

COCAINE-METYRAPONE INTERACTION STUDY

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1.0 SYNOPSIS

The primary goal of this study is to evaluate the safety of metyrapone (2-methyl-1,2-di-3-pyridyl-1-propanone) (MRP) for use in an outpatient study in which participants would be given two 750 mg doses of MRP per week. Secondary study goals are to evaluate the possible efficacy of MRP as a treatment for cocaine dependence and to compare three factors hypothesized to induce cocaine craving: cocaine cues, stress, and cocaine itself. The present study will utilize a double blind, placebo-controlled, crossover design with three factors: 1) medication (750 mg MRP vs. placebo), 2) relapse trigger (cue response vs. stress), and 3) infusion (cocaine vs. placebo). A total of 12 non-treatment seeking cocaine addicts will be recruited for this eleven-day inpatient study. On the third full day of hospitalization (i.e., Day-2), subjects will undergo three consecutive “initiation” infusions of 20 mg of cocaine, placebo, and 40 mg of cocaine. Starting on Day 4, each subject will experience either the cue response (CR), or the Stress Imagery (SI) procedures, followed by a cocaine (40 mg) or placebo infusion. These conditions will be completed twice, once on MRP and once on placebo. There will be a 96-hour washout period between the MRP and placebo conditions to eliminate possible carry-over effects. Safety measures will include heart rate, adverse events, electrocardiogram (ECG), and blood pressure. Efficacy measures will include visual analog scale (VAS) ratings of craving, drug effect, and mood. Pharmacological measures will include cortisol and adrenocorticotrophic hormone (ACTH). MRP and cocaine plasma levels will also be measured. It is hypothesized that the concomitant administration of MRP and cocaine will be well tolerated by study subjects. We also predict that MRP will block stress-induced plasma cortisol surges, will decrease cocaine craving elicited by CR and SI and will have no effect on VAS ratings of the subjective effects of cocaine. An outpatient MRP trial will be initiated upon determination that the combination of MRP and cocaine are well tolerated by study patients.

2.0 BACKGROUND/ STUDY RATIONALE

2.1 The Need for a Pharmacological Treatment of Cocaine Dependence

The latest available national survey¹ estimates that in 1997, there were approximately 2.6 million occasional cocaine users (people who used the drug at least once but less than 12 days in the previous year) and 682,000 frequent users (51 or more days of use per year). An estimated 1.5 million Americans were current cocaine users having used at least once in the month prior to the survey. The estimated number of current crack users in 1997 was 604,000. While these numbers have declined somewhat over the years, it is apparent that cocaine addiction continues to be a pervasive and persistent problem.

In 1997, the Office of National Drug Control Policy (ONDCP)² reported that cocaine, particularly in crack form, remained the most widely abused illicit drug. Treatment providers confirmed that cocaine/crack was the major drug of abuse among their presenting clients while law enforcement officials cited it as one of the most common drugs used by those involved in criminal activity. Cocaine continues to be the most cited drug in coroners’ reports

(47% of total drug citations in 1993³), and the second most cited drug after alcohol in emergency room visits (30% of total emergency room drug citations in the first half of 1997⁴).

The enormous suffering resulting from this addiction affects not only the individual addicts, but also their families, friends, and communities. Unfortunately, at the present time, there is no consistently effective treatment for cocaine addiction, and no specific pharmacological treatment whatsoever. Present-day treatment consists of psychosocial interventions, generally of a behavioral nature (e.g., relapse prevention techniques), or twelve-step programs. Although these treatment modalities help some patients in the short term, the long-term relapse rate is very high. Taking these factors into account, the National Institute on Drug Abuse (NIDA) has indicated that its number one priority is to develop an anti-cocaine medication that will effectively combat this stubborn addiction⁵. In preliminary, open label studies, medications such as bromocriptine, desipramine, and amantadine appeared to be efficacious in treating cocaine dependence^{7, 8}, but more recent controlled studies are less optimistic⁹.

2.2 The Possible Role of the Hypothalamic-Pituitary-Adrenal Axis in Cocaine Dependence

Until recently, the vast majority of cocaine research has focused on the dopamine hypothesis of cocaine dependence. However, dopaminergic agents tested to date have not yielded an effective pharmacological treatment and, thus, some investigators have started exploring the role of other systems in cocaine dependence. One area of particular interest is the neuroendocrine system.

Several lines of evidence have suggested that activation of hypothalamic-pituitary-adrenal (HPA) axis function may be important in mediating the physiological and subjective effects of cocaine use. The HPA axis is also felt to be a key system in the behavioral sensitization which develops after intermittent cocaine use, and which may be responsible for the relapsing nature of this illness. Animal studies have investigated the relationship between stress-induced elevations of plasma corticosterone (the primary glucocorticoid in the rat) and cocaine self-administration. Investigators have found a significant positive correlation between the amount of cocaine self-administered and the amount of plasma corticosterone present prior to exposure to cocaine.^{10,11,12}

Perhaps even more compelling are findings by Goeders and Guerin¹³ that adrenalectomized rats did not self-administer cocaine in response to low dose cocaine reinforcement; whereas, sham operated rats and adrenalectomized rats who were given steroid replacement continued to self-administer cocaine. These authors and others have also investigated the effects of "reversible pharmacological adrenalectomy" on cocaine self-administration in the rat model.^{14,15,16} They found that MRP and ketoconazole, both corticosterone synthesis inhibitors (via blockade of CYP450_{11β}), each decreased cocaine self-administration. The reverse of this was also found to be true; that is, increasing corticosterone levels in the rat, induced the acquisition and maintenance of psychomotor stimulant self-administration.^{11,17,18} The authors

interpret their findings to suggest that "corticosterone is not only important, but may be necessary for cocaine reinforcement."

Studies in humans have demonstrated that acute cocaine administration increases ACTH and cortisol secretion¹⁹ and, that the sympathomimetic effects of cocaine on heart rate and blood pressure parallel the rise in serum cortisol levels.²⁰ Monoaminergic neurotransmitters exert stimulatory control over cortisol releasing factor (CRF) in rats; thus, the neuroendocrine effects of cocaine appear to be mediated through adrenergic, dopaminergic and serotonergic mechanisms in the brain.^{21,22,23}

Recently, Ward et al²⁴ studied human cocaine dependent volunteers to determine whether reversible pharmacological suppression of cortisol, via administration of ketoconazole, would reduce the cardiovascular and subjective effects of cocaine and cocaine craving. In this study ketoconazole (600 or 1200mg) or placebo was administered to subjects one hour prior to smoking cocaine or placebo. Ketoconazole was found to reduce, in a dose-dependent fashion, cocaine-induced cortisol, but not ACTH release. It was also shown to attenuate the cocaine-induced increase in heart rate and blood pressure. However, suppression of cortisol secretion, by ketoconazole, was not associated with a reduction in ratings of the subjective effects of cocaine (e.g., high, stimulated).

While the negative results of this study suggest that the HPA axis may not be as important in mediating cocaine effects and craving in man as in other animal species, this one study cannot be considered a final indictment of this approach for several reasons. Ward, et al²⁴ is a very well done, but small study (8 participants) with a few limitations that have been acknowledged by the authors. Cortisol levels at the time of cocaine administration were never below 5 µg/dl, suggesting that ketoconazole, at the doses used, did not completely inhibit 11β-hydroxylase.²⁵ MRP or higher doses of ketoconazole may be more effective at completely suppressing cortisol production after a single dose. Ketoconazole plasma levels were not measured in this study. Since there may be ethnic or individual differences in the metabolism of ketoconazole, it is important to correlate effect with plasma levels.²⁶ In addition, order effects were not randomized in this study. Ketoconazole was always administered with placebo given first and the highest dose of ketoconazole (1200 mg) given last. Therefore, the effects of ketoconazole on the subjective measures may have been completely confounded with time in the study. This may have biased the results against a ketoconazole effect if the subjects became less apprehensive with time and were more able to appreciate the effects of the cocaine dose.

The Ward et al.²⁴ study was also problematic in that the measures of cocaine's subjective effects (e.g., high, stimulated, etc.) were taken at -70, 4, 30, 44, and 74 minutes after the smoked dose of cocaine. Our experience with human volunteers indicates that the peak response of subjective effects generally occur at 1 to 9 minutes following IV administration of cocaine. Ratings generally returned to normal within 30 minutes of the cocaine infusion. Since the time-course of the subjective effects of IV cocaine administration and smoked cocaine are similar, the peak of subjective measures may have been missed in this study. Finally, the Ward et al.²⁴ study measured ketoconazole's efficacy in blocking cocaine's subjective effects but did not measure its ability to block cue-induced or stress-induced

craving. This is particularly problematic since the pre-clinical literature suggests that ketoconazole is unlikely to completely block cocaine's euphoric effects but that it may reduce an individual's susceptibility to stress-induced relapse.²⁷ In the present study, we will specifically measure the effects of HPA axis suppression on cue-induced and stress-induced craving for cocaine.

2.3 Rationale for the use of metyrapone to treat cocaine addiction

We have chosen to use MRP as an inhibitor of steroidogenesis in this study rather than ketoconazole for the following reasons: 1) Ketoconazole is only FDA approved for the treatment of fungal infections. Metyrapone is indicated as a diagnostic agent for the assessment of HPA axis function (Prod. Info. Metopirone®, 1991). This test is used as an assessment of both pituitary and adrenal reserve and thus can be used in the diagnosis of both primary and secondary adrenal insufficiency. In addition to its FDA indication, MRP has also been studied as a treatment for Cushing's syndrome and depression.^{28,29,30,31,32} 2) Metyrapone produces its effects on corticosteroid biosynthesis by inhibiting primarily a single enzyme, CYP450_{11β}. This enzyme carries out the final step in cortisol biosynthesis, 11β-hydroxylation of 11-deoxycortisol to cortisol in the adrenal cortex. After a dose of 750mg of MRP, cortisol levels are rapidly and markedly reduced and stay low for several hours. In addition to inhibiting CYP450_{11β}, ketoconazole also has effects on other enzymes in the synthesis of adrenal steroids, including CYP450_{17α} and CYP450_{sc}. It is a more potent inhibitor of the biosynthesis of androgens and mineralocorticoids than is MRP.³³ 3) Metyrapone is preferred to ketoconazole since it is generally well tolerated with minor reported adverse reactions including nausea, vomiting, abdominal discomfort, headache, dizziness and sedation (Prod. Info. Metopirone®, 1991). Ketoconazole's use is associated with common, but reversible hepatic dysfunction, manifested by increased hepatic enzyme serum levels. Furthermore, its use has been limited because of the development of rare, but potentially fatal idiosyncratic hepatic dyscrasias.³³

Based on a review of the literature, we are predicting that MRP will reduce an addicted individual's reactivity to cocaine cues and stress and/or will decrease the pleasant effects of cocaine. The specific goal is to utilize MRP to interfere with craving in response to a stimulus and/or to decrease the reinforcing effects of a dose of cocaine and, thus, make relapse less likely. Based on MRP's rapid effect of blocking cortisol synthesis within the first hour of administration, MRP may have a particularly useful application for the cocaine addict who is often an episodic user. Episodes of use can be triggered by cues from the environment such as meeting a friend, getting a paycheck on Friday, or experiencing stress at work or home. We propose to use MRP to treat cocaine addiction in a rather unique way. The addict will use the drug much as an asthmatic would use an inhaled bronchodilator to prevent an asthmatic attack before an athletic event or prior to exposure to a known allergic trigger. For example, on a Friday evening when the addict would usually go out to use cocaine, he/she would take MRP in an effort to prevent uncontrolled craving and an episode of drug use. In this way, the addict is able to make a conscious decision to gain control in a situation, which formerly led to uncontrolled and unwanted behavior. Again, the present study is being conducted to evaluate the safety of using MRP in an outpatient study; this outpatient study will commence immediately upon the determination that MRP is safe for this purpose.

2.4 Safety of MRP

Metyrapone has been widely used as a diagnostic test agent for assessing HPA function since it was first introduced in 1959 as a test of pituitary reserve.^{34, 35} An acute dose of MRP, for diagnostic purposes (called the “overnight MRP test,” typically 30 mg/kg given orally in the evening), is generally well tolerated. In a review of 576 such tests performed in 293 patients, side effects were reported in seven patients.³⁵ These included three patients with nausea and vomiting, one with dizziness without postural hypotension, one with unusual limb sensations and feeling faint, one with nocturnal nightmares, and one with dizziness during his second test and feeling distant from the surroundings during his third test.

Repeated dosing of MRP for a short period of time has also been used widely since the “standard MRP test” calls for giving patients 750 mg of MRP every four hours over a twenty four hour period.³⁶ It is also used chronically for the treatment of Cushing’s syndrome.^{28,29} More recently, several clinical trials have utilized MRP for the treatment of major depression.^{37,32} Under these conditions, the dose of MRP is titrated to maintain normal cortisol levels, while patients receive hydrocortisone (e.g., 7.5 mg QID) as a physiological replacement dose.

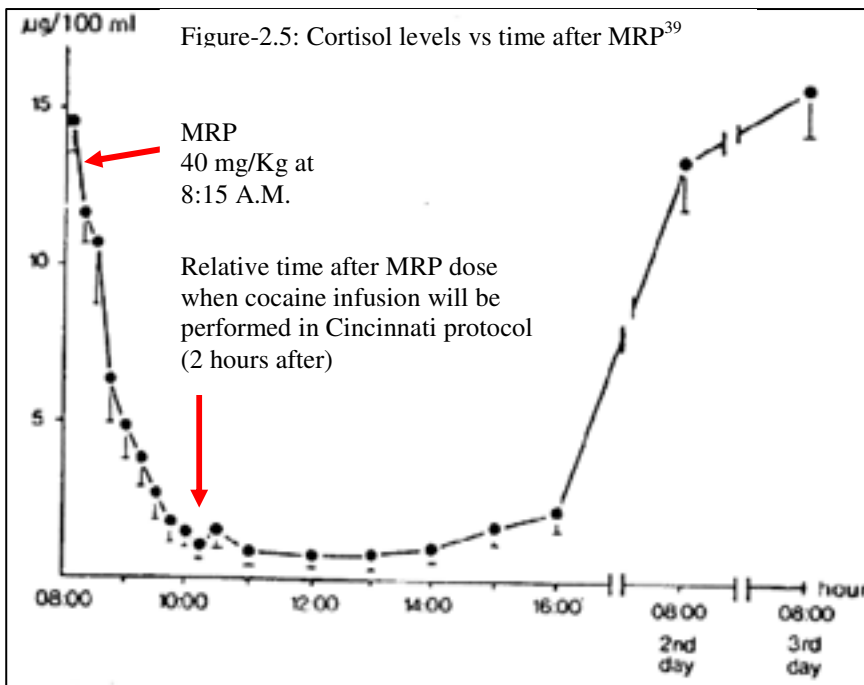
Although studies in human volunteers have shown that ketoconazole, another cortisol-synthesis blocker, significantly attenuates the increases in heart rate and in systolic and diastolic blood pressure following cocaine administration, one cannot automatically assume that the same effect will occur with MRP.²⁴ Also, subjects in that study were not exposed to other potential stressors, such as CR and SI. Since MRP blocks cortisol synthesis, it is possible, but unlikely, that subjects in our study may experience adrenal insufficiency in response to either the stress induction or to cocaine itself. Symptoms of adrenal insufficiency include nausea, vomiting, lethargy, hyperpyrexia and hypotension. If the condition goes untreated it may progress into cardiovascular collapse. Thus, it is prudent to carefully monitor cardiac parameters in this study. For these reasons the study will be conducted in a well-controlled inpatient setting with careful monitoring. If symptoms of acute adrenal insufficiency are observed, treatment can be initiated rapidly with a bolus intravenous infusion of 100 mg hydrocortisone followed by a continuous infusion of hydrocortisone at a rate of 10 mg/h. An alternative approach is to administer a 100-mg bolus of hydrocortisone intravenously every 6 hours³⁸.

2.5 Pharmacokinetics of Metyrapone and Duration of its Inhibitory Effect on the Synthesis of Cortisol

To determine the optimal timing of the cocaine and placebo infusions relative to the ingestion of MRP, and to determine a sufficient washout period from MRP to placebo dosing, it is necessary to know the plasma levels of cortisol as a function of time after acute dosing of MRP. This information can be obtained from several studies that have measured the effects of MRP on the synthesis of cortisol after acute dosing. The results of these studies will now be summarized.

2.5.1 Acute Dosing:

Schoneshofer et al.³⁹ administered 40mg/kg of MRP orally to four healthy adult males at 8:15 in the morning. Cortisol levels started to fall 15 to 30 minutes after drug administration and maximum suppression was reached 90 to 120 minutes after drug administration (see Figure 2.5). Note that by two hours after MRP ingestion the level of cortisol is clearly at a minimum (arrow in Figure 2.5). This is the time after MRP ingestion when the cocaine infusion will be performed in the present study. It is clear from the figure that the cortisol trough is very wide, thus small errors in the timing of the cocaine infusion will not result in significant changes in the cortisol plasma level. These results are consistent with the findings of Schoneshofer, et al.⁴⁰, that an orally administered 30mg/kg dose of MRP at midnight resulted in maximum blockade of 11-hydroxylase, as measured by cortisol, deoxycortisol, deoxycorticosterone and corticosterone, between 2 and 4 a.m. (i.e., two to four hours after MRP ingestion). Sawin et al.⁴¹ completed one measure of cortisol at two hours following a 9 AM oral dose of 750 mg or 1500 mg in five healthy males and found that the drop in cortisol was not significantly different between the two doses with a drop from 13.8 ± 5.7 to 1.4 ± 0.96 and 12.1 ± 4.1 to 1.7 ± 0.98 , respectively. Finally, Swano et al.⁴² reported that mean basal levels of plasma cortisol decreased from 14 ± 0.8 to 2.1 ± 0.06 $\mu\text{g}/\text{dl}$ 90 minutes after ingestion of 1g or 1.5g of oral MRP at 9 AM. Unfortunately, these authors did not provide the cortisol levels at other



time points but these findings seem to be consistent with those of other studies, described above, which find maximal suppression of cortisol occurring between 90 to 120 minutes post-dose.

2.5.2 Establishing the Length of Wash-Out Period

The half-life of MRP is 2 hours, the half-life of the active

metabolite, metyrapol, is 4 hours (Prod. Info. Metopirone®, 1991). Schoneshofer et al.³⁹ investigated the effect of an 8 AM dose of 40mg/kg po on a variety of adrenal steroids, and found that cortisol, corticosterone, deoxycortisol, deoxycorticosterone, and aldosterone were at normal, or close to normal, levels 24 hours after dosing. Progesterone and 17-OH-progesterone were higher than baseline 24 hours later but returned to normal levels by 48 hours post-dose. These findings suggest that the 96-hour washout period provided for in the

present study should be more than sufficient to prevent carry-over effects between the MRP and placebo conditions.

2.5.3 Establishing the Optimal Dose of Metyrapone

In animal studies, there was a dose response relationship in the effect of MRP on corticosterone and self-administration in the rat, with greater effect at higher doses.¹⁷ As described in section 2.5.1, it appears that in humans, a range of MRP doses have a similar effect on lowering plasma cortisol levels. Thus, higher doses of MRP may not be any more effective in inhibiting cortisol synthesis than are lower doses. Moreover, higher doses of MRP can cause gastrointestinal discomfort (Prod. Info. Metopirone®, 1991). Finally, MRP only comes in 250mg capsules. Thus, higher doses of MRP might decrease patient compliance because it would mean swallowing up to 10 large capsules at a time. To assure that the 750mg dose of MRP adequately inhibits cortisol synthesis we will be monitoring both MRP and cortisol plasma levels throughout the study.

2.6 Cue Response and Stress Imagery Procedures

As stated above, medications can effectively treat cocaine dependence by blocking the subjective effects of cocaine or by decreasing the addicts' susceptibility to cocaine cue- or stress-induced relapse. MRP's ability to block the subjective effects of cocaine will be assessed by VAS scales (e.g., high, good drug effect) completed during cocaine infusion. MRP's ability to block cue-induced craving will be measured with a cue response (CR) procedure in which participants will be exposed to cues associated with cocaine use (e.g., crack pipe, money). This procedure has been used to screen candidate medications for several years⁴³. MRP's ability to block stress-induced craving will be measured with the stress imagery (SI) procedure in which a research staff member will use a participant-generated script to guide the participant in imagining a non-drug related stressful scene from the participant's life. The SI procedure has recently been shown to increase craving and salivary cortisol levels in cocaine addicted individuals.⁴⁴

3.0 STUDY OBJECTIVES

Overview

The primary goal of this study is to evaluate the safety of conducting an outpatient MRP study in which participants would be given two 750 mg doses of MRP per week. The outpatients would be instructed to take a dose whenever they feel a strong need for cocaine, with the restriction that they could not take two doses within the same 24 hour period and that they are allowed a maximum of two doses per week. Thus, the present inpatient study will examine the safety of two consecutive days of dosing in patients who may use cocaine concurrently. Other goals are to evaluate the possible efficacy of MRP as a treatment for cocaine dependence and to compare three factors hypothesized to induce cocaine craving: cocaine cues, stress, and cocaine itself.

3.1 Primary Objectives

The primary objectives of this study are:

1. To demonstrate that a 750 mg dose of MRP is safe when used concomitantly with cocaine.
2. To demonstrate that a 750 mg dose of MRP is safe to use two days in a row.
3. To determine whether MRP can block the cocaine craving and physiological symptoms induced by cocaine cues (i.e., CR).
4. To determine whether MRP can block the cocaine craving and physiological symptoms induced by a personal stress situation (i.e., SI).
5. To determine whether MRP can modify the subjective and physiologic effects of cocaine.

3.2 Secondary Objectives

1. To determine whether MRP blocks the cortisol surge produced by:
 - cocaine administration
 - cocaine cues
 - stress
2. To determine whether cortisol levels or ACTH levels are more closely linked to craving and cocaine's effects.

4.0 METHODS

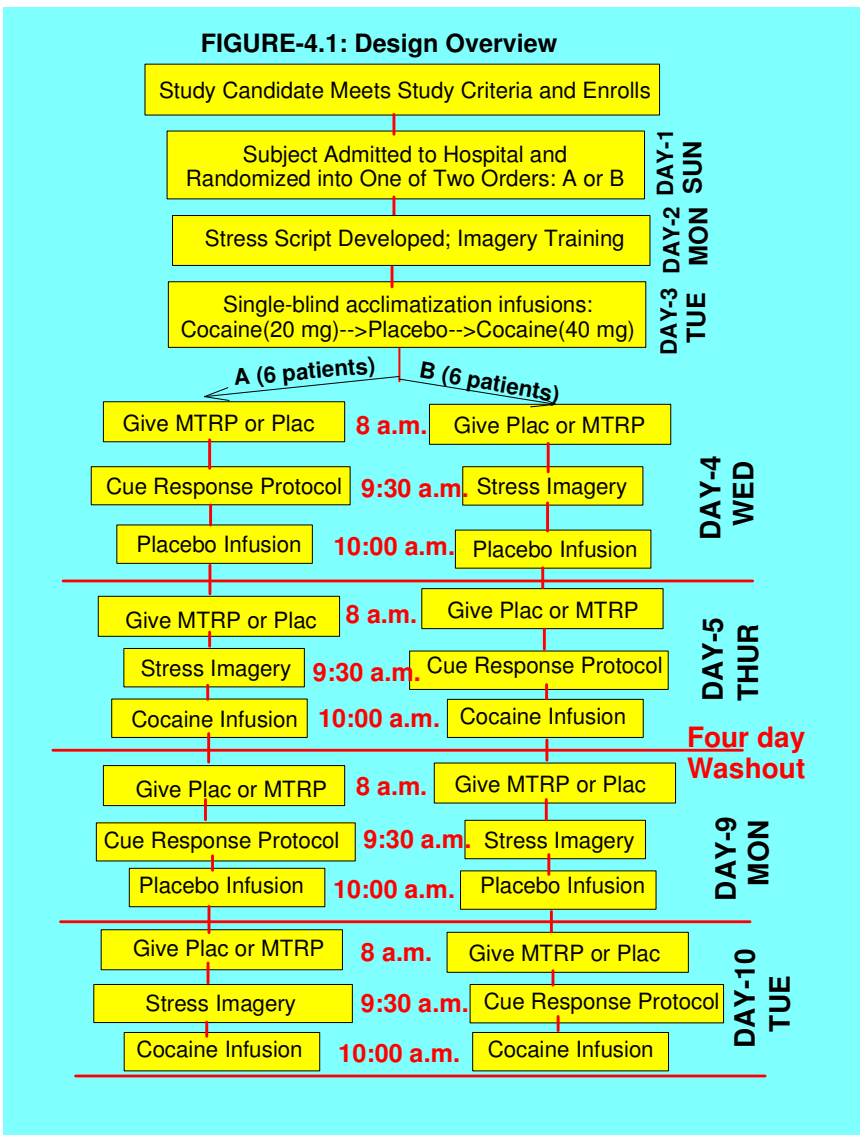
4.1 Study Design Overview

The safety, and possible efficacy, of using MRP to treat cocaine dependence will be evaluated in this double-blind, placebo-controlled, cross-over design with three factors: 1) Medication (750 mg MRP vs. Placebo), 2) Relapse Trigger (cue response vs. Stress), and 3) Infusion (40 mg Cocaine vs. Placebo). A total of 12 non-treatment seeking cocaine addicts will be recruited for this eleven-day inpatient study. Cortisol level is a critical factor in this trial,

thus, we plan to standardize the subjects' sleep-wake cycle starting two days prior to the first test day. Without this intervention, a treatment order effect might arise from the short-term effects that sleep-wake cycle changes have on the timing of the cortisol rise⁴⁵. During their inpatient stay, participants will be instructed to go to bed at 11:00 PM and to awaken at 7:00 AM. During the first full hospital day, a psychologist will provide the patient with imagery and relaxation training and will develop the participant's stress script in preparation for the stress imagery procedure.

The results of one of our previous interaction studies revealed that subjects were more reactive to the first infusion experienced. To avoid this novelty effect, we are including

“initiation infusions” on the second full day of hospitalization (i.e., Day-3) in which subjects will undergo infusion of 20 mg of cocaine, placebo, and 40 mg of cocaine. This will be done to ascertain that the participant can tolerate a cocaine infusion and to acclimatize the participants to the procedures that will be used during all subsequent infusions.



Starting on day-4 and ending on day-9, each subject will experience two days of Cue Response, and two days of Stress Imagery (see Figure 4.1 above). In addition, each subject will be given two single blind infusions of Cocaine (40 mg) and of Placebo. One set of infusions will be given after pretreatment with MRP and the other after pretreatment with placebo (in a double-blind manner). As shown in Figure 4.1, there will be a 96-hour washout period between the MRP and Placebo conditions to eliminate possible carry-over effects. The order of both the Medication and Relapse Trigger factors will be counterbalanced, which yields four potential orders as outlined in Table 4.1.

Table 4.1: Treatment Orders

Order	Medication Order*	Relapse Trigger 1	Infusion 1	Relapse Trigger 2	Infusion 2
1	Placebo-Days 4&5	cue response – Day 4	Placebo – Day 4	Stress Imagery – Day 5	Cocaine – Day 5
	MTRP – Days 9&10	cue response – Day 9	Placebo - Day 9	Stress Imagery - Day 10	Cocaine-Day 10
2	MTRP – Days 4&5	cue response – Day 4	Placebo – Day 4	Stress Imagery – Day 5	Cocaine – Day 5
	Placebo – Days 9&10	cue response – Day 9	Placebo – Day 9	Stress Imagery – Day 10	Cocaine – Day 10
3	Placebo – Days 4&5	Stress Imagery – Day 4	Placebo – Day 4	cue response – Day 5	Cocaine – Day 5
	MTRP – Days 9&10	Stress Imagery – Day 9	Placebo – Day 9	cue response – Day 10	Cocaine – Day 10
4	MTRP – Days 4&5	Stress Imagery – Day 4	Placebo – Day 4	cue response – Day 5	Cocaine – Day 5
	Placebo – Days 9&10	Stress Imagery – Day 9	Placebo – Day 9	cue response – Day 10	Cocaine – Day 10

*There will be a 96-hour washout period between the MTRP and Placebo conditions.

4.2 Outcome Variables

4.2.1 Primary Outcome Variables

Systolic Blood Pressure (SBP)

Diastolic Blood Pressure (DBP)

Heart Rate

Cardiac Rhythm

Electrocardiogram

Visual Analog Scales (VAS) for measuring cocaine craving and the subjective effects of cocaine (e.g., desire for cocaine, willingness to pay, drug effect) and mood.

4.2.2 Secondary Outcome Measures

Blood levels of ACTH and cortisol.

4.3 Major Safety Outcome Analytic Plan

Safety measures will be collected as outlined in Table 4.6.3.

Heart rate and rhythm will be monitored continuously from shortly prior to each cocaine/placebo infusion to 2 hours after dosing. A cardiac rhythm strip will be printed and sitting and postural blood pressure and heart rate will be measured prior to, during, and for the first hour after cocaine infusion. The subjects will be questioned in a non-leading manner about adverse events regularly during and after infusion.

Postural vital signs will be assessed as outlined in Table 4.6.1. Glucose and electrolyte levels will be measured on days three, four, five, seven, eight, nine, and eleven to assess for clinically significant hypoadrenalcorticism. This is very unlikely to occur in this study because metyrapone is a relatively specific inhibitor of glucocorticoid synthesis with much less effect on mineralocorticoid synthesis. Also, we are giving the drug at low dose and for a very short time. The study drug will be stopped and participation terminated if there is a clinically significant change in any of these measures, as determined by the P.I.

In accordance with FDA reporting requirements, all AEs occurring during the course of the clinical trial will be collected, documented, and reported by the principal investigator or sub-investigators according to the specific instructions detailed in this section of the protocol and Appendix I. The occurrence of AEs will be assessed at each study visit and an AE CRF completed weekly.

An AE is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial, whether or not the event is considered medication-related or clinically significant. For this study, AEs will include events reported by the subject, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant clinical laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs. All AEs must be recorded on the AE Form. The AE Form is also used to record follow-up information for unresolved events reported on previous visits. Each week, a study investigator must review the AE Form completed for the previous week for any events that were reported as continuing. All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed by study investigators until satisfactory resolution. AEs should be reported up to 4 weeks following completion of, or termination from treatment.

Each adverse event or reaction will be classified by the study investigator as serious or non-serious. Based on the seriousness of the adverse event or reaction appropriate reporting procedures will be followed. The International Conference on Harmonization (ICH) Guideline for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH-E2A March 1995, as implemented by the U.S. Food and Drug Administration defines serious adverse event (SAE) or reaction as any untoward medical occurrence that at any dose:

... results in death;

... is life-threatening; (*NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*)

... requires inpatient hospitalization or prolongation of existing hospitalization;

... results in persistent or significant disability/incapacity; or

... is a congenital anomaly/birth defect.

An unexpected event is one that is not described with respect to nature, severity, or frequency in the current Investigator's Brochure or product package insert.

Any SAEs due to any cause, that occur during the course of this investigation, whether or not related to the investigational agent, must be reported within 24-hours by telephone to: the Study Medical Monitor, the NIDA Project Officer, and the investigator-sponsor. The telephone report is to be followed by submission of a completed SAE Form with demographic information and a narrative explanation of the event. Attached to the SAE Form should be photocopies of the AE Form, the Concomitant Medication Form, and the Medical History Form from the subject's CRFs. All serious medical events are also to be reported to the responsible institutional review board according to local regulatory requirements. All participating investigators will be notified of any serious and unexpected AE requiring submission to the FDA in an IND safety report from the investigator-sponsor.

Any fatal or life-threatening SAE that is investigational agent related and unexpected must be reported initially to the FDA within 7 calendar days via telephone, facsimile or e-mail with a written follow-up within an additional 8 calendar days. Any additional clinical information that is obtained must be reported, as it becomes available to the FDA.

The investigator-sponsor will inform NIDA of all SAEs that occur during the study. The investigator-sponsor is required by FDA regulations to report these to the FDA in a timely fashion. All AEs that are both serious and unexpected must be reported to the FDA, in writing, within 15 calendar days of notification of NIDA of the SAE.

There can be serious consequences including ultimately, criminal and/or civil penalties for sponsors who fail to comply with FDA regulations governing the reporting of SAEs to FDA. The study investigators in this study have the responsibility of promptly reporting all SAEs to NIDA and the investigator-sponsor in order that the investigator-sponsor can comply with these regulations.

If a study subject withdraws from the study or if an investigator decides to discontinue the subject from the study because of a SAE, the subject must have appropriate follow-up medical monitoring. If the subject is hospitalized, medical monitoring will consist of not less than daily evaluation by physical examination, vital signs, laboratory evaluations, and if

applicable, ECG monitoring for significant treatment-emergent abnormalities. Monitoring will continue until the problem prompting hospitalization has resolved or stabilized with no further change expected or is discovered to be clearly unrelated to study medication or progresses to death.

4.4 Institutional Review and Subject Informed Consent

Before initiating this study, it will be submitted for approval by the University of Cincinnati institutional review board (IRB) as well as by the VA Medical Center R&D Committee. Once the study is underway, the investigator will promptly report to the IRB and to NIDA DTRD all changes in research activity and all unanticipated problems involving risks to human subjects or others. The investigator will not make any changes in the protocol without IRB approval, except where necessary to eliminate immediate hazards to human subjects.

The investigator will explain the purpose and nature of the study, including the risks to the prospective volunteers before his/her participation in the study. The investigator will inform the volunteer that he or she is free to withdraw from the study at any time after enrollment. The volunteer must sign, in the presence of a witness, the informed consent form supplied by the investigator in accordance with the FDA regulations (21 CFR Part 50) and approved by the institutional review board. A copy of the signed informed consent form will be provided to the volunteer.

4.5 Selection of Patients

A total of twelve non-treatment-seeking cocaine dependent persons with a history of intravenous drug use will be sought through referrals and advertisements and will be reimbursed for their participation.

4.5.1 Inclusion Criteria

The eligibility of the volunteers will be evaluated based on the following criteria:

1. male or female of any race, between 18 and 45 years of age.
2. cocaine dependent according to DSM-IV criteria.
3. currently use cocaine by smoked or intravenous route of administration and confirmed by positive urine screen for benzoylecgonine within 2 weeks prior to study enrollment. The subjects who currently use cocaine by smoked route must have a history of intravenous exposure to drugs of abuse.
4. stable physical and mental health as judged by interview and physical examinations.
5. female subjects test non-pregnant and use adequate birth control. All female subjects will have a serum pregnancy test performed prior to the first dose of study medication.
6. capable of providing written informed consent to participate in this study, able to comply with protocol requirements, and likely to complete all study treatments.
7. basal cortisol and ACTH levels within normal range.

4.5.2 Exclusion Criteria

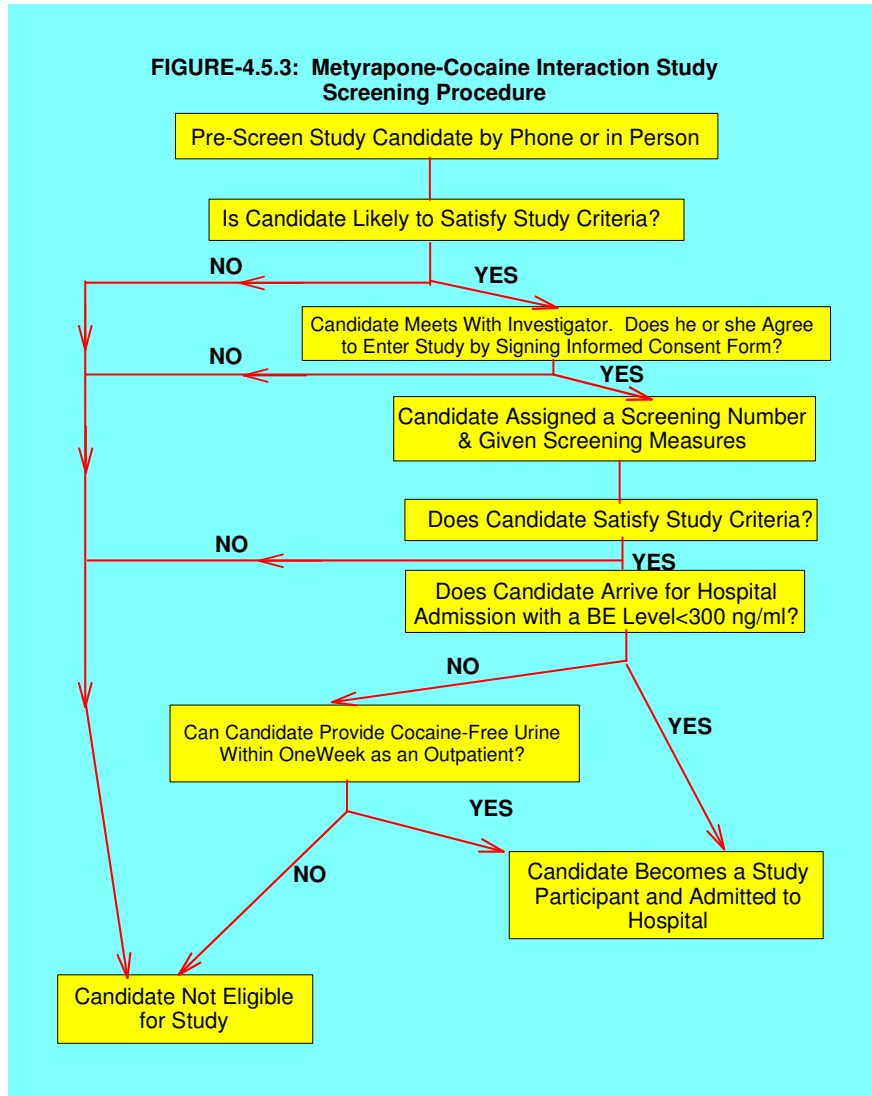
Subjects will be excluded from the study if they:

1. require detoxification from alcohol, opiates, or sedative-hypnotics.
2. have a history of significant hepatic, renal, endocrine, cardiac (i.e., arrhythmia requiring medication, angina pectoris, myocardial infarction), stroke, seizure, neurological, non-drug-related psychiatric, gastrointestinal, pulmonary, hematological or metabolic disorders.
3. have a history of adverse reaction to cocaine including loss of consciousness, chest pain, psychosis, or seizure.
4. have a history of adverse reaction/hypersensitivity to MRP.
5. test positive upon urine toxicology screen for opiates, benzodiazepines, barbiturates or related CNS depressants, amphetamines or related stimulants.
6. have a clinically significant laboratory abnormality in hematology, serum chemistries or ECG
7. have any significant active medical, or psychiatric illness which might inhibit their ability to complete the study or might be complicated by administration of the test drug.
7. have active hypertension as defined by the American Heart Association criteria.
8. currently receive any medications for the treatment of any significant medical conditions.

9. have a history of seizures or seizure disorder.
10. have any medical history or condition considered by the investigator(s) to place the subject at increased risk.
11. are receiving therapy with any of the opiate-substitutes (methadone, LAAM, buprenorphine) within 60 days of enrollment in this study.
12. have the diagnosis of adult asthma, including those with a history of acute asthma within the past two years, and those with current or recent (past 2 years) treatment with inhaled or oral beta-agonist or steroid therapy (due to potential serious adverse interactions with cocaine).
13. actively use albuterol or other beta agonist medications, regardless of whether they are diagnosed with asthma. (Inhalers are sometimes used by cocaine addicts to enhance cocaine delivery to the lungs.) If respiratory disease is excluded and the subject will consent to discontinue agonist use, he/she may be considered for inclusion.
14. may be suspect for asthma but carry no diagnosis, that is
1) history of coughing and wheezing, 2) history of asthma and/or asthma treatment two or more years ago, 3) history of other respiratory illness, e.g., COPD (exclude if on beta agonists), 4) use over the counter agonist or allergy medication for respiratory problems (e.g. Primatene Mist): a detailed history and physical exam, pulmonary consult, and pulmonary function tests should be performed prior to including or excluding from the study. Patients with FEV1 <70% of predicted should be excluded.
16. have an hematocrit value below 40 for men and 36 for women.

4.5.3 Screening

The sequence of procedures involved in the screening portion of this study is summarized in Figure-4.5.3. Table-4.5.3 lists the screening tests and procedures. There will be a pre-



screening evaluation where candidates who reply to advertisements are interviewed briefly over the phone or in person to see if they are likely to be viable candidates. If they are interested in participating in the full screening evaluation they must first be seen in person so that the study can be fully explained to them and so that they can sign the informed consent form. Afterwards they will enter the screening period, which will last a maximum of four weeks from the time the informed consent has been signed (see Figure-4.5.3). Enough candidates will be screened to identify a total of twelve who will be likely to complete the full study. The screening examinations

include the tests and procedures needed to determine if a given candidate satisfies all of the inclusion and exclusion criteria listed in sections 4.5.1 and 4.5.2. Some additional measures are desirable (e.g., the ASI-Lite CF and the HIV Risk Taking Behavior scale (HRBS)) but are not needed for determining study eligibility. These measures will be administered during the first full day of hospitalization.

Note that the tests and procedures listed in Table-4.5.3 have been divided into five groups. The pre-screening will generally be done by phone. The division of the majority of the screening measures into three days is for convenience only. It is often desirable to postpone the high resource measures (e.g., the physical exam, the SCID) until there are fairly clear signs that the candidate satisfies those study criteria which are easy to test (e.g., normal liver

function tests and negative serology for viral hepatitis). We will obtain 8 AM serum cortisol and ACTH levels during screening II. If the baseline cortisol level is outside the normal range, the individual will be excluded from the study or tested for pituitary/adrenal disease. The last section of the screening measures lists the urine toxicology screen. This must be done at the very end of the screening period, after the subject has arrived in the hospital to ensure that he

TABLE-4.5.3: SCREENING MEASURES	
FORM#	TEST OR PROCEDURE
PRE-SCREENING	
	Pre-Screening Interview
SCREENING I	
	Informed Consent
001	Study Enrollment Form
005	Urine Toxicology Screen
008	Electrocardiogram
009	DSM-IV screen for Cocaine Dependence
010	Vital Signs
SCREENING II	
002	Blood Chemistry Profile
003	CBC with Differential
004	Birth Control/Pregnancy Assessment
006	Urinalysis
007	Infectious Diseases (e.g., HIV, hepatitis B & C)
012	Psychiatric Measures Sum (SCID)
018	Cortisol and ACTH Levels
SCREENING III	
015	Medical History
016	Physical Examination
017	Prior Medications
STUDY DAY ONE	
004	Birth Control/Pregnancy Assessment
005	Urine Toxicology Screen

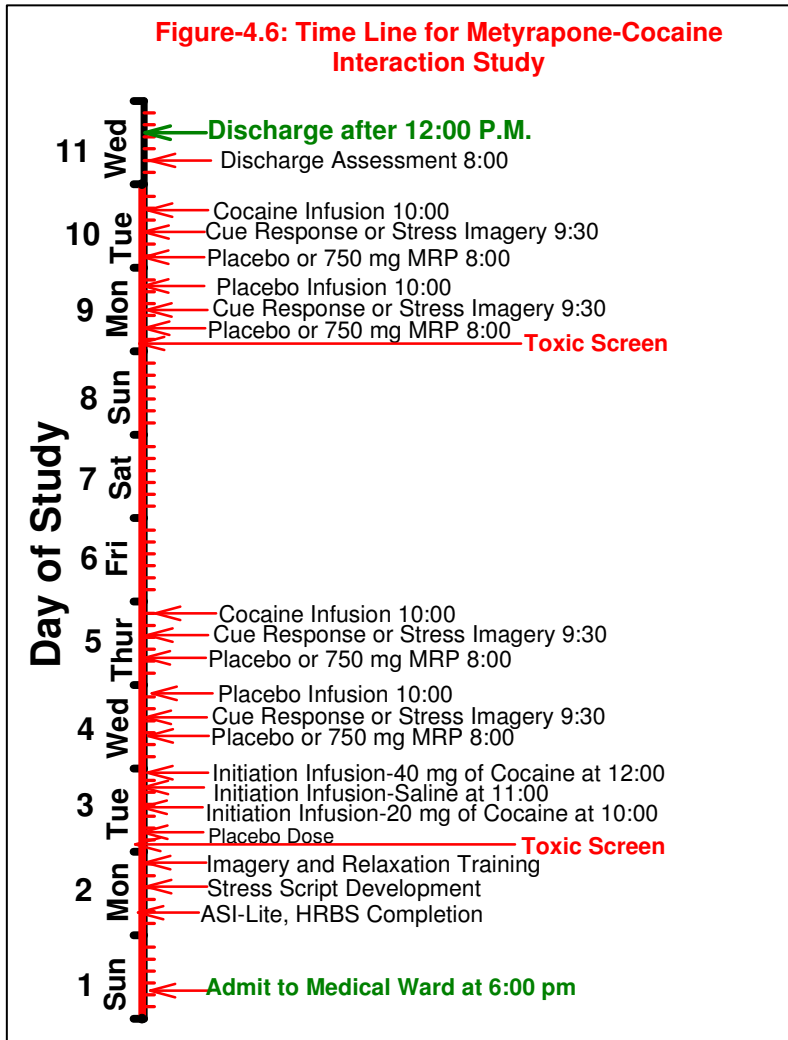
or she is negative for cocaine (see figure-4.5.3). This urine toxicology screen will be performed with a rapid assay triage kit. Thus, the drug status of each candidate will be known within one hour of admission. The results of the toxicology screen will be confirmed by the VA Laboratory Service, using standard methodology. Subjects who satisfy all inclusion and exclusion criteria will be enrolled into the study only if they arrive for their hospital admission with a negative urine BE level. Those with positive urine BE levels will be given a maximum of one week to provide cocaine-free urine samples (see Figure-4.5.3).

4.6 Conduct of Study

4.6.1 Overview

Participants who satisfy all study criteria and have a non-detectable urine BE level (< 300ng/ml) when they arrive to the hospital for admission will be admitted to a VA medical ward in the evening approximately 40 hours prior to the first cocaine infusion. Participants will be offered a nicotine patch to discourage cigarette smoking while in the hospital. However, the need to smoke will not disqualify a person from participation if the smoking activity does not interfere with the need for monitoring the participant's activities while in the hospital. During the inpatient period, subjects will be asked not to use any drugs (except

acetaminophen, aspirin, nicotine, or caffeine).



The participant will be allowed to leave the unit to attend VA activities at designated times and, if necessary, to smoke with permission from the research or nursing staff.

The protocol will be completed following the time-line in Figure-4.6 (see also table-4.6.1 for details). On all infusion days, the participant will be given breakfast by 30 minutes before receiving his or her dose of metyrapone or placebo. At 8:00, the appropriate dose (see Figure 4.6) of metyrapone or placebo will be administered in a double-blind manner. IV therapy will be notified to insert two heplocks, one into each of the participant's antecubital fossae or forearms. After breakfast on days 3 and

9 a urine specimen will be obtained for a rapid drug screen. If the drug screen is negative for cocaine metabolite, the study will proceed as outlined above. If the drug screen is positive, no further medication or procedures will be administered and, after an evaluation by the PI, the subject will be discontinued from the protocol and discharged home.

The participant will be taken to a VA telemetry unit, the Post-Anesthesia Care Unit (PACU), or will be connected to a cardiac monitoring unit in the medical ward for the infusion procedures. Prior to infusion, the physician will oversee the activation and calibration of

monitoring equipment. At 9:00 a.m. postural vital signs will be measured. At 9:30 a.m. on test days cue response or stress imagery procedures will be performed as described in section 4.6.3.

Cocaine or saline will be administered intravenously by infusion pump in a single-blind fashion, over one minute, through one of the heparin locks. Vital signs will be assessed as outlined in Tables 4.6.2 and 4.6.3. ECG will be done 15 minutes after the infusion and as needed if hypertension, chest pain or rhythm disturbance develops. Rhythm strip will be monitored continuously and hard copies recorded as outlined in Tables 4.6.2 and 4.6.3. The study physician will monitor the patient in-person for an hour following infusion and will remain readily accessible for the following four hours. The participant will be continuously monitored for at least two hours after the infusion. If vital signs and cardiac rhythm remain normal, the participant will be disconnected from cardiac monitoring. The participant will be allowed to leave the unit to smoke or to participate in VA activities with permission from the research assistant.

Table-4.6.1: Schedule of Measures, Blood Draws, and Procedures

Hospital Day -->	1	2	3	4	5	6	7	8	9	10	11
Day of Week -->	Sun	Mon	Tue	Wed	Thur	Fri	Sat	Sun	Mon	Tue	Wed
COCAINE INFUSION			ID	TD1	TD2				TD3	TD4	
CR or SI Procedure				X	X				X	X	
Urine Tox. Screen	X		X						X		
HRBS		X									
ASI-Lite		X									
Vital Signs			7X	12X	12X	X	X		12X	12X	X
Postural Vital Signs	X		5X	3X	3X	X		X	3X	3X	X
BD: Cocaine				1X	1X				1X	1X	
BD: Cortisol				9X	9X				9X	9X	1X
BD: ACTH				9X	9X				9X	9X	1X
BD: Gluc. & Electrolyte Pnl			1X	1X	1X		1X	1X	1X		1X
Total Blood Samples			4X	20X	20X		1X	1X	20X	19X	3X
Total Blood Volume (ml)			6	98	98		3	3	98	95	13
Rhythm strip			7X	5X	5X				5X	5X	
EKG			4X	2X	2X				2X	2X	
Adverse Events			8X	7X	7X				7X	7X	X
VAS			22X	11X	11X				11X	11X	
Cardiopulmonary Exam											X

Notes: Explanation of Column Headings: numbers 1 to 11 are the inpatient study days.

The heavily shaded areas represent regular infusion days (labeled test day (TD)1-4), the lightly shaded area is the initiation (acclimatization) day (labeled ID). If two or more samples are needed at the same time the total will be drawn and distributed into several tubes (see Table-4.6.3 for the timing of each blood draw). **Total blood drawn = 414 ml.**

4.6.2 Initiation (Acclimation) Infusions

Day 3 is the “initiation day” designed to assure the safety of a 40mg cocaine dose and to acquaint the participant to the procedures to be followed on the actual test days. The procedures followed on the initiation day differ from the test days in the following manner:

1. The patient will be given a single-blind placebo dose prior to the first initiation infusion.
2. There are three infusions during this initiation day. They are: the 20 mg cocaine dose at 10:00 a.m., followed by placebo at 11:00 a.m., followed by 40 mg cocaine at noon. See Table 4.6.2 for the schedule of these infusions and of the safety measures to be obtained.
3. Neither CR nor SI procedures are performed on this day.
4. The blood drawn at time 1, shown in Table-4.6.2, will be used for the Glucose and Electrolyte panel. In addition, a small amount of blood, approximately 1.0 ml, will be drawn from the heparin lock at the times 2-4, shown in table 4.6.2. These samples will be drawn to simulate the blood draws on the test days and will be discarded out of sight of the participant.
5. Various safety measures and VAS for drug effect will be obtained as shown in table 4.6.2.

TABLE-4.6.2: Schedule For Initiation Infusion Day

I←----- SCHEDULE OF PROCEDURES ----->I

Time of Day -->	8:30	9	10:00	10:15	10:30	11	11:15	11:30	noon	12:15	12:30	1:00	2:00
AM/PM	AM	AM	AM	AM	AM	AM	AM	AM	PM	PM	PM	PM	PM
Infusion			C 20mg			P			C 40mg				
Blood Draw		#1		#2			#3			#4			
ml blood		3.0		1.0			1.0			1.0			
Gluc & Electrolyte Pnl.		X											
Vital Signs			X		X	X		X	X		X	X	
Postural Vital Signs		X		X			X			X			X
Rhythm Strip		X		X	X		X	X		X		X	
Adverse Events		X		X	X		X	X		X		X	X
VASs*		X		X	X		X	X		X	X		
Toxic Screen	X												
ECG	X			X			X			X			

The shaded areas indicate infusions (**P** = placebo infusion; **C** = cocaine infusion)

*VAS measures are also taken at the following times: five minutes prior to each infusion and every five minutes after infusion for half an hour (i.e., six times following each infusion).

Note that there are 3 occasions when blood is drawn (1.0 ml each time) when no biochemical measures will be made. These samples are drawn to simulate the blood draws on the regular (test) days.

If it is established that the participant safely received the 40mg cocaine infusion and he or she wishes to proceed, he or she will continue in the study. Note that the reason for separating the 20 mg infusion from the 40 mg infusion by the placebo infusion is to avoid an accumulation of cocaine in the subject's body. Since there is a two-hour separation it is unlikely that this very short half-life substance will accumulate to dangerous levels.

4.6.3 Test Days

The schedule of procedures, safety measures, and efficacy measures to be performed on the four test days (Day 4, 5, 9, and 10; see Figure 4.1 and table 4.6.1) is shown in Table 4.6.3.

Each participant will undergo either the cue response (CR) or the stress imagery (SI) procedure at 9:30 on each test day, followed by an infusion of either 40 mg of cocaine or placebo. Blood will be drawn at various times for measuring the concentrations of various biochemical parameters. Numerous safety measures will be performed to monitor the safety of these procedures.

In addition, visual analogue scales (VASs) will be used to measure cocaine liking, craving, and various mood states resulting from the CR, SI, and cocaine infusion.

Note that during each test day a total of 98 ml (95 ml on Day 10) of blood will be drawn for the various biochemical measures. Thus, the total volume of blood drawn during all test procedure days plus the initiation day is **395 ml**. An additional 19 ml of blood will be drawn on non- infusion days. Thus a total of 414 ml will be drawn during this 11 day study. A small amount of additional blood will be drawn during the screening phase to determine study eligibility (see table 4.5.3).

TABLE-4.6.3: Schedule For Test Days

I←-----SCHEDULE OF PROCEDURES-----→I															
Time of Day	8	8:30	9	9:30	9:35	9:40	9:45	10	10:05	10:15	10:30	10:45	11	11:30	noon
AM/PM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	PM
MRP or Plac	X														
CR or SI Proc.				X	X	X	X								
Infusion								X							
Blood Draw:					#1	#2	#3			#4	#5	#6	#7	#8	#9
Cortisol					X	X	X			X	X	X	X	X	X
ACTH					X	X	X			X	X	X	X	X	X
Cocaine, BE										X					
Gluc & Elec Pnl**							X								
Total BDs					2	2	3			3	2	2	2	2	2
ml blood					10	10	13			15	10	10	10	10	10
Vital Signs [♦]				X	X	X	X	X	X	X	X	X	X	X	
Postural VS			X							X					X
Rhythm Strip							X		X	X		X		X	
AEs			X				X		X	X		X		X	X
VASs*				X	X	X	X		X	X	X				
Toxic Screen	X [♣]														
ECG							X			X					

Regular infusions will be performed on hospital days four, five, nine, and ten (see table 4.6.1 and figure 4.1).

**Glucose and Electrolyte panel completed on days four, five, and nine prior to infusion.

* **CR** = cue response procedure; **SI** = Stress Imagery procedure; **BD**=blood draw. The shaded columns indicate the times that CR or SI or an infusion are performed. Note that there are 9 occasions when blood is drawn for measuring various substances. Cortisol and ACTH are measured on each of the nine blood draws, cocaine, and BE are each measured once.

♦ Vital Signs are also taken at ten minutes post infusion.

*VAS measures are also taken five minutes prior to infusion and every five minutes after the infusion for half an hour.

♣Day 9 only.

Heart rate and rhythm will be monitored continuously from shortly prior to each cocaine/placebo infusion to 2 hours after dosing. For documentation purposes, a cardiac

rhythm strip will be printed according to the schedule in Table 4.6.3. In addition to sitting blood pressure and pulse, blood pressure and pulse will be recorded after the subject is standing for 60 seconds, three times during each test day. The subjects will be questioned in a non-leading manner about adverse events regularly during and after infusion. In addition, spontaneous complaints of adverse events at other times will be recorded. Subjective measures of drug effect, liking, and craving and mood will be taken to evaluate whether craving and good effects are paradoxically increased by concomitant MRP administration.

4.6.3.1 CR procedure

The CR procedure will entail a five minute baseline period, a five minute period of cocaine cue exposure, and a five minute relaxation period in which the participant will be asked to stop thinking about the cocaine cues and to relax. The cocaine cue exposure will entail viewing a 3-minute video of simulated cocaine use and handling cocaine related paraphernalia (e.g., crack pipe, etc.). Vital signs will be assessed, VASs administered, and blood drawn for cortisol and ACTH levels immediately following the baseline, cue exposure, and relaxation periods.

4.6.3.2 SI procedure

During the first full hospital day, a psychologist will provide the patient with imagery and relaxation training and will develop the participant's stress script in preparation for the SI procedure.

The SI procedure will entail a five minute baseline period, a five minute period of stress imagery, and a five minute relaxation period in which the participant will be asked to stop thinking about the stressful situation and to relax. Vital signs will be done, VAS administered, and blood drawn for cortisol and ACTH levels immediately following the baseline, stress imagery, and relaxation periods.

Following the CR or SI procedure, the participant will receive an infusion of 40 mg of cocaine or saline and measures will be collected as summarized in Table 4.6.3.

4.6.4 Summary of Blood Sampling

Blood samples will be obtained using vacutainer tubes through an intravenous catheter (heparin lock) in the forearm. Each blood sampling tube will be labeled with protocol number, subject number, date, and time of collection. The actual sampling time for each sample will be recorded. Upon collection, blood samples will be placed on wet ice and plasma will be separated by centrifugation within 30 minutes of blood collection. Plasma samples will be stored in properly labeled tubes and kept frozen at -70° C until assayed. A summary of all blood draws for this study is given in Table-4.6.1. Note that a total of **414** ml of blood will be drawn from each patient during the eleven-day inpatient period.

4.6.5 Measurements of Cocaine, Cortisol, and ACTH in Plasma

Samples collected for analysis of cocaine need to be stabilized in order to prevent *in vitro* hydrolysis. This can be accomplished most effectively by collecting samples in the presence of sodium fluoride and promptly placing them on ice. After plasma has been promptly separated by refrigerated centrifugation, samples will be maintained frozen until analysis. A summary of the times at which blood samples will be collected during each infusion day is summarized in Table-4.6.1. The details are given in Tables 4.6.2 and 4.6.3.

Analyses for cocaine in plasma will be performed at the Center for Human Toxicology, Salt Lake City, Utah. A sensitive and specific method utilizing gas chromatography mass spectrometry has been established and validated for cocaine. The quantitative limit for this assay is 2ng/mL of cocaine in the submitted sample, which meets our estimated sensitivity requirements as outlined above.

Plasma cortisol and ACTH levels will be processed through the Cincinnati VA laboratory. Plasma cortisol levels will be measured by competitive protein binding radioimmunoassay at the VA hospital in Cleveland, Ohio. Turnaround for this analysis is approximately 48 hours. ACTH levels will be measured by radioimmunoassay. The test will be performed at Associated Regional and University Pathologists, Inc in Salt Lake City, Utah. Turnaround time is approximately 48 hours.

4.6.6 Efficacy Measures

Subjects will enter their VAS ratings of mood, craving, drug effect, rush, liking, and amount they would pay for the infused substance, directly into a computer. Specifically, subjects will view an image resembling a CRF on the computer screen and will enter their ratings by clicking on the space which best reflects their subjective response. Subjects will receive training on how to correctly enter their VAS ratings prior to the first set of infusions.

4.6.7 Hospital Discharge and Follow-up

On study day 11, participants will be assessed to determine if they may be safely discharged from the hospital. The study physician will determine whether discharge is appropriate based on the following assessments:

1. Vital signs with postural blood pressure measurement
2. Glucose and electrolyte panel
3. Cardiopulmonary examination
4. Adverse events
5. Patient self-report of well-being

If any of the above measures is significantly abnormal, as determined by the study physician, the participant will remain in the hospital and the abnormal test(s) will be repeated as considered appropriate by the study physician. In addition to the assessments outlined above, the participant's 8 A.M. plasma cortisol and ACTH levels will also be determined. However, because the physical exam is adequately sensitive to determine acute adrenal insufficiency and because it will take longer than 48 hours to receive the cortisol and ACTH results, these levels will not be used to determine eligibility for discharge.

If the participant is found to be well, he/she will be discharged to home and will be scheduled to return for a follow-up visit in approximately one week. During that examination, vital signs and a cardiopulmonary examination will be performed. The participant may be brought back for additional follow-up visits at the discretion of the PI.

4.6.8 Acute Adrenal Insufficiency

During the course of this study, we will monitor the participants for signs of acute adrenal insufficiency so that, in the unlikely event that the syndrome occurs, it can be treated promptly. This syndrome usually occurs within the context of months of pituitary and adrenal suppression with exogenous corticosteroids and the addition of an overlying stress such as infection or surgery. This is particularly unlikely in our setting because the short duration of adrenal suppression (maximum of two days), and the absence of any pituitary suppression. The pituitary gland is actually stimulated by metyrapone. Signs of acute adrenal insufficiency include weakness, lethargy, hypotension, and dehydration. A subject who develops signs of this disorder would be treated with an intravenous infusion of 5% dextrose in normal saline and receive 100mg of hydrocortisone intravenously every six hours. Consultation would be obtained with the study endocrinologist, Dr. Robert Cohen. A subject could be transferred to the Intensive Care Unit if a higher level of care is needed, as determined by Dr. Singal or Dr. Cohen.

5.0 STUDY MEDICATIONS AND ADMINISTRATION

5.1 Study Medication Procurement

The 20mg and 40mg cocaine solutions will be obtained from NIDA DTRD. MRP 250mg gencaps are commercially available and will be purchased through the drug wholesale company, AmeriSource.

5.1.1 Study Drug Preparation

Cocaine

Sterile cocaine solutions for intravenous infusion will be prepared by the NIDA DTRD.

MRP

The study drug will be reformulated to conform to an identical placebo capsule. Each MRP 250mg gelcap will be encapsulated in an opaque gelatin capsule. Placebo capsules will be prepared by encapsulating placebo capsules within identical opaque gelatin capsules.

5.2 Study Drug Administration

The research staff will administer study medication in a double-blind fashion on test days. Each subject will take 3 capsules containing either MRP or placebo at 8:00am on each test day. Each subject will be take 3 capsules containing placebo in a single-blind fashion on the initiation infusion day.

Cocaine will be administered at a dose of 20 mg (on the initiation day) and 40 mg (on the initiation and test days) in a 20ml volume. The dose will be given by constant IV infusion over **1 minute** using a Baxter Infus O.R. syringe pump. The cocaine infusion will be administered 2 hours after the morning dose of MRP or placebo.

5.3 Dietary Restriction

Subjects will be given breakfast by 30 minutes prior to receiving the metyrapone or placebo dose on test days. Subjects will not be allowed to smoke for one hour before and four hours after each infusion. Standard meals will be provided to study subjects during their entire stay at the research facility.

6.0 STUDY MANAGEMENT AND ADMINISTRATIVE ISSUES

6.1 Concomitant Medications

Study participants will be asked not to use any psychoactive drugs or other drugs (except acetaminophen, aspirin, nicotine or caffeine) for at least 72 hours prior to admission and during the entire study period. If they require medications for an illness, an accurate record of all concomitant medications used (including names, dosage regimens, duration and purposes) must be documented.

6.2 Volunteer Discontinuation and Replacement

A volunteer may drop out of the study at any time if he or she so chooses or if the investigator feels it is clinically appropriate. A volunteer will be discontinued from the study due to a serious or unexpected adverse experience or a serious concurrent illness, as determined by the P.I. Dismissal will also be considered by the P.I., in the event that random drug testing indicates that the subject has used a drug of abuse outside of the study protocol. Cocaine intravenous administration will be discontinued if any of the following events occur:

1. Systolic blood pressure > 165 mm-Hg.
1. Diastolic blood pressure > 100 mm-Hg.
2. Heart rate > 130 bpm.

3. Behavioral manifestation of cocaine toxicity, e.g., agitation, psychosis, inability to cooperate with study procedures.

Further participation of the subject will be terminated if any of the following events occur:

1. Discontinuation criteria do not return to acceptable limits within appropriate timeframes (e.g. 30 minutes).
2. Discontinuation criteria are met for a second time within the protocol.
3. Systolic blood pressure > 180 mmHg sustained for 5 minutes or more.
4. Diastolic blood pressure > 120 mmHg sustained for 5 minutes or more.
5. Heart rate > $(220 - \text{age} \times 0.85)$ bpm sustained for 5 minutes or more.

Patients who experience significant adverse events from the MRP will not participate in cocaine challenges. Medical follow-up will be provided as necessary when subjects are discontinued and the occurrence of discontinuation criteria must be reported to the subject.

If a volunteer is discontinued prematurely due to adverse events, this subject will not be replaced. If a volunteer is discontinued prematurely due to administrative reasons, a substitute volunteer may be enrolled. The substitute volunteer will be assigned a new subject number and receive study treatments in the same order as the discontinued subject. The aim of this study is to have approximately 12 subjects completing the study as planned.

In the event that a subject is dismissed from a study prematurely due to a positive drug screen, he/she may be eligible for re-enrollment at a later time at the discretion of the PI.

6.3 Study Termination and Review Criteria

The study may be discontinued or terminated at any time if, in the opinion of the investigator, continuation of the study would present a serious medical risk to the subjects. After completion of the first subject, the study results (safety measures) will be reviewed prior to continuation of subject enrollment. If the rate of subject discontinuation due to adverse events is > 50% among the first 4 subjects enrolled, then subject enrollment will be discontinued and a safety review will be conducted to determine whether the study should be terminated.

7.0 DATA ANALYSIS

Data will be analyzed using SAS® statistical software. For all planned comparisons significance level will be set at $p=0.05$. Post-hoc adjustments will be made for all unplanned comparisons in order to maintain overall type I error rate.

7.1 The Effect of MRP on the Cardiovascular Effects of Cocaine

The effect of acute doses of MRP on cocaine induced changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) will be analyzed using simple statistics (mean, maximum, minimum) and repeated measures ANOVA with a crossover

design. Outcomes will be measured before infusion, during infusion, and 5, 10, 15, and 30 minutes after for a total of six repeated measures.

7.2 The Effect of MRP on the Subjective Effects of Cocaine

The effect of acute doses of MRP on cocaine induced changes in subjective measures will be analyzed using simple statistics (mean, maximum, minimum) and repeated measures ANOVA with a crossover design. Outcomes will be measured before infusion, during infusion, and 5, 10, 15, 20, 25, and 30 minutes after for a total of eight repeated measures.

7.3 The Effect of MRP on the Subjective Effects of CR and SI

The effect of acute doses of MRP on the subjective effects of CR and SI as recorded on VAS, will be analyzed using simple statistics and repeated measures ANOVA with a crossover design. Measures will be taken before the CR or SI procedure is performed, immediately following the procedure, and following a five minute relaxation period for a total of three repeated measures.

7.4 Pharmacokinetic Analysis of Plasma Cocaine, MRP, ACTH, and Cortisol

The effect of MRP on plasma levels of ACTH and cortisol in response to 40mg of cocaine, will be analyzed using repeated measures ANOVA with a crossover design. To determine the contribution of cortisol and ACTH levels to the cardio-vascular and subjective effects of cocaine, we will perform repeated measures analysis of covariance.⁴⁶

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APPENDIX I: Instructions For Evaluating and Reporting Adverse Events and Serious Adverse Events

A. GENERAL INSTRUCTIONS

1. The Adverse Event (AE) CRF must be completed daily and reviewed weekly by a study physician.
2. AEs will be reported as soon as the subject signs the informed consent.
3. Report the severity of the event following the guidance in section B below.
4. Report the relatedness of the event to the study agent administration according to the guidance in section C.

B. DEFINITIONS – SEVERITY OF EVENTS

Mild: Awareness of symptom, but easily tolerated.

Moderate: Discomfort enough to cause interference with usual activity.

Severe: Incapacitating with inability to work or do usual activity.

C. DEFINITIONS – RELATEDNESS OF EVENTS

The investigator is responsible for defining, in his/her best judgment, the relationship of the AE/SAE to the study drug/placebo. The degree of certainty for which the AE/SAE is attributed to the study drug or alternative causes (e.g. natural history of the underlying disease, concomitant therapies, etc.) should be determined by how well the experience can be understood in terms of one or more of the following:

- **Exposure:** Is there evidence that the subject was actually exposed to the drug/placebo?
- **Timing of the study drug/placebo:** Did the AE/SAE follow in a reasonable temporal sequence from administration of the drug test?
- **Consistency with study drug profile:** Known pharmacology and toxicology of the study drug in animals and man; reaction of similar nature having been previously described with the study drug.
- **Alternative explanations** for the adverse event such as concomitant medications, concurrent illness, non-medicinal therapies, diagnostic tests, procedures or other confounding findings.
- **Response to discontinuation** of the study drug/placebo.

Terms and definitions to be used in assessing the study agent relationship to the AE/SAE are:

- **Unknown:**
Use this category only if the cause of the AE/SAE is not possible to determine
- **Definitely Not Related:**
The subject did not receive the test drug, the temporal sequence of the AE/SAE onset relative to administration of the test drug is not reasonable, or there is another obvious cause of the AE/SAE.
- **Remotely Related:**
There is evidence of exposure to the test drug or there is another more likely cause of the AE/SAE.
- **Possibly Related:**
There is evidence of exposure to the test drug, the temporal sequence of the AE/SAE onset relative to administration of the test drug is reasonable, but the AE/SAE could have been due to another equally likely cause.
- **Probably Related:**
There is evidence of exposure to the test drug, the temporal sequence of the AE/SAE onset relative to administration of the test drug is reasonable, and the AE/SAE is more likely explained by the test drug than by any other cause.
- **Definitely Related:**
There is evidence of exposure to the test drug, the temporal sequence of the AE/SAE onset relative to administration of the test drug is reasonable, the AE/SAE is more likely explained by the test drug than by any other cause, and the AE/SAE shows a pattern consistent with previous knowledge of the test drug or test drug class.

D. SPECIFIC INSTRUCTIONS – LABORATORY/ECG ADVERSE EVENT

A laboratory or ECG AE is any clinically significant worsening in a test variable that occurs during the course of the study, whether or not considered to be study agent related. For each such change, provide the information requested on date of test, severity, likelihood of a relationship to investigational agent, change in investigational agent dosage due to the AE, and treatment required.

All laboratory AEs should be specified as an increased or decreased test result (e.g. “increased glucose”, “decreased potassium”) or as a term that implies an abnormality (e.g., hypercalcemia, azotemia).

E. SERIOUS ADVERSE EVENT AND UNEXPECTED ADVERSE EVENT REPORTING

24 hour Reporting Requirements

Any serious adverse event, including death due to any cause, which occurs to any subject from the time of admission through discharge whether or not related to the study drug/placebo, must be reported ***within 24 hours*** to the NIDA Medical Monitor, the NIDA Project Officer, and the principal investigator (IND sponsor).

The following information must be provided with the initial report of an SAE or unexpected AE:

- Name of person reporting the SAE/unexpected AE
- Subject's I.D. number
- Name of the principal investigator and institution
- Description of the SAE/unexpected AE
- Date and time of Onset
- Date/time of administration of last dose of study agent/placebo prior to the SAE/unexpected AE
- Severity of the SAE/unexpected AE
- Investigator's assessment of the relationship of the SAE/unexpected AE to study drug (related, possibly related, probably related, unlikely related, not related)
- Any action taken with the study drug, alteration to protocol defined schedule, diagnostics, and treatments secondary to the SAE/unexpected AE.

3-day Supporting Documentation Requirements

Written documentation for all SAEs/unexpected AEs must be received by the NIDA Medical Monitor/Alternate and the IND sponsor within 3 days of reporting the event. Required documents that must be submitted include the following:

- SAE Form
- Concomitant Medication CRF pages
- Adverse Events CRF pages
- Copies of source documents pertinent to the event (lab reports, ECG tracings, medical chart notes, etc.)
- Any other relevant information necessary to facilitate the investigator's judgment regarding the SAE's relatedness to the severity OR by request of the Medical Monitor/Alternate

Follow-Up of All Adverse Events/Serious Adverse Events

All adverse medical events must be followed until they are resolved, or until all attempts to determine the resolution of the AE/SAE are exhausted. This may require an extended inpatient period or a change in status from outpatient to inpatient. All treatments, outcomes and information regarding whether or not the subject was referred to their Primary Care Provider for additional follow-up must be recorded in the source document. All serious and unexpected adverse events occurring 30 days after administration of the last dose of study drug/placebo must be reported.

The investigator is required to provide the Medical Monitor/Alternate and the IND sponsor with all relevant follow-up information necessary to facilitate a thorough understanding of the event and judgment regarding the relationship to the study drug/placebo.

Reporting to the FDA

The principal investigator, who is the IND sponsor, is required to report SAEs to the FDA:

- in 7 days if the SAE is unexpected (or, if expected, unusually serious or rarely seen), life-threatening or lethal, and at least possibly related to the study agent, with a followup written report in 8 days;
- in 15 days if the SAE is unexpected (or, if expected, unusually serious or rarely seen), but not immediately life-threatening; and
- in an annual report in all other cases.