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Effects of oral contraceptives on acute cocaine response in female volunteers

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Abstract

A growing number of recent reports have demonstrated sex and menstrual cycle differences in the subjective, physiological and pharmacokinetic effects of stimulant drugs in humans. The present study was conducted to further investigate the relationship between gonadal hormones and cocaine effects by examining whether oral contraceptives (OCs) alter the acute effects of cocaine. Seven female volunteers, who were taking triphasic OCs and who were occasional users of cocaine, provided informed consent and participated in this placebo-controlled, four-visit study. Subjects were studied twice during days 6–10 of the menstrual cycle (equivalent to the follicular phase) and twice during days 21–28 of the menstrual cycle (equivalent to the luteal phase) and were challenged with an acute dose of intranasal (in) cocaine (0.9 mg/kg or placebo). There were no differences in cocaine-induced subjective, physiologic or plasma cocaine and metabolite levels during the times equivalent to the follicular and luteal phases of the menstrual cycle. Our findings provide evidence that OCs do not present an added risk of cocaine-induced cardiovascular effects and that exogenous administration of estrogen and progesterone at the physiologic doses found in OCs do not alter the subjective responses to acute cocaine.

Keywords: Cocaine; Oral contraceptives; Estrogen; Progesterone; Female subjects

1. Introduction

A growing number of recent reports have demonstrated sex and menstrual cycle differences in the subjective, physiological and pharmacokinetic effects of stimulant drugs in humans (Lukas et al., 1996; Kosten et al., 1996; Justice and de Wit, 1999; Sofuoglu et al., 1999; Evans et al., 1999, 2002). For instance, women have been shown to have fewer cocaine-related cerebral perfusion abnormalities than men (Levin et al., 1994), report greater nervousness following intranasal (in) cocaine than men (Kosten et al., 1996) and experience prolonged cardiovascular effects following smoked cocaine than men (Evans et al., 1999). In addition, women in the luteal phase of the menstrual cycle report diminished ratings of high, stimulation and desire to use following smoked cocaine than during the follicular phase of their cycle (Sofuoglu et al., 1999; Evans et al., 2002).

We previously reported that peak plasma cocaine levels following an intranasal dose of cocaine were significantly higher during the follicular phase (73.2 ± 9.9 ng/ml) than during the luteal phase (54.7 ± 8.7 ng/ml) of the menstrual cycle (Lukas et al., 1996). In addition, we reported that male subjects achieved significantly higher plasma cocaine levels and detected cocaine effects significantly faster than female subjects. These differences in pharmacokinetic profiles were present in spite of similar cocaine-induced changes in heart rate between men and women in the various phases of the menstrual cycle.

Even though the exact mechanisms mediating the sex and menstrual cycle differences in the effects of stimulant drugs have not been identified, it has been suggested that fluctuations in ovarian hormones during the menstrual cycle may play an important role in mediating these effects (Selye, 1971; Sharma et al., 1992; Church and Subramanian, 1997). This notion in supported by preclinical data demonstrating that exogenous administration of estradiol to female rats reduces the toxic effects of cocaine (Seyle, 1971), that progesterone administration increases cocaine-induced cardiovascular toxicity (Plessinger and Woods,

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1990) and that cocaine toxicity is increased during pregnancy, when endogenous progesterone levels are elevated (Sharma et al., 1992; Church and Subramanian, 1997). However, a few studies have found progesterone administration to not alter cocaine cardiotoxicity in rats (Glantz and Wood, 1994, 1995).

Further support for the notion that ovarian hormones modulate the behavioral effects of stimulant drugs comes from clinical studies. Justice and de Wit (1999) showed that the subjective effects of an oral dose of D-amphetamine (15 mg) were greater during the follicular phase compared to the luteal phase of the menstrual cycle and that estrogen levels during the follicular phase were positively correlated with amphetamine-induced increases in euphoria and energy. This correlation was not found during the luteal phase, when levels of both estrogen and progesterone are high, suggesting that estrogen may enhance the subjective effects of stimulant drugs in women but that progesterone may mask this effect. Consistent with this notion, Sofuoglu et al. (2002) recently reported that exogenous progesterone treatment during the early follicular phase attenuates some of the subjective responses to repeated cocaine administration without altering cocaine-induced cardiovascular responses.

Evans et al. (2002) recently reported greater cocaine-induced increases in heart rate and ratings of intoxication (“good drug effect,” “high” and “stimulated”) during the follicular phase compared to the luteal phase of the menstrual cycle. The reported increases in cocaine-induced “high” during the follicular phase are consisted with those from another study of a single dose of smoked cocaine (Sofuoglu et al., 1999). However, these menstrual cycle-related changes in reports of “high” following smoked cocaine administration were not observed after acute administration of intranasal cocaine (Lukas et al., 1996) or intravenous (iv) cocaine (Mendelson et al., 1999). In addition, the significant increases in cocaine-induced heart rate during the follicular phase reported by Evans et al. (2002) were not observed in other studies (Lukas et al., 1996; Mendelson et al., 1999; Sofuoglu et al., 1999).

Even though the involvement of ovarian hormone fluctuations in modulating cocaine’s effects has been demonstrated repeatedly in both animal and human studies, the exact nature of this involvement is not clear. The present study was conducted to better understand the interaction between ovarian hormones and acute cocaine effects by investigating whether oral contraceptives (OCs) eliminate the reported menstrual cycle differences in cocaine effects. It is also important to investigate whether OCs alter the acute effects of cocaine because an estimated 18 million women in the US take OCs (Clinical Proceedings from the Association of Reproductive Health Professionals, 2001) and almost half of all cocaine users in the US are women (Johnston et al., 2001). We hypothesized that the previously reported menstrual cycle differences in the subjective, cardiovascular and pharmacokinetic effects of cocaine would be eliminated in women taking OCs and that OCs would not result in increased cardiovascular responses to cocaine.

2. Methods

2.1. Subjects

Seven healthy female volunteers between the ages of 21 and 25 were recruited from the Boston metropolitan area via newspaper advertisements and flyers. Phone screens were conducted to determine initial eligibility for the study, which included current occasional intranasal cocaine use (at least once in the past 6 months but not more than three times in any 1 week) and current use of triphasic OCs. Subjects meeting initial study criteria were invited to the laboratory for a physical and mental status examination. Following the laboratory evaluations, subjects were accepted into the study if they met the following criteria: (1) were not taking psychotropic medications, (2) had normal electrocardiography (EKG), blood and urine laboratory findings, (3) had no history of neurological disease, mental illness or any chronic medical conditions, (4) did not meet criteria for current DSM-IV (American Psychiatric Association, 1994) defined Axis I disorders, (5) had no history of alcohol or drug dependence, (6) had been on triphasic OCs for at least 6 months and (7) were able to sign an informed consent form. Subjects provided informed consent before any study procedures were performed and then were paid for their participation in the study.

Subjects accepted into the study were asked to provide exact dates of their last menstrual period and were told that they would come to the laboratory four times, twice during days 6–10 after the onset of menstruation (equivalent to the follicular phase) and twice during days 21–28 after the onset of menstruation (equivalent to the luteal phase). Subjects were also told that they could receive either an active dose of cocaine or a placebo during the study visits. The study protocol was reviewed and approved by the McLean Hospital Institutional Review Board.

2.2. OC use

All of the women in the study were taking Ortho Tricyclen tablets containing the progestational compound norgestimate and the estrogenic compound ethinyl estradiol. This OC preparation was selected because it is the most commonly used OC in the US (Clinical Proceedings from the Association of Reproductive Health Professionals, 2001).

2.3. Demographics and drug use history of study sample

The women included in the study were on average 22.8 ± 1.3 (S.E.) years of age and had 16.1 ± 0.9 years of education. They reported using cocaine intranasally an

average of 9.77 ± 2.6 (S.E.) times per year, drinking alcohol an average of 5.71 ± 2.1 (S.E.) drinks per week and smoking marijuana an average of 1.6 ± 1.5 (S.E.) times per month.

2.4. Cocaine dose

Cocaine hydrochloride U.S.P. (Mallinkrodt, St. Louis, MO) flakes were self-administered intranasally in a dose of 0.9 mg/kg using a modified snort-stick device (see Lukas et al., 1994, 1996, 2001; Kouri et al., 2000, 2001). A small amount of lactose powder was added to each dose to bring the total weight of powder delivered to 1.0 mg/kg. The placebo preparation consisted of 5 mg of cocaine to which enough lactose powder was added to total a weight of 1.0 mg/kg. Subjects were instructed to snort the substance using both nostrils (one at a time), to snort slowly to avoid swallowing any of the substance and to snort the entire contents of the tube. The cocaine administration procedure lasted 30–60 s.

2.5. Experimental design

This was a randomized, placebo-controlled study investigating the effects of OCs on the subjective (Addiction Research Center Inventory (ARCI) and Visual Analog Scales (VAS)), physiologic (heart rate, blood pressure and skin temperature) and pharmacokinetic (plasma cocaine, benzoylecgonine (BE) and ecgonine methylester (EME) levels) effects of acute intranasal cocaine. Subjects came to the laboratory on four separate occasions: twice during the equivalent of the follicular phase and twice during the equivalent of the luteal phase of their menstrual cycle. To determine the time of testing, subjects were required to call the laboratory on the first day of menses and schedule their study visits. Each visit consisted of an acute intranasal challenge of either cocaine (0.9 mg/kg) or placebo. All treatment schedules were randomized prior to the beginning of the study so that each subject received a cocaine and a placebo challenge during the follicular phase and a cocaine and a placebo challenge during the luteal phase. Each visit lasted 4.5 h in the laboratory: 30 min of baseline monitoring followed by cocaine (or placebo) administration and a 4 h postadministration period during which subjects were monitored continuously.

On the morning of the study, subjects were asked to provide a urine sample to be tested for recent drug use with a urine screen kit (Triage, Biosite Diagnostics, San Diego, CA) and a breath sample to be tested for the presence of ethanol using an AlcoSensor (Intoximeter, St. Louis, MO). Subjects were given a pregnancy test (QuPid One-Step Pregnancy Test, Stanbio Laboratory, San Antonio, TX) prior to each of the four challenge visits. Subjects with positive breath ethanol levels or drug screens were not allowed to participate that day but were rescheduled for a later date. Female subjects with a positive pregnancy test were terminated from the study.

After verifying the negative urine screens and breath ethanol levels, subjects were escorted to an experimental chamber equipped with an intercom and closed circuit video camera. Subjects were seated in a reclining chair and were prepared with EKG electrodes, a skin temperature thermistor, a blood pressure cuff and a catheter for blood withdrawal. At the end of the study session, subjects were provided with a light lunch. All subjects were transported to and from the laboratory by taxicab and were not released until all signs of intoxication had diminished and psychological indices were back to baseline levels.

2.6. Subjective measures

At nine different intervals during the study, subjects were asked to complete the 49-item ARCI (Martin et al., 1971) and a set of 9 computerized VAS. The questionnaires were completed using a joystick device (Lukas et al., 1986, 1996), which subjects could use to move a cursor on a 100 mm line with the words "None" or "Extremely" at either end to answer the questions: "How GOOD do you feel right now?," "How HAPPY do you feel right now?," "How HIGH do you feel right now?," "How STIMULATED do you feel right now?," "How ANXIOUS do you feel right now?," "How BAD do you feel right now?," "How INTOXICATED do you feel right now?," "How strong is your DESIRE TO USE cocaine right now?" and "How strong is your DESIRE TO NOT USE cocaine right now?" The ARCI and VAS were presented on the subject's computer monitor 15 min before the cocaine administration and at 15, 30, 60, 90, 120, 150, 180 and 240 min post-administration.

2.7. Physiologic variables

Subjects' EKG activity was continuously monitored throughout the study using a five-lead placement of electrodes on their arms, legs and chest. A skin temperature thermistor (Hewlett-Packard 78352A) was attached to the subject's middle finger. An automatic blood pressure cuff was attached to the subject's arm and readings were taken immediately prior to each of the nine questionnaire sets.

2.8. Blood sampling procedures/plasma analyses

Immediately prior to the study, an intravenous catheter (Dakmed, Buffalo, NY) was inserted in the 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 1 ml/min. Blood samples were collected every 2.5 min, pipetted into glass vacutainer tubes containing sodium fluoride (to prevent cocaine hydrolysis), cooled and centrifuged. The plasma was removed from the centrifuged sample and frozen at −70 °C for quantitative analyses of cocaine, benzoylecgonine and EME (see Lukas

et al., 1996; Kouri et al., 2000, 2001). A solid phase extraction procedure was utilized to separate the analytes from the plasma and the extracts were subsequently analyzed by gas chromatography/mass spectrometry (GC/MS) (Cone et al., 1994).

2.9. Data analyses

Repeated-measures analysis of variance (ANOVA) was used to investigate baseline differences in subjective mood state, skin temperature, heart rate and blood pressure. As no differences in any of the variables were found as a function either of cocaine dose or menstrual cycle, raw data were used in all statistical analyses.

Responses on the ARCI and VAS items were analyzed using 2 (Dose: placebo, 0.9 mg/kg) × 2 (Menstrual cycle phase: follicular, luteal) × 4 (Timepoint: baseline, 15, 30 and 60 min after cocaine administration) repeated-measures ANOVAs, with dose, menstrual cycle phase and time as repeated factors. Data were truncated at 60 min as peak changes were found to occur within 60 min after cocaine administration.

Heart rate data were averaged over 5 min intervals for the 5 min period immediately preceding (to yield a baseline value) and 60 min after cocaine administration. Separate baseline heart rate values were calculated for each menstrual cycle phase. The baseline and peak heart rate values were used in a 2 (Timepoint: baseline, peak) × 2 (Menstrual cycle phase: follicular, luteal) repeated-measures ANOVA, with both time and menstrual cycle phase as the repeated factors.

Skin temperature data were averaged over 5 min intervals for the 5 min period immediately preceding (to yield a baseline value) and 60 min after cocaine administration. A baseline skin temperature value was calculated for each menstrual cycle phase. This baseline value was subtracted from each 5 min value obtained after cocaine administration to yield a change from baseline score. Maximal change values (either positive to indicate an increase in skin temperature or negative to indicate a decrease in skin temperature) were analyzed using a 2 (Dose: placebo, 0.9 mg/kg) × 2 (Menstrual cycle phase: follicular, luteal) repeated-measures ANOVA, with dose and menstrual cycle phase as repeated factors.

Blood pressure data were analyzed using 2 (Dose: placebo, 0.9 mg/kg) × 2 (Phase: follicular, luteal) × 4 (Timepoint: baseline, 15, 30 and 60 min after cocaine administration) repeated-measures ANOVAs, with all three variables as repeated factors. Systolic and diastolic blood pressure were analyzed separately. Data were truncated at 60 min as peak changes were found to occur within this time period.

Finally, repeated-measures ANOVA was used to examine differences in peak plasma cocaine, benzoylecgonine and EME levels as a function of menstrual cycle phase. Latency to these peak values also was examined using repeated-measures ANOVA.

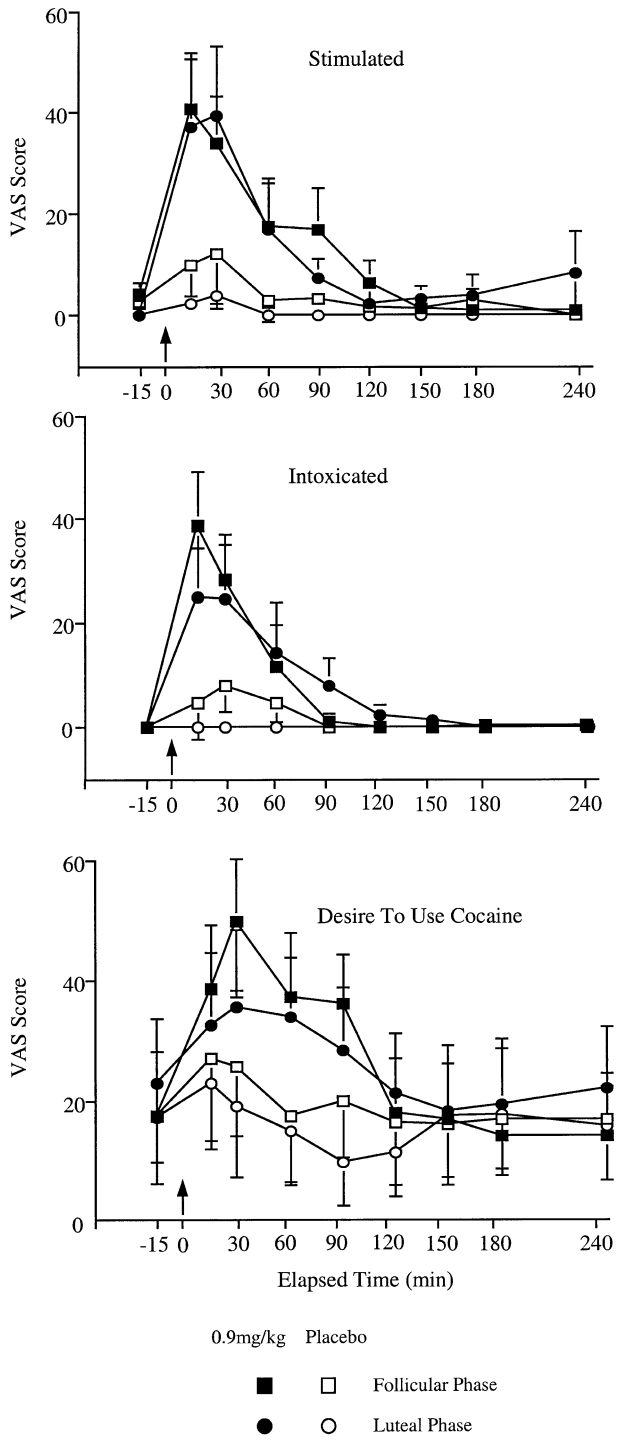

Fig. 1. Mean ± S.E.M. scores for the VAS "How STIMULATED do you feel right now?" (top panel), "How INTOXICATED do you feel right now?" (center panel) and "How strong is your DESIRE TO USE cocaine right now?" (bottom panel) following 0.9 mg/kg (filled symbols) or placebo (open symbols) intranasal cocaine administration. Data from follicular phase equivalent are depicted as squares and data from luteal phase equivalent are depicted as circles. Cocaine or placebo was administered at time 0 (arrow).

All statistical analyses were performed using programs and subprograms of Statistical Package for the Social Sciences (1995) with effects considered significant at the $P < .05$ level. Analyses investigating the statistical power of the data based on a sample size of seven subjects and α at .05 (one-tailed) revealed an estimated power between 73% and 79% for the subjective, physiologic and pharmacokinetic variables. This estimate was based on the ability to detect a moderate difference, had such differences existed. Power estimates were performed using the Power and Precision Software (Biostat, 2001).

3. Results

3.1. ARCI/VAS

A significant main effect for dose was found on the amphetamine [$F(1,6) = 7.05$, $P = .04$] scale of the ARCI, with subjects receiving higher scores on this scale following cocaine administration compared to placebo. There was a significant Menstrual cycle phase × Timepoint interaction [Hotelling's $T = 6.08$, exact $F(3,4) = 8.10$, $P = .036$] on the VAS item "Desire to Use Cocaine." Simple effects tests indicated that women in the follicular phase of the menstrual cycle reported a greater desire to use cocaine at 15 and 30 min after cocaine administration relative to baseline. Similarly, women in the luteal phase reported a greater desire to use cocaine at 30 min after cocaine relative to baseline. There were significant dose effects for the VAS items "Stimulated" [$F(1,6) = 9.51$, $P = .02$] and "Intoxicated" [$F(1,6) = 8.09$, $P = .03$], with subjects reporting feeling more stimulated and intoxicated subsequent to cocaine administration compared to placebo (Fig. 1). There were no significant differences as a function of menstrual cycle phase on any of the remaining ARCI or VAS items.

3.2. Heart rate

Heart rate was significantly increased from baseline by cocaine administration [$F(1,6) = 67.96$, $P < .001$]. Peak increases were similar during both the "follicular" and the "luteal" phases of the menstrual cycle and did not differ significantly as a function of menstrual cycle phase (Fig. 2). There were no differences in latency to peak heart rate.

3.3. Skin temperature

There were no significant dose or menstrual cycle phase effects on maximal changes from baseline in skin temperature.

3.4. Plasma levels

There were no significant differences in peak plasma cocaine, EME or benzoylecgonine levels as a function of menstrual cycle phase (Fig. 3). Analyses also failed to reveal differences in latency to these peak values.

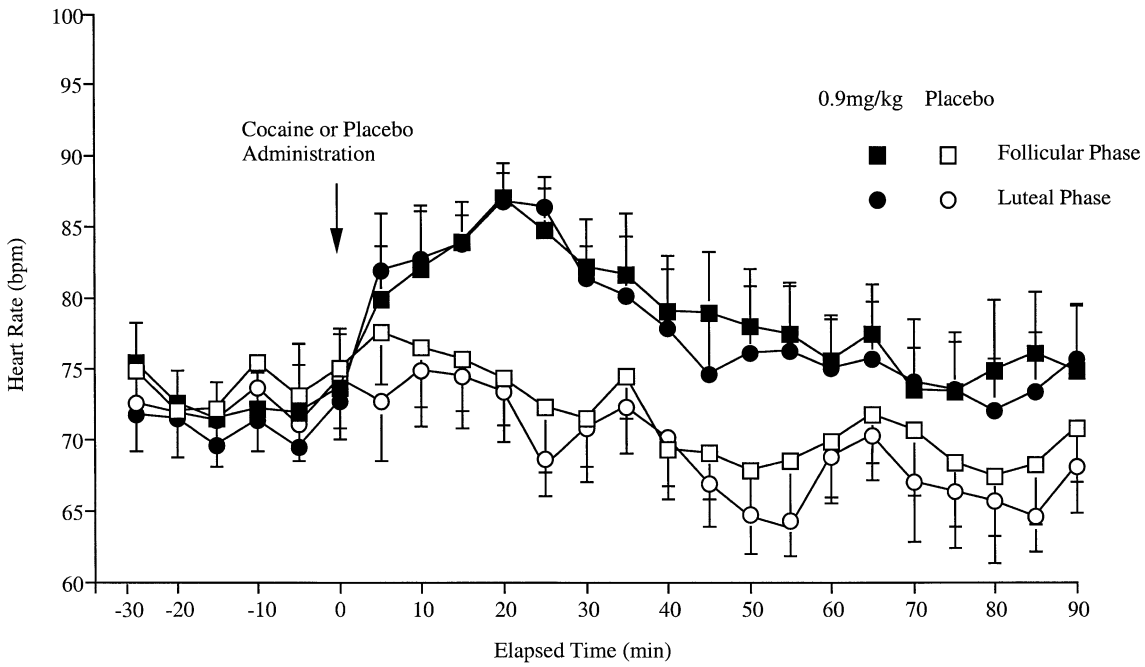

Fig. 2. Mean ± S.E.M. heart rate (bpm) following 0.9 mg/kg (filled symbols) or placebo (open symbols) intranasal cocaine administration during the days equivalent to the follicular (squares) and the luteal (circles) phases of the menstrual cycle in women taking OCs. Heart rates were calculated from continuous recordings and averaged over consecutive 5 min time intervals. Cocaine or placebo was administered at time 0 (arrow).

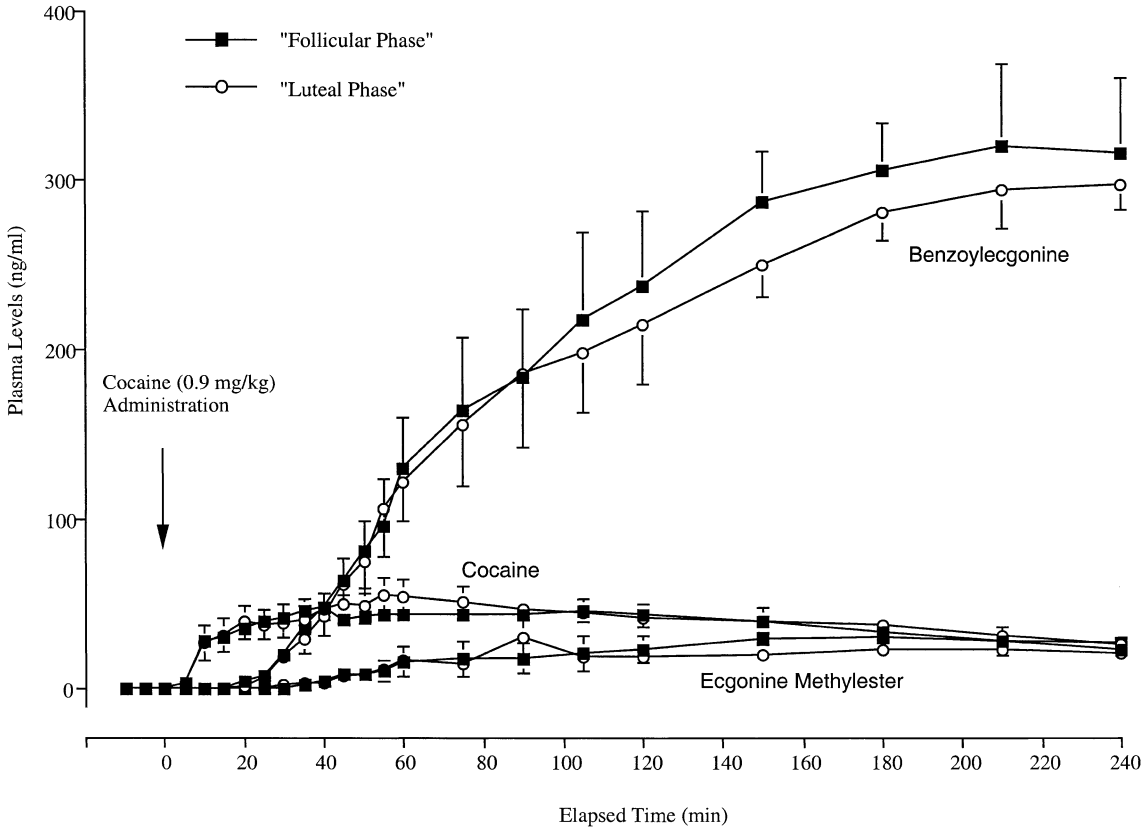

Fig. 3. Mean ± S.E.M. plasma cocaine, benzoylecgonine and EME levels after acute cocaine (0.9 mg/kg in) during the days equivalent to the follicular (squares) and the luteal (circles) phases of the menstrual cycle in women taking OCs. Cocaine was administered at time 0 (arrow).

3.5. Blood pressure

There was a significant main effect for dose on diastolic blood pressure [$F(1,6) = 6.54$, P=.043]. Diastolic blood pressure was significantly increased subsequent to cocaine administration (mean = 73.75 ± 4.69) compared to placebo (mean = 69.84 ± 6.35), irrespective of both menstrual cycle phase and time of measurement. There was also a main effect for time [Hotelling's $T = 9.23$, exact $F(3,4) = 12.31$, P=.017]. Post hoc tests indicated that diastolic blood pressure was significantly elevated at 15 (mean = 75.25 ± 6.39) and 30 min (mean = 72.75 ± 5.25) after cocaine administration relative both to baseline (mean = 69.79 ± 6.57) and to 60 min (mean = 69.39 ± 3.82) after cocaine administration. There were no menstrual cycle effects on diastolic blood pressure.

A significant main effect for dose was found on systolic blood pressure [$F(1,6) = 33.34$, P=.001], with systolic blood pressure significantly increased following cocaine administration (mean = 123.77 ± 7.41) relative to placebo (mean = 118.32 ± 7.95). There were no other effects.

4. Discussion

Data from the present study showed that women on OCs did not show the previously reported menstrual cycle-related differences in cocaine's effects (Lukas et al., 1996; Sofuoglu et al., 1999; Evans et al., 2002). Specifically, women taking OCs have similar subjective, cardiovascular and pharmacokinetic responses to cocaine regardless of the phase of the menstrual cycle in which they are tested. In addition, the profile and magnitude of cocaine's subjective and physiological effects observed in the present study were similar to those reported in our previous study of women not on OCs (Lukas et al., 1996), suggesting that OCs do not alter the acute subjective effects of intranasal cocaine. This is an important observation given the large number of women who take OCs in the US.

Investigating whether OCs alter the effects of acute cocaine is important because data from animal studies suggest that exogenous administration of gonadal steroids alters the response to cocaine. For example, administration of cocaine to progesterone-treated animals has been shown to be associated with increased cardiovascular responses (Plessinger and Woods, 1990; Sharma et al., 1992) and cocaine toxicity is enhanced during pregnancy, when endogenous progesterone levels are high (Church and Subramanian, 1997; Sharma et al., 1992). In addition, estradiol administration has been shown to reduce cocaine toxicity (Rapp et al., 1979; Selye, 1971).

The fact that the cardiovascular and subjective effects of cocaine were not altered by the OCs in the present study

might be explained by the fact that all the women were taking combination OCs, which contained both estrogen and progesterone. This particular type of OC was chosen for the present study because it is the most commonly used preparation in the US (Clinical Proceedings from the Association of Reproductive Health Professionals, 2001). If progesterone increases cocaine toxicity while estrogen decreases it, it is possible that the opposite effects of the two hormones negate any impact on the response profile. However, it is also possible that the doses of estrogen and progesterone in the OC preparation in the present study may be too low to alter acute cocaine effects. The changes in cocaine toxicity in animal studies were seen after supraphysiologic doses of estrogen and progesterone. Future studies investigating the acute effects of cocaine in women taking progesterone-only contraceptive pills would further elucidate the nature of this relationship.

Another important finding from our study is that most of the cocaine-induced changes in subjective reports were similar during the two phases studied, suggesting that the previously reported diminished ratings of cocaine-induced high during the luteal phase (Sofuoglu et al., 1999; Evans et al., 2002) and after progesterone administration (Sofuoglu et al., 2002) are eliminated by OCs. It is interesting to note, however, that one variable that showed a significant effect of menstrual cycle phase in this study was "desire to use cocaine." It is unclear why women in the follicular phase-equivalent period reported desire for cocaine 15 min earlier than they did during in the luteal phase-equivalent period. One possible explanation is that the onset of subjective effects was delayed or the magnitude of the effects was minimized in this period (i.e., follicular phase-equivalent), so that the subjects reported a greater desire for cocaine earlier in the session. Despite the statistical significance of this interaction, the biological significance is not as clear, as there were no phase-related differences in any other subjective effect measures.

In contrast to the findings from our previous study of women not taking OCs (Lukas et al., 1996), plasma cocaine and metabolite levels in the present study were similar regardless of whether the women were studied in the time period equivalent to the follicular or the luteal phase of their cycle. The plasma levels observed in the present study are similar to those we previously found during the luteal phase of women not taking OCs. In that study (Lukas et al., 1996), women not on OCs had the highest plasma cocaine levels during the follicular phase of the cycle, when estrogen levels are high and progesterone levels are low. Interestingly, these plasma cocaine levels occurred in the absence of any subjective or behavioral changes.

In conclusion, our findings provide evidence that combination OCs, the most commonly used type in the US, do not present an added risk of cocaine-induced cardiovascular effects. In addition, exogenous administration of estrogen and progesterone at the physiologic doses used in OCs do not alter the subjective responses to acute cocaine.

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