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Methylphenidate and cocaine: A placebo-controlled drug interaction study

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Abstract

Up to thirty percent of cocaine addicted individuals may meet diagnostic criteria for Attention-Deficit/Hyperactivity Disorder (ADHD). Methylphenidate (MPH) is a highly effective and commonly used treatment for ADHD but, like cocaine, is a cardiovascular and central nervous system stimulant with the potential to cause toxicity at high doses. The present study was undertaken to investigate the likelihood of a toxic reaction in individuals who use cocaine while concurrently taking MPH. Seven non-treatment seeking cocaine-dependent individuals completed this placebo-controlled, crossover study with two factors: Medication (placebo, 60 mg MPH, 90 mg MPH) and Infusion (saline, 20 mg cocaine, 40 mg cocaine). Physiological measures included vital signs, adverse events, and electrocardiogram. Subjective response was measured with visual analog scale (VAS) ratings of craving and drug effect. Cocaine pharmacokinetic parameters were calculated for each participant at each drug combination, using a non-compartmental model. MPH was well tolerated, did not have a clinically significant impact on cocaine's physiological effects, and decreased some of the positive subjective effects of cocaine. MPH did not significantly alter the pharmacokinetics of cocaine. The study results suggest that MPH at the doses studied can likely be used safely in an outpatient setting with active cocaine users.

Keywords: Cocaine; Methyphenidate; Cardiovascular effects; Subjective effects; Cocaine pharmacokinetics

1. Introduction

Approximately 15 to 30% of cocaine dependent individuals meet Diagnostic and Statistical Manual 4th Edition (DSM IV) criteria for adult Attention-Deficit/Hyperactivity Disorder (ADHD) (Gawin et al., 1985; Grabowski et al., 1997; Levin et al., 1998). Adult ADHD is associated with significant impairment in educational and occupational functioning, including fewer years of education, higher rates of unemployment, and lower paying jobs (Wilens et al., 2004). Adult ADHD is also related to problems in family functioning including greater family discord and higher divorce rates (Biederman et al., 1993). In addition to its detrimental effects on work and family life, adult ADHD is associated with more reckless driving as evidenced by more speeding tickets and severe accidents (Wilens et al., 2004). Psychostimulants are the mainstay of pharmacologic treatment for ADHD. More specifically, over 50 randomized controlled trials (Schachter et al., 2001), along with decades of clinical experience, has established the safety and efficacy of methylphenidate (MPH) in the treatment of ADHD (Greenhill et al., 1999).

For treating adults with ADHD, Spencer et al. (1995) have found that MPH is most effective at doses of up to 1 mg/kg/day. This could represent a daily dose of 90 mg or more in heavier patients. Both cocaine and MPH are sympathomimetics and psychomotor stimulants, with the potential to cause cardiovascular toxicity and increased central nervous system stimulation (Goldfrank and Hoffman, 1991; Hoffman and Lefkowitz, 1996). One double-blind, placebo controlled study of MPH for treating cocaine addicted individuals with ADHD used MPH up to 90 mg a day in three divided doses. In this study, Schubiner et al. (2002) reported no group differences in self-reported cocaine use, urine toxicology results, or cocaine craving, but significant improvement

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in ADHD on both physician-rated and self-rated global improvement scales. However, in this small study of 48 participants 25% of the MPH group had dose decreases compared to 8% of the placebo group, indicating that the use of high doses of MPH in a cocaine-dependent, ADHD population may be associated with significant side effects. Thus, it is important to systematically study the relationship between increasing MPH dose, concomitant cocaine use and adverse reactions.

In addition to concern over possible negative physiological effects, the psychological interactions between these stimulants must also be assessed. MPH shares subjective effects with cocaine in humans (Rush and Baker, 2001) and sensitizes animals to the reinforcing effects of cocaine (Schenk and Izenwasser, 2002). MPH is a Schedule II controlled substance with the potential for abuse when used alone (Llana and Crismon, 1999). There is a report of MPH inducing cocaine craving in some individuals (Gawin et al., 1985). However, two studies did not support this finding. Roache et al. (2000) did not report any increases in cocaine craving or abuse potential with a combination of sustained-release MPH and smoked cocaine. In an open-label trial of MPH for the treatment of 41 cocaine-dependent adults with a DSM-IV diagnosis of ADHD, Somoza et al. (2004) reported significantly less craving over the course of the 10-week trial. In a recent cocaine–MPH interaction study, Collins et al. (2006) found that MPH decreased some of the positive effects of cocaine in cocaine dependent participants with ADHD. It was thus predicted that MPH would not increase the positive effects of cocaine.

Any toxic or psychological interactions detected with a combination of MPH and cocaine may be an additive effect of using two psychomotor stimulants simultaneously or a result of a pharmacokinetic interaction between the two drugs. MPH is metabolized almost completely in the liver by esterification and cocaine is metabolized primarily by plasma and hepatic esterases (Bosron et al., 1997; Laizure et al., 1995; Parker et al., 1998), with a small fraction is metabolized by *N*-methylation in the liver. There are no reports in the literature that has examined whether a minor cocaine metabolic pathway could be influenced by high doses of MPH.

The primary objective of this study was to examine the safety of using doses of MPH, up to 90 mg daily, in cocaine-dependent individuals who may concomitantly use cocaine. It was our assumption that the physiological and subjective responses of cocaine dependent participants without ADHD to cocaine and MPH would be similar to those of cocaine dependent individuals with ADHD. Thus, study participants were recruited without regard to ADHD. The correctness of our assumption is supported, at least in part, by a recent study finding that cocaine abusers with and without ADHD had very similar physiological and subjective responses to cocaine infusion (Collins et al., 2006).

2. Methods

2.1. Participants

Each potential participant completed a two-week screening period consisting of medical and psychiatric history, physical examination, laboratory evaluation and electrocardiogram (ECG). Healthy men and women between the ages of 21 and 47 years, within 20% of ideal body weight, and with a current DSM-IV diagnosis of cocaine dependence were eligible for enrollment if they had a past history of intravenous exposure to any drug of abuse. Participants were excluded from the study if they required detoxification from alcohol, opiates or sedative-hypnotic drugs, if they had any serious physical or psychological illness, or if they had any of the following: glaucoma, a diagnosis or family history of Tourettes' Syndrome, abnormal thyroid function, or a history of seizures. Persons with a history of any adverse reactions or hypersensitivity to either cocaine or MPH 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.

All participants 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. Participants who satisfied criteria were enrolled in the study only if upon hospital admission they provided a urine specimen negative for the cocaine metabolite, benzoylecgonine (BE). A total of eight volunteers met inclusion criteria, and enrolled in the study.

2.2. Procedures

The present study utilized a placebo-controlled, crossover design with two factors: 1. Medication (placebo, 60 mg MPH, and 90 mg MPH) and 2. Infusion (saline, 20 mg Cocaine, and 40 mg Cocaine). MPH dosing was not blinded and was not counterbalanced. Rather, for all participants, the first cocaine infusion series was completed under placebo, the second cocaine infusion series was completed once the participant was stabilized on 60 mg of MPH and the third cocaine infusion series was completed once the participant was stabilized on 90 mg of MPH. Cocaine infusions were administered in a modified double-blind design. On the first test day of the first infusion series, participants were randomly assigned to receive either saline or 20 mg of cocaine. On the following day (the second infusion day) the participant received the substance not infused on the first day (i.e., 20 mg of cocaine or saline). This portion of the infusion process (the first two infusion days) was performed in a double blind fashion. On the third infusion day, each participant received a 40 mg cocaine infusion in a single-blind fashion. This procedure was chosen to assure the safety of the participants before the highest doses of cocaine and MPH were administered concomitantly. Once an order was assigned, it was followed for each of the three infusion series. All infusions were administered intravenously over two minutes, with the participant supine.

Participants were discharged on study day 21 with a prescription for a seven-day MPH taper. Following discharge, participants were seen in the outpatient clinic once a week for two weeks and were referred to a community treatment program if they desired.

2.3. Study drug preparation

2.3.1. MPH

Ten-milligram tablets of immediate release MPH (Ciba-Geigy) were used for all doses. The VAMC Inpatient Pharmacy staff

observed the administration of each dose at 8:00, 12:00 and 18:00. On infusion days, the morning MPH dose was given one hour prior to the infusion.

2.3.2. Cocaine

Human-use cocaine HCl powder was obtained from The National Institute on Drug Abuse through the Research Triangle Institute (Research Triangle Park, NC). The powder was weighed into dry, single-dose sterile vials. The vials were closed with a septum, crimp sealed and labeled. The vials were securely stored at controlled room temperature. On the day of use, the weighed cocaine HCl powder was dissolved in sterile normal saline for injection at a concentration of 1.12 g/l for the 20 mg dose and 2.24 g/l for the 40 mg dose. The solution was sterilized by filtration through a 0.22 μm filter into a sealed sterile vial (Abbott Laboratories, North Chicago, IL). All manipulations of the test drug were performed in a laminar flow hood. The sterile solution (21.5 ml) was drawn up into a 60 ml syringe (Becton Dickinson, Co., Franklin Lakes, NJ) and infused intravenously through an InfuseOR (Abbott) infusion pump at a rate of 10 ml/min. Each batch of cocaine HCl was tested for sterility and pyrogenicity (Celsis Laboratory Group, St. Louis, MO).

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, 60 mg MPH, or 90 mg MPH, was assessed with Visual Analog Scales (VASs) that included six separate scales (any drug effect, rush, good effects, bad effects, liking, and desire for cocaine). Participants were requested to quantify the degree of effect that they experienced in each of the six categories by making a mark along a 100-mm line from 0 (none) to 100 (extreme).

Physiological reactions to infusions were carefully monitored from shortly prior to each infusion to four hours afterward by conducting all procedures under continuous cardiac monitoring. The monitoring equipment continuously assessed heart rate and cardiac rhythm. The study physician or nurse obtained single lead rhythm strips directly from the cardiac monitoring equipment at the time points outlined in Table 1. In addition, systolic (SBP) and diastolic (DBP) blood pressure were also obtained periodically via the cardiac monitoring equipment. 12-lead electrocardiogram (ECG) tracings were also obtained during the course of each infusion as additional safety measures. Adverse events associated with the combination of MPH 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 MPH use alone were recorded as the participants reported them.

Table 1
Schedule of assessments relative to infusion procedures

Measures/ procedures	Infusion													
	Minutes relative to infusion*													
	−90	−30	−15	−2	−1	5	10	15	20	30	60	120	180	360
VAS+			x	x		x	x		x	x				
Vital signs			x	x	x	x	x	x		x				
12- lead ECG	x						x							
Rhythm strip			x			x	x				x	x	x	x
Adverse events			x			x	x			x	x	x		x
Blood draw — cocaine			x			x	x			x	x	x	x	x
Cardiac Monitoring	← Period of continuous cardiac monitoring →													

*Time $t=0$ marks the end of the two minute infusion. Positive numbers signify minutes post-infusion and negative numbers are minutes prior to the end of infusion.

2.5. Specimen collection and analysis

Blood samples were collected for pharmacokinetic analysis of cocaine as outlined in Table 1. In addition, blood samples were collected to assess MPH levels. The schedule for MPH blood sample collection was based on the administration of MPH, with the samples drawn at 3, 60, 120, 360, and 480 min following the A.M. dose. Blood samples were drawn into tubes containing sodium fluoride and potassium oxalate, through heparin locks, previously placed in the participants' forearm veins. Tubes were immediately placed in ice water and transported within 20 min to a cooled centrifuge 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 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). The limit of quantification was 5.0 ng/ml with 0.5 ml of plasma. The analyses of MPH were done on 1.0 ml of plasma. The method used deuterated internal standard, liquid–liquid extraction, derivatization with heptafluorobutyryl-L-propyl chloride and gas chromatographic–mass spectrometry with negative ion chemical ionization essentially as described by Lin et al. (1999) except that the derivatizing agent no longer provided chiral separation. The limit of quantification was 0.75 ng/ml with 1 ml of plasma.

2.6. Data analysis

2.6.1. Physiological and subjective measures

Data were analyzed using Statistica (StatSoft, Inc., 2004). Significance levels were set at $p<0.05$ for all analyses. The effects of the Infusion, Medication, and the Infusion by Medication interaction on the subjective and physiological measures were analyzed using simple statistics and repeated measures ANOVAs with a crossover design. As can be seen in Table 1, there were seven repeated measures for subjective assessments. There were six and two repeated measures, respectively, for vital signs and the 12-lead ECG. There were some missing data for both the subjective and physiological measures (e.g., missed assessment, technical problem). For the subjective measures, all but 11 out of the expected 378 ratings were completed (i.e., 3% missing data). For blood pressure, all but one out of the expected 441 readings were completed (i.e.,<1% missing data). For these

measures, missing data were imputed by taking the group mean. For HR, the research staff failed to capture 80% of the HR data for two participants; these two participants were not included in the HR analyses and, thus, these analyses are based on five participants. There were no missing data for the ECG analyses.

2.6.2. Pharmacokinetic analysis

Pharmacokinetic analysis for cocaine at 20 and 40 mg doses was performed using pharmacokinetic software, WinNonlin, version 1.5 (Pharsight, CA). The plasma cocaine concentration vs. time data of individual participants was fitted to a non-compartmental pharmacokinetic model. The following parameters were calculated for each participant at each dosage combination: maximum concentration obtained in plasma (C_{max}); elimination rate constant (λ_z); elimination half-life ($t_{1/2}(\lambda_z)$); area under the concentration–time curve from time zero to infinity (AUC_∞); volume of distribution (V_d); and clearance (Cl).

Mean and standard deviation were calculated for each pharmacokinetic parameter. We used Proc Mixed (SAS™), with participant as a random effect and cocaine and MPH dose as fixed effects, to determine whether MPH dose influenced the pharmacokinetics of cocaine. The dependent variables in the model were the pharmacokinetic parameters defined above.

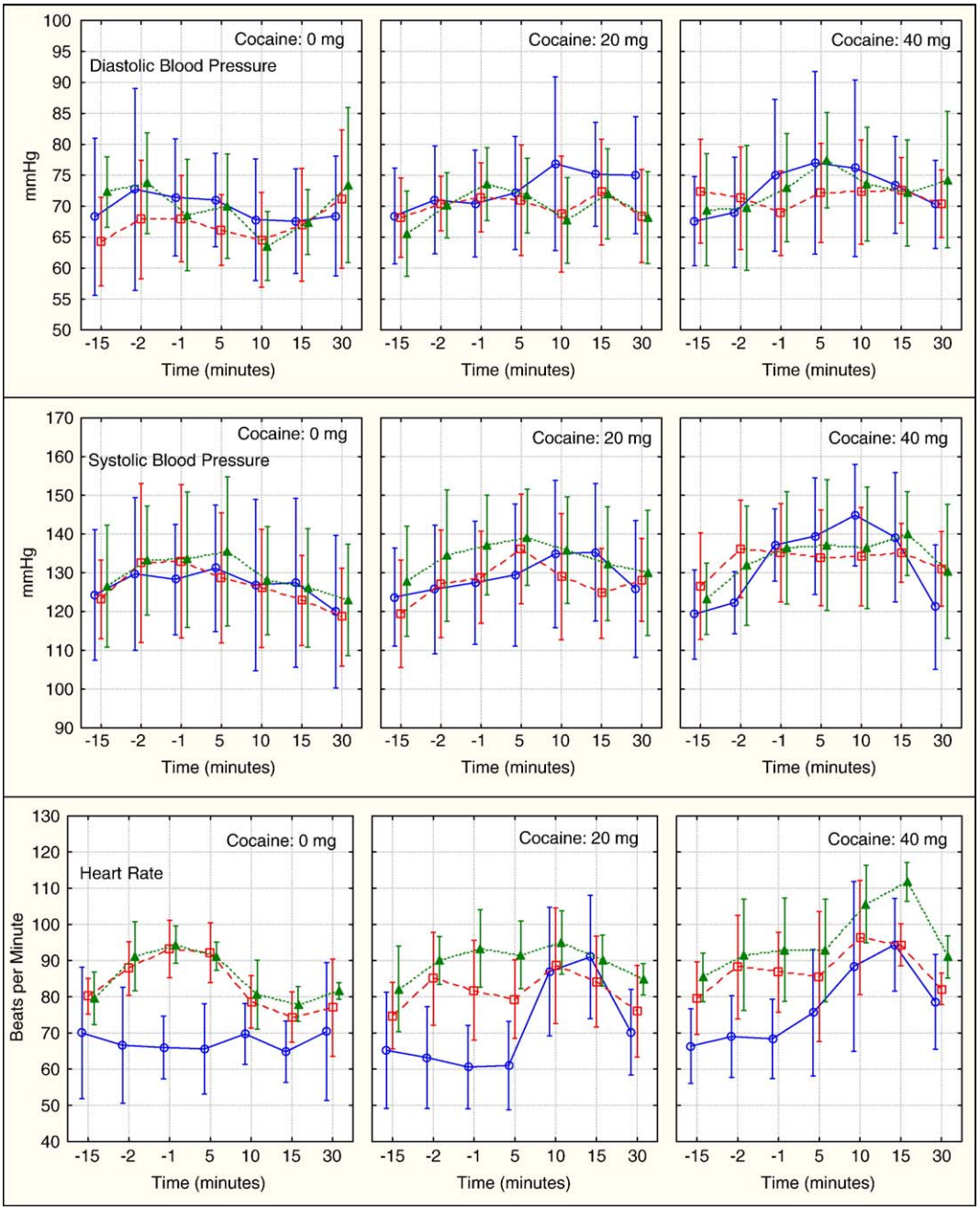

Fig. 1. Physiological responses as a function of Medication, Infusion, and Time (minutes from infusion). –o– 0 mg MPH; –□– 60 mg MPH; …▲… 90 mg MPH. Vertical bars denote .95 confidence intervals. Horizontal time axis not to scale.

The pharmacokinetics analyses identified outliers empirically, because they had unusually high concentrations at a given time point or did not show the expected elimination phase. Of the 294 data points, 10 (i.e., 3.4%) were considered outliers: one data point for participant #2: 20 mg cocaine with 60 MPH obtained 12 min post infusion; one data point for participant #3: 40 mg cocaine with 0 mg MPH obtained 60 min post-infusion; one data point for participant #4: 90 mg cocaine with 40 mg MPH obtained 14 min post infusion; and seven data points for participant #8: 40 mg cocaine with 0 mg MPH for all time points. Data were analyzed both with and without outliers. Most outliers were eliminated because C_{max} was unusually high for the cocaine dose received. When these outliers were eliminated C_{max} at 40 mg of cocaine was, as expected, approximately twice that for the 20 mg cocaine dose (431±84 ng/ml vs. 193± 43 ng/ml).

3. Results

Eight volunteers met inclusion criteria, passed the screening examination, and were enrolled in the study. One participant was dropped from the study because he tested positive for cocaine during a non-infusion period. His data were excluded from the analysis. The seven participants who completed the study were primarily male (71%), African American (71%; 29% were Caucasian), and reported cocaine use an average of 20 days in the past 30 (SD=7). The average age of the participants was 40 (SD=5.3).

3.1. Physiological response

3.1.1. Vital sign analysis

As expected, there was a significant Infusion by Time interaction effect on SBP ($F(12,72)=2.58$, $p<.01$), DBP ($F(12,72)=2.08$, $p<.05$), and HR ($F(12,48)=11.82$, $p<.001$). There were no significant Medication effects on SBP or DBP. There was a significant Medication by Time interaction effect on HR ($F(12, 48)=7.01$, $p<.01$). As can be seen in Fig. 1, HR while the participants were on either 60 mg or 90 mg of MPH, compared to 0 mg MPH, was significantly higher across multiple time-points. There was no significant Medication by Infusion interaction effect on HR.

The highest individual SBP, DBP and HR recordings during and within 30 min of infusion are shown in Table 2. There were no SBP or DBP values recorded above the moderate hypertension range and no sustained hypertension was detected. The highest SBP recorded across all conditions within 30 min of the cocaine/saline infusions was 177 mm Hg at 15 min post-infusion whereas the highest DBP recorded was 108 mm Hg during infusion. Both of these pressures were recorded under placebo conditions in the absence of methylphenidate. The highest HR recorded for any subject up to 30 min after infusion was 118 beats/min at 15 min post-infusion and this occurred while the participant was receiving 40 mg of cocaine while on 90 mg of methylphenidate. There were no episodes of sustained tachycardia and no episodes of serious dysrhythmia like atrial flutter or fibrillation, ventricular premature beats or ventricular tachycardia.

3.1.2. ECG analysis

Four ECG parameters, QRS duration, PR interval, QTc duration, and ST segment, were analyzed. There were no significant effects for QRS duration. There was a significant Infusion by Time interaction effect on PR interval ($F(2,12)=5.66$, $p<.05$), QTc interval ($F(2,12)=15.43$, $p<.01$), and ST segment ($F(2,12)=5.16$, $p<.05$). The PR interval decreased by 6.1 ms (4.3%) with the 20 mg cocaine infusion, and by 6.6 ms (4.6%) with the 40 mg infusion. The QTc interval increased by 9.7 ms (2.4% change) with the 20 mg cocaine infusion and by 18.8 ms (4.6% change), with 40 mg infusion. The ST segment (as measured in leads V2 and V3) decreased by 0.14 mm (21.4% change) with the 20 mg cocaine infusion and by 0.55 mm (74.2% change) with the 40 mg infusion. There were no significant Medication effects on the ECG parameters.

During the period of constant monitoring no patient had any clinical symptoms of ischemia; however, there was one study participant who developed altered cardiac parameters. He was a 31 year old African American male with a past history of a septal myocardial infarct. His ST segment (in leads V2 and V3) decreased from an average of 0.67 mm before the 20 mg cocaine infusion to zero at 10 min post infusion, and also dropped from an average of 0.70 mm before the 40 mg infusion to −1.3 mm post infusion,

Table 2
Highest individual physiological reading taken during and 30 min after infusion as a function of medication and infusion

Physiological measure	Infusion								
	Placebo			Cocaine 20 mg			Cocaine 40 mg		
	MPH=0 mg	MPH=60 mg	MPH=90 mg	MPH=0 mg	MPH=60 mg	MPH=90 mg	MPH=0 mg	MPH=60 mg	MPH=90 mg
Systolic blood pressure (mm Hg)									
During Infusion	167	169	167	162	148	168	146	156	154
Post Infusion	177	152	172	168	153	161	165	155	162
Diastolic blood pressure (mm Hg)									
During Infusion	108	86	90	89	83	82	100	85	92
Post Infusion	87	90	95	100	89	84	100	86	97
Heart rate (beats/min)									
During Infusion	78	103	103	74	101	106	80	103	112
Post Infusion	97	104	94	107	106	105	117	112	118

suggesting the effects of ischemia. In addition, his QTc increased as a result of the 40 mg cocaine infusion from 400 mg pre-infusion to 425 at 10 min post-infusion. There was no evidence that MPH exacerbated these effects of cocaine. In fact at the highest cocaine infusion, his QTc intervals were 440, 427, and 409 ms, respectively for MPH doses of 0, 60 mg, and 90 mg. His ECG parameters recovered to baseline values after the infusion.

3.2. Subjective response

Subjective effects were measured on 6 VASs. As expected, infusion of cocaine, compared to placebo, had a significant effect on the participants' subjective responses. Specifically, there were significant Infusion by Time interaction effects for all scales except "bad effects."

Unexpectedly, MPH decreased some of the positive subjective effects of cocaine. There was a significant Infusion by Medication by Time interaction effect for two VASs: desire for cocaine ($F(20,120)=2.17$, $p<.01$) and good drug effects ($F(20,120)=2.12$, $p<.01$). As can be seen in Fig. 2, it appears that MPH served to decrease participant ratings of "desire for cocaine" and "good effects." Tukey HSD post-hoc analyses revealed that participant ratings of "desire for cocaine" at 0 mg of MPH compared to 90 mg MPH differed at several time points during the 20 mg and 40 mg cocaine infusions (see Fig. 2). Tukey HSD post-hoc analyses revealed that participant ratings of "good effects" at

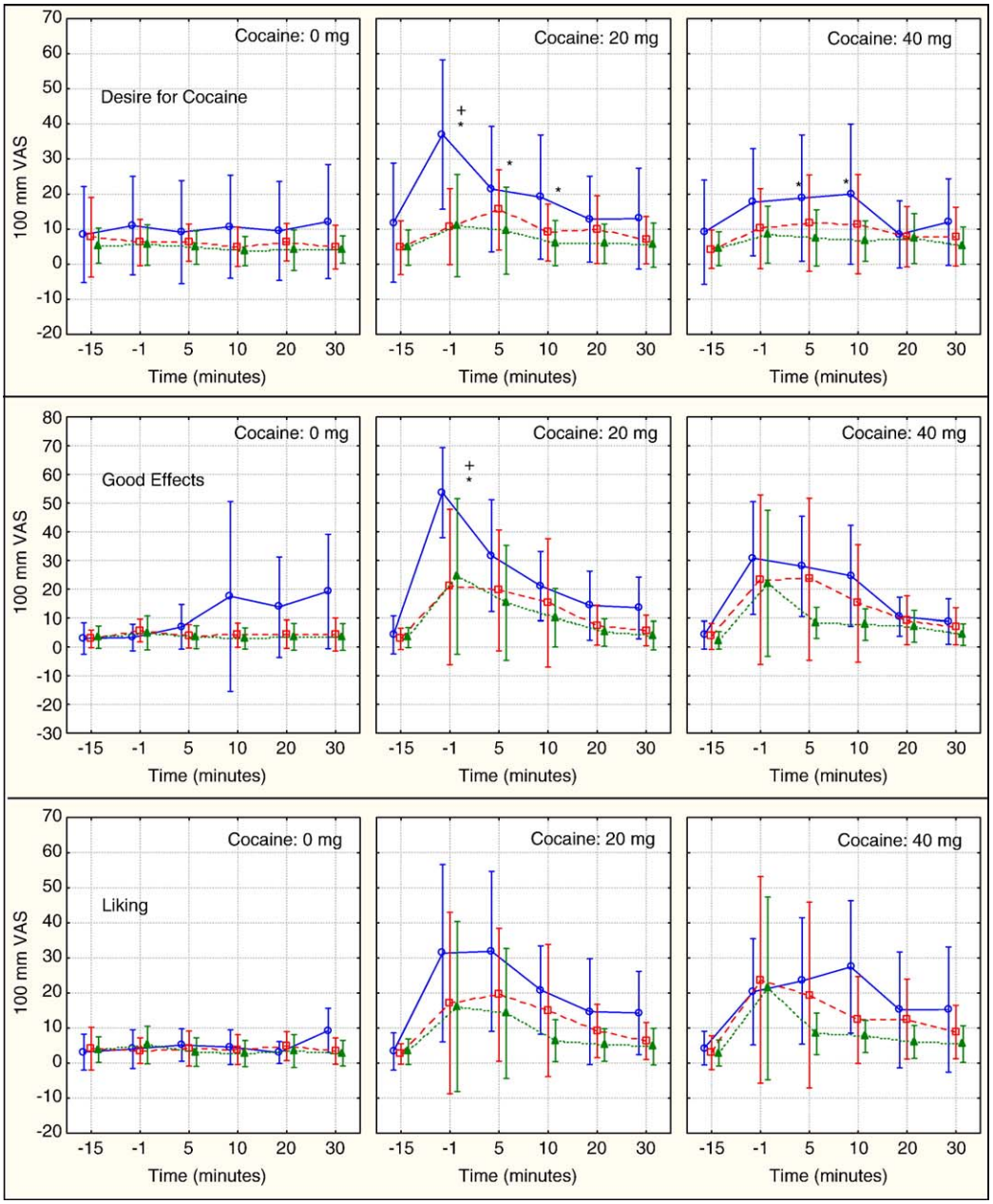

Fig. 2. Subjective responses as a function of Medication, Infusion, and Time (minutes from infusion). –o– 0 mg MPH; –□– 60 mg MPH; …▲… 90 mg MPH. Vertical bars denote .95 confidence intervals. $^{+}p<.05$ on Tukey HSD for 0 MPH vs. 60 MPH. $^{*}p<.05$ on Tukey HSD for 0 MPH vs. 90 MPH. Horizontal time axis not to scale.

Table 3
"Possibly related" adverse events reported as a function of medication and infusion

Cocaine infusion	MPH steady state dose level		
	0 mg	60 mg	90 mg
Placebo (saline)	Chest pain (1)[a]	Lightheadedness (1) Nervousness (1)	None reported
20 mg	Lightheadedness (1)	None reported	Headache (1)
40 mg	Lightheadedness(1) Nervousness (2) Tingling (1)	Nervousness (1)	None reported

[a] (*n*) indicates number of patients reporting.

0 mg of MPH, compared to both 60 mg MPH and 90 mg MPH, differed at only one time point during the 20 mg cocaine infusion (see Fig. 2).

There was a significant Medication by Time interaction effect for three VASs: "liking" ($F(10,60)=2.22$, $p<.05$), "rush" ($F(10,60)=2.08$, $p<.05$), and "any drug effect" ($F(10,60)=2.11$, $p<.05$). Tukey HSD post-hoc analyses revealed no significant differences for "rush" or "any drug effect" ratings (data not shown). As can be seen in Fig. 2, there was a trend for participant rating of "liking" to be decreased by MPH. Tukey HSD post-hoc analysis of the Medication by Time interaction effect revealed that liking was significantly lower at the 5 and 10 min post-infusion time-points when the participants were on 90 mg compared to 0 mg of MPH.

3.3. Tolerability

MPH was well tolerated by all study participants. No participant was withdrawn from the study because of adverse events. Most adverse events were rated as mild to moderate though one participant reported severe diffuse joint pain that became progressively worse throughout the day. Physical examination showed no abnormalities. This event occurred while the participant was taking MPH 90 mg. It did not occur during an infusion period and, therefore, was not related to a drug interaction between cocaine and MPH. A hypersensitivity reaction to MPH was one possible explanation for the event. The participant was prescribed a single dose of prednisone 60 mg. The participant became symptom free within 30 min of treatment and continued on the MPH with no further complaints. The signs and symptoms and the response to treatment were unusual and the exact cause of the adverse event was never determined.

There were no significant adverse events reported during infusion periods possibly related to a drug interaction between cocaine and MPH (see Table 3). Interestingly, participants reported more adverse events during infusions in the absence of MPH than while taking either dose of MPH. This may suggest an interaction between the two drugs or more likely the result of an order effect. Since all participants received the first infusion series in the absence of MPH, they may have experienced more apprehension or nervousness prior to this infusion series than during later infusions when they were taking MPH.

3.4. Pharmacokinetic parameters

Table 4 shows the pharmacokinetic parameter estimates for the two doses of cocaine in the absence and in the presence of two steady-state dose levels of MPH (60 mg and 90 mg) when outliers were excluded (parameters shown in bold lettering) and included (parameters shown in parentheses) as defined under *Data Analysis*. Statistical analyses of the six main pharmacokinetic parameters were assessed for the effects of cocaine dose, MPH dose and the interaction between concurrent administration of MPH and cocaine. There was a significant effect of cocaine dose on all parameters except V_d: C_{max} ($df=1$, $F=21.76$, $p<0.05$); λ_z ($df=1$, $F=9.19$, $p<0.05$); $t_{1/2}(\lambda_z)$ ($df=1$, $F=6.25$, $p<0.05$); AUC_∞ ($df=1$, $F=79.93$, $p<0.05$); Cl ($df=1$, $F=9.72$, $p<0.05$). Medication did not significantly affect any of the cocaine pharmacokinetic parameters. The interaction of Infusion and Medication showed a significant effect on V_d only when outliers were included in the analysis ($df=2$, $F=4.29$, $p=0.042$).

Table 4
Cocaine pharmacokinetic parameters as a function of medication and infusion

Parameter	MPH steady state dose level						Mean values across MPH conditions	
	0 mg		60 mg		90 mg			
	Cocaine infusion dose							
	20 mg	40 mg	20 mg	40 mg	20 mg	40 mg	20 mg	40 mg
C_{max} (ng/ml)	240±53	411±68 (918±469)	214±63.3 (435±209)	501±104	125±11.7	382±79	193±43 (267±91)	431±84 (600±487)
λ_z (min^{-1})	0.014±0.001	0.012±0.002	0.013±0.001	0.01±0.001	0.013±0.001	0.012±0.001	0.013±0.001	0.011±0.002
$t_{1/2}(\lambda_z)$ (min)	49.0±2.7	69.77±16 (81.4±17.5)	55.5±4.6	74.4±6.2	58.5±8.4	60.8±5.9	54.3±5.2	68.3±19.4 (72.2±19.4)
AUC_∞ (ng/ml/min)	10,872±556	31,232±6133 (35,821±6765)	11,461±1326 (13,807±1842)	28,510±2304	10,911±1384	27,327±2564 (29,530±3938)	11,081±1089 (11,863±1261)	29,023±7593 (31,287±8160)
V_d (l)	131±7.9	132.3±6.1 (133.33±14.13)	153±22.5 (128±18.9)	152.7±10.9	156±8.5	130.95±9.5 (126.6±12.7)	142.7±30 (137.9±31.2)	
Cl (l/min/kg)	0.0243±0.0013	0.0192±0.0034 (0.018±0.0033)	0.0251±0.0036 (0.0211±0.0031)	0.0189±0.0016	0.026±0.0030	0.0202±0.0021 (0.0194±0.0025)	0.025±0.003 (0.024±0.002)	0.0194±0.004 (0.019±0.004)

C_{max}=maximum concentration obtained in plasma; λ_z=elimination rate constant; $t_{1/2}(\lambda_z)$=elimination half-life; AUC_∞=area under the concentration–time curve from time zero to infinity; V_d=volume of distribution; Cl=clearance. *Note*: Parameter estimates represent mean±SD. Where outlier exclusion changed a pharmacokinetic parameter, the parameter estimate with the outlier(s) included is provided in parentheses.

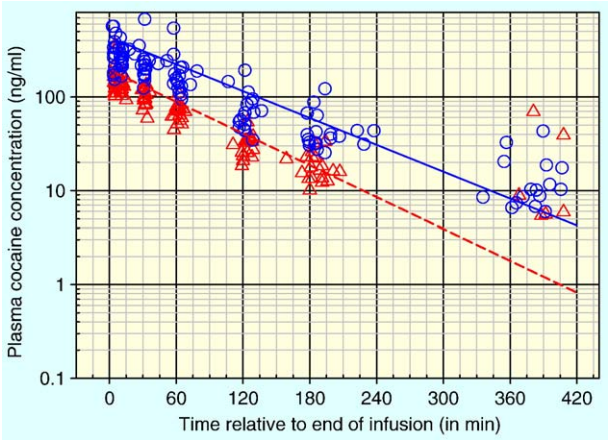

Fig. 3. Plasma cocaine concentration as a function of time from infusion (semi-log plot). All individual data points are represented by the red triangles (for the 20 mg cocaine infusions) or blue circles (for the 40 mg cocaine infusions) regardless of the medication condition. The corresponding lines represent the pharmacokinetic curves assuming (a) a half life $t_{1/2}(\lambda_z)$ of 54.3 min for 20 mg of cocaine and 68.3 min for 40 mg of cocaine and (b) the concentrations at time $t=0$ of: 193 ng/ml for the 20 mg cocaine infusion and 431 ng/ml for the 40 mg infusion as given in Table 4. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 3 displays the plasma cocaine concentrations for 20 mg and 40 mg of infused cocaine as a function of time. Note that at the final time point (360 min) the cocaine concentration was undetectable for some samples, thus, they do not appear on the graph.

3.5. Plasma MPH concentrations

The average MPH concentration over all study participants, cocaine infusion dosages, and times was 7.5 ng/ml for the 60 mg dose and 8.1 ng/ml for the 90 mg dose. There was a great deal of variability in the MPH plasma concentrations. For example, the maximum MPH concentration observed for the 60 mg per day dose ranged from 5.91 to 16.6 ng/ml, and from 4.9 to 19.3 for the 90 mg dose.

4. Discussion

The present study evaluated the likelihood of a toxic reaction in individuals who use cocaine while concurrently taking MPH, up to 90 mg daily. The results of this study indicate that MPH in combination with cocaine was well tolerated. No Infusion by Medication interaction was found for SBP, DBP, or HR. The significant Medication by Time interaction effect for HR suggests that MPH does significantly increase HR but the lack of a significant Infusion by Medication interaction suggests that MPH does not significantly exacerbate the effects of cocaine on heart rate. There were no clinically significant ECG findings related to the interaction of cocaine and MPH. Thus, the study suggests that the combination of MPH and cocaine is safe at the doses studied. These findings are consistent with a recent MPH–Cocaine interaction study that evaluated the effects of MPH up to 60 mg (Collins et al., 2006). Additionally, the present study found that MPH did not significantly alter the pharmacokinetics of cocaine.

To our knowledge, the present paper is the first to publish pharmacokinetic parameter estimates for a 20 mg cocaine dose (0.26 mg/kg). Three prior studies (Hart et al., 2000; Chow et al., 1985; Cone et al., 1988) have calculated pharmacokinetic parameters for doses equivalent to the 40 mg cocaine dose utilized in the present study. Table 5 displays the values from the present study together with those of the three previous studies. As can be seen in Table 5, the consistency in these parameters is greatest for Cmax. Our value of cocaine's half life (at a dose of 0.52 mg/kg) is within 30% of Hart et al. (2000) and Chow et al. (1985), and 45% higher than that of Cone et al. (1988). Our value of clearance is virtually identical to that of Hart et al. (2000), but 36% lower than that of Chow et al. (1985) and Cone et al. (1988). Our AUC value is 9% lower than that of Cone et al. (1988), and 43% lower than that of Hart et al. (2000). These differences are likely to be due to metabolic differences among the individuals participating in these studies. Our analysis of MPH plasma concentrations revealed a great deal of variability in concentration levels, which is consistent with previous research (Kimko et al., 1999; Gualtieri et al., 1982).

Contrary to prediction, the study results suggest that MPH decreased some of the positive subjective effects of cocaine. These decreases were most marked for the "Desire for Cocaine" and "Good Effect" ratings. While not predicted, this finding is consistent with those of Collins et al. (2006) who found that MPH decreased some of the positive subjective effects of cocaine including the rating of "Good Effect" for 48 mg/70 kg of cocaine under the 60 MPH condition compared to the placebo MPH condition.

Although this study provides evidence for the safe use of MPH in a cocaine-abusing population, there are several deficiencies in this study that may affect the conclusions and generalizability of the results. First, the study was not fully blinded and the order of the MPH doses was not counterbalanced. All participants received open-label MPH in the same dose-escalating regimen. Participants were then randomized to receive either placebo or the lower cocaine dose first in the three cocaine infusion series. The highest cocaine dose was always administered

Table 5
Comparisons of cocaine pharmacokinetic parameters from various studies

Pharmacokinetic parameter	Present study 20 mg cocaine (0.26 mg/kg)	Present study 40 mg cocaine (0.52 mg/kg)	Hart et al. (2000) (0.5 mg/kg)	Chow et al. (1985) (0.478 mg/kg)	Cone et al. (1988) (0.585 mg/kg)
AUC (ng/min/ml)	11,081±1089	20,023±7593	28,628±4598		21,838±2970
$t_{1/2}$ (min)	54.3±5.2	68.3±19.3	87±7.19	48±13	37.3±1.8
Cl (l/min/kg)	0.025±0.003	0.0194±0.004	0.019±0.0024	0.03±0.0047	0.0298±0.004
C_{max} (ng/ml)	193±43	431±84	444±93.54		470±70

last. Safety was the primary reason for this study design. It was important for the participants to receive a lower cocaine dose prior to the higher dose to ensure tolerability. The second reason involved the timeliness of the study. If MPH doses were randomized a washout period would have been needed if the higher doses of MPH were given before the lower doses. This would have increased the length of an already long study (21 inpatient days).

The lack of blinding may have affected the study results. However, the results of the present study are consistent with those of the Collins et al. (2006) study, which was double-blinded. The failure to counterbalance the order of MPH dosing is problematic in that the subjective effects and perhaps the cardiovascular effects of cocaine in the presence and absence of MPH might have been inextricably confounded with time in the hospital. Early in the study there may have been more anxiety related to the novelty of the study procedures, more recent experience with street cocaine, and less identification with staff members, producing a heightened response when compared with that elicited during the last days of the study.

Another concern is that the results may not generalize to the entire cocaine abusing population and more importantly to those with ADHD who are candidates for MPH treatment. The seven subjects completing this study were recruited without regard to ADHD and were extensively screened to insure good health. Persons were eliminated during screening if they had any evidence of cardiovascular disease including hypertension. Essential hypertension, in particular, is very prevalent in the population and is likely to be present in a substantial number of cocaine abusers. It may be hard to extrapolate a lack of toxicity seen in screened normal individuals to those with hypertension or heart disease, who may be treated in the general population. Finally, in terms of safety, another concern associated with the results of this study is the dose of cocaine used. Cocaine dependent individuals are likely to use more than 40 mg of cocaine. Moreover, street cocaine is likely to be adulterated with other substances. In this study 40 mg was the maximum dose of cocaine, resulting in the possibility that there are risks associated with concomitant use of MPH and cocaine that were unable to be assessed by the present study design.

The results from the present study suggest that treatment of cocaine dependent persons with higher doses of MPH, up to 90 mg daily, may not pose an increased risk to healthy individuals who continue to use cocaine.

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