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Antiandrogen Pretreatment Alters Cocaine Pharmacokinetics in Men

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Abstract

Among cocaine users, men experience more adverse brain and vascular effects than their female counterparts. This could be caused by testosterone, which may potentiate some of cocaine's effects. We examined whether antiandrogen (flutamide, FL) pretreatment alters cocaine's acute behavioral, physiologic, and pharmacokinetic effects in men with histories of occasional cocaine use. Participants ($N = 8$) were pretreated with oral FL (250 mg) and placebo on separate study days followed by intravenous (IV) cocaine (0.4 mg/kg). Vital signs, subjective ratings, and blood samples for cocaine and metabolites were obtained at baseline and for 90 minutes after cocaine administration. FL, itself, had no effects on physiologic or subjective responses; however, after cocaine, heart rate recovered faster with FL pretreatment. Flutamide reduced peak plasma cocaine levels (Wilcoxon signed-rank $z = 2.1$, $P < 0.04$) and area under the curve (AUC; $z = 1.96$, $P < 0.05$). Additionally, FL reduced EME levels ($z = 1.96$, $P < 0.05$) and AUC for BE and EME ($z = 2.38$, $P < 0.02$ and $z = 1.96$, $P < 0.05$, respectively). These results suggest that FL may alter cocaine pharmacokinetics in men. Because cocaine and BE are vasoconstrictive, the data imply that FL might reduce some of cocaine's cardiovascular effects.

Keywords

cocaine; flutamide; gonadal hormones; benzoylecgonine; ecgonine methyl ester

Cocaine continues to be a major drug of abuse in the United States¹ and has been associated with structural and functional abnormalities in the brain.² Its effects on blood flow may result in brain and cognitive impairments,^{3–5} which have been commonly reported. A growing number of studies have identified significant sex and menstrual cycle differences in the subjective, physiologic, and pharmacokinetic effects of cocaine in both animals and humans.^{6–11} In human chronic cocaine users, men seem to be more vulnerable to cocaine's adverse brain and vascular effects than women.^{12–17} These findings suggest that gonadal hormones may modulate some of cocaine's physiologic effects.

Cocaine has potent sympathomimetic actions affecting cerebral, cardiac, and peripheral vascular resistance.^{18–22} Testosterone also increases vascular resistance,²³ it impairs

agonist-induced vasorelaxation,^{23–25} and it increases apoptotic signaling, adversely affecting myocardial function following ischemia.²⁶ Further, chronic testosterone or androgen administration to hypercholesterolemic subjects both enhanced aortic vasoconstriction and reduced vasodilation.²⁷

Given that cocaine and testosterone by themselves can promote vascular dysfunction and that when present together, in vitro, there is evidence for potentiated vascular dysfunction,²⁸ we hypothesized that antiandrogen treatment might have beneficial effects in cocaine-exposed men. This preliminary study was conducted to assess the safety and efficacy of administering cocaine in the presence of an antiandrogen, FL, as well as to test the hypothesis that androgen receptor blockade would reduce cocaine's acute effects on cardiovascular measures in men who have a history of occasional cocaine use. Previous studies to date have found no evidence that intravenous cocaine administration alters cocaine use patterns in occasional cocaine users.^{29,30}

METHODS

Participants

Healthy men with histories of occasional cocaine use between the ages of 21 to 35 years were recruited from the Boston metropolitan area via newspaper and Internet advertisements. Phone screens were conducted to determine initial eligibility, which included: 1) a history of cocaine use, 2) no current use of prescription medications, 3) and no history of asthma or claustrophobia. Participants meeting initial study criteria were invited to the laboratory for a physical examination, including an assessment of health status and drug use. Participants were accepted into the study if they: 1) had normal electrocardiograms (ECG), blood, and urine laboratory findings; 2) had no history of neurologic disease, mental illness, or any chronic medical conditions; and 3) did not meet criteria for history of alcohol or drug dependence, as assessed by a trained addiction psychiatrist. Participants provided written, informed consent before any study procedures were performed and were paid for their participation. The study protocol and informed consent were reviewed and approved by the McLean Hospital Institutional Review Board.

Demographics and Drug Use History of Study Sample

Participants in this study were 8 white men, with an average weight ($\pm$ SD) of 81.42 ± 10.9 kg and average age of 24.8 ± 1.7 years at the time of their first visit. They reported using cocaine exclusively via the intranasal route for a mean ($\pm$ SD) 12.6 ± 9.2 lifetime uses, 3.8 ± 1.2 times per year, with last use 2.6 ± 2.9 months before the study.

FL Dose

Two Eulexin (Schering, Kenilworth, NJ) capsules containing 125 mg each of FL (USP), an acetanilide, nonsteroidal, orally active antiandrogen, or placebo (lactose) capsule similar to the Eulexin (Schering) capsules were administered orally. This was a randomized, placebo-controlled, crossover trial.

Cocaine Dose

Cocaine hydrochloride (USP) for injection (provided by the National Institute on Drug Abuse Drug Supply Program, in 20-mg/mL ampoules) was administered in a single-blind manner, as an intravenous 60-second infusion (0.4 mg/kg) as per NIDA guidelines.

Subjective Measures

Initially, participants were seated in a “natural settings” room where they completed a manual Visual Analogue Scale (VAS) 10 minutes before FL/placebo pretreatment (130 minutes before cocaine administration), and did so again 90, 60, 30, and 10 minutes before cocaine administration. They were then brought in to the Behavioral Psychopharmacology laboratory where they sat comfortably in a reclining chair for the remainder of the study. Participants completed a computerized version of the VAS at 5, 10, 20, 30, 40, 60, and 90 minutes after cocaine administration. In the Behavioral Psychopharmacology laboratory, the VAS was presented on a computer monitor and participants responded by using a joystick device,⁷ which allowed them to move a cursor on a 100-mm line with the words “None” or “Extremely” at either end to answer the questions: “How GOOD, HIGH, HAPPY, STIMULATED, ANXIOUS, BAD, INTOXICATED do you feel right now, how much is your DESIRE TO USE, and how much is your DESIRE NOT TO USE cocaine right now?” Additionally, participants indicated latency and duration of cocaine-related euphoria, dysphoria, and detection at any time after the cocaine administration by using a separate computer keypad device.

Physiologic Measures

Participant's electrocardiograms (ECG) were monitored by using a vital signs monitor (Welch-Allyn, Beaverton, OR) on a continuous basis throughout the study using a 3-lead electrode placement under the left and right collarbones and lower left rib with heart rate reported as 5-minute averages. As an additional safety measure, pulse oximetry, a noninvasive method for monitoring hemoglobin oxygen saturation, was used to continuously assess heart rate via an SPO₂ fingertip probe placed on the right index finger. Blood pressure was measured every 5 minutes after cocaine for 1 hour and finally at 90 minutes after cocaine by using an automatic blood pressure cuff attached to the participants' left upper arm. Blood pressure is reported as mean arterial pressure (MAP) calculated by using the formula: diastolic pressure + 1/3 (systemic pressure – diastolic pressure).

Baseline and post study blood pressure readings were taken in an examination room by using a manual blood pressure cuff attached to the participants' left upper arm. Readings were taken 10 minutes before FL and placebo pretreatment and 10, 30, 60, and 90 minutes before cocaine infusion.

Blood Sampling Procedures/Plasma Analysis

An intravenous (IV) catheter (Dakmed, Buffalo, NY) was inserted in each subject's antecubital vein for blood withdrawal. The distal end of the catheter tubing was attached to a 10-mL syringe and mounted on a withdrawal syringe pump set to withdraw blood at a continuous rate of 2 mL per minute. Syringes containing sodium fluoride (to prevent cocaine hydrolysis) were changed every 5 minutes, immediately centrifuged, and plasma was removed and frozen at –70°C for subsequent quantitative analysis of cocaine and metabolite (benzoylecgonine-BE and ecgonine methyl ester-EME) levels.^{7,31,32} Plasma was obtained at baseline, 2, 5, 10, 20, 30, 40, 60, and 90, minutes after cocaine administration. A solid phase extraction method was used to separate analytes from plasma and extracts were analyzed by gas chromatography/mass spectrometry (GC/MS).³³ The lower limit of quantification for cocaine and cocaine metabolites was 4.5 ng/mL with assay linear to 500 ng/mL. Quality control samples were extracted with each analytical run and the coefficients of variation (CVs) for cocaine, BE, and EME at 50 ng/mL were 8.7%, 5.1%, and 2.8%, respectively, at 100 ng/mL the CVs were 4.8%, 5.9% and 5.2%, respectively, and at 200 ng/mL the CVs were 4.6%, 2.1% and 2%, respectively.

Experimental Design

Participants were scheduled to come in for 2 laboratory visits separated by at least 4 weeks. They were required to fast and abstain from caffeine- or nicotine-containing products from midnight before each study day, as well as to abstain from alcohol for 24 hours and illicit drugs for 4 days before the study. Before beginning each study session, participants were screened for recent drug (urine screen kit, Triage, Biosite Diagnostics, San Diego, CA) and alcohol (breath test, AlcoSensor, Intoximeter, St. Louis, MO) use. They also were assessed for breath carbon monoxide levels (Breath Test, Vitalograph, Lenexa, KS). Participants with positive drug screens, carbon monoxide (CO) levels higher than 15 ppm (indicating recent cigarette consumption), or any measurable breath alcohol level were not allowed to participate that day and were rescheduled for another date. Participants cleared to participate were escorted to the “natural settings” room and were seated to complete their first VAS assessment. Next, participants received pretreatment with oral FL or placebo and were assessed on subjective and physiologic measures, as described earlier, for 2 hours.

Participants were then transferred into the Behavioral Psychopharmacology laboratory, equipped with an intercom, computer monitor, and closed circuit video camera, and were seated in a reclining chair. They were prepared with vital sign monitoring equipment as described above. A physician, certified in Advanced Cardiopulmonary Life Support with experience conducting cocaine infusion studies, administered cocaine via an iv catheter 2 hours after FL/placebo-pretreatment.

Data Analysis

Repeated-measures analysis of variance (ANOVA) was used to investigate FL effects on pre- and postcocaine subjective mood state, heart rate, and blood pressure.

VAS ratings, vital sign measures, and cocaine and cocaine metabolite levels were analyzed by using a randomized block ANOVA with treatment (FL, placebo) as the first within-subjects dependent measure and time (reported at specific time-points for 90 minutes after cocaine) as the second within-subjects dependent measure.

Cocaine, benzoylecgonine, and ecgonine methyl ester levels were analyzed by using WinNonlin Professional Version 4.1 (Pharsight Corp, Mountain View, CA). The following variables were calculated for these substances by using noncompartmental analysis for both the placebo and FL conditions: time to maximum concentration (T_{max}), maximum concentration (C_{max}), elimination half-life ($T_{1/2}$), and area under the curve (AUC_{0-90}). These variables were determined using data from time 0 to 90 minutes, and at least 3 data points from the elimination phase of the plasma concentration over time curve were used to determine the $T_{1/2}$ for each subject.

Because of the small sample size, data for subjective latency and duration of euphoria, dysphoria, and detection of cocaine were analyzed by using Wilcoxon signed-rank test (Wilcoxon), as were the pharmacokinetic parameters. Participants with any missing data points on a given measure were not included in the analysis of that measure. All statistical analyses were performed by using StatView 5.0.1 (1998) with a statistical significance threshold set at $P < 0.05$.

RESULTS

VAS

No significant effects of FL pretreatment were found on precocaine subjective mood ratings. After cocaine administration, VAS scores increased immediately on responses to: “How

GOOD, HIGH, HAPPY, STIMULATED, INTOXICATED do you feel right now, and how strong is your DESIRE TO USE cocaine right now?" (GOOD $F_{11,33} = 5.7$, $P < 0.0001$, HIGH $F_{11,55} = 78.1$, $P < 0.0001$, HAPPY $F_{11,22} = 7.9$, $P < 0.0001$, STIMULATED $F_{11,22} = 11.9$, $P < 0.0001$, INTOXICATED $F_{11,66} = 32.1$, $P < 0.0001$, DESIRE TO USE $F_{11,55} = 19.9$, $P < 0.0001$) and then decreased by 90 minutes after cocaine. FL pretreatment did not alter cocaine-mediated VAS ratings changes on any subjective measure.

Latency and Duration of Cocaine Experience

There were no significant FL effects on latency to detect cocaine or duration of cocaine detection, euphoria, or dysphoria (Table 1).

Cardiovascular Measures

Average baseline heart rate before FL and placebo pretreatment was within the normal range and did not differ statistically between FL and placebo sessions. Average baseline MAP was slightly higher before placebo pretreatment (Wilcoxon $Z = 2.02$, $P < 0.05$). Heart rate and MAP did not change significantly after FL or placebo pretreatment before cocaine administration. After cocaine infusion both heart rate and mean arterial pressure (MAP) increased significantly ($F_{8,48} = 19.9$, $P < 0.0001$ and $F_{8,56} = 17.2$, $P < 0.0001$, respectively; Table 2). No statistically significant differences were noted between FL and placebo trials for peak heart rate or MAP. However, the AUC for heart rate $\times$ time product after cocaine infusion was significantly lower in the FL condition (Wilcoxon $Z = 2.1$, $P < 0.04$; Fig. 1). Effects of pretreatment drug administration order were not significantly different between FL and placebo conditions. By 90 minutes after cocaine administration, MAP had returned to baseline: 82.5 ± 7 mm Hg and 84.1 ± 7.3 mm Hg under both FL and placebo conditions, respectively.

Plasma Cocaine and Metabolite Levels

Plasma cocaine levels increased then decreased rapidly after cocaine infusion. By contrast, metabolite levels increased linearly throughout the duration of the study. Peak plasma cocaine levels (C_{max}) averaged 164.1 ± 40.9 and 193.6 ± 56.9 ng/mL after FL and placebo treatment, respectively (Wilcoxon $Z = 2.1$, $P < 0.04$). Average 90-minute BE level after FL and placebo was 161 ± 38.1 and 183.7 ± 43.2 ng/mL, respectively, whereas average 90-minute EME level was 16 ± 2.7 and 19 ± 3.4 ng/mL, respectively (Wilcoxon $Z = 1.8$ and 2 , $P < 0.07$ and 0.05 ; Fig. 2). Analysis of AUCs revealed decreased levels of cocaine, BE and EME after FL pretreatment; average areas for cocaine $\times$ time products were $8,980 \pm 2,630$ and $10,300 \pm 2,700$, for BE $\times$ time products $9,960 \pm 3,300$ and $11,720 \pm 2,860$, and for EME $\times$ time products 990 ± 260 and $1,260 \pm 250$, for FL and placebo respectively ($Z = 2.0$, 2.0 , and 2.4 , and $P < 0.05$, 0.05 , and 0.02 , cocaine, BE, and EME, respectively; Fig. 3). No significant order effects for drug pretreatment administration were found for any of the above measures.

The clearance rate for cocaine with FL was 2.56 ± 0.96 L per minute and with placebo, 2.35 ± 0.8 L/min ($Z = 0.98$, $P > 0.33$). The volume of distribution for cocaine with FL was 199.3 ± 60.9 L and with placebo, 171.9 ± 72.3 L ($Z = 0.98$, $P > 0.33$).

DISCUSSION

Intravenous cocaine induced cardiovascular and subjective (VAS) effects consistent with previous findings.^{15,34–38} Flutamide pretreatment reduced plasma cocaine C_{max} , cocaine by time product AUC, and BE and EME levels 90 minutes after cocaine injection. This suggests that FL treatment may alter cocaine pharmacokinetics in men. Additionally, heart rate after cocaine infusion recovered to baseline more quickly when participants were

pretreated with FL. Yet, there were no MAP differences and FL pretreatment did not alter cocaine's subjective effects. Thus, FL does not seem to produce detrimental physiologic or behavioral effects when administered before cocaine.

Flutamide's alteration of cocaine pharmacokinetics in the absence of any effects on subjective mood, detection, or euphoria is not surprising because the peak behavioral effects occurred 2 to 4 minutes after injection. By contrast, FL-induced changes in cocaine kinetics did not begin to appear until 8 to 20 minutes later. Detection was over by 40 minutes and so any alteration in plasma levels of cocaine or its metabolites would not have impacted cocaine's acute behavioral effects. However, although heart rate and blood pressure changes correspond with plasma cocaine levels, cocaine's vascular effects evolve over time and are recurrent as a function of increasing plasma cocaine metabolite levels.³⁹ Reducing the plasma levels of cocaine and BE—both of which are vasoconstrictive—could alleviate some of cocaine's adverse vascular effects.

The liver is a primary distribution site for cocaine.^{40,41} Ba et al⁴² found that FL increases hepatic blood flow and oxygen delivery in adult male rats and such increases in hepatic blood flow could lead to increased liver extraction of cocaine and metabolites, as has been demonstrated with alcohol.^{43,44} This sequence could decrease plasma cocaine, BE, and EME levels, as was observed in the present study. This effect could be beneficial to brain, heart, and other organs, which would then be exposed to lower cocaine and metabolite levels. The consequence of such effects on hepatic structure and function are not known, although in mice, cocaine-induced liver damage is dose-related,⁴⁵ is amplified by testosterone treatment,⁴⁶ and is likely a function of norcocaine metabolism in the liver.¹¹ Because the current study did not assess norcocaine levels, increased norcocaine levels and their potential hepatic effects cannot be ruled out.

Flutamide itself has been associated with beneficial cardiovascular effects. It relaxed isolated aortic rings and small intestinal blood vessels.^{47,48} It improved cardiac output, stroke volume, and ventricular performance parameters (eg, hepatic microvascular blood flow and maximal rate of pressure increase and decrease) in male rats undergoing trauma hemorrhage.^{43,49} By improving vascular performance, FL could increase blood flow to the liver during cocaine exposure, effectively shunting cocaine and its 2 major metabolites out of the plasma.

Our study is limited by a number of factors that should be considered when interpreting the data. The participants were only occasional cocaine users and thus it is not clear whether our findings extend to heavy cocaine users. In this regard, there is evidence that chronic cocaine users have diminished levels of cholinesterase enzymes that metabolize cocaine and that this contributes to an increased incidence of cocaine-induced cardiac impairments.⁵⁰ Because participants in our study did not demonstrate cardiac impairment, it is unlikely that the current observations are a result of altered cholinesterase enzyme levels. It is conceivable that FL modulation of cocaine pharmacokinetics would differ in heavy cocaine users. Furthermore, because all our participants were white, it is unknown how the present results might apply to other racial or ethnic groups, which exhibit different cardiovascular responsiveness in general.^{51,52} Additionally, plasma cocaine metabolite changes evolve beyond the 90-minute time frame of our study and it is likely that pharmacokinetic effects occurred beyond that time frame that went undetected. Furthermore, we did not measure peripheral blood flow or vascular resistance, which are decreased and increased, respectively, by cocaine.^{53,54} Measuring peripheral and hepatic blood flows might have provided us with a more definitive relationship between FL and cocaine responses and is something that will be assessed in future studies. Additionally, although we saw parallels in cocaine C_{max} and heart rate in both conditions, the scope of the assessments in the current

study was not broad enough to speak to the issue of cocaine pharmacodynamics adequately. Future studies should be designed to address pharmacodynamics specifically. In addition, our sample size was small and it is not clear whether our findings reflect cohort or population characteristics. However, our within-subjects design, by reducing intersubject variability, is a relatively strong model for pharmacokinetics studies.

Notwithstanding these limitations, our preliminary findings suggest that FL, by altering cocaine pharmacokinetics, could have beneficial effects in cocaine-abusing men. This finding may have therapeutic implications, because among chronic cocaine users, men develop more severe brain and peripheral vascular dysfunction than women.^{12,13,16,17,55} These effects have potential applications for drugs, such as methamphetamine, which demonstrates similar sex differences in its adverse vascular effects.⁵⁶ Because cocaine and androgen combinations are associated with enhanced vascular dysfunction in vitro^{19,28} and in animal models,¹⁹ and because cocaine induces vasoconstriction in a dose-related manner,^{19,20,35,36,57} treatments such as FL that block androgen receptors and possibly reduce plasma cocaine and metabolite levels may protect an individual from cocaine's toxic effects. With regard to the latter effect, others are pursuing treatment strategies that reduce plasma cocaine and metabolite levels,^{58–60} which can reduce cocaine toxicity.^{61,62} Finally, although it is recognized that young men might be averse to taking antiandrogenic drugs, selective androgen receptor modulators are being developed to target a variety of pathologies.⁶³ Some may be useful for modulating cocaine pharmacokinetics or other effects.

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FIGURE 1.

Heart rate as 5-minute averages after cocaine infusion with (inset) integrated (AUC) heart rate after cocaine infusion. Open symbols-placebo; filled symbols-flut-amide. Data are means $\pm$ SE (* $P < 0.05$). The "0" timepoint reflects the average heart rate for the 5 minutes immediately before cocaine administration.

FIGURE 2.

Peak plasma cocaine and 90-minute EME levels after flutamide pretreatment compared with placebo. Open symbols-placebo; filled symbols-flutamide. Data are means $\pm$ SE (* $P < 0.05$).

FIGURE 3.

Plasma cocaine and metabolite levels across time after cocaine administration with insets of the integrated (AUCs); (A) cocaine, (B) BE, and (C) EME levels after flutamide (FL) pretreatment compared with placebo. Open symbols-placebo; filled symbols-FL. Data are means $\pm$ SE (* $P < 0.05$).

TABLE 1

Subjective Latency and Duration of Cocaine Detection, Euphoria, and Dysphoria

Measure	N	Detect Cocaine		Euphoria		Dysphoria	
		Flutamide	Placebo	Flutamide	Placebo	Flutamide	Placebo
Latency	8	2.6 ± 0.8	2.0 ± 1.1	4.3 ± 3.6	3.9 ± 2.5	No response	3.0 ± 0.1 (n = 2)
Duration	8	40.9 ± 19.4	41.9 ± 13.3	15.3 ± 6.5	10.5 ± 4.6	0 ± 0	5.4 ± 3.3 (n = 2)

Values are means ± standard deviations with time in minutes.

With regard to latency and duration of dysphoria, no subject reported dysphoria after flutamide pretreatment and cocaine.

The data for the placebo condition reflects 2 participants who reported dysphoria.

TABLE 2

Cardiovascular Parameters at Baseline, Effects of Flutamide or Placebo Pretreatment, and Effects of Acute Intravenous Cocaine Infusion (0.4 mg/kg)

	Heart Rate (BPM)	MAP (mm Hg)
Baseline		
Pre-flutamide	62.2 ± 8.3	84.8 ± 4.8
Pre-placebo	63.3 ± 7.2	90.1 ± 8.6
Z	-1.01	-2.02
P	0.31	0.05*
Pre-cocaine		
Post-flutamide	62.1 ± 10.6	86.0 ± 6.5
Post-placebo	63.5 ± 6.9	84.4 ± 7.2
Z	-0.68	-1.12
P	0.5	0.26
Peak effect after cocaine		
Flutamide pretreatment	98.1 ± 24.9	97.8 ± 7.6
Placebo pretreatment	102.4 ± 19.8	97.7 ± 6.1
Z	-1.12	-0.17
P	0.26	0.87
Area under the curve after cocaine		
Flutamide pretreatment	9340.0 ± 1500.0	7440.0 ± 510.0
Placebo pretreatment	9960.0 ± 1650.0	7570.0 ± 500.0
Z	-2.1	-1.5
P	0.04*	0.12