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Abstract

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Grant Number: 5P50DA005273-100001
PI Name: WALSH, SHARON L.
PI Email:
PI Title:
Project Title: INPATIENT STUDY

Abstract: This is a proposal to conduct a series of studies on the clinical pharmacology of levo-alpha acetylmethadol (LAAM), which are directly relevant to its safety and clinical efficacy as an opiate maintenance/detoxification agent. Using within- and between-subject experimental designs, these studies will be conducted under rigorously controlled, double-blind conditions. Healthy adult volunteers, who are either opioid-dependent or opioid-experienced, will participate in these studies as inpatients on a residential research laboratory. The broad clinical issues to be addressed include characterization of the acute pharmacodynamic properties of LAAM, assessment of the opioid blockade properties of LAAM, and evaluation of various LAAM induction procedures. Specifically, the first study will assess the acute pharmacodynamic properties of LAAM when given orally and intravenously, and will provide information regarding safety, dose-effects, time course, and parenteral abuse liability. The second study will assess the development of cross- tolerance in response to LAAM maintenance, with a particular emphasis on the duration of blockade and the dose response relationships. The third study will characterize the time course and magnitude of withdrawal symptoms during transition from a short-acting opioid to LAAM, using the current FDA recommended dosing schedule for induction. The fourth study will characterize the crossover from methadone to LAAM in order to assess the therapeutic value of short-term methadone treatment prior to LAAM induction in unstabilized heroin addicts, and to assess the efficacy, safety and patient acceptability of the current induction schedule of LAAM in methadone-maintained patients. In summary, these studies will provide information on the pharmacodynamic properties of LAAM relevant to its clinical utility, efficacy and safety as a pharmacological adjunct for the treatment of intravenous opioid abusers. The development of new and effective pharmacotherapies for substance abuse, such as LAAM, will serve to reduce the medical complications stemming from intravenous drug abuse, including a reduction in the spread of HIV infection and AIDS.

Thesaurus Terms:
drug abuse chemotherapy, drug screening /evaluation, human therapy evaluation, methadylacetate, opiate alkaloid
clinical trial, drug administration rate /duration, drug withdrawal, hospital patient care,

methadone, morphine, naloxone, pharmacokinetics
human subject, intravenous administration, oral administration

Institution:	JOHNS HOPKINS UNIVERSITY 3400 N CHARLES ST BALTIMORE, MD 21218
Fiscal Year:	1997
Department:	
Project Start:	
Project End:	
ICD:	NATIONAL INSTITUTE ON DRUG ABUSE
IRG:	

Version 2.0

Abstract

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Grant Number:	5R01DA010753-02
PI Name:	WALSH, SHARON L.
PI Email:	swalsh@jhmi.edu
PI Title:	ASSOCIATE PROFESSOR
Project Title:	THERAPEUTIC POTENTIAL OF KAPPA-OPIOIDS AGAINST COCAINE

Abstract: DESCRIPTION: (Applicant's Abstract) While recent epidemiological studies suggest that the prevalence of illicit cocaine use has plateaued over the past few years, cocaine abuse continues to pose a significant public health problem in the United States. Despite a vigorous research effort directed towards developing an effective medication, no pharmacotherapies to date have well demonstrated clinical efficacy against cocaine abuse. This project proposes to evaluate the potential efficacy of kappa-opioid compounds to alter the euphorigenic effects of cocaine and to reduce cocaine use. There is a substantial amount of preclinical evidence which suggests that compounds with kappa-opioid activity can decrease the neurochemical, behavioral, and reinforcing effects of cocaine. A series of four controlled laboratory studies are proposed that will systematically evaluate the safety and efficacy of two kappa agonists in humans when given alone and in combination with cocaine. Enadoline, a novel agent which acts selectively at kappa sites as a full agonist, and butorphanol, an agent with mixed opioid activity which acts as a partial agonist at kappa sites, will be tested. An initial within-subject dose-ranging study will evaluate and compare the safety and pharmacodynamic profiles of enadoline and butorphanol over a range of doses. The second study will evaluate and compare the effects of enadoline and butorphanol when administered under acute dosing conditions in combination with cocaine in an effort to determine the safety of concomitant administration of these agents. This within-subject study will also assess the ability of enadoline and butorphanol to alter the subjective response to intravenous cocaine and cocaine self-administration, as an index of their potential efficacy for reducing cocaine use. The third and fourth studies will evaluate the safety of chronic treatment with enadoline and butorphanol, respectively, characterize the tolerance that develops following chronic administration of these drugs, and evaluate their ability to alter cocaine self-administration and the pharmacodynamic effects of cocaine during chronic dosing. These studies will contribute importantly to our understanding of the interaction between cocaine and kappa opioids in humans and will systematically evaluate this class of drugs for their potential efficacy against cocaine abuse. These studies are relevant to the treatment of cocaine abuse and may lead to the development of an effective pharmacotherapy, thereby, reducing the HIV and other health risks associated with cocaine abuse and intravenous drug abuse.

Thesaurus Terms:
cocaine, drug abuse chemotherapy, drug addiction, drug addiction antagonist, human therapy evaluation, opioid
clinical trial, drug abuse prevention, drug interaction, drug tolerance, opioid receptor, pharmacokinetics, receptor binding, relapse /recurrence, self medication
clinical research, human subject, intravenous administration

Institution:	JOHNS HOPKINS UNIVERSITY 3400 N CHARLES ST BALTIMORE, MD 21218
Fiscal Year:	1997
Department:	PSYCHIATRY AND BEHAVIORAL SCIS
Project Start:	30-SEP-1996
Project End:	31-JUL-2001
ICD:	NATIONAL INSTITUTE ON DRUG ABUSE
IRG:	SRCD

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Grant Number:	5R29DA010029-02
PI Name:	WALSH, SHARON L.
PI Email:	swalsh@jhmi.edu
PI Title:	ASSOCIATE PROFESSOR
Project Title:	COCAINE WITHDRAWAL--HUMAN LABORATORY STUDIES

Abstract: APPLICANT'S ABSTRACT: The purpose of this project is to develop a controlled laboratory method for evaluating the effects of chronic cocaine use and withdrawal from cocaine in human cocaine abusing volunteers. The DSM-IV describes cocaine withdrawal as a syndrome characterized by dysphoric mood, changes in appetite, fatigue, and sleep disturbances, and it is believed that these symptoms and neurobiologic disruptions consequent to cocaine use contribute to relapse. Clinical studies assessing these phenomena have been conducted primarily in cocaine abusers undergoing detoxification. These studies have significantly contributed to our understanding of the cocaine withdrawal syndrome; however, there are elements of experimental control lacking in this open-label methodology. By developing a laboratory method for cocaine stabilization, it will be possible to control critical factors related to the emergence of withdrawal symptoms, such as the time since last cocaine use, amount of cocaine use, and recency of other drug use. This project proposes a series of three inpatient studies that will develop such a method, and will apply that method to evaluate the consequences of chronic cocaine and cocaine withdrawal in humans. The first study uses a within-subject ascending dose procedure to evaluate the safety, pharmacodynamic, and pharmacokinetic profiles of repeated oral dosing with cocaine across a range of doses. The oral route of administration was selected for use in this model for both safety and pharmacological reasons. The objective is to identify a dosing procedure that produces sustained plasma drug levels in the range commonly achieved during illicit use. The second experiment will assess the time course, magnitude, and nature of cocaine withdrawal under double-blind, placebo-controlled conditions using a between-groups design. Cocaine withdrawal in volunteers who have been stabilized on oral cocaine and abruptly transferred to placebo will be compared to spontaneous withdrawal in placebo-maintained volunteers. The dependent measures will include changes in mood, sleep, appetite, motor activity, and neuroendocrine function. The third experiment will evaluate the effects of chronic cocaine on brain dopamine systems using positron emission tomography. Dopamine-D receptor binding potential will be measured at different times during controlled withdrawal from cocaine in cocaine abusers, and these data will be compared to data obtained from normal drug-free volunteers. In summary, this project proposes to develop a safe and controlled laboratory method of cocaine stabilization and

abrupt cessation to evaluate the effects of chronic cocaine in humans. Data from the present studies may lead to a better understanding of the physiological, behavioral, and neurobiological consequences of chronic cocaine abuse. This method may provide an improved strategy for the development of medications that may be useful in preventing relapse and treating cocaine dependence.

Thesaurus Terms:
cocaine, drug addiction, drug withdrawal, neuropharmacology, psychopharmacology
appetite disorder, corpus striatum, dopamine receptor, endocrine disorder, mood disorder, psychomotor disorder, receptor binding, sleep disorder
clinical research, drug administration rate /duration, human subject, positron emission tomography, questionnaire, urinalysis

Institution:	JOHNS HOPKINS UNIVERSITY 3400 N CHARLES ST BALTIMORE, MD 21218
Fiscal Year:	1997
Department:	PSYCHIATRY AND BEHAVIORAL SCIS
Project Start:	01-JUL-1996
Project End:	31-MAY-2001
ICD:	NATIONAL INSTITUTE ON DRUG ABUSE
IRG:	SRCD