Attachment 1: Mock IRB Protocol

THE EFFECTS OF INFUSION RATE ONF PHYSIOLOGICAL AND BEHAVIORAL RESPONSES TO COCAINE

PRECIS

Cocaine abuse occurs by several routs of administration which vary in their toxicities and abuse liabilities. Drug delivery rate differences between routes may account for much of this variation. However, this issue has not been systematically studied. The purpose of this study is to determine whether the rate of infusion (shich corresponds to drug delivery rate) is an important determinant of cocaine's physiological and subjective effects in humans.

Using a double-blind, ascending-dose, within-subjects design, human volunteers will receive three doses of cocaine (10 mg, 25 mg, 50 mg) delivered intravenously over three infusion durations (10 seconds, 30 seconds, 60 seconds) over nine experimental sessions. Continuous cardiovascular, neurological, and psychological assessments will be made and analyzed for dose and infusion rate effects.

Knowledge of how rate of infusion moderates cocaine's physiological and subjective effects will aid in consolidating information on cocaine abuse, developing cocaine administration guidelines for future studies, and exploring the potential of slow cocaise delivery systems (eg. Patch or gum) to aid in the treatment of cocaine abuse.

The potential risks of this research are cocaine-related cardiovascular and neurological events; however, these risks will be minimized with the dosed of cocaine proposed, which have been safely used in many prior studies conducted at the Addiction Research Center (ARC) and elsewhere. In addition, subjects will receive extensive

cardiovascular and neurological evaluation prior to, during and following cocaine administration.

II. OBJECTIVES

The hypotheses in this study are:

1) The rate of cocaine infusion will affect the magniture of the measured physiological and subjective effects on intravenously administered cocaine.

1a) For a given dose, faster infusion rates will produce more rapid and larger cardiovascular effects and more intense subjective effects.

1b) The influence of infusion rate on physiological and subjective measures will differ in relative magnitude.

1c) Interaction effects exist between cocaine dose and infusion rate which may not be simply addictive.

2) If 1b and/or 1c are true, it will be possible to derive a dose and infusion rate range for human cocaine administration which yields significant subjective effects while producing minimal physiological effects.

The justifications for performing this research in humans are:

1) No replicable model exists for the quantitative prediction of cocaine's subjective effects in humans based on animal data.
2) Putative treatments for cocaine abuse will require safety and efficacy testing in the laboratory with human cocaine users receiving both the treatment and cocaine prior to testing in outpatients. Thus, empirically-derived guidelines for the administration of cocaine to humans are needed.

III. INTRODUCTION

Clinically, cocaine's behavioral effects, abuse, potential and toxicity are known to vary across routes of administration (Levine, et. al., 1991;Hollander and Hoffman, 1991), Infusion rate differences between the various routes may account for many of the differential effects observed; however, with other route-specific factors involved, this cannot be well-studied in the natural environment.

Experimentally, drug delivery has been shown to be an important variable in determining the physiological effects of many drugs, including cocaine, with increasing infusion duration associated with decreasing magnitude of corresponding physiological effect. (Resnick and Kasetenbaum, 1977, Fischman et. al., 1985, Kumor, et. al, 1989; Foltin and Fischman, 1991).

Drug delivery has also been to be an important determinant of abuse liability, with faster rates producing increased behavioral and reinforcing effects for several drugs of abuse. This phenomenom has been observed in humans pentobarbital (de Wit, et. al., 1992), diazepam (de Wit, et. al., 1993) and nicotine (Henningfield, et. al., 1993), and in animals for cocaine (Balster and Schuster, 1973). Research with nicotine-replacement therapy has found that nicotine, when administered at very slow infusion rates (i.e. via patch or gum), has little abuse potential while promoting cigarette abstinence (Henningfield, et. al., 1993). The creation of similar products as adjuncts for the treatment of cocaine abuse has been suggested.

The testing of putative pharmacological adjuncts for cocaine abuse treatments involves administering both the adjunct medication and cocaine to human cocaine uses in

a laboratory setting to determine drug safety and efficacy prior to outpatient clinical trials. Currently, guideline for the cocaine infusion rates to be used in these and other experimental studies have principally relied upon past experimenter experience or arbitrary standards. These rates have frequently varied across laboratories, thus neglecting a potentially important source of variance. Failure to account for infusion rate effects may affect both a study's verisimilitude to the natural environment and its safety, as "benign" cocaine dosed given over shorter infusion durations may prove problematic. The provision of empirically-derived guidelines for intravenous cocaine administration could improve both the efficacy and safety of such studies by specifying dose and infusion rate parameters which yield the subjective effects of interest while minimizing physiological responses.

Although results from animal studies can often indicate the direction and relative magnitude of a drugs physiological effects in humans, no animal data can adequately indicate a drug's subjective effects in humans (Fischman and Schuster, 1982, Katz, 1990). This severely limits the utility of animal studies where knowledge of subjective effects is essential, as with cocaine abuse.

In this study intravenous cocaine doses will be administered to human volunteers (10 mg, 25 mg, 50 mg) at various infusion durations (10seconds, 30 seconds, 60 seconds). Past research has utilized these dosing and infusiton parameters in humans without adverse events. For example, Kumor, et. al, (1989) at ARC administered "loading doses" of 60 to 80 milligrams of intravenous cocaine to eight experience cocaine users over a two to five-second time period and showed average systolic blood pressure and heart rate increases (three minutes post-administration) of 12mmHg and 25

bpm, respectively, without an adverse cardiovascular effect. Similarly, Jaffe et. al. (1989) administered 40 milligrams of cocaine intravenously over a two-second time period to nine experience IV cocaine users. Muntaner et. al. (1898, at theARC safely administered 40 milligrams of intravenous cocaine to eight male cocaine users over a twelve second infusion duration. In that study, subjects demonstrated systolic and diastolic blood pressure and heart rate increases (two minutes post-adminsitration) of 17 mmHg, 3 mmHg, and 40 bpm, respectively. Folton and Fishcman (1991) showed very similar effects on blood pressure and heart rate for 32 milligrams of cocaine administered, at 15 minute intervals, sequential doses of 35 mg. smoked cocaine-base to human cocaine users (over 10-15 second inhalation intervals) up to 350 mg. total, without incurring problems.

In another study protocol 25 subjects received a total of 601 IV cocaine injections of 25 mg (approximately 0.33 mg/kg) over a ten second infusion Durant (2.5 mg/second) with concurrent ECG and Holter monitor recordings. One benign adverse cardiovascular event occurred in close temporal relation to cocaine adminsitation; this consisted of ten minutes of asymptomatic S-T segment depression beginning 15 minutes after cocaine injection. Three other subjects were disqualified for displaying brief episodes of cardiac abnormality on 24-hour Holter monitors (all occurring at least 9 hours subsequent to the last cocaine administration). All subjects were asymptomatic at the time of occurrence, with follow-up assessments showing no evidence of permanent cardiovascular sequalae (Frankfield, et.al. 1994, submitted to Drug and Alcohol Dependence).

The occurrence of cocaine-related adverse events in humans at present is not predictable, although from emergency room reports it appears that much larger cocaine

doses than those used in human research (including this study) are usually involved (Gitter, et.al., 1991). To the greates extent possible, this study will reduce this risk by: 1) extensively screening subjects to exclude those in whom there is evidence of pre-existing health problems, especially cardiovascular or neurological abnormalities; 2) using only cocaine doses and infusion rates which have been used in humans in the past without recorded adverse health consequences; and 3) using only subjects whose self-report histories appear reliable and indicate extensive experience with cocaine at or above the doses and infusion rates proposed in this protocol without adverse consequences.

The present protocol follows the methods utilized in previous single dose intravenous cocaine administration studies done at the ARC with the addition of mechanized means of delivering intravenous drug at a steady, precisely defined infusion rate.

The ARC has the task of furthering the development of pharmacological treatments for drugs of abuse. Part of the development process involves administering both the treatment and abused drug under controlled circumstances to assess the probable efficacy and safety of these treatment sin the natural environment. This protocol addresses questions relevant to both the verisimilitude and safety features of this design.

Cocaine abuse remains a serious public health problem in this country, with numerous cocaine-related deaths occurring every year. To date, no effective treatment for cocaine abuse and/or dependence has appeared, making the development of new treatments and of safe, efficacious methods for testing these treatments a high priority at the ARC, which has a long history of performing innovative research in the area of human cocaine administration.

IV. METHODS

A. SUBJECT SELECTION AND RECRUITMENT

Description of Subject Recruitment/Screening: Up to twenty subjects ages 21 to 35 will be recruited and consented for this study to ensure that twelve subjects complete the protocol, as past experience at the ARC has indicated typical subject drop-out rated from all causes to be roughly 40%. As results of this study will be used in the development of guidelines for further cocaine administration studies and as characterization of interaction effects between drug dose and infusion rate are of importance, subject number is slightly higher than typically used within-subjects designs (N= eight to ten). Research Institute Contractors will perform recruitment using standard procedures described in the ARC Policy and Procedures Manual. We expect the demographic characteristics of this group to reflect those of the population on intravenous cocaine users in the Baltimore area. As this protocol requires the administration of intravenous cocaine and does not include treatment for cocaine abuse, participants will be considered subjects and will not be permitted into the study if they are seeking treatment.

In the addition to the standard requirements in the ARC Medical Policy Procedures Manual regarding screening of potential volunteers for research, including specific directives for research involving cocaine administration, all potential subjects will be questioned by the intake evaluator, the medically responsible investigator, and the nursing staff regarding their experiences taking intravenous cocaine in the natural environment and will be excluded if they: 1) indicate a history of never using cocaine at doses at least as great as the maximum

amounts to be administered in this study; 2) have never injected an intravenous dose of cocaine in ten seconds or less; 3) are not using cocaine at least three days a week; 4) display significant discrepancy in their histories of past cocaine use upon repeat questioning. These requirements are designed to ensure that subjects are not exposed to cocaine doses, frequencies, routes or rates of administration which they have not previously experienced. Other inclusion and exclusion criteria are listed above.

INCLUSION CRITERIA

1) Between 21 and 35 years of age.

2) A history of intravenous cocaine use of at least one year's duration, including use on at least six occasions in the past 30 days.

3) In good health as verified by medical history, physical exam, and screening laboratory tests as outlined in the ARC Medical Policy and Procedures Manual.

4) No family history of premature coronary artery disease, defined as history of documented coronary artery disease or report of "heart attack" in any first degree relative before the age of 50. No history of classical migraine headaches, Raynaud's phenomenon or adverse reaction to a medication known to cause vasospasm.

5) No evidence of underlying cardiovascular disease or significant abnormality, as assed by the following (inclusion criteria):

a) Standard twelve-lead electrocardiogram (interval parameters: PR 0.12-0.20

sec., QRS 0.06-0.12 sec., QT 0.36-0.44 sec., J-point elevation not to exceed two millimeters in two corresponding leads) with no ST-T evidence of ischemia, conduction system abnormalities, eg. AV block or bundle branch block, or pre-excitation abnormality.

b) Three minute rhythm strip (Rate 50-100 bpm, normal sinus rhythm).

c) Signal-averaged ECG (duration of QRS vector complex less than 110 milliseconds, duration of low-amplitude signal in terminal part QRS vector complex less than 32 milliseconds, root mean square voltage of the terminal 40 milliseconds greater than 25 microvolts).

d) 24-hour Holter monitor report (No episodes of ventricular tachycardia, idioventricular rhythm, couplets, pauses, multiformed PVC's, bigeminy or trigeminy. Normal sinus rhythm other than for the occasional occurrence of premature ventricular contractions (less than one per minute) premature atrial contractions (less than three per minute) per ARC Medial Policy and Procedure Manual guidelines. NO ST-T segment changes indicative of ischemia, in the opinion of a board certified cardiologist).

e) Echocardiogram (Ejection fraction greater than 0.45, ventricular wall thickness less than or equal to 1.2 centimeters, no evidence of significant valvular disease, pulmonary hypertension, or aortic root enlargement, upon review by board certified cardiologist).

f) Standardized Exercise Stress Test (No ST-T changes consistent with ischemia and exercise capacity falling within age-based norms).

6) No evidence of neurological diseases, focal neurological deficits or increased

vulnerability to stroke or seizure activity as assessed by the following (Inclusion criteria):

a) An extensive neurological examination performed by a board-certified neuropsychiatrist (No focal or lateralizing neurological signs, and all other tests of functions must be within normal limits).

b) a sixteen-lead standard electroencephalogram performed by a trained technician and reviewed by a board-certified neuropsychiatrist (No focal slowing or spike activity; all frequencies within two standard deviations of age-matched norms when tested under resting, photic drive, and hyperventilation conditions).

c) A CAT scan of the head (no evidence of structural brain lesions).

d) An assessment of Internal Cartoid Artery blood flow by Doppler Ultrasound using the QFM technique (Internal Cartoid Artery Flow 6-11 ml/sec. See Appendix III).

e) An assessment of Middle Cerebral Artery blood flow by Transcranial Doppler (MCA flow velocity within age-based normal limits without evidence of localized constriction. See Appendix III).

f) An extensive neuropsychological examination by a licensed neurologist (No response patterns indicative of either localized brain deficits in brain function).

7) Must have adequate venous access.
8) Resting blood pressure must consistently be less than 140 mmHG systolic and 90 mmHG diastolic.
9) Liver enzyme functions must show an ALG and AST of less than 80.

(Subjects with selected clinical laboratory measures outside the range of

normal which are not known to increase cocaine-related risks will be permitted to enroll).

10) A urine toxicology screen must be positive for cocaine use.

11) If female, a urine pregnancy screen must be negative at time of enrollment; in addition, the subject must have a history of receiving either a hysterectomy or tubal ligation, be using an adequate contraceptive method (birth control pills, IUD, or barrier method with spermicidal gel), or sign a document stating that she is sexually abstinent and agrees to remain so until study completion.

12) Must understand and sign a written consent form.

EXCLUSION CRITERIA

1) Seeking treatment for cocaine abuse or with a history of being in a treatment setting anytime in the past twelve months.
2) History indicative of a cocaine-related adverse reaction, including any history of acute chest pain, duspnea, or psychosis associated with cocaine use.
3) A history of hypertension or blood pressure reading markedly or consistently above 140 mmHg systolic or 90 mmHg diastolic.
4) A history of any of the following: heart disease, seizures, head trauma resulting in unconsciousness, cardiac arrhythmia, chest pain or non-chest wall etiology, hyperthyroidism or glaucoma. Family history of premature coronary artery disease in a first degree relative.
5) Evidence of heart block, rate or rhythm disturbance, cardiovascular disease, or changes consistent with past or present ischemia on a twelve-lead resting

ECG, three minute rhythm strip, signal-averaged ECG, 24-hour Holter monitor report, echocardiogram, or exercise stress test, including heart-rate variability at rest (i.e. vagal tone) outside age-matched norms.

6) Evidence of past present stroke, seizure head trauma, impairment or abnormal neurological functioning on either neurological examination, sixteen-lead EEG, head CAT scan, Cartoid Doppler Ultrasound, Transcranial Doppler Ultrasound, or by neuropsychological testing.
7) Current physical dependence on alcohol, sedative-hypnotics, or opiates.
8) Currently pregnant or lactating female.

Women and Minority Considerations: Male and female subjects will be recruited with equal vigor for this research study. Members of minority groups in whom cocaine use is prevalent will be routinely recruited and encouraged to participate.

Special Recruitment Considerations: All potential subjects will be offered the opportunity to receive free HIV antibody testing with pre- and post-test counseling. However, HIV status will not be a criteria for inclusion or exclusion, as it is not known to influence responses to or risks associated with acute cocaine exposure in otherwise healthy individuals. Universal precautions will be used with all subjects.

Potential subjects who are severely cognitively impaired or educationally disadvantaged that informed consent cannot be clearly obtained will be excluded. Other educationally or economically disadvantaged individuals will not be excluded from participation as this would result in a subject sample unrepresentative of the population of intravenous cocaine users; however,

homeless and other populations with enhanced vulnerability will not be specifically targeted.

B. PROCEDURES

Prior to inclusion in this study, a potential subject will receive a complete medical and drug use history, physical examination including repeat blood pressures, detailed neurological exam, screening blood tests, sixteen-lead EEG, twelve-lead ECG, three minute rhythm strip, signal-averaged ECG, 24-hour Holter monitor, echocardiogram, exercise stress test, head CAT scan, carotid Doppler ultrasound, transcranial Doppler ultrasound, and neuropsychological testing. If the subject is deemed medically appropriate for participation by these procedures, informed consent will be obtained and the subject will be enrolled in the study.

This study will proceed using a double-blind, pseudo-Latin Square within-subjects design, with all subjects receiving one of three doses of cocaine (10 mg, 25 mg, and 50 mg) over one of three infusion times (10 seconds, 30 seconds, and 60 seconds) during a given experimental session. Each subject will thus receive all nine possible combinations of drug dose and infustion time over the course of nine daily sessions. The doses of cocaine will be presented in an ascending order, i.e., subjects will receive three dosed of 10 mg, followed by three doses of 25 mg, and lastly, three dosed of 50 mg. this orfer is for safety reasons to ensure that no subject receives a high dose of cocaine prior to displaying an ability to tolerate a lower dose. However, within each dose level, the infusion time is ordered in a random counter-balanced manner using a Latin Square for the first nine subjects and an random order for the last three. This randomization is

deemed crucial to the validity of results as infusion rate is the primary independent variable of interest and as order effects are known to influence results in drug administration studies (Millar, 1983).

This study will be performed on an inpatient basis at the residential research unit of the Addiction Research Center. Each subject will be admitted for up to four weeks, during which time the experiment will be completed. Experimental sessions will run only on Monday through Friday in order to minimize effects due to change of routing and staff which occurs on weekends. Subjects will undergo an orientation and adaptation session during which they will be introduced to the experimental setting and will follow all procedures for a session except for receiving normal saline in lieu of cocaine. Then for ten weekdays, subjects will run through daily morning experimental sessions during which they will receive one dose of intravenous cocaine (or placebo) administered over a pre-set infusion rate. Each session will start at the same time each morning for a given subject in order to minimize effects due to time of ay or diurnal rhythms. In addition, time will be allowed for a review of the previous session's ECG, EEG, and Holter monitor data in order to determine if the subject should be permitted to continue the study. Thus a minimum of 48 hours will separate the administration of each cocaine dose. Non invasive periodic monitoring of heart rate, blood pressure, respiratory rate, skin and body core temperature, motor activity, EEG activity, and subjective and cognitive state will be performed from one-half hour prior to the cocaine administration and for a minimum of one hour post-administration, continuing until all physiological parameters return to within normal limits and the subject displays no evidence of persisting cocaine-relate effects. Assessment of Cartoid Artery blood flow will be

performed prior to and after cocaine administration for the highest dose. In addition, continuous ECG monitoring will also be performed for a minimum of 25 minutes following each cocaine administration. A full timeline is included in the appendix.

An ACLS certified physician will be present for the administration of the cocaine dose and for a minimum of 25 minutes thereafter to monitor the subject for any adverse effects, remaining readily accessible for two hours following cocaine administration. A crash cart will be present during the experimental sessions and ready access to consultation with a cardiologist will be available. At the scheduled time for cocaine administration, if a subject's systolic or diastolic blood pressure exceeds 140 mmHG or 90 mmHG, respectively, or if his heart rate exceeds 105 bpm, the cocaine will not be given and the session terminated for that day.

Any subject who experiences one of the following after receiving cocaine will be disqualified from receiving further cocaine doses: 1) a systolic blood pressure reading above 200 mmGH, 2) a diastolic blood pressure above 110 mmGH, 3) recorded heard rate exceeding a value of 8085 multiplied by (220 minus a subjects age), e.g. HR > 161 for a 30 year old subject, 3) any occurrence of ectopy other than either single premature ventricular contractions (less than one per minute) and/or single premature atrial contractions (less than three per minute) within 25 minutes of cocaine dosing, 4) reported or observed manifestations of acute or delayed dysphoric drug effects, 5) reported or observed chest pain or acute dyspnea during or after dosing, 6) ECG abnormalities indicative of ischemia, 7) spiking, focal slowing or occurrence of wave activity outside of two standard deviations of age-based norms (other than an expected increase in Beta wave activity) in or 8) changes in other physiological parameters indicative of the

occurrences of a potentially health-threatening response to the cocaine, (e.g., significantly increased or un remitting elevation in core body temperature). In addition the subject may request termination from the study at any time.

After completion of the tenth experimental session, the subject will remain on the residential research unit for 48 hours to monitor for the occurrence of any delayed sequelae to the administered cocaine; prior to discharge the subject will receive a physical exam to rule out the occurrence of any adverse health consequences incurred during the study.

Free outpatient treatment at the Clinic will be offered to all subjects upon completion. If appropriate treatment cannot be given in the Clinic, the subject will be referred to an appropriate community program,

DRUG ISSUES

Drug Preparation: Pure cocaine hydrochloride suitable for human use will be obtained through the ARC pharmacy. This cocaine will be dissolved in sterile saline and prepared for intravenous injection by ARC pharmacy personnel, using the guidelines set by the ARC to ensure fidelity and safety.

Drug Dose and Administration Procedures (See also Appendix II): This study