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Metyrapone and cocaine: A double-blind, placebo-controlled drug interaction study

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Abstract

Pre-clinical research suggests that suppression of adrenocorticosteroid synthesis might decrease susceptibility to stress-induced relapse. Metyrapone effectively suppresses cortisol synthesis and thus might have promise as a cocaine dependence treatment. The present inpatient study evaluated the interaction of metyrapone and cocaine to assess the safety of conducting an outpatient trial. Twelve nontreatment-seeking cocaine-dependent individuals completed this double-blind, placebo-controlled, crossover study with two factors: medication (750 mg of metyrapone vs. placebo) and infusion (40 mg of cocaine vs. saline). Safety measures included vital signs, adverse events, and electrocardiogram. Efficacy measures included visual analog scale (VAS) ratings of craving and drug effect. Neuroendocrine measures included cortisol and ACTH. As predicted, metyrapone was well tolerated and did not exacerbate cocaine's physiological effects. Also as predicted, metyrapone did not significantly alter cocaine's subjective effects. The results of the present study suggest that metyrapone at the dose studied can likely be used safely in an outpatient study with active cocaine users.

Keywords: Cocaine; Metyrapone; Cortisol; Cardiovascular effects; Subjective effects

1. Introduction

Cocaine dependence represents a public health problem (SAMHSA/OAS, 2002, 2003) for which no consistently effective pharmacotherapy has been identified and for which no Food and Drug Administration-approved medication exists. 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; thus, some investigators have started exploring the role of other systems in cocaine dependence. One system of particular interest is the hypothalamic–pituitary–adrenal (HPA) axis. Cocaine has an activating effect on the HPA axis as evidenced by increases in ACTH (Mendelson et al., 1992) and cortisol (Baumann et al., 1995) in humans, and ACTH and corticosterone in rats (Moldow and Fischman, 1987).

A number of pre-clinical studies 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 (Goeders, 1997; Piazza and Le Moal, 1996; Piazza et al., 1991). In addition, pre-clinical research has found that that administration of corticosterone at a level similar to that produced by stress results in cocaine-seeking reinstatement (Deroche et al., 1997) and that ketoconazole, which inhibits adrenocorticosteroid synthesis, can block stress-

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induced reinstatement (Mantsch and Goeders, 1999). In humans, it has been found that experimentally induced stress significantly increases the craving, anxiety, salivary cortisol, and heart rate of cocaine-dependent individuals (Sinha et al., 1999). Two studies of cocaine cue exposure in humans have found that cocaine cue exposure increases cortisol and craving in cocaine-dependent patients (Reid et al., 2003; Sinha et al., 2003). When considered with the pre-clinical data, these findings raise the intriguing possibility of a role for cortisol synthesis suppression in helping to reduce a cocaine-dependent person's susceptibility to stress-induced and cue-induced craving.

Two FDA-approved medications, ketoconazole and metyrapone, suppress cortisol synthesis and, thus, might be of interest as pharmacological treatments for cocaine dependence. However, metyrapone possesses several properties that make it a more favorable candidate medication. Specifically, compared to ketoconazole, metyrapone has greater specificity in inhibiting cortisol (Schimmer and Parker, 1996), has a more favorable side-effect profile, and is approved by the FDA as a diagnostic agent for the assessment of HPA axis function (Prod. Info. Metopirone®, 1991). Based on metyrapone's rapid effect of blocking cortisol synthesis within the first hour of administration (Schoneshofer et al., 1980), metyrapone may have a particularly useful application for the cocaine-dependent individual who is an episodic user. Episodes of use can be triggered by cues from the environment such as meeting a friend, getting a paycheck, or experiencing stress at work or home. Metyrapone might be used pro re nata (PRN), with the dependent individual using metyrapone when he or she experiences craving following exposure to cues or stress. In addition, if the dependent individual is aware of the triggers of his or her craving, he or she could use metyrapone 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, an individual whose cocaine use is triggered by money could take metyrapone an hour before getting his or her paycheck. In this way, the dependent individual is able to make a conscious decision to gain control in a situation, which formerly led to uncontrolled and unwanted behavior. The finding that cortisol levels normalize within 72 h after a large oral dose of metyrapone (e.g., 2.8 g; Schoneshofer et al., 1980) suggests that such PRN dosing would be feasible.

Prior to completing an outpatient study of metyrapone for cocaine dependence, it is important to determine the safety of administering metyrapone to participants who are actively using cocaine. An interaction study of ketoconazole and cocaine in humans (Ward et al., 1998) suggested that the suppression of cortisol in combination with cocaine does not pose a safety risk. A recent interaction study of metyrapone and methamphetamine in humans found that two of eight participants evidenced significant premature ventricular complexes; the authors concluded that metyrapone might not be safe to use with methamphetamine users (Harris et al., 2003).

The interaction study of ketoconazole and cocaine found that ketoconazole did not decrease the subjective effects of cocaine (Ward et al., 1998). This finding is not surprising in that pre-clinical research has found that the ability to attenuate cocaine self-administration through inhibiting adrenocorticosteroid synthesis is limited to low doses of cocaine and, thus, is unlikely to be a successful treatment approach in humans (Winhusen and Somoza, 2001). Conversely, as stated above, pre-clinical research suggests that ketoconazole does block stress-induced reinstatement of cocaine-seeking (Mantsch and Goeders, 1999) and, thus, suppression of adrenocorticosteroid synthesis might decrease susceptibility to relapse related to environmental stressors. Again, the potential promise of adrenocorticosteroid synthesis suppression is not based on its ability to alter the subjective effects of cocaine but, rather, its potential to reduce the likelihood that the addicted individual will seek cocaine in response to stress or cue-induced craving.

In the present study, the safety of participants and their subjective responses to cocaine was carefully monitored. It was predicted that there would be no significant safety issues arising from the interaction of cocaine and metyrapone. It was also predicted that, consistent with the finding of Ward et al. (1998), metyrapone would not significantly alter the subjective effects of cocaine.

2. Methods

2.1. Participants

Potential participants were recruited from Cincinnati with the use of flyers and newspaper advertisements for individuals who use cocaine frequently and do not want substance abuse treatment. Eligible participants were between 18 and 45 years of age; had a history of intravenous drug use; had basal cortisol, ACTH levels, and hematocrit values within normal range; and were in good physical health as determined by a medical history, physical exam, electrocardiogram, and standard laboratory tests. In addition, participants were required to currently use cocaine by smoked or intravenous route of administration, to have a positive urine toxicology screen for benzoylecgonine (BE) within 2 weeks prior to study enrollment, and to meet DSM-IV criteria for cocaine dependence as assessed by the Structured Clinical Interview for DSM-IV (SCID; First et al., 1996). Participants were excluded from the study if they required detoxification from alcohol, opiates, or sedative–hypnotic drugs, or if they had urine toxicology screens positive for opiates, benzodiazepines, barbiturates or related CNS depressants, and amphetamines or related stimulants. Other exclusion criteria included any serious psychological or physical illness, including a history of seizures. Persons with a history of any adverse reactions or hypersensitivity to either cocaine or

metyrapone were also excluded from the study. Women were ineligible for the study if they were pregnant or unwilling to use an adequate method of birth control. Finally, participants were required to have a urine toxicology screen negative for cocaine prior to the first cocaine infusion.

All subjects signed an informed consent approved by the University of Cincinnati Institutional Review Board and the Cincinnati Veterans Affairs Medical Center (VAMC) Research and Development Committee.

2.2. Procedures

The present study utilized a double-blind, placebo-controlled, crossover design with two factors: 1) medication (750 mg of metyrapone for 2 days vs. placebo for 2 days), and 2) infusion (cocaine vs. saline). The 750 mg MRP dose was selected since it has been demonstrated that this dose effectively suppresses cortisol synthesis (Sawin et al., 1971), and the use of this lower dose should reduce the likelihood of gastrointestinal discomfort that can be caused by higher doses of MRP (Prod. Info. Metopirone®, 1991). Infusions were single-blind, with cocaine and saline infusions completed in the same order for all participants. Specifically, the cocaine infusions were administered on the second day of medication dosing (either placebo or metyrapone) to assess the interaction of cocaine and metyrapone after 2 days of dosing. A 96-h washout period between the metyrapone and placebo conditions was included to eliminate possible carryover effects. All infusions were conducted by a board-certified anesthesiologist or emergency medicine physician with current certification in ACLS. ECGs were reviewed by a cardiologist.

Cortisol level was a critical factor in this trial; thus, an attempt was made to standardize the participants' sleep–wake cycle starting 2 days prior to the first interaction 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 rise (Davidson et al., 1991). During their inpatient stay, participants were instructed to go to bed at 11:00 pm and to awaken at 7:00 am. Study day 3 entailed "initiation" infusions designed to familiarize participants with the study procedures and to assess the participant's ability to tolerate the 40 mg dose of cocaine utilized in the study. The initiation day procedures differed from the test day procedures in that a urine toxicology screen was completed prior to any other procedure, the participant was given a single-blind placebo medication dose prior to the first initiation infusion, there were three infusions given (20 mg of cocaine at 10:00 a.m., placebo at 11:00 a.m., and 40 mg of cocaine at noon), and only a small amount of blood was drawn (approximately 1 ml per draw) since the intention was to simulate the test day blood draws but not to analyze the blood samples.

In order to successfully complete the initiation infusions, a participant could not evidence any of the following: (1) systolic blood pressure greater than 180 mm Hg sustained for more than 4 min or systolic blood pressure greater than 165 mm Hg that did not return to below 165 mm Hg within 30 min; (2) diastolic blood pressure greater than 120 mm Hg for more than 4 min or diastolic blood pressure greater than 100 mm Hg that did not return to below 100 mm Hg within 30 min; (3) heart rate greater than 220 (participant age×0.85) beats/min for more than 4 min or heart rate greater than 130 beats/min that did not return to below 130 beats/min within 30 min. Following the successful completion of the day 3 infusions, the participant was randomized to one of two medication orders (MRP–placebo or placebo–MRP). The procedures on the four interaction days (days 4, 5, 9, and 10) were identical, with a dose of placebo or 750 mg of metyrapone given at 8:00 and infusion (cocaine or saline) administered at 10:00. The timing between medication dosing and infusion was based on past research suggesting that maximum suppression of cortisol is reached approximately 90–120 min after metyrapone administration (Schoneshofer et al., 1980).

2.3. Study drug preparation

2.3.1. Cocaine

Human-use cocaine HCl solution (10 mg/ml) was obtained from The National Institute on Drug Abuse through the Research Triangle Institute (Research Triangle Park, NC). The solution was diluted in 0.9% sodium chloride. The cocaine solution or saline control was infused intravenously during a minute time frame through an InfuseOR (Abbott) infusion pump at a rate of 10 ml/min.

2.3.2. Metyrapone

Metyrapone (2-methyl-1,2,-di-3-pyridyl-1-propanone) obtained from Sigma/Aldrich Chemical (St. Louis, MO) was tested for USP purity by Celsis Laboratory Group (St. Louis, MO 63123). Metyrapone capsules were compounded locally at the Cincinnati VA Medical Center Investigational Drug Service and encapsulated in Gallipot 0102202 (St. Paul, MN) size 0 blue opaque gelatin capsules. Each capsule contained 250±5 mg of metyrapone powder and 150 mg of lactose. Placebo capsules contained only lactose. Total capsule weight was 497±10 mg. FDA approval was granted to prepare the medication locally.

2.4. Measures

The schedule of assessments relative to the infusion procedures is provided in Table 1. Subjective reaction to the infusion procedures, in the presence of placebo or metyrapone, was assessed with visual analog scales (VAS) that included 11 separate scales (stimulated, depressed, anxious, high, drug worth, liking of drug, desire for drug, likelihood of using drug, any drug effects, good drug effects, and bad drug effects). Participants were requested to quantify the degree of effect that they experienced in each of the 11 categories by making a mark along a 100-mm line from 0

Table 1
Schedule of assessments relative to infusion procedures

Measures/procedures	Infusion													
	Minutes relative to infusion													
	−120	−15	−5	0	5	10	15	20	25	30	45	60	90	120
Medication dose taken	x													
Visual analogue scales			x		x	x	x	x	x	x				
Vital signs		x		x	x	x	x			x				
ECG		x					x							
Adverse events		x			x		x				x		x	x
Blood draw for cortisol		x					x			x	x	x	x	x
Blood draw for ACTH		x					x			x	x	x	x	x

(none) to 100 (extreme). Neuroendocrine reactions to the infusion procedures, in the presence of placebo or metyrapone, were assessed by blood draws for cortisol and ACTH, which were obtained from an indwelling heparin lock. Physiological reactions to infusion, in the presence of placebo or metyrapone, were assessed with vital signs readings including heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP). In addition, infusion procedures were performed with participants on continuous telemetry monitoring from 30 min before to 4 h after each cocaine or placebo infusion and a 12-lead electrocardiogram (ECG) was used as an additional safety measure. Adverse events associated with the combination of metyrapone and cocaine were recorded during infusion periods by questioning participants in a non-leading manner at the time points noted in Table 1. On non-infusion days, adverse events related to metyrapone use alone were recorded as the participants reported them.

2.5. Specimen collection and analysis

2.5.1. Cocaine

Blood was drawn into tubes containing sodium fluoride and potassium oxalate, through heparin locks previously placed in the subjects' forearm veins. Tubes were immediately placed in ice water and transported within 20 min to a cooled centrifuge (4 °C) for separation of plasma. Tubes containing plasma were labeled and stored, in duplicate, at −70 °C until shipped on dry ice to the analytical laboratory (Center for Human Toxicology, Salt Lake City, Utah). The analyses for cocaine and BE were done on 0.5 ml of plasma. The method used deuterated internal standards, solid-phase extraction and liquid chromatographic tandem mass spectrometry with atmospheric pressure chemical ionization (Lin et al., 2001).

2.5.2. Cortisol

Blood was collected in tubes containing no preservatives, immediately stored on ice, and transported within 20 min to a cooled centrifuge (4 °C) for separation of serum. Tubes containing serum were stored at −70 °C until processed at the Cincinnati VA Medical Center clinical laboratory by an electrochemiluminescence immunoassay (Elecsys® Systems; Roche Diagnostics, Indianapolis, IN). Precision and accuracy studies in serum demonstrated inter- and intra-assay coefficient of variation of 3%.

2.5.3. ACTH

Blood collected in tubes containing EDTA was processed as described above for cocaine. Plasma samples were analyzed using a chemiluminescent immunoassay (Associated Regional and University Pathologists, Salt Lake City, Utah). Precision and accuracy studies in plasma demonstrated inter-assay CV ranging from 10% for low measurements to 4% for maximal measurements. Intra-assay CV ranged from 2% to 8.6% for high and low measurements, respectively.

2.6. Data analysis

Data were analyzed using Statistica (StatSoft, Inc., 2001). Significance levels were set at $p<.05$ for all analyses. The effects of the infusion, medication, and the infusion×medication interaction on the subjective, physiological, and neuroendocrine measures were analyzed using simple statistics and repeated-measures ANOVAs with a crossover design. As can be seen in Table 1, there were seven, six, and seven repeated measures, respectively, for the subjective, physiological (i.e., vital signs), and neuroendocrine measures. One participant was given a cocaine infusion on all four interaction days; hence, the data from this participant were not included in the infusion analyses. In addition, one patient left the VAS for "high" blank during one of the time points and, thus, the analysis of "high" is for 10 participants.

3. Results

Fifteen participants were enrolled into the study to achieve the target of 12 completed participants. Two of the participants experienced such a strong subjective response to the 20 mg of cocaine initiation infusion that they requested to be discontinued from the study. A third participant was terminated from the study due to having a urine drug screen positive for cocaine prior to the initiation

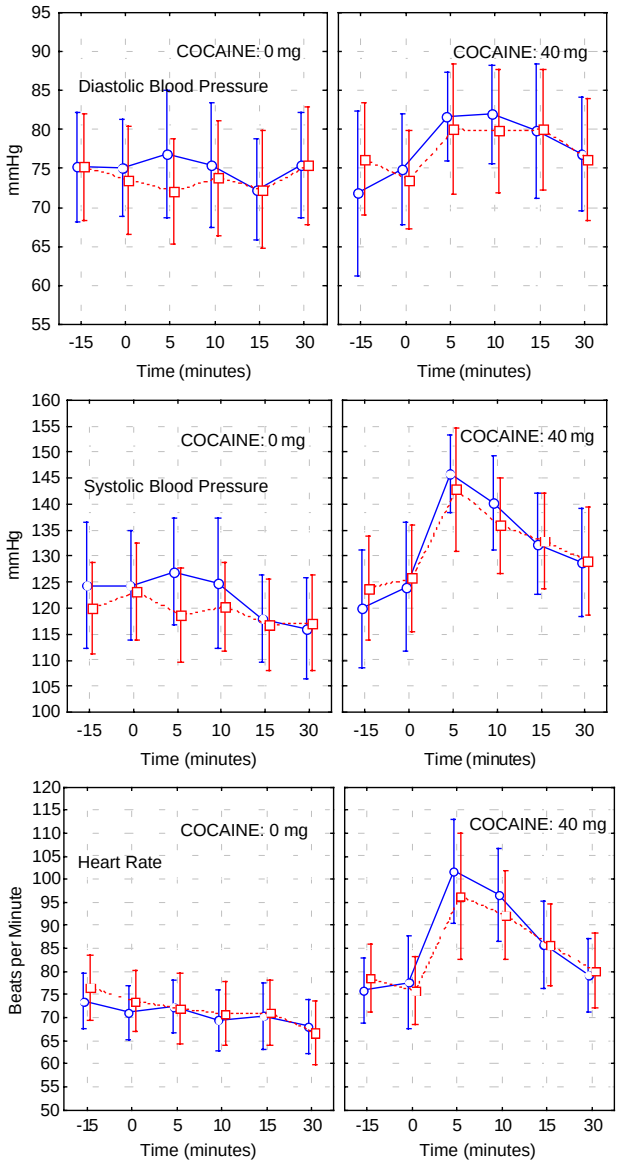

Fig. 1. Physiological responses as a function of medication, infusion, and time (minutes from infusion). (—○—) 0 mg of metyrapone; (---□---) 750 mg of metyrapone. Vertical bars denote .95 confidence intervals.

infusions. The participants who completed the study were very similar to the three participants who did not complete. The 12 participants who completed the study were primarily male (75%), were African American (75%; 25% were Caucasian), were crack cocaine users (100%), reported cocaine use on an average of 12.75 days in the past 30 days (S.D.=10.04), and reported an average of 10 years of lifetime cocaine use (S.D.=4.51). Most of the participants were employed at least part time (66%). One third of the sample had never been married and no participant reported currently being married. The average age of the participants was 39.7 years (range: 35–44 years). The three participants who were enrolled but did not complete were primarily male (67%), were African American (100%), were crack cocaine users (100%), reported cocaine use on an average of 20 days in the past 30 days (S.D.=1.7), and reported an average of 12 years of lifetime cocaine use (S.D.=0). Most of the participants were employed at least part time (67%). One (33%) had never been married and the other two (67%) were divorced. The average age of these three participants was also 39.7 years (range: 33–45 years).

3.1. Physiological response

3.1.1. Vital sign analysis

As expected, there was a significant infusion×time interaction effect on SBP ($F(5,50)=14.10$, $p<.001$), DBP ($F(5,50)=6.70$, $p<.05$), and HR ($F(5,50)=27.74$, $p<.001$). There were no significant infusion×medication or infusion×medication×time interaction effects. As can be seen in Fig. 1, metyrapone did not exacerbate the effects of cocaine on any of the vital sign measures. The highest individual SBP, DBP, and HR recordings during and within 60 min of infusion are shown in Table 2. There were no values recorded above the moderate hypertension range and no sustained hypertension was detected.

3.1.2. ECG analysis

During the period of constant monitoring, there were no cardiac rhythm abnormalities noted except for sinus tachycardia, sinus bradycardia, and non-specific ST segment and T wave changes. In addition, one patient had a rightward axis at baseline and throughout the entire study.

3.2. Neuroendocrine response

The neuroendocrine effects of cocaine were assessed by cortisol and ACTH plasma levels. As can be seen in Fig. 2, cortisol levels prior to infusion (i.e., at the −15 min assessment) were between 10 and 15 μg/dl for placebo, while they were below 5 μg/dl for metyrapone, indicating that metyrapone effectively suppressed baseline cortisol levels. Metyrapone's suppression of cocaine's increase of

Table 2
Highest individual physiological reading taken during and 60 min after infusion as a function of medication and infusion

Physiological measure	Infusion			
	Placebo		Cocaine=40 mg	
	MRP=0 mg	MRP=750 mg	MRP=0 mg	MRP=750 mg
Systolic blood pressure (mm Hg)				
During infusion	154	150	158	145
Post infusion	160	167	161	164
Diastolic blood pressure (mm Hg)				
During infusion	86	87	92	85
Post infusion	100	94	106	100
Heart rate (beats/min)				
During infusion	90	90	102	98
Post infusion	93	96	131	133

MRP=metyrapone.

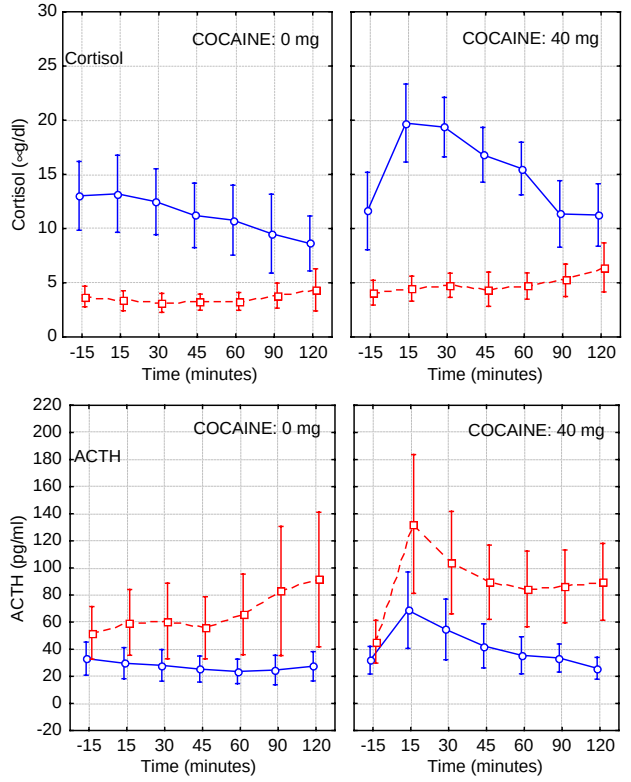

Fig. 2. Neuroendocrine responses as a function of medication, infusion, and time (minutes from infusion). (—○—) 0 mg of metyrapone; (---□---) 750 mg of metyrapone. Vertical bars denote .95 confidence intervals.

cortisol is reflected by a significant medication×infusion×time interaction effect ($F(6,60)=3.18$, $p<.01$). Bonferroni post-hoc analyses examining the significant interaction effect revealed that cortisol under the placebo condition was significantly greater than cortisol under metyrapone at every time point except 120 min post saline infusion.

The analysis of the ACTH results revealed a significant medication×infusion×time interaction effect ($F(6,60)=3.18$, $p<.01$). Bonferroni post-hoc analyses examining the significant interaction effect revealed that ACTH under the placebo condition was significantly less than ACTH under metyrapone at every time point except the pre-infusion point (−15 min) for saline and cocaine. This suggests that metyrapone increased ACTH, regardless of whether saline or cocaine was infused.

3.3. Subjective response

Subjective effects were measured on 11 VAS. As expected, infusion of cocaine, compared to placebo, had a significant effect on the participants' subjective responses. Specifically, there were significant infusion×time interaction effects for all scales except "how depressed do you feel." The effects of metyrapone on participant response to cocaine infusion should be reflected by infusion×medication and infusion×medication×time interaction effects. There was a significant infusion×medication interaction effect for two VAS: "does the drug have any good effects" ($F(1,10)=6.70$, $p<.05$) and "how much do you like the drug" ($F(1,10)=5.44$, $p<.05$). The graphs for these VAS are shown in Fig. 3.

As can be seen in Fig. 3, it appears that metyrapone served to increase the participants' subjective ratings of saline and to decrease their ratings of cocaine. However, this interpretation was not supported by the Tukey HSD post-hoc analyses examining the significant infusion×medication interaction effect for "good drug effect" and "drug liking." These analyses revealed that the effect of metyrapone on participant rating of good drug effect and drug liking was dependent upon the infusion received (cocaine or saline; $p<.05$). In contrast, the effect of cocaine on participant rating of good drug effect and drug liking was not dependent upon the medication received (MRP or placebo; $p>.05$). These results suggest that metyrapone significantly increased participant liking of saline while not significantly affecting the subjective effects of cocaine.

3.4. Tolerability

Eleven participants (92%) reported at least one adverse event (AE) during the 11-day inpatient stay. A total of 57 AEs were reported. Of these, 12 AEs were considered related to study drug, although seven of these AEs were reported on

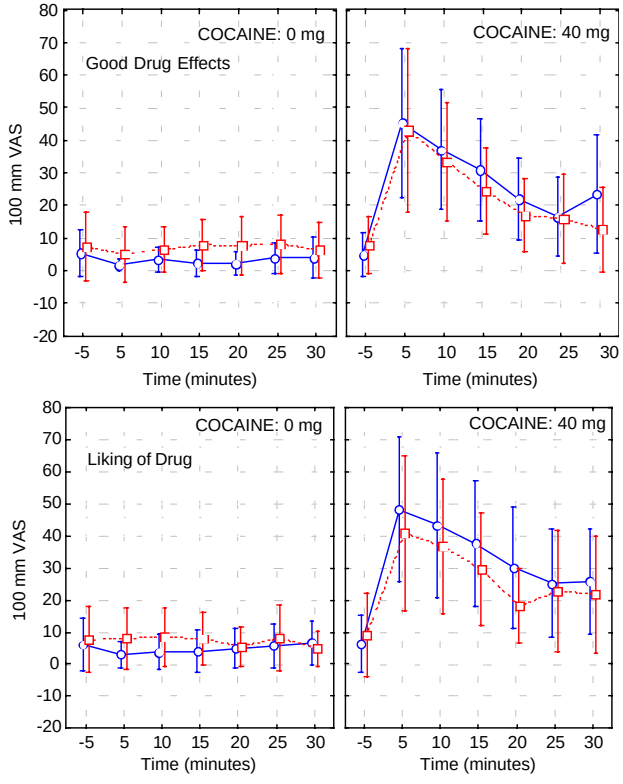

Fig. 3. Subjective responses as a function of medication, infusion, and time (minutes from infusion). (—○—) 0 mg of metyrapone; (---□---) 750 mg of metyrapone. Vertical bars denote .95 confidence intervals.

non- infusion days. All AEs occurring on metyrapone and cocaine infusion days were considered mild. Single occurrences of nausea and muscle spasm were considered related. No serious adverse events (SAE) occurred and no subjects were discontinued because of an AE.

4. Discussion

The goal of this study was to evaluate the safety of metyrapone for eventual use in an outpatient study with active cocaine users. It was predicted that there would be no significant safety issues arising from the interaction of cocaine and metyrapone. It was also predicted that, consistent with the finding of Ward et al. (1998), metyrapone would not significantly alter the subjective effects of cocaine. As predicted, the physiological and adverse event measures indicated that the interaction of cocaine and metyrapone at the doses studied did not illicit any safety concerns. This finding is consistent with that of Ward et al. (1998) in their interaction study of ketoconazole and cocaine. The results of this study, combined with Ward et al.'s (1998) results, suggest that metyrapone is likely to be safe for evaluation in an outpatient trial at the doses studied in the current trial.

While there were two statistically significant infusion×medication interaction effects on subjective ratings, post-hoc analyses suggest that the results seen were not due to metyrapone lessening the effect of cocaine, but rather to metyrapone significantly increasing participant liking of saline while not significantly affecting the subjective effects of cocaine. The finding that metyrapone did not significantly affect participant response to cocaine is consistent with the findings of Ward et al. (1998).

It is hypothesized that metyrapone might help to reduce a cocaine-dependent person's susceptibility to stress-induced and cue-induced craving. Although not reported in the present paper, we attempted to evaluate metyrapone's effects on the participants' reactions to laboratory stress and conditioned craving procedures. The stress and conditioned craving procedures did not significantly alter participants' VAS ratings; thus, the potential effects of metyrapone on stress- and cue-induced craving could not be evaluated. Testing the effectiveness of metyrapone as a cocaine dependence treatment will require an outpatient double-blind placebo-controlled trial. The results of the present study suggest that metyrapone at the doses studied can likely be used safely in an outpatient study with active cocaine users. Given the FDA-approved dosing schedule for metyrapone, its use as a cocaine dependence treatment may be limited to the use of short-term single doses on an as-needed basis. This would be consistent with the PRN use of metyrapone by episodic users or by those who have initiated abstinence but need assistance in avoiding a stress- or cue-induced relapse.

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