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Methodological Issues in the Administration of Multiple Doses of Smoked Cocaine-Base in Humans

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HATSUKAMI, D. K., P. R. PENTEL, J. GLASS, R. NELSON, L. H. BRAUER, R. CROSBY AND K. HANSON. *Methodological issues in the administration of multiple doses of smoked cocaine-base in humans.* PHARMACOL BIOCHEM BEHAV **47**(3) 531-540, 1994.—Many methodological issues exist in human laboratory research with smoked cocaine-base that include safety, precision of dose delivery of smoked cocaine, and the lack of an adequate placebo. All of these issues are particularly apparent with studies involving multiple doses of cocaine. Addressing these concerns is important in conducting parametric studies that require examining dose-response effects. The purposes of this study were to determine: 1) the safest interval between doses to deliver smoked cocaine; 2) the accuracy or reproducibility of administering precise and multiple doses of cocaine; 3) the potential for using a control dose of cocaine; and 4) the influence of multiple doses on these parameters. Six black males were given 10 doses of either 5 or 35 mg of cocaine-base at 15-, 30-, and 45-min intervals. The dependent measures included physiological, subjective, and performance responses. These measures were taken prior to dosing and at specific time intervals after each dose of smoked cocaine. The results showed: 1) dosing at 30-min intervals allowed sufficient time for recovery of blood pressure and heart rate to permit up to 10 doses to be safely administered; 2) reproducible blood cocaine levels were obtained with repeated dosing using a heated wire-coil device; 3) significant differences were observed between the 5- and 35-mg dose with 5 mg being a low enough dose to produce minimal effects; 4) acute tolerance was evidenced with multiple doses of cocaine for most of the measures; and 5) considerable between- and within-subject variability was observed in the pattern of responses to cocaine.

Smoked cocaine-base Human laboratory Methodology

SMOKED cocaine (crack, free-basing) use recently has gained prominence and given rise to a great deal of concern in the United States. In spite of this concern, few parametric laboratory studies have been undertaken. One reason is the major methodological concerns with regard to conducting studies with smoked cocaine. These concerns include the safety of administering multiple doses of smoked cocaine, the problems associated with administering precise and reproducible doses of cocaine, and the lack of a placebo dose (16). Various devices have been used in laboratory settings to deliver smoked cocaine. These devices include tobacco cigarettes containing cocaine paste (21), a glass pipe containing free-base cocaine immersed in a silicone oil bath (15,22) or an electrically heated flask (16), a modified corncob pipe containing cocaine-base (10), or a smokeless filtered cigarette with cocaine-base contained in an aluminum canister (10). These devices pose several problems in delivering precise doses: the delivery of products other than cocaine (e.g., tobacco with cigarettes); the conversion of cocaine into pyrolysis products due to burning the cocaine at high temperatures; and/or the lack of control over smoking topography.

We have developed a device in which a wire coil is coated with a specific amount of cocaine. This wire cocaine is placed in a glass mouthpiece and a current is passed through the coil

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to rapidly heat it to 178 to 183°C, a temperature that volatilizes but does not pyrolyze the cocaine [see (13) for details]. This device has been shown to reliably deliver single doses of cocaine, although the precision of delivering multiple doses of cocaine with it has not previously been studied.

Another methodological issue is the lack of an adequate placebo in the smoked cocaine area that is sometimes crucial in parametric studies. Human cocaine IV studies (5) and smoked cocaine animal studies (2) have used lidocaine as a placebo. However, it is not known whether lidocaine can safely be smoked, and the doses delivered in a multiple dose study might well be toxic. In the current study we evaluated the use of a very low dose of smoked cocaine that might provide both the behavioral aspects of receiving cocaine and the oral mucosal anesthesia associated with cocaine use yet produces minimal systemic activity.

Few studies have delivered multiple doses of smoked cocaine. Of the studies that exist, the maximum number delivered was approximately four to seven 50-mg doses of cocaine-base every 15 min (9). No adverse events were observed in the study nor were any subjects terminated due to excessive increase in blood pressure or heart rate. This present study examined the safety of administering a greater number of repeated doses of cocaine at various time intervals. Our intent was to find an interval that did not result in withholding a dose due to accelerated heart rate or increased blood pressure, an important consideration in studies of self-administration of cocaine involving controlled dose delivery.

A final goal of this study was to examine the effects of multiple doses of cocaine, specifically with regard to how they might influence the choice of a suitable cocaine dosing regimen. Some previous studies with smoked or IV cocaine have shown development of acute tolerance with cocaine given IV (1,6,8), insuffation (25), or smoked (8); other studies have shown no evidence of acute tolerance (18,19) to IV infusion of cocaine. Determining the rate of development and extent of tolerance observed with a given dosing paradigm is clearly important because it will influence the choice of cocaine dose and dosing interval. Individual variability also requires close examination. Studies have consistently shown variability between subjects in peak blood cocaine levels and time to peak (16). Between-subject differences have also been observed with subjective and physiological responses (10) and are demonstrated by the large standard deviations observed with these responses (8). Further, within-subject differences have also been observed in responses to cocaine (11). A closer look at individual variability when specific doses are administered at controlled intervals is important because these individual differences may have implications for treatment and safety, and may also provide insights into the mechanisms of cocaine action or toxicity. In summary, the goals of this study were to determine:

1. the safest interval between doses to deliver smoked cocaine;
2. the accuracy or reproducibility of administering multiple doses of cocaine;
3. a potential control dose of cocaine; and
4. the influence of multiple doses of cocaine on these parameters.

METHOD

Subjects

Male cocaine abusers (N = 9) between the ages of 18 and 40 were recruited by word-of-mouth or flyers requesting volunteers for a cocaine study at various sites within the Twin Cities communities. Interested subjects were asked to contact the investigators to undergo an initial telephone screening. This screening included questions on demographic characteristics, health, cocaine and other drug use habits, and a brief mental health history. Potential subjects who met the initial screening criteria were then invited to the laboratory and informed written consent was obtained. Subjects underwent a comprehensive examination. They were thoroughly interviewed for drug and psychiatric history and given a complete physical examination, ECG, pulmonary function test, chest x-ray, urine analysis, and blood chemistry work up that included tests for hepatitis, HIV, and pseudocholinesterase deficiency. The inclusion criteria were comprised of the following:

1. a history of smoked cocaine use of $\geq$ 1 g daily at least twice weekly over a 6-month period;
2. no current problems with substance abuse other than cocaine and cigarettes;
3. no immediate desire to stop using cocaine or having received drug abuse counseling within the past year;
4. no history of suicide attempts, affective disorders, schizophrenia, or anxiety disorders;
5. no history of major medical illnesses;
6. a normal 12-lead electrocardiogram and resting blood pressure < 140/90;
7. current state of good health;
8. seronegative for HIV; and
9. not under the supervision of the legal system.

Subjects were paid $25/day for their participation.

Procedure Overview

Subjects were given 10 doses of either 5 or 35 mg of cocaine-base in a semi-double-blind manner (the physician monitoring the physical state of the subject was aware of the dose of cocaine in case of a medical emergency) at 15-, 30-, and 45-min intervals. Subjects were required to attend eight experimental sessions and stay at the General Clinical Research Center (GCRC) for 12 days. They were asked to refrain from using all drugs 48 h prior to admission and were told that a urine screen would be obtained to determine their compliance (even though some drugs are detectable in urine even after 48 hours). This "bogus" procedure was used to maximize compliance. Subjects were admitted at noon on the first day. During the next day subjects were acquainted with the apparatus and experimental procedures, and baseline physiological, performance, and subjective measures were taken. On the third day, subjects were escorted to the laboratory located on the GCRC. All experimental sessions were run in the evenings. The subjects were fitted with an 18-ga catheter placed on the nondominant forearm to obtain blood samples and were attached to the ECG (12 lead) and blood pressure device. Subjects were then asked to sit quietly for the next 30 min, during which time baseline readings of heart rate and blood pressure were obtained. After this 30-min period, subjects were administered a battery of measures including self-report visual analogue scales, the Addiction Research Center Inventory, and a performance measure (see below). Physiological measures and a blood sample were subsequently obtained. In a random and semi-double-blind fashion, subjects were then given one of two cocaine doses, 5 or 35 mg, for up to 10 doses. Half the subjects received the 35-mg dose during the first session and half the subjects received 5 mg first. The doses were alternated to minimize the potential cumulative effects from the highest dose of cocaine. They were administered as two inhalations 1 min apart with each inhalation on separate coils. Each coil held one-half the dose to minimize overloading the wire coils

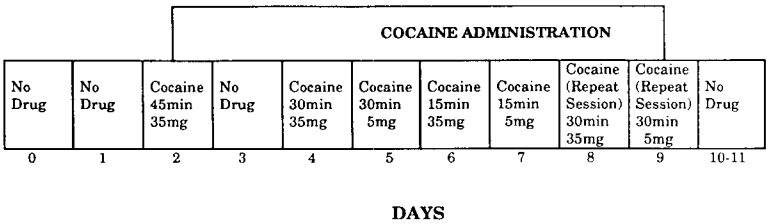

FIG. 1. Experimental procedure for the study. The 5-mg, 45-min interval was dropped due to the impracticality of having subjects sit in the laboratory for over 7 h on a low-dose day.

with cocaine, which could have resulted in insufficient burning of all the cocaine. Subjects were asked to inhale each dose of cocaine as deeply as possible and hold their breath. No specific instructions were given on puff and inhalation duration. The interval between doses was either 15, 30, or 45 min. The 45-min interval for the 5-mg dose was omitted because pilot subjects became irritated with the length of the session when such minimal amounts of cocaine were administered. This session was substituted with a no-cocaine day. The intervals proceeded from the longest to the shortest. Thus, subjects were tested at each interval with each dose of cocaine. Three of the subjects also repeated and successfully completed the 30-min interval to obtain reliability data. Figure 1 shows an example of the sequence of events.

Table 1 shows the measures and times when each of the measures was taken. Physiological measures were recorded immediately before and at specific times after each cocaine dose. Subjective and performance measures were obtained only after each cocaine dose. Blood samples were also obtained after each dose of cocaine. During the session, specific amounts of food were provided for the subjects during the

TABLE 1

TIME SCHEDULE FOR THE ADMINISTRATION OF MEASURES

Minutes	Measure	
−2.5	Heart rate/blood pressure (HR/BP)	
0	Cocaine dose #1	
1	Cocaine dose #2	
2.5	HR/BP	
3	VAS	
4	EKG	
4.5	HR/BP	
6	Blood draw	
9.5	HR/BP	
10	Performance	
13	ARCI	
14.5	HR/BP	15-min interval
15	VAS	
19.5	HR/BP	
24.5	HR/BP	
25	VAS	
29.5	HR/BP	30-min interval
34.5	HR/BP	
35	VAS	
39.5	HR/BP	
44.5	HR/BP	45-min interval

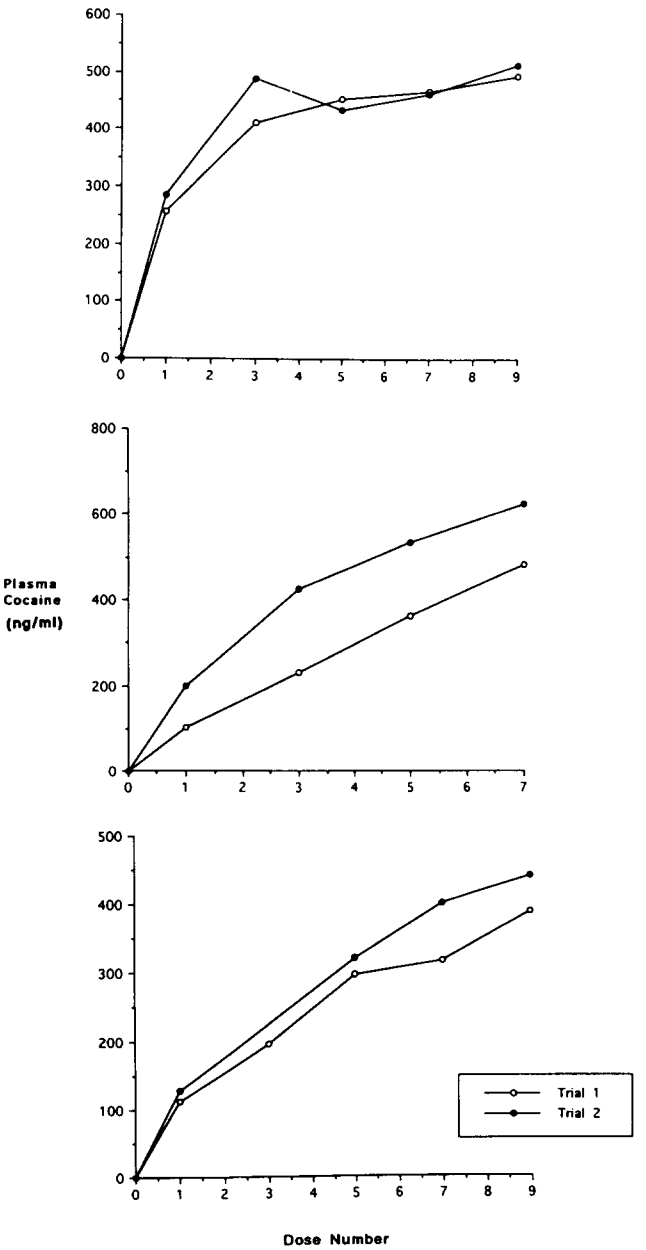

FIG. 2. Mean ± SE plasma cocaine concentrations for repeated administrations of 10 doses of 35 mg smoked cocaine-base given at 30-min intervals within three different subjects.

session to minimize the effects of food deprivation. Before and after laboratory sessions, subjects were free to move around the GCRC and engage in leisure activities. On the last 2 days (days 10 and 11), subjects no longer had access to cocaine and were simply monitored. Physiological and subjective measures, as well as the sleep scale and withdrawal symptom checklist, were taken at 0900 and 1500. Subjects were held on the GCRC until 1200 on day 11 to ensure that their behavior and physiological parameters stabilized before they were released.

Several precautions were taken to minimize the use or effects from other drugs. During the subjects' stay on CRC, random urine samples were taken to ensure that they did not use any drugs other than the cocaine provided by the investigators. The subjects were also monitored for 24 h and were only allowed to leave the unit when accompanied by research staff. To remove the possibility of drug exchanges, guests were not allowed to visit. The use of caffeine was maintained at the same level throughout the study. Cigarettes were provided for the subjects to minimize the possibility of tobacco withdrawal. However, subjects were not allowed to smoke during the experimental sessions.

Safety. Specific criteria were developed to ensure the safety of the subjects. Subjects were allowed to have the next dose of cocaine only if the systolic blood pressure was ≤ 150 mmHg, diastolic was ≤ 90 mmHg, and heart rate ≤ 110 bpm. Subjects were disqualified from the study if the systolic blood pressure was $\geq 170/110$ mmHg, the heart rate was ≥ 170 bpm, or if they developed significant symptoms such as cardiac arrhythmia, chest pain, headaches, shortness of breath, etc.

Physiological Measures

Heart rate and blood pressure. Heart rate was continuously monitored using an ambulatory ECG monitor (Marquette Electronics model 8500, Milwaukee, WI). Blood pressure was monitored using a Dinamap S X/P with the cuff left in place throughout the study. Blood pressure was recorded every 2–5 min, and heart rate was monitored continuously.

Subjective Measures

Addiction Research Center Inventory (ARCI). The short form of the 550-item ARCI (20) was used. This form consists of 49 items that have been shown in previous studies to be sensitive to the effects of cocaine (7–9,25). These items were taken from a sedative scale (Pentobarbital Chlorpromazine Alcohol General, PCAG), three stimulant scales (Benzedrine General, BG; Morphine Benzedrine General, MBG; and Amphetamine, A) and a scale measuring dysphoric and psychomimetic changes (LSD).

Self-report 100-mm Visual Analogue Scales (VAS). This questionnaire, which was compiled from scales used in other studies (5), consisted of 16 lines, each 100 mm long. The lines are labeled "desire for more cocaine," "pleasantness," "high," "energy," "hungry," "down," "sedated," "anxious," "stimulated," "fatigued," "paranoid/suspicious," "alert," "able to concentrate," "confused," "full of pep/lively," and "heart racing or pounding." Subjects indicated how they felt by placing a mark along each line labeled at the left side as "not at all" and at the right side as "extremely."

Performance Measures

Vigilance task. In this task (26), subjects pressed a button as soon as possible when a circle with a dot at 12 o'clock appeared on a screen. Subjects were to inhibit responding whenever a dot occurred at the 6 o'clock position. Presentations of the stimulus were made at 2-s intervals. The length of the task was approximately 3 min. This test measures reaction time and the total number of errors of omission (nonresponses to the dot at 12 o'clock) as well as impulsivity or failure to inhibit response by the number of errors of commission (responses to dot at 6 o'clock). In a previous study, we found that this test was sensitive to tobacco deprivation effects (12,17). Subjects who were tested during tobacco deprivation had significantly longer reaction times than the control group.

Biochemical Measures

Blood. For measurement of plasma cocaine concentrations, blood was collected in lavender top (EDTA) venipunc-

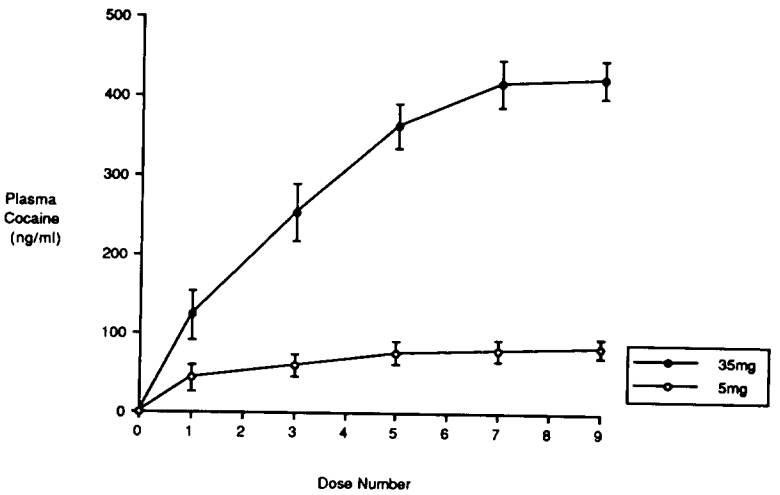

FIG. 3. Mean ± SE plasma cocaine concentrations after the administration of 35 mg vs. 5 mg of smoked cocaine-base given at 30-min intervals.

ture tubes containing 0.35 ml of saturated sodium floride solution and immediately centrifuged. Plasma was stored at −70°C for no more than 4 weeks and was assayed for cocaine by gas chromatography with a nitrogen-phosphorous detector using a capillary column (24).

Data Analysis

Comparisons of plasma cocaine concentrations across time intervals were made using a within-subjects analysis of variance (ANOVA) consisting of three time intervals (15, 30, and 45 min), five dose administrations (doses 1, 3, 5, 7, and 9), and two cocaine doses (5 mg and 35 mg). Because all blood samples across most subjects and time intervals were collected for five dose administrations, they were the only ones examined. Comparisons of outcome measures from only the 30-min interval between the 35-mg and 5-mg conditions were made using a within-subjects ANOVA containing two cocaine doses (5 mg and 35 mg) and administration of multiple doses. The 15-min interval was not examined because it resulted in too many doses withheld; the 45 min interval was not examined because it produced an excessively long and tedious experimental session that in the long run would not be practical in future experiments. Data obtained only at the 2-min (for physiological measures) and 3-min (for VAS) postdose interval for each dose were included in these analyses because this was the time at which peak effects occur.

RESULTS

The six black males who completed most phases of the study were examined for the final results. Three subjects were disqualified from the study: the first demonstrated an apprehension toward IV needles, the second subject was ruled out when an abnormal EKG was detected after admission to the GCRC but prior to any of the experimental sessions, and the third exceeded the blood pressure criteria for termination (systolic blood pressure ≥ 170 mmHg) after his third dose of cocaine during the 45-min interval session so that minimal data was available for him. The mean age of the remaining six subjects was 30.7 years (range = 23–35), the mean duration of cocaine use 10.0 years (range = 2–20 years), the mean frequency of cocaine use 6.2 times/week (range = 5–7 times/week), and the mean self-reported amount of use 3.22 g/day (range = 1.0–7.0 g/day). The majority of the subjects (five out of six, exception was subject #3) had a history of marijuana use 5–7 times/week; one subject (#6) had a history of stimulant and PCP abuse; and another subject (#1) had a history of sedative abuse. The current use of drugs revealed only two subjects who may be considered to be heavy alcohol drinkers (subject #6 drank 1–4 times/week, 1–2 pints/occasion; subject #2 drank 2–3 times/week, 8 beers/occasion). All others drank alcohol no more than 3 times weekly and no more than 4 beers/occasion. Only one other subject reported current use of drugs with the use of two joints of marijuana, twice a week. Most of these subjects were unemployed or worked at temporary services.

Safety

Safety in this study was defined as not being prematurely discharged from the study or having deliveries withheld because of potential adverse effects or of exceeding the blood pressure/heart rate criteria. Besides the subject mentioned earlier, only one other subject was discharged prematurely. This subject had a 5-min episode of left shoulder pain after receiving two 35-mg doses of cocaine 15 min apart. The ECG showed nonspecific ST-T wave changes in the inferior and anterior leads that resolved in 15 min. The subject's exam, serial serum creatine kinase levels, and subsequent ECGs remained normal. He was discharged from the study even though this episode was felt to be clinically unimportant. Doses were withheld for two out of six subjects for the 15-min interval, one subject for the 45-min interval, and none of the subjects for the 30-min interval. (Doses were withheld for failure to return to < 150/90 mmHg when the next dose was due.) Because significant differences were observed in the plasma concentrations across the three time intervals, $F(8, 2)$

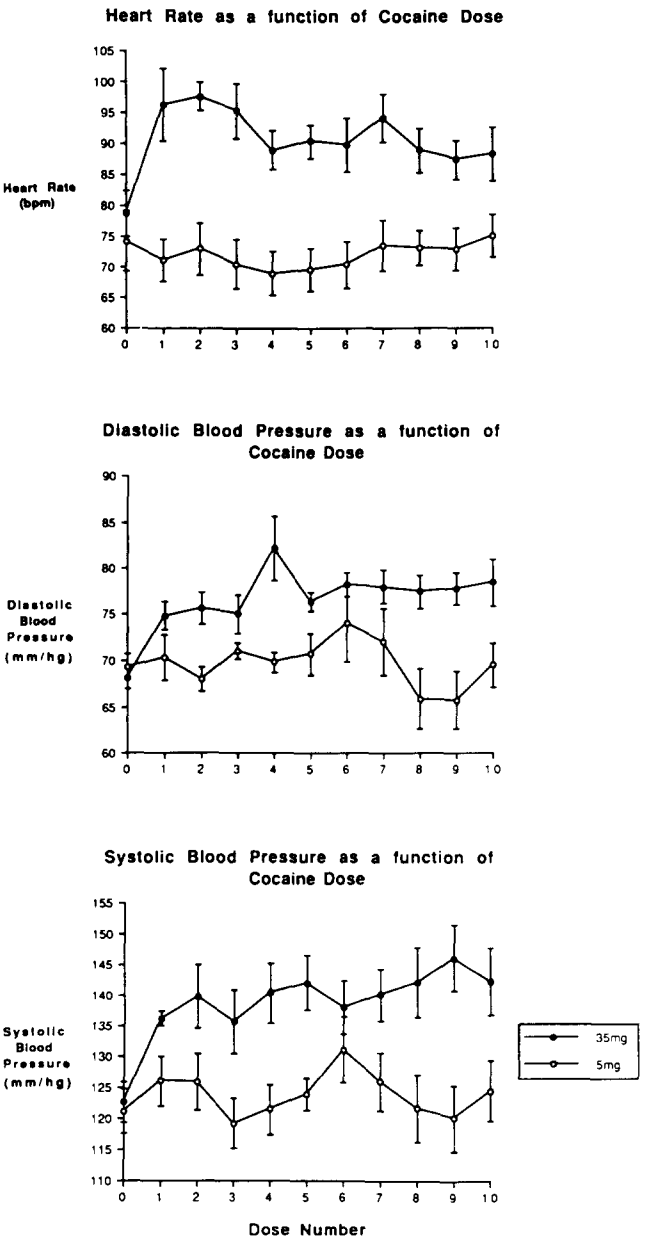

FIG. 4. Physiological measures (mean ± SE) that showed significant differences between 35 mg and 5 mg of smoked cocaine-base administered at 30-min intervals for 10 doses.

= 6.88, p = 0.02, withholding doses for the 15-min interval was likely to be caused by higher plasma cocaine concentrations (mg/ml) attained compared to the other intervals (mean ± SE peak = 788.6 ± 265.9 for the 15-min, 434.8 ± 25.7 for the 30-min, and 334.6 ± 73.2 for the 45-min intervals). Withholding doses for the 45-min intervals was possibly a function of the subject becoming accustomed to the smoke delivery device.

Reproducibility

Figure 2 shows the reproducibility of plasma cocaine concentrations during sessions with each of the three subjects who received repeated doses of cocaine at 30-min intervals.

Effective Control Dose

Because of the excessive amount of data, lack of a 5-mg dose available for the 45-min interval, and missing values for the 15-min interval, only the results from the 30-min interval are described.

Plasma cocaine concentrations. Significant differences were obtained in plasma cocaine levels between the 5- and 35-mg condition, $F(5, 1) = 102.41$, $p < 0.001$ (see Fig. 3). Figure 3 also points to the low cocaine concentrations attained at the 5-mg dose (mean peak level ± SD = 84.2 ± 11.1 ng/ml).

Physiological effects. Significant differences were observed between the 5- and 35-mg condition for heart rate, $F(5, 1) = 15.03$, $p = 0.01$, diastolic, $F(5, 1) = 25.11$, $p = 0.004$, and systolic blood pressure, $F(5, 1) = 31.65$, $p < 0.002$ (see Fig. 4).

Subjective effects. Among all the variables measured on the VAS, significant differences between 5 mg and 35 mg were observed for "desire for cocaine," $F(6, 1) = 11.8$, $p < 0.001$; "high," $F(6, 1) = 123.6$, $p < 0.001$; "stimulated," $F(6, 1) = 55.3$, $p < 0.001$; "sedated-relaxed," $F(6, 1) = 8.1$, $p < 0.01$;

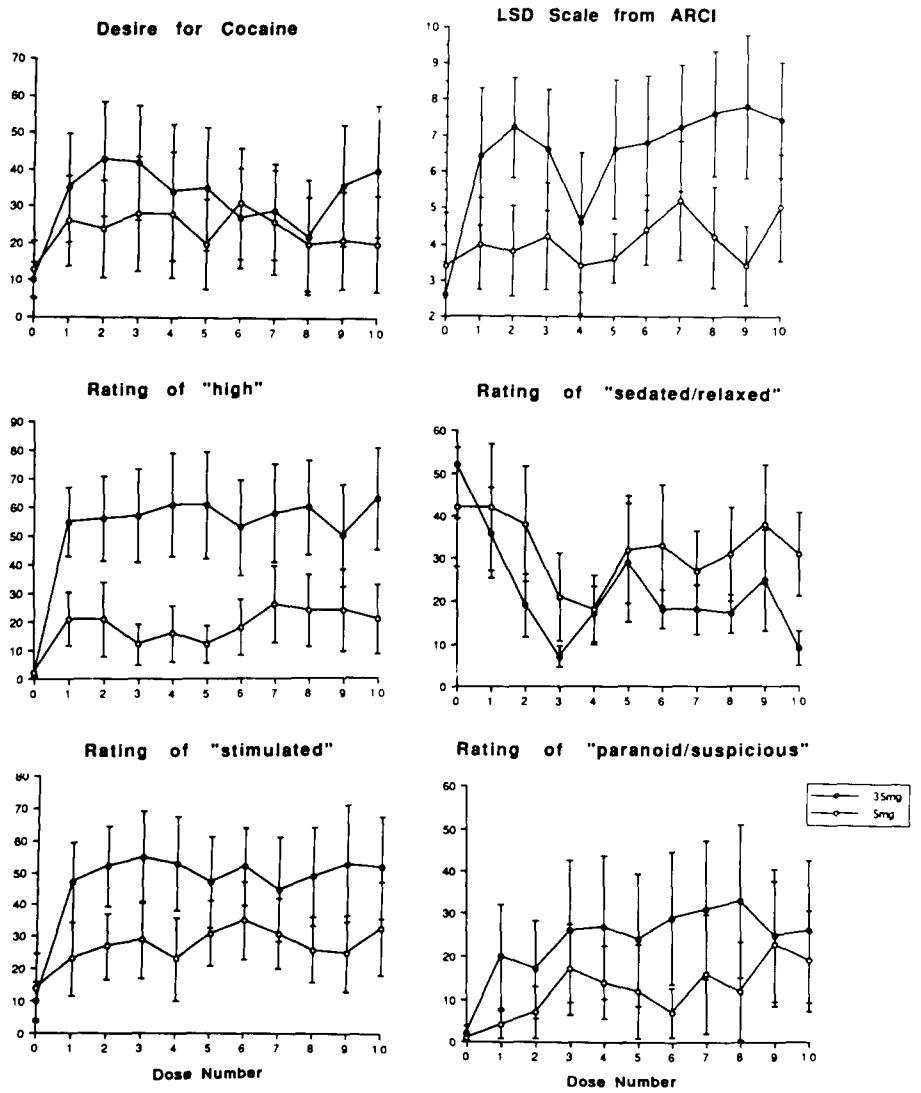

FIG. 5. Subjective measures (mean ± SE) that showed significant differences between 35 mg and 5 mg of smoked cocaine-base administered at 30-min intervals for 10 doses.

and "paranoid-suspicious," $F(6, 1) = 16.3$, $p < 0.001$ (see Fig. 5). Near significant results were observed for "desire for sex," $F(6, 1) = 3.5$, $p = 0.06$, and "confused," $F(6, 1) = 3.6$, $p = 0.06$. For the 35-mg dose the subjects reported higher levels on each of the scales except "sedated-relaxed" and "desire for sex" than they had for the 5-mg dose. Of all the scales on the Addiction Research Center Inventory, only the LSD scale showed near significant differences between the two doses, $F(4, 1) = 6.86$, $p = 0.06$, with the 35-mg dose showing higher levels than the 5-mg dose.

Vigilance task. No significant differences were observed between repeated doses of the 5- or 35-mg dose of cocaine on reaction time, errors of commission, errors of omission, or standard deviation (variability) of reaction time.

Effects of Multiple Doses of 35 mg of Cocaine

For the 35-mg dose, the physiological parameters and the subjective variables demonstrated acute tolerance with an increase in responses for the initial dose(s) and then an asymptote in response to cocaine. Partial hysteresis plots of plasma cocaine concentrations vs. heart rate and "high" demonstrated the occurrence of this acute tolerance to cocaine, as shown in Fig. 6. Diastolic blood pressure, however, showed less tolerance effect than the other measures.

Individual data were examined for heart rate and "high" and found to show variability in the pattern of responses to cocaine. Figure 7 shows the response pattern of three individuals to the multiple doses of cocaine on the measure for "high." Subject #2 indicated experiencing a subjective "high" with each dose of 35 mg of cocaine with a return to baseline levels between doses. On the other hand, subject #4 reported an immediate increase and persistent experience of feeling high from cocaine throughout the experimental session (note data from doses 8-9 are missing). Subject #3 reported feeling increasingly "high" with each repeated dose of cocaine. Figure 8 shows heart rate responses for all the data points collected. Again, individual variability in the pattern of responses is observed. Subject #6 showed an increase in heart rate with each dose of 35 mg of cocaine and a return to baseline values between doses. Subject #5 showed an increase in heart rate that was maintained throughout the experimental session. Subject #1 showed an initial increase and then a gradual decrease in heart rate over time.

Data were also examined to determine the pattern of responses to cocaine in a given individual across various measures. Results showed similarities across measures in some subjects and differences in other subjects. For example, Fig. 9A shows that subject #3 experienced parallel increases in heart rate and a rating of "high" during the experimental session. On the other hand, subject #2 (Fig. 9B) showed an increase in heart rate that was maintained at a consistent level over the course of the multiple doses of cocaine. However, for "high," the subject reported experiencing an increase with each dose of cocaine and a return to baseline.

Effects of Multiple Doses of 5 mg of Cocaine

Figures 7–9 demonstrates that with a 5-mg dose of cocaine, minimal responses were observed and the pattern of response was consistently flat across subjects.

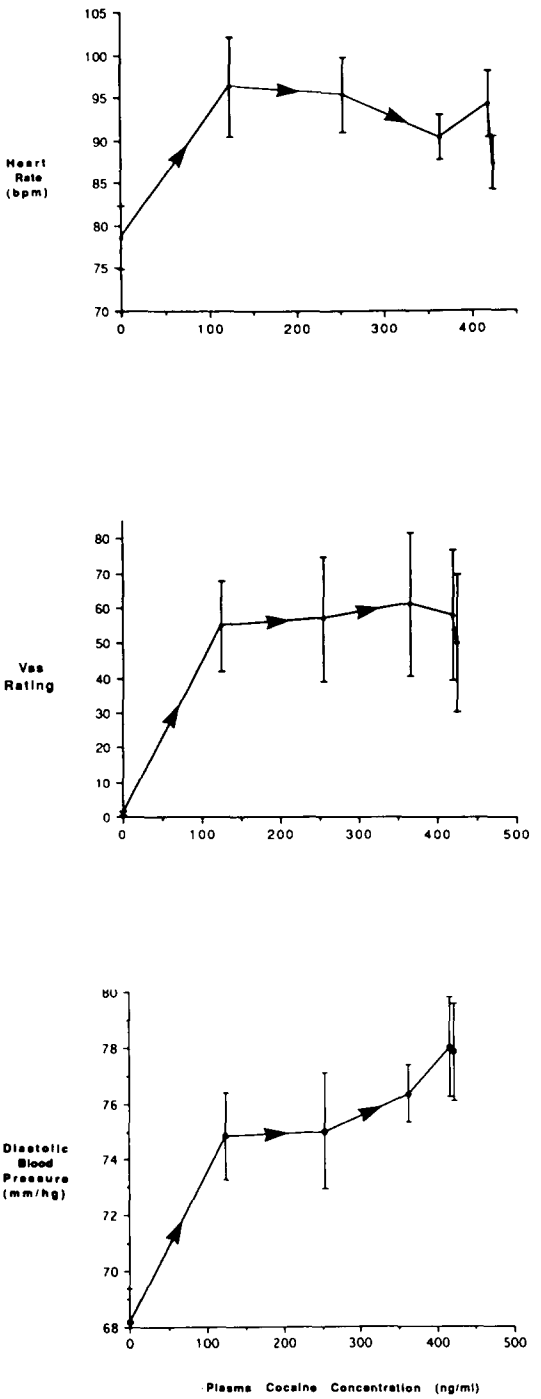

FIG. 6. Partial hysteresis plots for selected physiological and subjective measures across plasma cocaine concentrations and time (indicated by arrows).

DISCUSSION

Safety

The 30-min interval showed the least interference in the administration of cocaine due to increases in vital signs when using a 35-mg dose of cocaine. Other studies with repeated IV or smoked doses of cocaine have used 15-min intervals between doses. In one self-administration study, between 15% and 20% of the 32-mg IV cocaine sessions required withholding doses because vitals were above criterion levels. The sub-

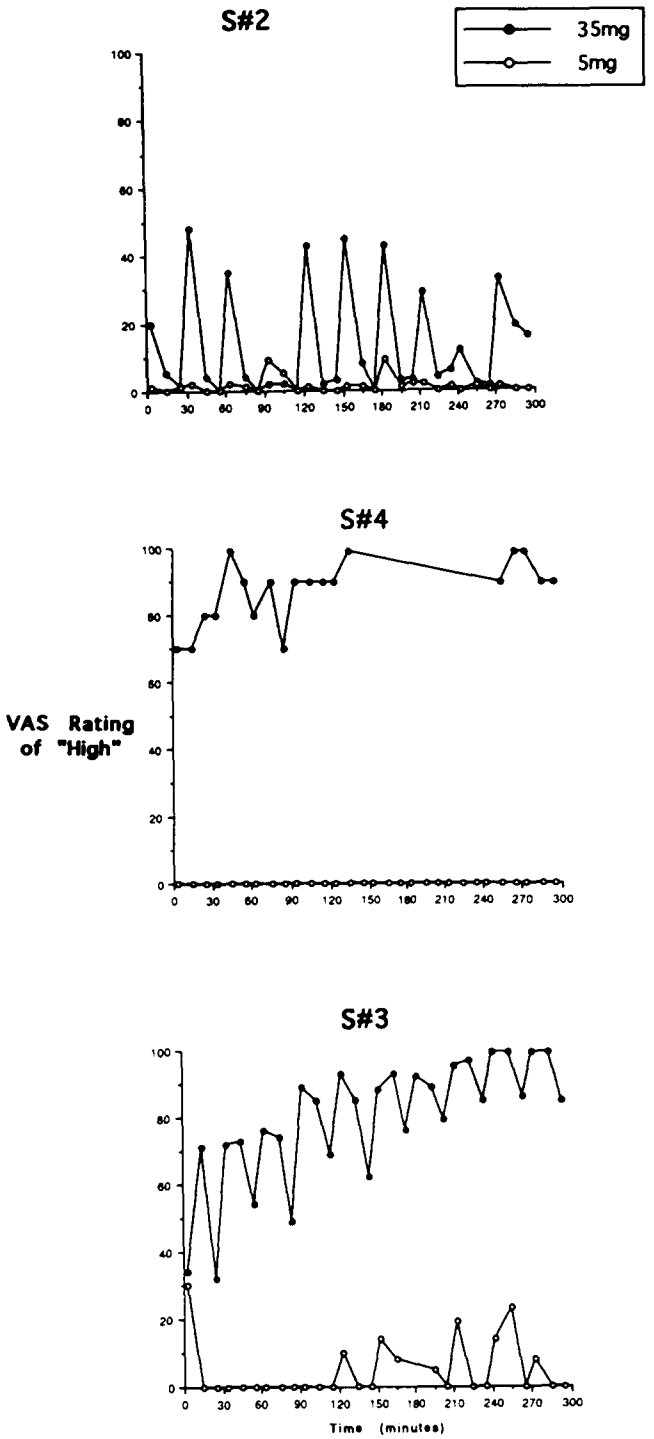

FIG. 7. Pattern of responses for self-rated high on a 100-mm VAS scale among three different subjects after the administration of 10 doses of 35 mg and 5 mg of smoked cocaine-base given at 30-min intervals.

jects consequently could not be administered a requested dose of cocaine (4). In other studies, however, no reports were made of withholding doses in subjects who were administered potentially 4–7 consecutive doses of smoked (25 and 50 mg) (9,10) and/or IV (16–32 mg) cocaine every 14 min (9). The difference between the present and previous studies could have been caused by the amount of cocaine delivered, although plasma cocaine concentrations attained with the 35-mg dose of smoked cocaine in this study were similar to those attained with 50- and 32-mg doses of smoked and IV cocaine, respectively, in the other studies. Another potential cause may be the fact that blood pressure and heart rate criteria for withholding doses were higher in previous studies.

Reproducibility

Although the reproducibility of the plasma concentrations during repeated sessions were examined only in three subjects,

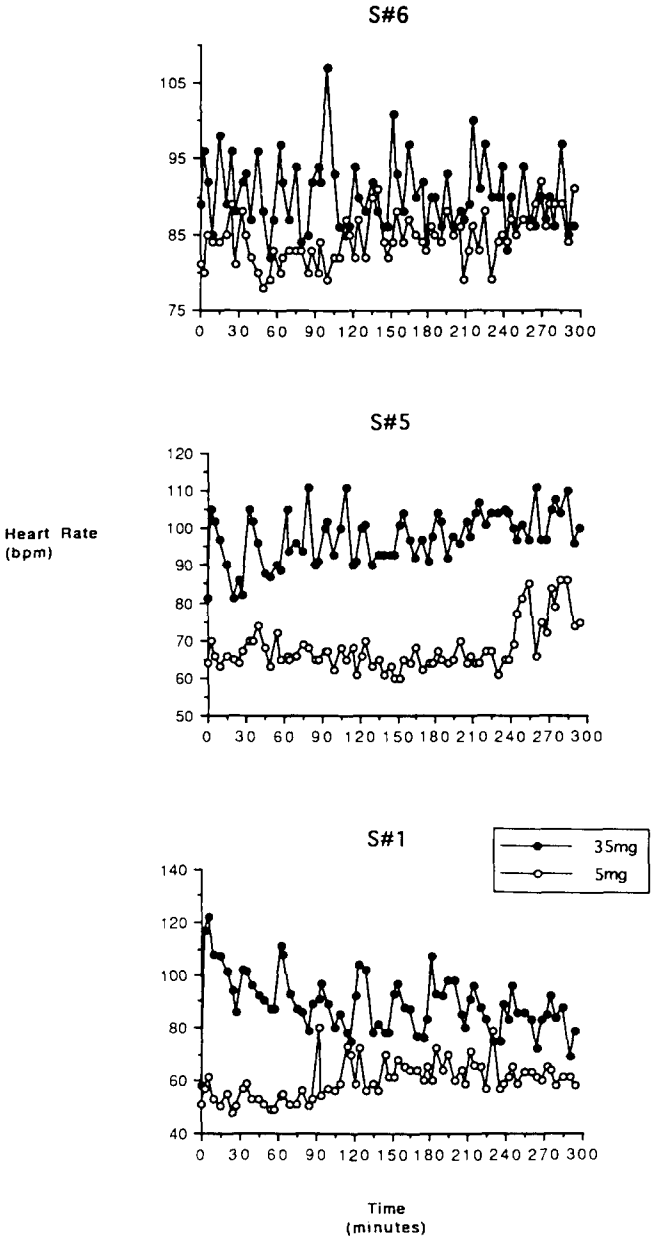

FIG. 8. Pattern of heart rate responses among three different subjects after the administration of 10 doses of 35 mg and 5 mg smoked cocaine-base given at 30-min intervals.

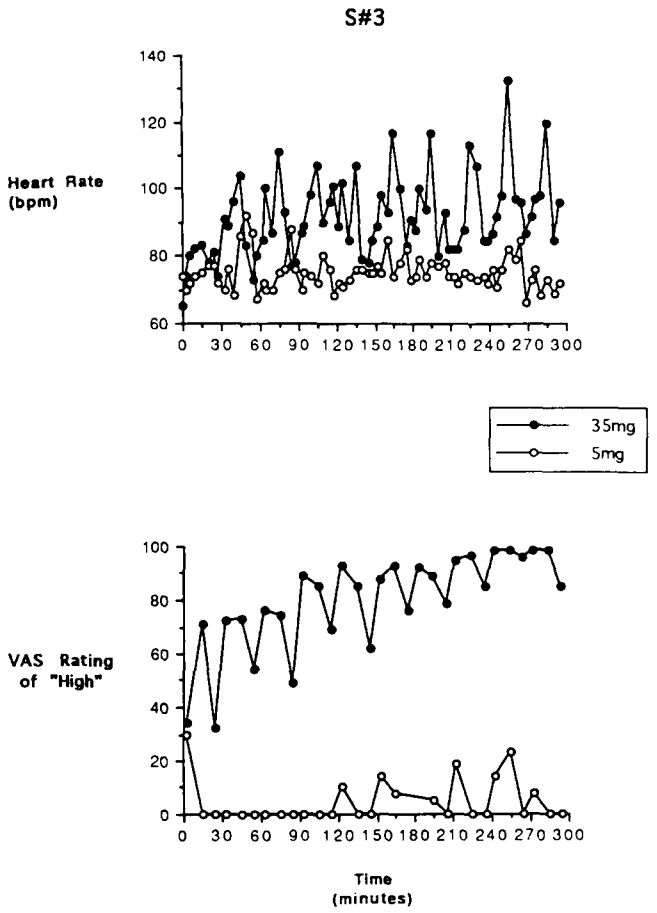

FIG. 9A. Pattern of responses for heart rate and self-rated high on a 100-mm VAS scale for subject #3 after the administration of 10 doses of 35 mg and 5 mg of smoked cocaine-base given at 30-min intervals.

these results seem consistent with the single-dose reproducibility from a previous study (13) in two of these three subjects. The 100 ng/ml difference found in one of the subjects may have been a result of procedural error (e.g., insufficient time for cocaine to dry on the coils or flaking of cocaine from the coils). The ability to dose precisely is most important when undertaking parametric studies.

Effective Control Dose

Significant differences were observed on both physiological and subjective parameters between the 5- and 35-mg doses of cocaine. Further, a 5-mg dose of cocaine produced essentially no effect on blood pressure or heart rate and minimal effects on subjective measures compared to baseline values. Because of these facts, 5 mg can be considered for use as a control condition, even though it is not a true placebo. Another study has used inhalation on the smoke delivery device with no cocaine as the control condition (9). However, this placebo control does not allow one to undertake research using a double-blind procedure. Therefore, a dose of cocaine that produces the least effects would make a better control condition until a safe smoked-placebo drug is tested.

Effects of Multiple Doses of Cocaine

The subjective and physiological changes that were observed from 35 mg of smoked cocaine-base were similar to those obtained from previous studies (8). Of note in this study was the increase in subjects' reports of "suspicious-paranoid" thinking. Nurses in another study also observed increases in suspiciousness-paranoia among subjects who were given 4 h of continuous IV cocaine infusions, although the subjects themselves did not report these feelings (23). The undiminished level in desire for cocaine during the administration of 35 mg of cocaine in our study was also similar to findings from other studies (4). Finally, this study demonstrated no effect on a reaction time task with the administration of multiple doses of cocaine.

Acute tolerance with smoked cocaine has been noted in other studies (1,3,6,8,9,14,16,25). Although the current study clearly demonstrated tolerance to both physiological and subjective effects, a great deal of between-subject variability was also observed, despite the small number of subjects. That is, subjects showed different patterns of response to multiple doses of cocaine. This study does not pose explanations for differences in tolerance. Individual differences in the plasma cocaine concentrations do not readily explain this between-subject variability, as all subjects had increasing concentra-

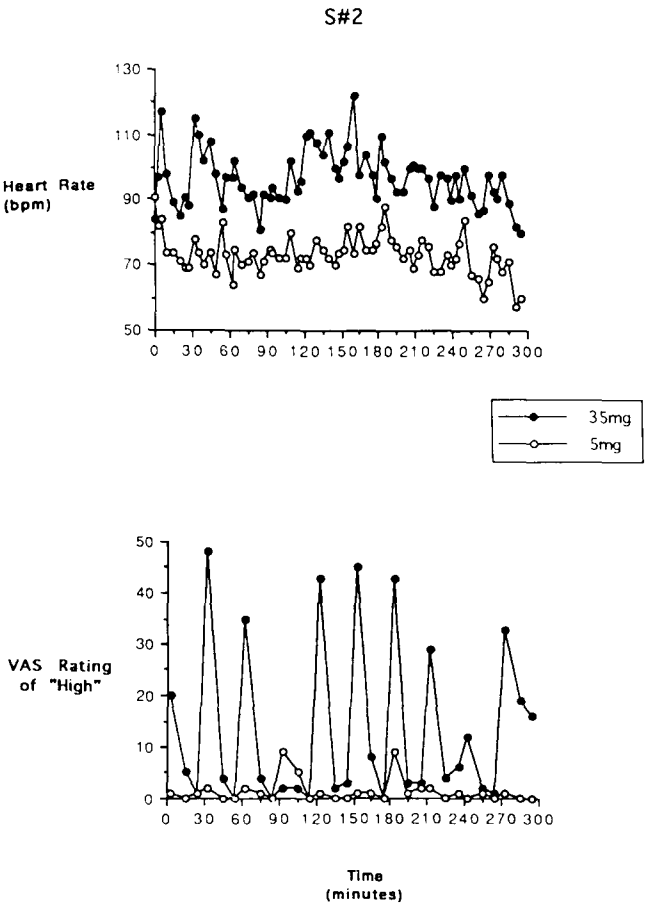

FIG. 9B. Pattern of responses for heart rate and self-rated high on a 100-mm VAS scale for subject #2 after the administration of 10 doses of 35 mg and 5 mg of smoked cocaine-base given at 30-min intervals.

tions over the experimental session. Other studies have also demonstrated this variability (10,11) directly or indirectly from the wide standard deviations that were observed for some of the measures (8). In addition to these findings, the pattern of responses also varied across physiological and subjective measures within subjects. Therefore, individuals may show greater acute tolerance to some measures than to others. Foltin et al. (11) also found the development of acute tolerance with repeated doses of intranasal cocaine in some measures (e.g., heart rate, feeling "stimulated") but lack of tolerance to pressor effects.

Further study of this potential variability will be of interest to determine whether it influences the acquisition, maintenance, or treatment of cocaine abuse. For example, those crack users who have increasing levels of high with each drug dose may be affected by a different treatment than those crack users who develop rapid tolerance. Further, variability in response across measures may have implications regarding safety. An individual who demonstrates acute tolerance to a subjective high but not to some of the cardiovascular measures may be at increased risk of cardiovascular toxicity.

Future studies also need to include females because relatively little information exists regarding the direct effects of cocaine in this population. When using females as subjects, it would be important to address and control for the menstrual cycle phase.

In summary, this study has shown that administering repeated doses of 35 mg of smoked cocaine-base every 30 min was safe and did not result in withholding doses in any of the subjects. We also found such significant differences between the 5- and 35-mg dose of cocaine that 5 mg, though not a true placebo, can serve as a control condition because of its minimal effects. Finally, although the results showed acute tolerance to cocaine-base, individual variability may exist across subjects and across measures within subjects as to the pattern of responses to smoked cocaine-base.

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