	(27.9%)
Paranoia	18	(26.5%)
Ringing in Ears	16	(23.5%)
Headaches	15	(22.1%)
Decreased Sex Drive	14	(20.6%)
Fatigue	14	(20.6%)
Auditory Mallucinations	14	(20.6%)
Feel Hot	13	(19.1%)
Decreased strength	12	(17.6%)
Vomiting	9	(13.2%)
Feeling of Detachment	9	(13.2%)
Increased Appetite	5	(7.4%)
Decreased Anxiety	5	(7.4%)

TABLE FOUR
SELF-REPORTED SYMPTOMS WHEN CHRONIC PCP USE IS DISCONTINUED
N = 68

EXPERIENCES

Craving for PCP	35	(51.5%)
Increased Need for Sleep	33	(48.5%)
Poor Memory	31	(45.6%)
Depression	30	(44.1%)
Laziness	30	(44.1%)
Increased Appetite	26	(38.2%)
confused Thoughts	24	(35.3%)
Flashbacks	22	(32.4%)
Irritable	21	(30.9%)
Feeling Weak	21	(30.9%)
Increased Anxiety	15	(22.1%)
Headaches	11	(16.2%)
Insomnia	10	(14.7%)
None	10	(14.7%)
Recurring Tastes	9	(13.2%)
Panic	8	(11.8%)
Decreased Appetite	6	(8.8%)
Decreased Need for Sleep	3	(4.4%)
Feeling Speedy	1	(1.5%)
Feeling Hot	1	(1.5%)
Ringing in Ears	1	(1.5%)

TABLE FIVE
SELF-REPORTED UNWANTED BEHAVIORS UNDER THE INFLUENCE OF PCP
N = 68

BEHAVIOR	
Lost Money	33 (48.5%)
Got Lost	27 (39.7%)
Took Drugs	24 (35.3%)
Got Into Fight	21 (30.9%)
Hurt Yourself	18 (26.5%)
Hurt Someone Else	16 (23.5%)
Unwanted Sexual Encounter	13 (19.1%)
Attempted Suicide	9 (13.2%)
Committed Crime	8 (11.8%)
Had Car Accident	7 (10.3%)

REFERENCES

1. Burns, RS, Lerner SE, Corrado R, et al: Phencyclidine; States of Acute Intoxication and Fatalities. West J Med, 123: 345-349, 1975.

2. Chen G, Ensor CR, Russell D, et al: The Pharmacology of 1-(1-Phenylcyclohexyl) Piperidine HCC. J Pharmacol Exp Ther, 127:241-250, 1959.

3. Balster RL, Chait LD: The Behavioral Effects of Phencyclidine in Animals. In: Peterson RC, Stillman RC, eds. Phencyclidine (PCP) Abuse: An Appraisal. National Institute on Drug Abuse: Research Monograph Series, 1978.

4. Luby ED, Cohen BD, Rosenbaum G, et al: Study of a New Schizophrenomimetic Drug-Sernyl. Arch Neurol Psychiatr, 81: 363-369, 1959.

5. Siegel RK; Phencyclidine and Ketamine Intoxications: A Study of Four Populations of Recreational Users. In: Peterson RC, Stillman RC, eds. Phencyclidine (PCP) Abuse: An Appraisal. National Institute on Drug Abuse: Research Monograph Series, 1978.

6. Munch JC: Phencyclidine: Pharmacology and Toxicology. Bulletin on Narcotics, 26:131-133, 1974.

7. Leonard BE, Tonge SR: The Effects of Some Hallucinogenic Drugs Upon the Metabolism of Noradrenaline. Life Sci, 8: 815-825, 1969.

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Effect of Chronic Heroin Exposure on Pregnant Rats and Their Offspring

Ian S. Zagon and Patricia J. McLaughlin

INTRODUCTION

In the last 15 to 20 years a dramatic increase in the use of narcotic drugs has occurred, particularly among young women. Of the more than 500,000 persons estimated to be using heroin regularly in the United States in 1976, 150,000 were female of childbearing age (NIDA 1979). Heroin readily crosses the placenta and enters the fetal circulation and has been detected in the milk of lactating humans (Perlmutter 1974). As a consequence of maternal narcotic consumption, the fetus and neonate are known to become passively addicted. Although a great deal of attention has focused on the neonatal withdrawal syndrome, as well as on intrauterine growth. retardation (Perlmutter 1974; Cobrinick et al. 1959; Zelson et al. 1971; Naeye et al. 1973; Vargas et al. 1975), concern for the long-term sequelae associated with perinatal narcotic exposure has only recently been expressed (NIDA 1979; Beschner and Brotman 1977; Blinick et al. 1976; Wilson 1975; Wilson et al. 1975, 1979).

In order to more clearly elucidate the short- and long-term effects. of perinatal heroin exposure on the developing organism, and to begin to ascertain the risks involved with human drug addiction, the present laboratory study was undertaken. In this investigation, we have explored the effects of various dosages of heroin, administered either subcutaneously or intraperitoneally, on pregnant rats and their offspring.

METHODS

Male (250-300 g) and primiparous female (180-200 g) Sprague-Dawley rats (Charles River Laboratories, Wilmington, MA) and their offspring were utilized in this study and all rats were housed under controlled conditions (Zagon and McLaughlin 1977, 1978), with water and Purina Laboratory Chow available ad libitum. Adult animals were quarantined 5 days prior to the beginning of experimentation.

Females were randomly divided into groups of 5-10 animals (5 rats/cage) and each group received either dally intraperitoneal (i.p.)

injections of 3, 5, 7, 10, or 20 mg/kg heroin (diacetylmorphine, National Institute on Drug Abuse) or daily subcutaneous (s.c.) injections of 1, 2.5, 5, or 10 mg/kg heroin; equivalent volumes of saline were administered either by the i.p. or s.c. route to two different groups of control rats. Females were weighed every 3 days and dosage adjustments made. Heroin was prepared weekly by dissolution of the powder into sterile water.

Five days after the beginning of injection, females were mated (one male to one female) and the presence of sperm in vaginal smears indicated day 1 of gestation. On the 18th day of gestation, females were placed in separate solid-bottomed cages to deliver their offspring. Drug injections continued daily throughout gestation and lactation until postnatal day 21 (weaning).

Litter size was maintained at eight pups per mother with an equal distribution of males and females. Offspring were weighed at birth and on postnatal days 6, 10, and 21. Gestation time, litter size, and infant mortality were recorded. Pups found dead within 2 hr of birth were considered stillborn.

For each route of administration, gestation time and litter size were analyzed with the Mann-Whitney U test (Winer 1971), whereas the number of stillborn pups, mortality in the first 3 days, and body weights of preweaning offspring were evaluated using a one-way analysis of variance. Subsequent comparisons between dosages and their respective controls were made using the Newman-Keuls procedure (Siegel 1956).

RESULTS

Subcutaneous Drug Administration

Mortalities were not noted in the s.c. heroin groups prior to mating; however, two rats in the 2.5-mg/kg group and three rats in the 10-mg/kg group died during gestation (TABLE 1). Two rats each in the 2.5- and 5-mg/kg groups and 1 animal in the 10-mg/kg group did not have sperm-positive smears. Female rats receiving dosages of 2.5 mg/kg and 10 mg/kg tended to have longer gestation times than controls, but only rats in the 2.5-mg/kg group were significant in this regard. Litter size in the 5- and 10-mg/kg groups were somewhat smaller than that of controls, but these differences were not Statistically reliable. In comparison to control values, the number of stillborn rats and the number of pups that had died by 3 dsys were significantly increased in the 2.5; 5; and 10-mg/kg groups.

The effects of maternal s.c. injections of heroin on the body growth of rat offspring are presented in TABLE 2. Mean birthweight of all groups of heroin-subjected pups was significantly reduced from control values, with reductions of 14-24% being noted. On day 6, all offspring subjected to heroin were subnormal in body weight, and on day 10 rats in the 2.5; 5; and 10-mg/kg groups were lower in body weight than controls. At weaning, all groups of heroin-exposed pups weighed 11% to 36% less than control animals.

TABLE I

Effects of subcutaneous Heroin Administration of Pregnant Rats and Their Offspring

	Dosage (mg/kg)				
	Control	1.0	2.5	5.0	10.0
Number of females rated	8	5	8	8	8
Number of females delivered	8	5	4	6	4
Length of gestation (days) $\overline{X}$ ± S.E.	21.75 ±0.25	21.00 +0.41	23.75† ±0.95	22.33 ±0.72	23.50 ±0.87
Litter size, $\overline{X}$ ± S.E.	12.50 ±0.68	12.25 ±0.47	13.50 ±1.55	10.66 ±1.89	10.50 ±0.64
Mean number Of stillborns/ litter	0	0	0.75**	1.0**	0.75**
Mean mortality at 3 days	0	0	3.50**	1.33**	0.75**

Significantly different from controls at p<0.01 (**) using analysis of variance.
Significantly different from controls at p<0.02 (†) using Mann-Whitney U test.

TABLE 2

The Effects of Subcutaneously Administered Heroin to Maternal Rats on the Body Growth of Their Offspring

Age (days)	Dosage (mg/kg)				
	Control	1.0	2.5	5.0	10.0
0	7.409±0.14	6.41±0.10**	5.97±0.10**	6.02±0.10*	5.71±0.10**
6	13.78±0.14	12.44±0.28**	12.74±0.07*	12.70±0.16*	11.44±0.16**
10	24.74±0.12	24.28±0.24	19.01±0.59**	21.97±0.20**	20.90±0.29**
21	40.00±0.66	43.45±0.99**	36.49±1.22**	41.35±0.87**	31.24±1.38**

Mean body weights (g) + S.E. for 8-16 rats per group. Significantly different from controls at p<0.0.05 (*) and p<0.01 (**) using analysis of variance.

Intraperitoneal Drug Administration

No mortalities were recorded in the i.p. heroin groups prior to mating, but two female rats each in the 5-, 7-; 10-, and 20-mg/kg groups died during gestation (TABLE 3). The length of gestation of heroin-treated and control females was similar; however, one rat each in the 7 and 10 mg/kg groups apparently resorbed their litters and did not deliver. Litter size was abnormally small for all heroin-treated groups, with reductions of 15-27% being recorded. In a manner similar to the observations noted for rats born of s.c.-injected mother, the number of stillborns and infant mortality by 3 days was generally increased in all i.p.-heroin litters.

TABLE 3

Effects of Intraperitoneal Heroin Administration on Pregnant Rats and Their Offspring

	Dosage (mg/kg)					
	Control	3.0	5.0	7.0	10.0	20.0
Number of females mated	0	4	10	8	0	10
Number of females delivered	0	4	8	4	5	0
Length of gestation (days) $\bar{X}$ ± S.E.	21.66 ±0.23	21.50 +0.28	21.72 ±0.24	22.50 +0.29	22.00 ±0.32	22.37 ±0.62
Litter size, X ± S.E.	12.64 ±0.33	10.75† ±1.65	9.64† ±0.60	10.75† ±0.48	9.20† ±1.16	9.87† ±0.74
Mean number stillborns/ litter	0	0.75**	1.18**	0.50**	0.60**	1.25**
Mean mortality at 3 days	0.12	1.25**	0.90**	0.50	2.40**	3.50**

Significantly different from controls at $p<0.01$ (**) using analysis of variance.
Significantly different from controls at $p<0.02$ (†) using the Mann-Whitney U test.

Newborn pups of mothers given i.p. injections of heroin were subnormal in body weight, with reductions of 16% to 27% being recorded (TABLE 4). Growth retardation was evident in all 6- and 10-day-old offspring subjected to heroin, with heroin-exposed pups weighing 56% to 88% of control levels. At weaning, rats in the 3-mg/kg group were comparable to controls in body weight, but animals in all of the other heroin-exposed groups had reductions in mean body weights of 15% to 24%.

TABLE 4

The Effects of Intraperitoneally Administered Heroin to Maternal Pats on the Body Growth of Their Offspring

Age (days)	Dosage (mg/kg)					
	Control	3.0	5.0	7.0	10.0	20.0
0	6.91 ±0.10	5.81** ±0.25	5.03** ±0.11	5.25** ±0.19	5.53** ±0.10	5.45** ±0.11
6	13.77 ±0.21	12.13** ±0.37	9.15** ±0.17	11.11** ±0.13	8.68** ±0.39	9.46** ±0.22
10	24.94 ±0.39	14.98** ±0.79	16.35** ±0.22	15.11** ±0.30	13.87** ±0.32	14.60** ±0.49
21	49.28 ±0.64	40.95 ±1.3.1	41.67** ±1.08	38.09** ±0.98	37.56** ±1.19	37.45** ±1.59

Mean body weights (g) ± S.E. for 8-16 rats per group. Significantly different from controls at $p<0.05$ (*) and $p<0.01$ (**) using analysis of variance.

DISCUSSION

Although the dosages of heroin used in this study were well below the LD_{50} level of 100 mg/kg for the s.c. route in rats (Way et al. 1960), and no mortalities were recorded in either the s.c. or i.p. heroin groups prior to mating, a number of heroin-injected rats died during gestation. These results are similar to those by Buchenauer et al. (1974) and Zagon and McLaughlin (1977, 1978) showing an adverse effect of another opiate, methadone, during gestation. At this time it is not known whether drug disposition and susceptibility are altered during gestation, but it does appear that exposure to narcotics during pregnancy has a profound influence on maternal viability.

The present data indicate that chronic heroin exposure of female rats prior to and during pregnancy has little effect on the estrous cycle, fertility, or length of gestation, although some increase in gestation time was noted in animals of the 2.5-mg/kg-s.c. group. These data parallel those of clinical studies in which the fecundity of heroin addicts has been reported to be unaffected (Blinick 1971).

The effects of heroin on litter size were dependenton the route of administration. All groups of females receiving heroin by i.p. injection had markedly smaller litters than controls, whereas only the 5- and 10-mg/kg groups receiving heroin s.c. showed some tendency to have fewer pups than controls. The reasons underlying the discrepancy between the s.c. and i.p. routes in terms of litter size is unclear; however, differences in drug metabolism and/or the possibility of intrauterine placement of the i.p. injections could account for these results. Maternal heroin consumption did result in an increase in the number of stillborn pups in groups from both routes of drug administration, as well as an abnormal increase in infant mortality within the first 3 days. This increase in infant mortality nay well have been the result of narcotic withdrawal, even though these pups were still receiving heroin by way of the maternal milk. These findings of infant mortality are consonant with reports of human addiction wherein up to 71% of the Infants delivered by addicts demonstrate some objective evidence of withdrawal, and, if left untreated, these infants will eventually begin to convulse and some may die (Perlmutter 1974).

One of the most consistent facts of *in utero* heroin exposure found in this study was a reduction in birthweight. A dose-response relationship was not found in this regard, but birthweights of all groups of pups subjected to heroin were abnormally reduced in body weight. Not only does heroin appear to be related to *in utero* growth retardation, but body weight gain during the preweaning period was also reduced. At weaning (day 21), decreases in body weight were evident in all but the 3-mg/kg-i.p. group and, with both routes of heroin administration, a dose-response effect could be observed. These results are consistent with clinical findings in which low birthweights have been reported for neonates of heroin-addicted mothers, with these babies being small for gestational age rather than premature (Perlmutter 1974; Naeye et al. 1973;

Reddy et al. 1971; Kandall et al. 1976). In addition, our data in regard to deficits in body weight gain can be correlated with the results of Wilson and colleagues (1975, 1979), which have shown that heroin-exposed children from 3 to 6 years have alterations in growth. These children were often found to be lighter in weight and shorter in stature than controls and to have head circumference measurements considerably below those of controls.

In conclusion, these observations reveal that maternal exposure to heroin can be detrimental to growth of the fetus and neonate. Furthermore, our results can be correlated with those seen in clinical situations. The question as to what other short- and long-term developmental, and possibly neurobiological, abnormalities may be occurring in heroin-exposed offspring needs investigation.

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REFERENCES

Beschner, G. and Brotman, R., eds, Symposium on Comprehensive Health Care for Addicted Families and Their Children. National Institute on Drug Abuse Services Research Report, 1976.

Blinick, G. Fertility of narcotic addicts and effects of addiction on the offspring. Soc Biol, 18: s34, 1971.

Blinick, G., Wallach, R.C., Jerez, E., and Ackerman, B.D. Drug addiction in pregnancy and the neonate. Am J Obstet Gynecol, 125: 135-142, 1976.

Buchenauer, D., Turnbow, M., and Peters, M.A. Effect of chronic methadone administration on pregnant rats and their offspring. J Pharmacol Exp Ther, 189: 66-71, 1974.

Cobrinik, R.W., Hood, T.R., and Chusid, E. The effect of maternal narcotic addiction on the newborn infant. Pediatrics, 24: 288-304, 1959.

Kandall, S.R., Albin, S., Lowinson, J., Berle, B., Eidelman, A.I., and Gartner, L.M. Differential effects of maternal heroin and methadone use on birthweight. Pediatrics, 58: 681-685, 1976.

Naeye, R.L., Blanc, W., Leblanc, W. and Khatamee, M.A. Fetal complications of maternal heroin addiction: abnormal growth, infections, and episodes of stress. J Pediatr, 85: 1055-1961, 1973.

National Institute on Drug Abuse, Drug Dependence in Pregnancy Clinical Management of Mother and Child, National Institute on Drug Abuse Research Monograph. DHEW Pub. No. (ADM) 79-678. Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., 1979, pp. 16-49.

Perlmutter, J.F. Heroin addiction and pregnancy. Obstet Gynecol Sur, 29: 439-446, 1974.

Reddy, A.M., Harper, R.G., and Stern, G. Observations on heroin and methadone withdrawal in the newborn. Pediatrics, 48: 353-358, 1971.

Siegel, S. Nonparametric Statistics. New York: McGraw-Hill Book Company, 1956, 312 pp.

Vargas, G.C., Pildes, R.S., Vidyasagus, D., and Keith, L.G. Effects of maternal heroin addiction on 67 liveborn neonates. Clin Peds,

14: 751-757, 1975.
Way, E.L., Kemp, J.W., Young, J.M., and Grassetti, D.R. The pharmacologic effects of heroin in relationship to its rate of Biotransformation. J Pharmacol Exp Ther 129: 144-154, 1959.
Wilson, G.S. Somatic growth effects of perinatal addiction. Addict Dis, 2: 333-345, 1975.
Wilson, G.S., Desmond, M.M., and Verniaud, W.M. Early development of infants of heroin-addicted mothers. Am J Dis Child, 126: 457-462, 1973.
Wilson, G.S., McCreary, R., Kean, J., and Baxter, J.C. The development of preschool children of heroin-addicted mothers: a controlled study. Pediatrics, 63: 135-141, 1979.
Winer, B.J. Statistical Principles in Experimental Design. New York: McGraw-Hill Book Company, 1971. 907 pp.
Zagon, I.S. and McLaughlin, P.J. The effects of different schedules of methadone treatment on rat brain development. Exp Neural, 56: 538-552, 1977.
Zagon, I.S. and McLaughlin, P.J. Perinatal methadone exposure and brain development: a biochemical study. J Neurochem, 31: 49-54, 1978.
Zelson, C., Rubio, E., and Wasserman, E. Neonatal narcotic addiction: 10 year observation. Pediatrics, 48: 178-189, 1971.

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Direct Relationship of Brain Concentration of Methadone with Analgesia in Chronic Morphine-Implanted and Acute Naloxone-Treated Rats

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Roth chronic morphine pretreatment and acute naloxone treatment have been shown to decrease or block methadone analgesia. We have shown that the analgesic effect of methadone is directly related to the brain concentration of methadone. The present study was initiated to investigate the effect of morphine and naloxone pretreatment on the brain concentration of methadone and the possible mechanism of effect involved. Rats rendered tolerant to morphine analgesia, by s.c. implantation of 2 pellets containing 75 mg of morphine base each for 3 days, showed cross-tolerance to methadone analgesia with or without subsequent removal of the morphine pellet. The brain concentration of ^{14}C-methadone at 1 and 2 hr after administration of ^{14}C-methadone was markedly decreased (ranging from 25-58 percent of control values) by morphine implantation without pellet removal. In contrast, the urinary volume as well as urinary excretion of ^{14}C-methadone and total ^{14}C were markedly increased by this pretreatment. Essentially the same results were obtained in morphine-implanted rats in whom the pellets were removed 6 hr before the experiments were performed. This increased urinary excretion of ^{14}C-methadone and total ^{14}C was apparently due to cross-tolerance to methadone-induced antidiuresis in morphine-implanted rats. Naloxone (0.6, 1.8 and 5.4 mg/kg, i.p.) given 20 min before administration of ^{14}C-methadone (5 mg/kg, s.c.) antagonized methadone-induced antidiuresis and caused a dose-related increase in urinary volume and urinary excretion of ^{14}C-methadone and total ^{14}C. The same naloxone treatment caused a dose-related decrease (49-64 percent of controls) in the brain concentration of ^{14}C-methadone. When naloxone (5.4 mg/kg, i.p.) was given 30 min after administration of ^{14}C-methadone (5 mg/kg, s.c.), it also decreased the brain concentration of ^{14}C-methadone but caused no significant effect on urinary volume and urinary excretion of ^{14}C-methadone. When naloxone was given 20 min before administration of a low dose of methadone (1 mg/kg, s.c.), which produced no analgesia or antidiuresis, it exerted no significant effect on either brain concentration or urinary excretion of methadone. These results indicate that the observed decreases in brain concentration of

methadone in chronic morphine-implanted and acute naloxone-treated rats were not due to direct effects of morphine and naloxone on the biotransformation of methadone. Rather the results suggest that the cross-tolerance to antidiuresis seen in morphine-implanted rats and the naloxone-induced antidiuresis seen in naloxone-treated rats could be partly responsible for the rapid excretion of methadone and the decrease in brain concentration of methadone. This decrease in the brain concentration of methadone could, in turn, cause the observed blockade or decrease in methadone analgesia in the morphine-implanted and naloxone-treated rats.

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Psychological and Physiological Reponse to Hydromorphone: An Opponent Process View of Addiction

Joseph W. Ternes and Charles P. O'Brien

INTRODUCTION

Drug Addiction, especially dependence upon narcotic drugs such as heroin, is frequently cited to demonstrate the temporal dynamics of affect in the opponent-process model (Solomon & Corbit, 1974). Typically, the narcotic drug is described as the affect-arousing stimulus. The euphoria which the narcotic induces is described as the A state, the primary affective reaction, and the narcotic abstinence syndrome is described as the B state, the opponent-affective reaction. Each administration of the drug elicits an a process and indirectly engages an opponent, the b process. The intensity of the A state is determined by the algebraic summation of these underlying processes. Redosing produces an increase or "growth" in the b process. As the b process grows in strength, the B state becomes more aversive and of longer duration. Tolerance is seen as a natural result of the growth of the b process. This mans that as the b process becomes more intense, a larger dose of drug is needed to achieve the same amount of positive affect.

According to an opponent-process analysis of drug addiction, withdrawal agony motivates the addict to seek ways of relieving the pain. Various coping procedures may be engaged in and then discarded. Eventually redosing occurs and abstinence symptoms are relieved. This selectively reinforces the drug-seeking operants at the expense of other less effective responses. Thus the addict learns to relieve his withdrawal symptoms by using the drug to return to normal. But redosing indirectly elicits the b process which eventually leads to withdrawal symptoms, and so forth.

Stimuli which comprise drug preparation and self-injection rituals naturally become associated with the drug (the UCS) through the process of Pavlovian conditioning. They my be thought of as conditioned stimuli (CSs) which are specifically paired with the A state and which come to elicit a conditioned

response (CR) which is similar to the a process. Since eliciting the a process always engages the b process, it seem reasonable to predict that a conditioned a process will also engage the b process. When the conditioned a process decays, a B state will result. Therefore, a conditioned opiate state (either delay of withdrawal symptom or relief of symptoms) should be followed by increased opiate hunger. This is one way the opponent-process theory accounts for "conditioned withdrawal."

Other stimuli which occur earlier in the chain of events preceding redosing, such as the copping corner, the pusher, and bags of heroin, are encountered near the onset of withdrawal, the B state. As such they may be thought of as CSs which predict the end of the drug effect. These stimuli are specifically paired with the B state and therefore may acquire the power to elicit a CR which is hedonically opposite to the A state. This is anotherway in which the opponent-process theory accounts for "conditioned withdrawal." Whether these CS's prolong or induce further growth of the b process is unknown. However, it is known that presentation of a drug-related stimulus such as a syringe may elicit withdrawal signs in both methadone-maintenance and detoxified addicts (Ternes et al 1979). The opponent-process model predicts that "conditioned withdrawal" and, by implication, relapse to opiate addiction, is influenced by Pavlovian conditioned responses to environmental stimuli as well as by the nonassociative responses of the nervous system which counteract strong affective states.

Procedure

Although anecedotal accounts and clinical knowledge of the phenomenolgy of addiction appear to fit the opponent-process model, an empirical demonstration of these features would be important. Since the model describes the temporal dynamics of affect, one obviously would want to monitor the hedonic quality of emotional states which are associated with both the presentation and withdrawal of an opiate drug (the affect-arousing stimulus). Psychological variables which we used to infer affect were derived from the subjective ratings of our subjects. Since we were studying human subjects, we obtained self-reports in response to a short series of questions about their subjective experience of high and withdrawal. Since "high" and "withdrawal" are emotional states, we also measured several psychophysiological variables. Due to space limitations, we will only present data for two measures, subjective ratings and skin temperature. Thus we intended to characterize the opiate-induced A and B states of addicts in terms of their psychological and psychophysiological correlates.

An experiment was performed in the following manner: Four detoxified heroin addicts who were abstinent from opiates for

at least 24 hours prior to the experiment were exposed to four experimental conditions, two unsignalled drug administrations; hydromorphone infusion and saline infusion, and two signalled drug administrations, hydromorphone self-injection and saline self-injection. Each session lasted 60 minutes and consisted of a baseline period of at least 20 minutes followed by either an infusion or a self-injection and at least 20 minutes of monitoring post-administration.

Results

The purpose of the unsignalled hydromorphone infusion session was to demonstrate the A state which is produced by a potent opiate. In this instance we equate the post drug infusion period with the A state. Figure 1 shows a psychophysiological measure, skin temperature. When the drug was infused, skin temperatures increased (figure 1a). Figure 2 shows two psychological measures, the subject's self-reports of high and withdrawal. The subjects reported feeling "high" and relief of withdrawal symptom following the hydromorphone infusion (figure 2a). These data suggest that autonomic variables track the onset and the presence of the drug. The psychological measures also track the phenomenon and indicate the positive hedonic quality of the drug-elicited A state.

Figures 1b and 2b show the saline-infusion condition. Since our subjects were in withdrawal while they were undergoing detoxification (twenty four hours after their final dose of methadone), the saline-infusion condition provided an example of the B state. It demonstrates what happens when opiates are not present in the addicts' system. The psychophysiological and subjective measures both suggest a withdrawal state characterized by low skin temperatures and subjective reports of withdrawal. We feel these physiological patterns and negative affects generally characterize opiate withdrawal, the B state.

Figures 1c and 2c show the hydromorphone self-injection condition. When the subjects began to self-inject, skin temperature decreased. We interpret these physiological changes as representing an anticipatory response, a CR in anticipation of the drug effects. (This type of CR has been suggested as the mechanism of tolerance by Siegel's (1975) Pavlovian conditioning theory of tolerance.) After the injection the subjects' skin temperature increased, and they reported feeling "high" and no withdrawal.

The saline self-injection was designed to be a test trial for Pavlovian conditioning which may have accompanied previous drug use in the natural environment. The psychophysiological data for the group did not seem to be typical of either opiate or opiate-withdrawal effects. Skin temperature was depressed during the injection and then increased following the injection

SKIN TEMPERATURE

Figure 1

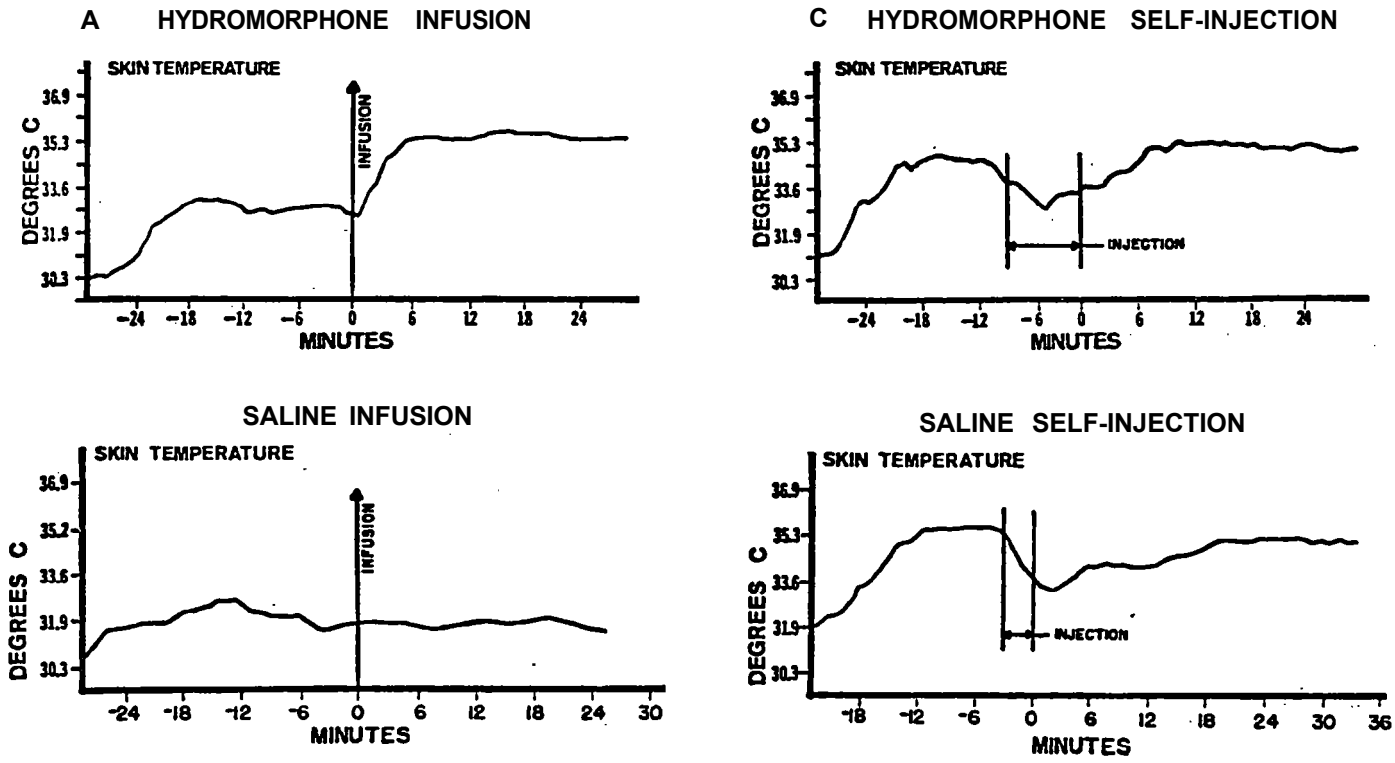
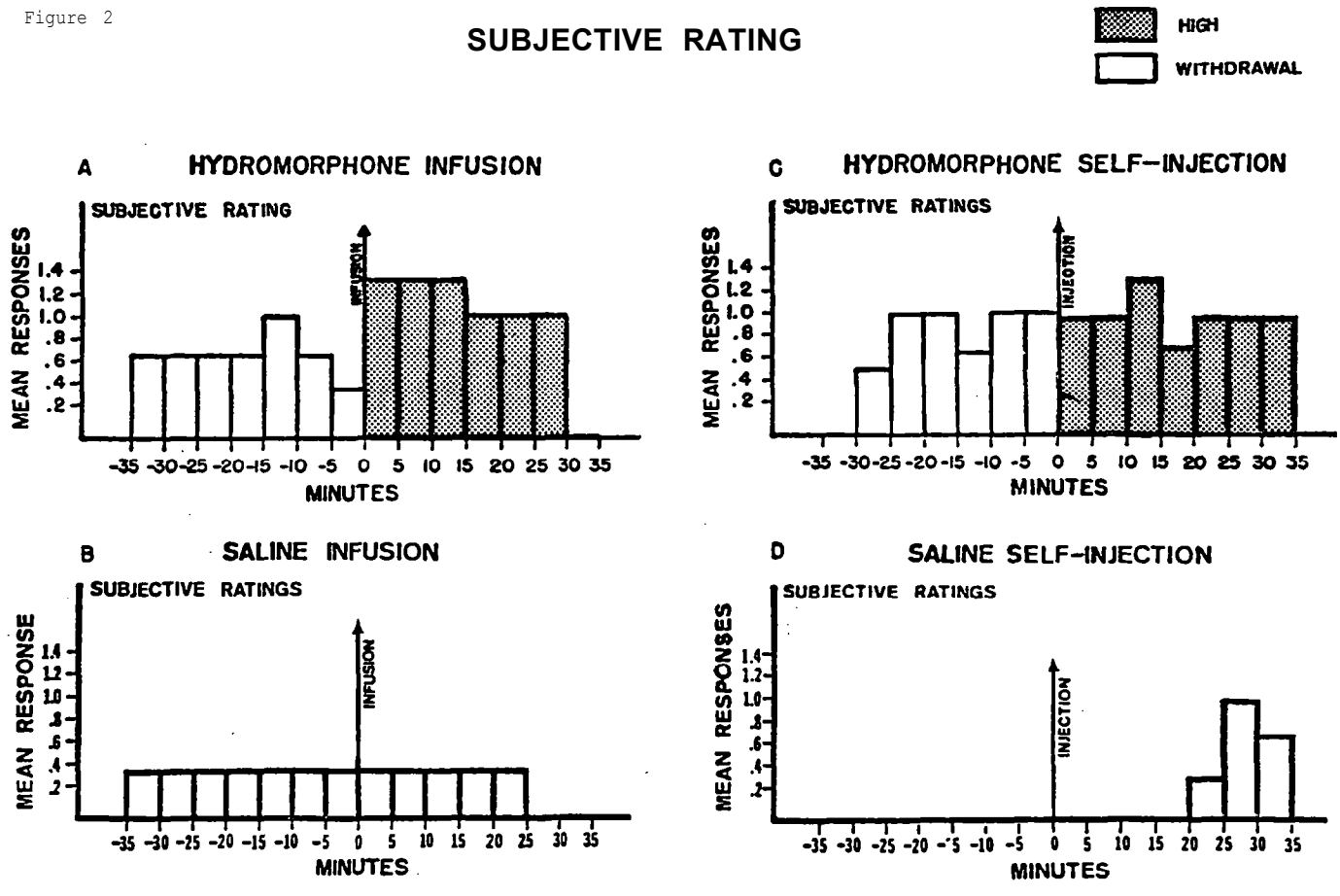


Figure 2


SUBJECTIVE RATING
HIGH
WITHDRAWAL
A HYDROMORPHONE INFUSION
SUBJECTIVE RATING
MEAN RESPONSES
INFUSION
MINUTES
C HYDROMORPHONE SELF-INJECTION
SUBJECTIVE RATINGS
MEAN RESPONSES
INJECTION
MINUTES
B SALINE INFUSION
SUBJECTIVE RATINGS
MEAN RESPONSE
INFUSION
MINUTES
D SALINE SELF-INJECTION
SUBJECTIVE RATINGS
MEAN RESPONSES
INJECTION
MINUTES

but did not attain its previous baseline (figure 1d). The subjective ratings indicated that no report of withdrawal symptoms occurred until approximately 15 minutes after the saline injection (figure 2d).

DISCUSSION

The unsignalled infusion data demonstrate two opiate-elicited states. The "high" state occurs in the presence of the opiate. This is an A state in opponent-process terms. The "withdrawal" state occurs in the absence of the opiate. This is a B state. We also appear to have physiological evidence for two different CRs which could be responsible for "conditioned withdrawal": the anticipatory CR (for example, the pre-injection response to the injection ritual, figures 1c an 1d); and the placebo CR (for example, the post-injection temperature increase following saline injection, figure 1d). Both Siegel's conditioned-tolerance theory and Solomon's opponent process theory can account for the withdrawal symptoms, albeit in quite different ways.

The conditioning theory focuses on the expected drug positive effects which the CS predicts. Given this positive expectancy, the injection CSs elicit a compensatory CR which tends to mitigate the drug effects. However, this compensatory CR may be misinterpreted as narcotic withdrawal if it is unopposed by the opiate. This is similar to Wikler's counter adaptive CR theory of relapse to opiates. Essentially this position suggests that conditioning is at first an adaptive process which acts in the interest of preserving the homestatic balance of the organism. Therefore the large physiological reactions which some drugs cause are counteracted by CBs which change in the opposite direction. However, after several repetitions of the drug, the CR becomes quite strong and overshoots the adaptive level. This could be "counteradaptive." In the instance of opiate addiction, the adaptive CR produces tolerance, but presentation of the CS in the absence of the US (for example, a placebo injection) may precipitate withdrawal symptoms.

An opponent-process analysis can account for the withdrawal symptoms following the saline injection in two different ways: in the first case, the injection procedure may serve as a CS which is associated with the B state (withdrawal) which, usually precedes opiate injection and therefore results in a CB which resembles B., the withdrawal state. In the second case, the injection procedure may serve as a CS which is associated with the A state ("high") which immediately follows an opiate injection. Therefore it results in a CB which resembles the A state. However, when the conditioned a-process decays, the B state (withdrawal symptoms) should follow. The data are consistent with this latter version.

SUMMARY

This paper has described the affective and psychophysiological correlates of addictive states in detoxified opiate addicts. These data tend to fit the opponent-process model of the temporal dynamics of affect. Two types of autonomic conditioned drug reactions were also demonstrated: an anticipatory CR which is oppositeto the expected drug effects and a placebo CR which is similar to the drug effect. However, both of these. brief autonomic CRs tend to be followed by an increase in negative affect and drug hunger. Although "conditioned withdrawal" can be predicted with both the opponent process and the Pavlovian conditioning theories, the present data are more compatible with opponent-process theory.

REFERENCES

Hoffman, H.S., and Solomon, R.L. An opponent process theory of motivation: III. Affective dynamics in imprinting. Learning and Motivation, 5:149-164, 1974.

Siegel, S. Evidence from rats that morphine tolerance is a learned response. Journal of Comparative and Physiological Psychology, 89, 498-506, 1975.

Solomon, R.L., and Corbit, J.D. An opponent process theory of motivation: I. Temporal dynamics of affect. Psychological Review, 81, 119-145, 1974.

Solomon, R.L., the opponent process theory of acquired motivation: The costs of pleasure and the benefits of pain. American Psytchologist, 35, 691-712, 1980.

Ternes, J.W., O'Brien, C.P., Grabowski, J., Wellerstein, H., and Jordan-Hayes, J. Conditioned drug responses to naturalistic stimuli. Proceedings of the 41st Annual Meeting, Committee on Problems of Drug Dependence, NIDA Research Monograph, 1980.

Wikler, A. Conditioning successive adaptive responses to the initial effects of drugs. Conditional Reflex, 8, 193-210, 1973.

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AUTHORS

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Postulated Origin of Narcotic Antagonist Activity in Novel N-Methyl benzomorphans

Gail Hashimoto, Stanley Burt, and Gilda Loew

Addition of a 3-alkanone ($-CH_2CH_2C=OR$) side chain to position 9ß of metazocine results in compounds which demonstrate potent narcotic antagonism when the R group reaches a crucial length. For example, an analog with R = n-C_3H_7 is a potent pure agonist, while one with R = n-C_5H_{11} is a potent agonist and antagonist. Similar behavior is observed for the pair of analogs R = phenyl, R = CH_2-phenyl.

In order to understand the origin of antagonist activity with chain lengthening, energy-conformational studies were performed for these two pairs of analogs using both an empirical energy and a semiempirical quantum mechanical method (PCILO).

For all four analogs, two types of low-energy conformers were found, one involving internal H-bonding interactions between the carbonyl group and the protonated amine nitrogen, and the other corresponding to an extended chain conformer of the $-CH_2CH_2COR$ group. Since they are common to all analogs, -both of these conformations are plausible candidates for interaction at the receptor site leading to agonist activity.

Significantly, however, an additional low-energy conformation was found for the longer-chain analogs of each pair (i.e., R = C_5H_{11} and R = $CH_2\phi$) which was not present in the shorter-chain analogs. In this conformation the R group was directly above the protonated amine group and would interfere with its contact with an anionic. site thought to be a postulated requirement for agonism.

This conformer, then, could represent an antagonist mode of binding to the receptor which is accessible only as R is lengthened to five or more carbon atoms and could account for the onset of antagonist activity 'in these longer-chain analogs.

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Naltrexone and Psychotherapy

Nannette Stone-Washton, M.S., Richard B. Resnick, M.D., and Arnold M. Washton, Ph.D.

We previously reported a preliminary controlled study in detoxified opiate addicts comparing the efficacy of naltrexone combined with psychotherapy as opposed to naltrexone treatment alone. Our findings suggested that the combined treatment yielded better clinical outcome than naltrexone alone, but our conclusions were limited by methodological problem and incomplete follow-up data.

The present study is an extension of our earlier work with the following modifications and improvements: (a) only detoxified heroin addicts were included in the subject sample, and patients detoxified from long-term methadone maintenance were excluded; (b) there was greater consistency among therapists with regard to theoretical orientation and techniques; (c) stronger efforts were made to obtain the necessary follow-up information; and (d) the duration of the study was extended to 18 months.

METHODS

The subjects were 22 recently detoxified heroin addicts who took at least on dose of naltrexone, and stated willingness to accept random assignment to either of the two treatment conditions. All were at least 18 years of age, and had at least one year addiction history, no serious medical or psychiatric illness, and no recent methadone-maintenance treatment.

After signing an informed consent, each volunteer was randomly assigned to either naltrexone and psychotherapy (Hi Intervention) treatment or naltrexone alone (Lo Intervention) treatment. The Hi-Intervention treatment consisted of naltrexone maintenance requiring three clinic visits per week and assignment to an experienced psychodynamically oriented therapist who provided a minimun of one individual therapy session per week and additional sessions including group or family therapy, as indicated. The therapist maintained a high level of availability for crises and other problems that arose between scheduled sessions, and emphasis was placed on developing a strong therapeutic alliance with the

patient. The Lo-Intervention treatment consisted of naltrexone maintenance requiring three clinic visits per week and assignment to a case manager who provided crisis intervention and concrete services only. The case manager did not attempt to engage the patient in a therapeutic alliance or to encourage discussions of personal problems. No attempts were made to reach out to Lo-Intervention patients who missed clinic visits. Subjects in both groups were given access to the usual medical services of the clinic.

RESULTS

Pre-treatment demographic and drug&history variables, such as gender, ethnicity, employment, and percent of time drug-free since first becoming addicted, were similar for the two treatment groups. Table 1 shows that Hi-Intervention subjects stayed in

TABLE 1

Mean Time on Naltrexone Treatment (Weeks)

	HI	LO
All subjects	18.8 wks	6.0 wks
Subjects currently opiate-free	30 wks	8.5 wks
Subjects currently opiate-dependent	3.0 wks	7.0 wks

naltrexone treatment significantly longer than Lo-Intervention subjects. Within the Hi-Intervention group, subjects were more likely to be opiate-free at a 6- to 18-month follow-up than Lo-Intervention subjects (59% vs. 20%). Additionally, if re-addicted at follow-up, Hi-Intervention subjects were more likely to be in methadone-maintenance treatment, whereas Lo-Intervention subjects were likely not to be in treatment and using heroin.

TABLE 2

Follow-up status at 6-18 months

	Hi (N=12)		Lo (N=10)	
	N	(%)	N	(%)
Opiate free or in MMTP	10	(84%)	4	(40%)
On Heroin	1	(8%)	5	(50%)
unknown	1	(8%)	1	(10%)

Only 8% of Hi-Intervention subjects were using heroin at follow-up as compared with 50% of Lo-Intervention subjects. Within the Hi-Intervention group, subjects who were opiate-free at follow-up had a longer history of psychotherapy treatment before the study (1.6 years) than subjects who were re-addicted (0.7 years). However, treatment outcome was unrelated to the length of previous methadone-maintenance treatment.

DISCUSSION

Consistent with our earlier study[1] the combination of naltrexone and psychotherapy fostered better retention in treatment and greater likelihood of opiate abstinence than naltrexone alone. Five of the seven Hi-Intervention patients who are opiate-free at 6-18 months after starting naltrexone experienced at least one short relapse to heroin use: However, their engagement in psychotherapy appeared to help minimize the duration and potentially damaging effects of these relapses. Perhaps treatment outcome is better measured by the cummulative time in opiate-free status rather than status at an arbitrarily designated point in time. This is consistent with the fact that cycles of relapse and recovery are to be expected during the treatment process. Transient episodes of relapse during continued involvement in psychotherapy may be viewed as part of a continuing growth process rather than as treatment failures.

REFERENCES

1. Resnick, R. Washton, A., Stone-Washton N., and Rawson, R. Psychotherapy and Naltrexone in Opioid Dependence. In: Harris, L.S., ed. Problem of Drug Dependence 1980. National Institute On Drug Abuse Research Monograph 34. DHHS Pub. No. (ADM) 81- Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., 1981: pp. 109-115.

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Subject Index

MCV 4169 (NIH 9614, UM 1269)
See (-)-9-Hydroxy-4,7-dimethyl-C-homobenzomorphan Hydrobromide

MCV 4170 (NIH 9618)
See cis-3-(Octahydro-1ß,2-dimethyl-4aH-2-pyrindin-4a-yl)phenol, (Z)-2-butenedioic acid salt

MCV 4172 (NIH 9616)
See cis-3-Octahydro-1α, 2-dimethyl-4H-2-pyrindin-4a-yl) phenol, (Z)-2-butenedioic acid salt

MCV 4173 (NIH 9617)
See cis-2-(1,2-Dimethyl-4-propyl-4-piperidinyl)phenol (Z)-2-butenedioic acid salt

MCV 4175 (NIH 9624, UM 1258)
See dl-1-[(2α,6α,11S)-1-(1,2,3,4,5,6-Hexahydro-8-hydroxy-3,6,11-trimethyl-2,6-methano-3-benzazocin-11-yl)]-3-octanone methanesulfonate

MCV 4176 (NIH 9625A)
See 1-[(2α,6α,11S)-(±)-1-(1,2,3,4,5,6-Hexahydro-8-hydroxy-3,6,11-trimethyl-2,6-methano-3-benzazocin-11-yl)]-6-methyl-3-hepatanone methanesulfonate

MCV 4187 (NIH 9724, UM 1212)
See L-Tyrosyl-D-alanylglycyl-L-N-α-allyl-phenylalanine amide acetate

MCV 4190 (NIH 9650, UM 1198)
See N-4-Methylpentylnorketobemidone hydrobromide

MCV 4192 (zopemirac, NIH 9730, UM 1217)
See Sodium 5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrole-2-acetate

MCV 4195 (NIH 9735, UM 1223)
See N-Cyclopropylmethyl-7,8-dihydronormorphinone

MCV 4196 (NIH 9736, UM 1224)
See N-Cyclobutylmethyl-3-hydroxy-6-methylene-8ß-methyl-morphinan

MCV 4197 (NIH 9737, UM 1225)
See 17-Cyclopropylmethyl-7,7-dimethyl-3-methoxy-4,5α-epoxymorphinan-6-one

MCV 4199 (NIH 9738, UM 1226)
See Nitronaltrexone

MCV 4201 (NIH 9342, UM 1124)
See (-)-m-[2-(Cyclopropylmethyl)-1,2,3,4,4a,5,6,7,8,8a α-decahydro-4aß-isoquinolyl]phenol succinic acid salt

MCV 4206 (NIH 8834A, UM 972)
See (-)-13ß-Amino-5,6,7,8,9,10,11,12-octahydro-5α-methyl-5,11-methanobenzocyclodecen-3-ol hydrobromide

MCV 4208 (NIH 9787)
See 17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-6-fluoro-3-acetoxymorphinan

MCV 4210 (NIH 9791, UM 1238)
See N-Methyl-L-tyrosyl-D-serylglycyl-N-methyl-L-phenylalanyl-D-serinamide monoacetate

MCV 4212 (NIH 9804, UM 1245)
See (-)-(1R,5R,9R,2"S)-(5,9-Dimethyl-2'-hydroxy-2-(2-methyltetrahydrofurfuryl)-6,7-benzomorphan) L-tartrate

MCV 4213 (NIH 9805, UM 1246)
See (-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(2-methoxyisobutyl)-6,7,benzomorphan

MCV 4217 (NIH 9809)
(-)-(1R,5R,9R,2"S)-5,9-Dimethyl-2'-hydroxy-2-(2-methoxypropyl)-6,7-benzomorphan hydrobromide

MCV 4218 (NIH 9810)
See 2,3-Dihydro-2-methyl-3-[2-(dimethylamino)-propyl]-3-phenyl-1H-indol-1-carboxaldehyde methanesulfonate

MCV 4219 (NIH 9821, UM 1252)
See Oripavine hydrochloride

MCV 4220 (NIH 9824, UM 1253)
See (-)-trans-3-(Octahydro-2-methyl-4a(2H)-isoquinoline) phenol hydrobromide
See also (-)-trans-[(2-Methyl)-1,2,3,4,4a,5,6,7,8,8aα-decahydro-4aß-isoquinolyl]phenol hydrobromide

MCV 4221 (NIH 9825, UM 1254)
See (+)-trans-3-(Octahydro-2-methyl-4a(2H)-isoquinoline) phenol hydrobromide
See also (+)-trans-[2-(Methyl)-1,2,3,4,4a,5,6,7,8,8aα-decahydro-4aß-isoquinolyl]phenol hydrobromide

MCV 4222 (Oxazepam, NIH 9826)
See 7-Chloro-1,3-dihydro-3-hydroxy-5-phenyl-2H-1,4-benzodiazepin-2-one

MCV 4223 (flurazepam, NIH 9829)
See 7-Chloro-1-[2-(diethylamino)ethyl]-5-(O-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one dihydrochloride

MCV 4225 (NIH 9839, UM 1259)
See (-)-trans-3-(Octahydro-2-methyl-1H-2-pyrindin-4a-yl) phenol, (Z)-2-butanedioate

MCV 4226 (NIH 9840, UM 1260)
See (+)-trans-3-(Octahydro-2-methyl-1H-2-pyrindin-4a-yl)phenol, (Z)-2-butanedioate

MCV 4227 (NIH 9832, UM 1261)
See N-(6,14-Endoetheno-7,8-dihydromorphine-7α-carbonyl)-L-leucine ethyl ester hydrochloride

MCV 4288 (nabilone, NIH 9872, UM 1266)
See dl-trans-3-(1-1-Dimethylheptyl)-6,6aß,7,8,10,10aα-hexahydro-1-hydroxy-6,6-dimethyl-9Hdibenzo[b,d]pyran-9-one

MCV 4229 (NIH 9873)
See 3-(2-Ethyl-4,6-dimethyl-2-morpholinyl)phenol

MCV 4230 (NIH 9874, UM 1322)
See 17-Cyclopropylmethyl-4,5α-epoxy-6,6-difluoro-3-acetoxymorphinan

MCV 4231 (NIH 8508A, UM 809)
See (-)-5-(m-Hydroxyphenyl)-2-methylmorphan hydrochloride

MCV 4232 (NIH 8509A, UM 810)
See (+)-5-(m-Hydroxyphenyl)-2-methylmorphan hydrochloride

MCV 4233 (NIH 9886)
See (-)-5-(m-Hydroxyphenyl)-2-n-pentylmorphan hydrochloride

MCV 4235 (NIH 9895)
See (+)-4-Allyl-1-methyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1H-4-benzazonine

MCV 4236 (NIH 9896)
See (-)-4-Allyl-1-methyl-10-hydroxy-2,3,4,5,6,7-hexahydro-1,6-methano-1H-4-benzazonine

NIH 4591 (dextrophan, UM 106, UM 1262)
See d-3-Hydroxy-N-methylmorphinan tartrate

NIH 7958 (pentazocine, MCV 4268, UM 381)
See (±)-2'-Hydroxy-5,9α-dimethyl-2-(3,3-dimethylallyl)-6,7-benzomorphan

NIH 8439 (UM 747)
See (-)-5,9α-Diethyl-2'-hydroxy-2-methylenecyclopropyl-methyl-6,7-benzomorphan hydrochloride

NIH 8508A (MCV 4231, UM 809)
See (-)-5-(m-Hydroxyphenyl)-2-methylmorphan hydrochloride

NIH 8509A (MCV 4232, UM 810)
See (+)-5-(m-Hydroxyphenyl)-2-methylmorphan hydrochloride

NIH 8805 (UM 952)
See Buprenorphine

NIH 8833 (UM 961)
See (-)-cis-2-(Dimethylamino- m-hydroxybenzyl)cyclohexanol hydrochloride

NIH 8834 (NIH 8834A, MCV 4206, UM 972)
See (-)-13ß-Amino-5,6,7,8,9,10,11,12-octahydro-5α-methyl-5,11-methanobenzocyclodecen-3-ol hydrobromide

NIH 8834A (NIH 8834, MCV 4206, UM 972)
See (-)-13ß-Amino-5,6,7,8,9,10,11,12-octahydro-5α-methyl-5,11-methanobenzocyclodecen-3-ol hydrobromide

NIH 8835 (UM 973)
See 2,3,5,6,11,11b-Hexahydro-11,11b-dimethyl-1H-pyrido[3',2':4,5]pyrrolo[3,2-g]indolizine dihydrochloride

NIH 8863 (UM 983)
See N-(α-Pyridyl)-N-(1-ß-phenylethyl-4-piperidyl)-ethylcarbamate hydrochloride

NIH 9112 (UM 1076)
See (±)-3-Allyl-1,3-dimethyl-4-phenyl-4-propionoxy-piperidine hydrochloride

NIH 9256 (UM 1103)
See 2-Cyclopropylmethyl-9α-ethyl-2'-hydroxy-5-methyl-6,7-benzomorphan

NIH 9342 (MCV 4102, UM 1124)
See (-)-m-[2-(Cyclopropylmethyl)-1,2,3,4,4a,5,6,7,8,8aα-decahydro-4aß-isoquinolyl]phenol succinic acid salt

NIH 9521 (UM 1160)
See 3-α-(1,2ß,3ß,4-Tetramethyl-4-piperidinyl)phenol hydrobromide

NIH 9540 (MCV 4145, UM 1169)
See trans-3-(1,2-Dimethyl-4-propyl-4-piperidinyl)phenol hydrobromide

NIH 9541 (UM 1170)
See 4ß-(m-Methoxyphenyl)-1,3-dimethyl-4 α-piperidinol propionate hydrochloride

NIH 9549 (clonidine, MCV 4155, UM 1151)
See 2-(2,6-Dichloroanilino)-2-imidazoline hydrochloride

NIH 9576A (MCV 4157, UM 1242)
See (-)-cis-(Octahydro-2-methyl-1H-2-pyrindin-4a-yl) phenol, (Z)-2-butenedioic acid salt

NIH 9580 (phencyclidine, NIH 9580A, MCV 4158, UM 1264)
See 1-(1-Phenylcyclohexyl)piperidine hydrochloride

NIH 9580A (phencyclidine, NIH 9580, MCV 4158, UM 1264)
See 1-(Phenylcyclohexyl)piperidine hydrochloride

NIH 9585 (UM 1218)
See N-Cyclohexylmethylnorketobemidone hydrobromide

NIH 9596 (levonantradol, MCV 4161, UM 1265)
See (-)trans-5,6,6aß,7,8,9,10aα-Octahydro-1-acetoxy-9ß-hydroxy-6ß-methyl-3-(5-phenyl-2-pentyloxy)-phenanthridine hydrochloride

NIH 9612 (MCV 4167, UM 1267)
See (±)-9-Hydroxy-4,7-dimethyl-C-homobenzomorphan hydrobromide

NIH 9613 (MCV 4168, UM 1268)
See (+)-9-Hydroxy-4,7-dimethyl-C-homobenzomorphan hydrobromide

NIH 9614 (MCV 4169, UM 1269)
See (-)-9-Hydroxy-4,7-dimethyl-C-homobenzomorphan hydrobromide

NIH 9616 (MCV 4172)
See cis-3-Octahydro-1α,2-dimethyl-4H-2-pyrindin-4a-yl)phenol, (Z)-2-butenedioic acid salt

NIH 9617 (MCV 4173)
See cis-2-(1,2-Dimethyl-4-propyl-4-piperidinyl)phenol, (Z)-2-butenedioic acid salt

NIH 9618 (MCV 4170)
See cis-3-(Octahydro-1ß,2-dimethyl-4aH-2-pyrindin-4a-yl)phenol, (Z)-2-butenedioic acid salt

NIH 9624 (MCV 4175, UM 1258)
See (±)-1-[(2a,6α,11S)-1-(1,2,3,4,5,6-Hexahydro-8-hydroxy-3,6,11-trimethyl-2,6-methano-3-benzazocin-11-yl)]-3-octanone methanesulfonate

NIH 9625A (MCV 4176)
See 1-[(2α,6α,11S)-(±)-1-(1,2,3,4,5,6-Hexahydro-8-hydroxy-3,6,11-trimethyl-2,6-methano-3-benzazocin-11-yl)]-6-methyl-3-heptanone methanesulfonate

NIH 9637 (UM 1195)
See s-N-sec-Butylnormorphine hydrochloride

NIH 9650 (MCV 4290, UM 1198)
See N-4-Methylpentylnorketobemidone hydrobromide

NIH 9674 (UM 1200)
See (-)-4-Hydroxy-N-methylmorphinan-6-one hydrobromide

NIH 9677 (UM 1201)
See (-)-4-Hydroxy-N-methylmorphinan hydrochloride

NIH 9724 (MCV 4187, UM 1212)
See L-Tyrosyl-D-alanylglycyl-L-N-α-allyl-phenylalanine amide acetate

NIH 9730 (zopemirac, MCV 4192, UM 1217)
See Sodium 5-(4-Chlorobenzoyl)-,4-dimethyl-1H-pyrrole-2-acetate

NIH 9735 (MCV 4195, UM 1223)
See N-Cyclopropylmethyl-7,8-dihydronormorphinone

NIH 9736 (MCV 4196, UM 1224)
See N-Cyclobutylmethyl-3-hydroxy-6-methylene-8ß-methyl-morphinan

NIH 9737 (MCV 4197, UM 1225)
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NIH 9738 (MCV 4199, UM 1226)
See 2-Nitronaltrexone

NIH 9741 (UM 1221)
See N-2-Hexylnorketobemidone hydrobromide

NIH 9787 (MCV 4208)
See 17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-6-fluoro-3-acetoxymorphinan

NIH 9789 (UM 1237)
See 5-Hydroxypentylnorketobemidone hydrobromide

NIH 9791 (MCV 4210, UM 1238)
See N-Methyl-L-tyrosyl-D-serylglycyl-N-methyl-L-phenylalanyl-D-serinamide monoacetate

NIH 9804 (MCV 4212, UM 1245)
See (-)-(1R,5R,9R,2"S)-(5,9-Dimethyl-2'-hydroxy-2-(2-methyltetrahydrofurfuryl)-6,7-benzomorphan)-L-tartrate

NIH 9805 (MCV 4213, UM 1246)
See (-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(2-methoxyisobutyl)-6,7,benzomorphan

NIH 9809 (MCV 4217)
See (-)-(1R,5R,9R,2"S)-5,9-Dimethyl-2'-hydroxy-2-(2-methoxypropyl)-6,7-benzomorphan hydrobromide

NIH 9810 (MCV 4218)
See 2,3-Dihydro-2-methyl-3-[2-(dimethylamino)-propyl]-3-phenyl-1H-indol-1-carboxaldehyde methanesulfonate

NIH 9821 (MCV 4219, UM 1252)
See Oripavine hydrochloride

NIH 9824 (MCV 4220, UM 1253)
See (-)-trans-3-(Octahydro-2-methyl-4a(2H)-isoquinoline) phenol hydrobromide
See also (-)-trans-[2-(Methyl)-1,2,3,4,4a,5,6,7,8,8aα-decahydro-4aß-isoquinolyl]phenol hydrobromide

UM 747 (NIH 8439)
See (-)-5,9α-Diethyl-2'-hydroxy-2-methylenecyclopropyl-methyl-6,7-benzomorphan hydrochloride

UM 809 (NIH 8508A, MCV 4231)
See (-)-5-(m-Hydroxyphenyl)-2-methylmorphan hydrochloride

UM 810 (NIH 8509A, MCV 4232)
See (+)-5-(m-Hydroxyphenyl)-2-methylmorphan hydrochloride

UM 952 (NIH 8805)
See Buprenorphine

UM 961 (NIH 8833)
See (-)-cis-2-(Dimethylamino-m-hydroxybenzyl)cyclohexanol hydrochloride

UM 972 (NIH 8834A, MCV 4206)
See (-)-13ß-Amino-5,6,7,8,9,10,11,12-octahydro-5α-methyl-5,11-methanobenzocyclodecen-3-ol hydrobromide

UM 973 (NIH 8835)
See 2,3,5,6,11,11b-Hexahydro-11,11b-dimethyl-1H-pyrido[3',2':4,5]pyrrolo[3,2-g]indolizine dihydrochloride

UM 983 (NIH 8863)
See N-(α-Pyridyl),N-(1-ß-phenylethyl-4-piperidyl)-ethylcarbamate hydrochloride

UM 1076 (NIH 9112)
See dl-3-Allyl-1,3-dimethyl-4-phenyl-4-propionoxy-piperidine hydrochloride

UM 1103 (NIH 9256)
See 2-Cyclopropylmethyl-9α-ethyl-2'-hydroxy-5-methyl-6,7-benzomorphan

UM 1124 (NIH 9342, MCV 4201)
See (-)-m-[2-(Cyclopropylmethyl)-1,2,3,4,4a,5,6,7,8,8aα-decahydro-4aß-isoquinolyl]phenol succinic acid salt

UM 1151 (clonidine, NIH 9549, MCV 4155)
See 2-(2,6-Dichloroanilino)-2-imidazoline hydrochloride

UM 1160 (NIH 9521)
See 3α-(1,2ß,3ß,4-Tetramethyl-4-piperidinyl)phenol hydrobromide

UM 1169 (NIH 9540, MCV 4145)
See trans-3-(1,2-Dimethyl-4-propyl-4-piperidinyl)phenol hydrobromide

UM 1170 (NIH 9541)
See 4ß-(m-Methoxyphenyl)-1,3-dimethyl-4 -α-piperidinol propionate hydrochloride

UM 1195 (NIH 9637)
See s-N-sec-Butylnormorphine hydrochloride

UM 1198 (NIH 9650, MCV 4190)
See N-4-Methylpentylnorketobemidone hydrobromide

UM 1200 (NIH 9674)
See (-)-4-Hydroxy-N-methylmorphinan-6-one hydrobromide

UM 1201 (NIH 9677)
See (-)-4-Hydroxy-N-methylmorphinan hydrochloride

UM 1212 (NIH 9724, MCV 4187)
See L-Tyrosyl-D-alanylglycyl-L-N-α'-allyl-phenylalanine amide acetate

UM 1217 (zomepirac, NIH 9730, MCV 4192)
See Sodium 5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrole-2-acetate

UM 1218 (NIH 9585)
See N-Cyclohexylmethylnorketobemidone hydrobromide

UM 1221 (NIH 9741)
See N-2-Hexylnorketobemidone hydrobromide

UM 1223 (NIH 9735, MCV 4195)
See N-Cyclopropylmethyl-7,8-dihydronormorphinone

UM 1224 (NIH 9736, MCV 4196)
See N-Cyclobutylmethyl-3-hydroxy-6-methylene-8ß-methyl-morphinan

UM 1225 (NIH 9737, MCV 4197)
See 17-Cyclopropylmethyl-7,7-dimethyl-3-methoxy-4,5α-epoxymorphinan-6-one

UM 1226 (NIH 9738, MCV 4199)
See 2-Nitronaltrexone

UM 1237 (NIH 9789)
See 5-Hydroxypentylnorketobemidone hydrobromide

UM 1238 (NIH 9791, MCV 4210)
See N-Methyl-L-tyrosyl-D-serylglycyl-N-methyl-L-phenylalanyl-D-serinamide monoacetate

UM 1242 (NIH 9576A, MCV 4157)
See (-)-cis-(Octahydro-2-methyl-1H-2-pyrindin-4a-yl) phenol, (Z)-2-butenedioic acid salt

UM 1243
See 1,2,3,4,10,14b-Hexahydro-2-methyldibenzo{c,t} pyrazino{1,2a}azapine(mianserin)

UM 1245 (NIH 9804, MCV 4212)
See (-)-(1R,5R,9R,2"S)-(5,9-Dimethyl-2'-hydroxy-2-(2-methyltetrahydrofurfuryl)-6,7-benzomorphan L-tartrate

UM 1246 (NIH 9805, MCV 4213)
See (-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(2-methoxyisobutyl)-6,7,benzomorphan

UM 1252 (NIH 9821, MCV 4219)
See Oripavine hydrochloride

UM 1253 (NIH 9824, MCV 4220)
See (-)-trans-3-(Octahydro-2-methyl-4a(2H)-isoquinoline) phenol hydrobromide
See also (-)-trans-[(2-Methyl)-1,2,3,4,4a,5,6,7,8,8aα-decahydro-4aß-isoquinolyl]phenol hydrobromide

UM 1254 (NIH 9825, MCV 4221)
See (+)-trans-3-(Octahydro-2-methyl-4a(2H)-isoquinoline) phenol hydrobromide
See also (+)-trans-[2-(Methyl)-1,2,3,4,4a,5,6,7,8,8a α-decahydro-4aß-isoquinolyl]phenol hydrobromide

UM 1258 (NIH 9624, MCV 4175)
See dl-1-[(2α,6α,11S)-1-(1,2,3,4,5,6-Hexahydro-8-hydroxy-3,6,11-trimethyl-2,6-methano-3-benrazocin-11-yl)]-3-octanone methanesulfonate

UM 1259 (NIH 9839, MCV 4225)
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UM 1260 (NIH 9840, MCV 4226)
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UM 1261 (NIH 9832, MCV 4227)
See N-(6,14-Endoetheno-7,8-dihydromorphine-7α-carbonyl)-L-leucine ethyl ester hydrochloride

UM 1262 (dextrorphan, NIH 4591, UM 106)
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UM 1263 (ketamine)
See dl-2-(o-Chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride

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UM 1267 (NIH 9612, MCV 4167)
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