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NIDA Treatment Research and Development Division

A Phase 1 Parallel-Group, Double-Blind, Placebo-Controlled Cardiovascular and Behavioral Study Assessing Interactions Between Single Doses of Oral Reserpine and Intravenous Methamphetamine

1. Specific Aims

Reserpine will soon enter clinical trials for methamphetamine dependence. Even if reserpine is an effective pharmacotherapy for methamphetamine dependence, it is likely that addicts will take some illicit methamphetamine during reserpine therapy. Although concurrent use of methamphetamine and reserpine could occur at any time, the likelihood is greatest early in therapy. The pharmacologic effects of reserpine after the first few doses may be different from those after sustained administration. These early pharmacologic effects may be similar to the acute effects of methamphetamine. If the effects of acutely administered reserpine and methamphetamine are similar, additive toxicity could occur. Therefore, it is important to assess acute pharmacologic interactions before exposing patients to reserpine therapy.

In this parallel group clinical pharmacology laboratory experiment, we will assess pharmacodynamic interactions (with a focus on cardiovascular effects) of a 15 mg intravenous methamphetamine dose and single oral doses of reserpine (0.5 and 1.0 mg) or placebo.

The cardiovascular interactions between methamphetamine and reserpine will be assessed using a combination of complementary indices including:

a) Heart rate (HR), systolic and diastolic blood pressure, and pulse pressure (SBP, DBP and PP) to assess basic cardiovascular function.
b) Cardiac conductivity and myocyte repolarization assessed with electrocardiogram (ECG) and ECG heart rate corrected QT interval (QTc).
c) Systemic vascular resistance and cardiac output measured by impedance cardiography (IC).

CNS norepinephrine turnover (using the surrogate measure of urinary MHPG-sulfate excretion) will be used to assess the effects of methamphetamine and reserpine on CNS norepinephrine turnover.

Subjective symptom and mood effects will be measured using Adjective Scales and Visual Analog Scales (VAS) and craving measured by Brief Substance Craving Scale (BSCS).

2. Hypothesis

We predict that a single 0.5 or 1.0 mg oral dose of reserpine given 12 hours before methamphetamine will alter the pharmacological response to methamphetamine by increasing:

a) Heart rate and blood pressure response
b) Peripheral vascular resistance
c) Sympathetic tone
d) Urinary MHPG-sulfate excretion
e) Intoxication

f) Beck Depression Inventory scores on the days following methamphetamine administration

We predict that reserpine will not alter the effects of methamphetamine on:

a) Pulse pressure
b) Cardiac conduction and repolarization
c) Cardiac output
d) Vagal tone
e) Craving for methamphetamine

3. Background and Significance

A variety of pharmacological strategies are being pursued in the search for an effective treatment for methamphetamine addiction. One approach has been to target the dopaminergic neurotransmitter system involved in the reward mechanism to interrupt the reinforcing action of methamphetamine and thus reduce its use and prevent relapse (Hyman and Nestler 1996; Mendelson and Mello 1996; Ling and Shoptaw 1997). Methamphetamine is thought to produce its major effects through dopaminergic mechanisms in the midbrain. Methamphetamine causes dopamine release and blocks the reuptake of dopamine; the consequent excess of dopamine stimulates the midbrain reward centers. One therapeutic strategy is to develop and test dopamine antagonists to see if blocking dopamine can reduce methamphetamine abuse. A second, and diametrically opposed, therapeutic strategy is to develop and test dopamine agonists, agents that increase dopamine release or dopaminergic activity, to determine whether methamphetamine abuse can be reduced. This second strategy is based on a combination of theory and data suggesting that chronic methamphetamine use depletes brain dopamine and that this depletion is experienced as methamphetamine craving; the aim is to reduce methamphetamine craving and use by restoring the depleted dopamine system to normality.

Reserpine is one of the active extracts of Indian Snakeroot (*Rauwolfia serpentina*). Reserpine inhibits the action of the vesicular monoamine transporter (VMAT), producing a depletion of neuronal monoamines and decreased CNS sympathetic activity. Methamphetamine is an indirect sympatho-mimetic agonist. Acute doses block the reuptake of monoamines and serotonin and promote the release of transmitter from vesicular stores with a net effect of increasing synaptic neurotransmitter levels. Transmitter that is released but is not reaccumulated into synaptic vesicles diffuses out of the synaptic cleft and is metabolized. Continued exposure to methamphetamine eventually depletes neurotransmitter stores, resulting in a condition similar to reserpine treatment.

Acute treatment with reserpine might increase the acute effects of methamphetamine because reserpine, like methamphetamine, blocks the reuptake of monoamine neurotransmitters. Therefore, in the first few days of reserpine treatment, synaptic transmitter levels may be increased. Thus, reserpine may behave as an indirect sympathetic agonist and potentiate the actions of methamphetamine. The combination of two indirect sympathomimetic agonists could increase morbidity and even mortality.

The results of a preclinical acute methamphetamine-reserpine interaction study suggest that reserpine potentiates methamphetamine-induced lethality (MPI document, personal communication). In this study, 6 groups of male Crl: CD-1 (ICR) BR mice were treated with reserpine 0 or 3 mg/kg and then at 1 and 24 hours postreserpine were challenged with 0, 20, 40 and 60 mg/kg of methamphetamine. The study found no statistically significant interactions between reserpine and methamphetamine on neuro-behavioral measures of stereotypy, tremor, convulsions, or body weight. Reserpine alone had no effect on mortality. Although not statistically significant, there was a trend for the combination of reserpine and methamphetamine to increase the lethality of methamphetamine. Methamphetamine alone was lethal

in 1 of 8 animals in the 40 mg condition and 5 of 8 in the 60 mg/kg conditions. The combination of reserpine 3 mg/kg and methamphetamine increased lethality in a dose dependent manner, with 3, 5, and 7 of 8 animals dying in the reserpine 3 mg/kg and methamphetamine 20, 40, and 60 mg/kg groups, respectively. Animals expired between 2 and 5 days after combined drug challenges, suggesting that more than a simple additive cardio- or neurotoxic event occurred. Behavior was observed and no obvious behavioral or clinical findings were noted in the animals that expired compared with those who did not. Although there was no statistically significant increase in lethality and the mechanism responsible may not be cardiac, assessing the acute pharmacologic interactions between reserpine and methamphetamine is advisable before proceeding with clinical trials.

The effects of methamphetamine exposure in people treated with reserpine for longer periods of time are harder to predict. Depletion of vesicular transporter by reserpine should decrease the effects (shift the dose response curve to the right) of an indirect agonist like methamphetamine. Methamphetamine could further deplete transmitter stores, increasing reserpine effects but not impacting acute methamphetamine effects. Less likely, reserpine could blunt methamphetamine-induced transmitter depletion, possibly increasing some acute methamphetamine effects. In theory, reserpine will attenuate some of the acute stimulant effects without exacerbating the dysphoria produced by chronic methamphetamine exposure.

Prior to a randomized outpatient clinical trial, it is necessary to gather early phase 1 data to demonstrate that reserpine can be used safely in a population likely to use methamphetamine concurrently with reserpine and to explore whether and how reserpine might affect methamphetamine pharmacodynamics.

Pharmacology of Methamphetamine

Methamphetamine inhibits the reuptake and increases release of norepinephrine, serotonin, and dopamine. The dopaminergic activity is thought to contribute to the reinforcing effects of methamphetamine, and actions at dopamine and norepinephrine terminals may contribute to its sympathomimetic effects. Following i.v. administration, methamphetamine is eliminated with a $t_{1/2}$ of 12 ± 3.2 hours. Methamphetamine is metabolized by N-demethylation to amphetamine (Lin et al. 1997) and by hydroxylation to 4-OH methamphetamine (Lin et al. 1995). Both of these reactions are catalyzed by cytochrome P450 2D6 (CYP2D6). Approximately 38% of the administered dose is excreted in the urine unchanged (Mendelson et al. 1995). Methamphetamine and amphetamine also inhibit CYP2D6 with an apparent K*i* of 25 µM and 26.5 µM, respectively (Wu et al. 1997). This could shift metabolism during chronic administration towards urinary excretion of the parent compound.

We propose using a dose of 15 mg of intravenous methamphetamine. In prior studies, a 30 mg i.v. dose of methamphetamine produced peak plasma concentrations of 140 ng/mL (Mendelson et al. 1995). Logan et al. (1998) quantified methamphetamine levels in the postmortem blood of individuals involved in traffic fatalities that had detectable levels of methamphetamine. Levels ranged from 50 to 2,600 ng/mL (median 350 ng/mL). Thus, the dose of methamphetamine to be used in this study is representative of the levels in blood of methamphetamine users while at the same time being a safe dose to administer in the human laboratory setting.

In a pharmacokinetic and interaction study with alcohol, we reported the cardiovascular effects in 8 subjects following i.v. administration of 30 mg of methamphetamine (Mendelson et al. 1995). Blood pressure peaked at 2 minutes and heart rate peaked at 10 minutes. Both measures returned from peak values to a plateau level (20 mm Hg above and about 15 bpm above premethamphetamine baseline) 15 minutes following i.v. administration. These plateau levels slowly returned to baseline levels over the

rest of the day. Heart rate and blood pressure responses were dramatic in some individuals (50 mm Hg elevations in systolic blood pressure occurred). A few subjects exhibited a baroreceptor reflex response with a brief (less than 5 minute) relative bradycardia with heart rates of 55 to 60. All subjects had a robust, predictable response to the 30 mg dose with immediate intoxication ratings of about 50 (0=none, 100= max). In the interaction part of this study, methamphetamine (30 mg i.v.) was administered in combination with ethanol (1 gm/kg). Methamphetamine pharmacokinetics were not altered by the concurrent administration of ethanol, with the exception of lowering the apparent volume of distribution at steady state for methamphetamine. Based on these data, we concluded that doses around 30 mg produced at least half-maximal acute subjective and cardiovascular responses.

Methamphetamine is a substrate for CYP2D6 (Lin et al. 1997), so that its inhibition by co-administered drugs may affect the pharmacokinetics of methamphetamine. The biodisposition of reserpine is complex and probably proceeds through both oxidation and hydrolysis and reserpine is not a known substrate for 2D6. Therefore, it is unlikely that a metabolic interaction between reserpine and methamphetamine will occur.

Pharmacology of Reserpine

Reserpine has been approved for human use for more than 50 years. Although not currently widely used in the United States, the low cost, therapeutic efficacy, and overall excellent safety of reserpine make it a popular therapeutic agent in poor and developing countries. Reserpine is one of the active extracts of Indian Snakeroot (*Rauwolfia serpentina*) and was initially used in Hindu medicine to treat snakebite (hence, *serpentina*). Reserpine was an early and effective antihypertensive but an ineffective antipsychotic drug (Hardman et al. 1996). Currently, clinical use of reserpine is rare, having been supplanted by newer drugs, and is confined mostly to patients who initiated treatment long ago. The effects of reserpine are due to inhibition of the action of the vesicular monoamine transporter (VMAT), resulting in a depletion of neuronal monoamines and decreased CNS sympathetic activity. Synaptic terminals lose their ability to concentrate and store norepinephrine, dopamine, and serotonin. Reserpine-induced depletion of biogenic amines correlates well with antihypertensive actions.

Binding of reserpine to VMAT is probably irreversible, with recovery of sympathetic function dependent on the synthesis of new enzyme and storage vesicles. The cardiovascular and antihypertensive effects of the drug are the best studied. Pharmacodynamic effects begin shortly after the first dose, but it takes several weeks (possibly even months) before maximal effects plateau.

Little human pharmacokinetic data for reserpine are available, probably due to limitations in analytic technologies when the drug was widely used. Because reserpine binds tightly to its site of action and may not be in equilibrium with plasma, it is unlikely that plasma concentrations will be related to pharmacologic effects.

Reserpine undergoes extensive metabolism and none of the drug is excreted unchanged in the urine. However, some reserpine molecules do seem to escape metabolism, since significant amounts of intact reserpine have been found in fecal samples taken from both experimental animals and human beings after either oral or parenteral drug administration (Stitzel 1976). There are no data on the pharmacologic activity of the reserpine metabolites. Orally administered reserpine is readily absorbed from the GI tract. During this process, at least a portion of the drug is metabolized by the intestinal mucosa and then presumably is acted upon by serum esterases. Methylreserpate and trimethoxybenzoic acid are the primary metabolites which result from the hydrolytic cleavage of reserpine. The relative contributions of serum esterases versus hepatic metabolism in the biotransformation of reserpine in vivo are not known.

However, very little unmetabolized reserpine is eventually eliminated in the urine. In the liver, it is quite likely that both microsomal oxidative and hydrolytic enzymes contribute to the metabolism of reserpine.

Reserpine and Amphetamine Interactions

Interactions between amphetamine and reserpine were extensively investigated 50 years ago and helped to define mechanisms of amphetamine effects. Because most of this literature predates Medline, we have summarized the data below. Reserpine acts rapidly. After single doses of reserpine, brain monoamine levels decline within 24 hours and take several weeks to recover (Haggendal and Lindqvist 1964).

In rodents, reserpine decreases locomotor activity whereas the amphetamines increase activity. Pretreatment with reserpine usually attenuates or antagonizes the effects of subsequently administered amphetamine. For example, pretreatment with 2.5 mg/kg of reserpine antagonized the anorexic effects of racemic amphetamine in food-deprived rats, but had little effect on amphetamine-induced locomotion (Neill and Grossman 1971). In contrast, the same dose of reserpine, given either 3.5 hours or 21.5 hours before amphetamine, eliminated amphetamine-induced locomotor activity in rats; subsequent administration of amphetamine restored hyperactivity. In spontaneously hypertensive rats, treatment with d-amphetamine increases stereotypy. However, pretreatment with reserpine eliminates strain differences between spontaneously hypertensive and normotensive rats (McCarty et al. 1980). Reserpine pretreatment also decreases stereotyped responses to cocaine, pemoline, and methylphenidate in cats (Wallach and Gershon 1972).

These effects are probably not due to an alteration in amphetamine kinetics, as reserpine pretreatment decreases the duration of amphetamine effects without altering peak amphetamine levels (Dougherty and Ellinwood 1984). The dose response curve for amphetamine reversal of reserpine effects on locomotor activity indicates that maximal effects occur when reserpine is given 25 hours before amphetamine (Stolk and Rech 1967). To some, these data suggest that d-amphetamine is a directly acting sympathomimetic amine in the brain (Smith 1965).

A number of environmental factors influence the actions of amphetamines in mice and rats. Increasing environmental temperature or noise level or subjecting animals to crowded conditions increases the toxicity of amphetamines. When reserpine is administered to aggregated rats, there is a marked depletion of heart but not brain stores of norepinephrine and the number of mice dying from amphetamine treatment is reduced (Moore 1964).

Chronic treatment with reserpine produces a different spectrum of effects than brief (single or only a few doses) treatment with reserpine. In contrast to the reversal of reserpine-induced hypolocomotion by d-amphetamine, rats chronically treated with reserpine are more sensitive to the acute stimulant effects of d-amphetamine. Although chronic reserpine-treated mice show an increased sensitivity to the toxic effects of amphetamine, no increase in lethality was seen (Stolk and Rech 1968). Chronic reserpine and amphetamine seem to produce similar effects with decreased self-stimulation responding in animal models (Leith and Barrett 1980).

Explicit mortality data was not presented in any of the studies described above. However, there were no comments suggesting an increased mortality in animals treated with reserpine and amphetamine (or cocaine).

4. Methods

a. Study Design

This 7-day double-blind, parallel-group, placebo-controlled inpatient study will compare the effects of 15 mg of intravenous methamphetamine given 60 hours before and 12 hours after a single oral dose of reserpine (0.5 or 1.0 mg) or placebo.

Subjects will be randomized to one of three parallel groups. A parallel group design (as opposed to a crossover design) is needed because the duration of action of even a single dose of reserpine is unpredictable. Reserpine irreversibly binds to the vesicular monoamine transporter; reversal of this effect requires synthesis of new transporter, a process that can take from one week to one month.

b. Methods of Data Analysis

As appropriate, statistical group comparisons will be made with PC-SAS's general linear model procedure (SAS Institute Inc., Release 6.04 Edition, Cary, NC, 1990) and with multifactor repeated-measures analysis of variance using SAS (UNIX) or SuperANOVA (Macintosh) software applications. Physiologic data will be transformed to change scores (post-treatment minus pre) and analyzed by repeated measures analysis of variance (ANOVA). After a significant F test, pairwise comparisons will be performed using the least squares means analysis. Effects will be considered statistically significant at $P = 0.05$.

We have computed the power of our main measures from a prior methamphetamine study (Mendelson et al. 1995) similar to the study we propose. In this study, 30 mg of intravenous methamphetamine was administered and changes in heart rate (20±17; mean±SD) were the smallest differences between active drug and placebo conditions. Based on Cohen's (1988) effect size formula, data from a study with a sample size of 6 would yield a power of 0.80. However, because the parallel group design increases between-subject variance, a larger n is needed. Therefore, correcting for the slightly small effect size, we estimate that a sample size of 10 per group will be sufficient to achieve a power of .80, using a two-tailed alpha = 0.05.

c. Subject Selection

1) Who and Why

Methamphetamine-experienced subjects between the ages of 21 and 45 years, in good physical and mental health, with no cardiovascular pathology will be accepted into the study.

2) Total Number — 30 Subjects

3) Inclusion/Exclusion Criteria

Inclusion Criteria

Subjects will be included in the study if they:

1) Are normotensive and between the ages of 21 to 45.
2) Are in good physical and mental health and have a body mass index between 18 and 30.
3) If female and have childbearing potential, are using an acceptable method of contraception and are not pregnant.
4) Are able to give voluntary informed consent.

Exclusion Criteria

Subjects will be excluded if:

1) They are currently dependent (using DSM–IV criteria) on alcohol or other psychoactive drugs (except nicotine and caffeine).
2) They have positive qualitative urine screens for drugs of abuse on admission the morning of dosing or during the screening examinations.
3) They have significant medical or psychiatric illnesses that might impair their ability to safely complete the study, that might be complicated by study medication, or that may interfere with absorption, distribution, metabolism or excretion of drugs.
4) They have a history of major depression or pharmacotherapy for depression or anxiety within the last year.

Subjects will not be allowed to take concomitant medications (other than birth control pills), whether prescription or over-the-counter (OTC); subjects needing regular doses of prescription medications will be excluded.

d. Subject Recruitment

1) Sources and 2) Initial Contact Method

Subjects will be recruited through advertisements placed on Craig's list (a community Internet site) and advertisements in Bay Area newspapers.

e. Consent Process and Documentation

Informed consent will be obtained prior to study procedures in all subjects.

f. Procedures

1) Study Procedures

Screening. During their first visit to the laboratory, subjects will complete routine screening questionnaires, undergo a 12-lead EKG, and provide blood and urine samples for screening chemistries. Their second visit will involve a detailed history and physical exam by a physician (JM, or DH).

Drug Doses and Conditions

Reserpine Dosing. Subjects will be admitted to the GCRC for the entire study duration and at least 1 day before the first methamphetamine challenge. Reserpine (or placebo in the placebo group) will be administered at approximately 10 PM on the 4th hospital day. After successful screening, subjects will be randomly assigned to one of 3 parallel groups each containing 10 subjects. All groups receive methamphetamine 15 mg 60 hours before and 12 hours after reserpine. Groups are:

1. Reserpine 0.5 mg
2. Reserpine 1.0 mg
3. Placebo for reserpine

Methamphetamine Dosing. Methamphetamine 15 mg will be given on day 2 (60 hours before) and 12 hours after reserpine or placebo on day 4. Methamphetamine will be administered over 1 minute under infusion pump control.

Subjects will not be dosed if they have a positive qualitative urine test for abused drugs on the morning of dosing. Caffeine-containing beverages will not be allowed for 12 hours before each methamphetamine dose. No smoking will be allowed at any time after GCRC admission; nicotine patches will be offered to all smokers but discontinued 12 hours prior to methamphetamine doses. Although subjects will be in mild nicotine withdrawal at the time of methamphetamine dosing, avoiding drug-drug interactions between nicotine and methamphetamine or reserpine should decrease variability and improve our ability to detect subtle interactions between methamphetamine and reserpine.

Physiological Monitoring. On the days without methamphetamine challenges (days 0, 2, 3, and 5), subjects will have vital signs (heart rate, standing and supine blood pressure, respiratory rate, oxygen saturation, core temperature, and weight) and the noninvasive cardiac profile determined daily at 10 AM, 4 PM, and 8 PM. Vital signs will be obtained using a Critikon or Escort II monitor or a similar bedside device and noninvasive cardiovascular parameters measured using the instruments described above. On the days methamphetamine challenges are performed (study days 1 and 4), vital signs and the noninvasive cardiac profile will be obtained 15 minutes before and 5, 15, 30 and 60 minutes and at 1, 2, 3, 4, 6, 8 12, 18, 24, 30 36 and 48 hours after the infusion.

Subjective Measures. Subjective measures will be obtained daily at 8 AM, 4 PM, and 8 PM on study days 0, 2, 3 and 5. On days 1 and 4, when methamphetamine is administered, measures will be obtained starting 15 minutes before, and at 5, 15, 30, and 60 minutes, and 1, 2, 3, 4, 6, 8 12, 18, 24, 30 36, and 48 hours after the infusion. Items will include "any drug effect," "good drug effect," "bad drug effect," "headache," "dizziness," "desire for methamphetamine," and "craving for methamphetamine." The Beck Depression Inventory (Beck et al. 1996) will be administered daily at 4 PM.

Biosample Measures. All urine will be collected in 24-hour intervals and assayed for MHPG-sulfate by HPLC. On days 1, 4, and 6, aliquots will be sent for qualitative drugs of abuse screens.

Cardiovascular Measures. A series of non-invasive complementary cardiovascular measures assessing ventricular function (impedance cardiography), cardiac conductance and repolarization (ECG QTC interval), and peripheral vascular dynamics (impedance cardiography) will be obtained frequently throughout hospitalization. Data acquisition for the entire non-invasive panel requires about 10 minutes.

Methamphetamine produces a sustained rise in systolic and diastolic blood pressure, most likely due to peripheral vasoconstriction. Peripheral vasoconstriction increases systemic vascular resistance (SVR). In the past, accurate measurement of SVR required right heart catheterization with attendant risks and complications. A new technique, Impedance Cardiography, allows accurate, rapid, and reproducible recording of several cardiovascular parameters, including SVR, noninvasively (Nelesen et al. 1999; Arthur and Kaye 2001). We will use impedance cardiography to measure the effects of methamphetamine-induced vasoconstriction on vascular resistance and cardiac work. Methamphetamine increases cardiac output, although the heart rate may be reflexively slowed (Mendelson et al. 1995). Subjects in this study are likely to experience some effect on left ventricular (LV) function after exposure to methamphetamine. Since clinical assessment cannot detect changes in LV function (Hardman et al. 1996), we will use impedance cardiography to measure LV function after methamphetamine.

Impedance cardiography will be measured using a computerized system consisting of a personal computer with customized data processing software, a transmitting unit with 4 pairs of electrodes for analyses of the thoracic impedance field. Two of these 4 electrodes will be placed above the sterno-cleidomastoid region of the subject's right and left neck; 2 more pairs will be placed in the midclavicular line on each side at the lower thoracic aperture at the xiphoid level.

Safety Criteria. Vital sign and behavioral abnormalities will be used to determine the safety of continued study participation. Vital signs must be within acceptable limits before reserpine (or placebo) is administered. Criteria for holding reserpine (or placebo) and terminating study participation are:

1. Supine heart rate >150 or <50, systolic blood pressure >180 or <95, diastolic blood pressure >120 or <50, respiratory rate >24 or <8.
2. Orthostatic systolic blood pressure change greater than 10 mmHg and/or heart rate change greater than 10 beats per minute.
3. Reported chest pain or dyspnea.
4. Subject confusion, agitation or inability to properly complete test procedures.
5. Any other significant adverse effect regarded as being due to the experimental procedures.

If any of the following occur during or within 2 hours of methamphetamine dosing in the first challenge session, the subject will not continue in the study:

1. Supine heart rate > 80% predicted maximal for age or <50, systolic blood pressure >210 or <90, diastolic blood pressure >120 or <50, respiratory rate >24 or <8.
2. Significant arrhythmia defined as ≥6 beats nonsinus supraventricular tachycardia or =3 beats ventricular tachycardia.
3. Reported chest pain or dyspnea.
4. Subject confusion, agitation or inability to properly complete test procedures.
5. Any other adverse effect regarded as being due to methamphetamine or the experimental procedures.

If unexpected abnormal vital signs occur, subjects will be closely observed with vital sign measurements every 5 minutes until the abnormalities abate. If stopping criteria are exceeded, subjects will be closely observed for at least 24 hours before being discharged from the GCRC.

Alterations in CNS norepinephrine turnover produced by methamphetamine and reserpine will be assessed using urinary MHPG-sulfate excretion. Methamphetamine pharmacokinetic profiles will not be obtained because it is unlikely that alterations in the biodisposition of methamphetamine will be related to any pharmacodynamic effects. Reserpine pharmacokinetic profiles will not be obtained because venous levels are unrelated to pharmacologic effects. Subjective pharmacodynamic effects will be assessed with symptom reports and measured with visual analog scales.

Biological Samples

Urine Samples. All urine will be collected in 24-hour intervals (starting at 9:30 AM daily) and analyzed for MHPG-sulfate. A drug of abuse screen will be performed on admission and every 48 hours while on the GCRC and just before each methamphetamine dose.

2) Time (Frequency and duration of each study procedure; total amount of time)

Screening. The first visit to the laboratory will last 1 to 2 hours; subjects will complete routine screening questionnaires, undergo a 12-lead EKG, and provide blood and urine samples for routine labs. If subjects are called for a second visit, they will be compensated (see k below); this visit will involve a detailed history and physical exam by a physician and stress echocardiography, and will last approximately 2 to 3 hours.

Study Sessions. Subjects will be admitted to the UCSF General Clinical Research Center (GCRC) at Moffitt Hospital 24 hours before the first methamphetamine challenge. They will remain on

the ward until 48 hours after the last methamphetamine challenge dose. The total duration of GCRC admission is 5 nights.

3) Study Sites

Study procedures will be carried out at the UCSF General Clinical Research Center.

g. Risks/Discomforts

The most common side effects with intravenous methamphetamine are palpitations, euphoria, anxiety, panic, or dyspnea. In multiple prior experiments where similar or larger doses of intravenous methamphetamine have been administered (up to 0.5 mg/kg), few adverse effects have been seen or reported. Based on our prior experience, we expect the effects of the proposed 30-mg dose to be mild in intensity and brief in duration.

We will administer a single oral 0.5 or 1.0 mg dose of reserpine. This dose is safe, has pharmacologic activity, and is generally well tolerated. Adverse reactions are dose related and usually mild, with the majority affecting the CNS. Sedation and inability to concentrate are commonly reported. With *repeated* doses *greater* than 1.0 mg/day, depression and suicide can occur. Although serious depression with daily doses less than 1.0 mg per day has been reported, a history of depression is often present. Depression usually occurs insidiously, over a period of weeks or months and resolves with discontinuation of the drug; there are no reports of depression or suicide following a single dose of reserpine. Other reported side effects include nasal congestion and dyspepsia (Hardman et al. 1996).

There is a moderate amount of pain, discomfort, bruising, and a very remote potential for infection associated with the placement of needles in arm veins for drug administration.

There is also likely to be some stress from the fact the subject will be living on a hospital ward, and will be subjected to repeated blood sampling, physiological monitoring, questionnaires, and other study procedures. We will make every effort to minimize such stress.

h. Treatment and Compensation for Injury

This will be according to standard UCSF policy. The following statement is included in the consent form: "If I am injured as a result of being in this study, treatment will be available. The University of California, depending on a number of factors may cover the costs of such treatment. The University does not normally provide any other form of compensation for injury. For further information regarding this, I can either discuss it with the investigators or, if this is not clarified to my satisfaction, I can call the UCSF Committee on Human Research Office at (415) 476-1814."

i. Alternatives

The alternative is not to participate

j. Costs to the Subject

There will be no costs to the subject.

k. Reimbursements of Subjects

Subjects will earn compensation starting with the second screening session. This session involves undergoing a comprehensive physical examination and a stress echocardiogram. This session is expected to require 2 to 3 hours; compensation of $30.00 will be provided. They will receive $150.00 for

each night they stay on the research ward plus a 10% bonus if they complete all procedures; the total amount participants can earn is $858.00.

If a subject does not complete the experimental series, they will be paid their earnings up to that time, but will get no bonus. Subjects who actively abuse illicit drugs while on the GCRC will lose all compensation. Payment will be by University of California check. Subjects must provide their home address and a social security number to receive payments for participating in this study.

l. Confidentiality of Records

Subject confidentiality is always a primary concern. Privacy will not be guaranteed. For hospitalized volunteers, there are many possible confidentiality leaks. Prospective subjects will be told of this clearly. Anyone with strong concerns about being identified as a research subject will be encouraged not to participate. Research forms and files are coded by individual code numbers, kept in secure files or on protected computer disks with any identifying information linking to name only available to research personnel involved in the study. In any UCSF hospital patient records, sufficient medical information must be included to conform with JCAH and UCSF hospital record requirements, but possibly embarrassing information will be mentioned, if at all, in only the most circumspect way.

5. Qualifications of Investigators

Dr. Mendelson is a general internist who has extensive experience in pharmacologic studies similar to the one proposed. He has studied the cardiovascular and neuropsychopharmacologic effects of MDMA, methamphetamine, and cocaine. Dr. Jones is a psychiatrist and clinical psychopharmacologist who has been doing studies like this for almost 30 years at UCSF. Dr. Harris is a psychiatrist trained in substance abuse research and pharmacology who is experienced in psychiatric diagnosis and human laboratory studies of drug administration. Dr. Nath is an internist who has trained in clinical psychopharmacology for over 7 years with Drs. Jones and Mendelson.

6. Reference to Special Requirements and Attachments

None.

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