Correlation Between Pharmacological Effects and Plasma Cocaine Concentrations after Smoked Administration

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Abstract
The relationship between blood cocaine concentrations and pharmacological effects is of both theoretical and practical interest. This study utilized a computer-assisted smoking device for the delivery of three active doses (10, 20, and 40 mg) of cocaine base to seven human volunteers. Doses were administered in an ascending dose design with random placement of placebo. Physiological, subjective, and performance measures were collected concurrently with blood samples. Mean peak plasma cocaine concentrations were achieved at 2 min after the 20-mg and 40-mg doses and at 5 min after the 10-mg dose. Maximal responses in systolic and diastolic blood pressure, "feel", "good" drug, and drug "liking" subjective effects were also achieved immediately after drug administration. Pupil diameter and heart rate increases demonstrated a modest counter-clockwise hysteresis in relation to plasma cocaine concentrations shortly after dosing. Systolic and diastolic blood pressure, heart rate, and some subjective and performance measures of drug effect demonstrated a biphasic response after smoked cocaine. Initial increases above baseline levels were followed by an apparent compensatory decrease below baseline levels at a later time after smoked cocaine. Despite evidence of hysteresis and biphasic responses for some measures, linear correlation was obtained between mean plasma cocaine concentrations and several pharmacological effects over a period of 4 h after dosing. Several subjective and cardiovascular measures returned to baseline levels in the presence of detectable concentrations of cocaine.

Introduction

The proposal that the activity of a drug depends on blood concentration and not on dose was made in the 1940s (1). This proposal became the basis of therapeutic drug monitoring of blood concentrations for a variety of medications. Therapeutic ranges considered to be indicative of adequate therapy have been developed for many drugs. Exceeding the recommended maximal drug range often results in toxic effects. In clinical practice, determining plasma concentrations of drugs has helped explain individual variability in drug response, differentiate reversible and non-reversible receptor binding of drugs, and identify drugs that act through active metabolites (1). This concept has been extended to include drugs of abuse, where plasma concentrations of drug and metabolites are evaluated to determine their possible role in the pharmacological and toxic responses observed in individuals. For this approach to be valid, one must assume that specific plasma drug concentrations produce measurable physiological and/or behavioral effects in the majority of individuals who self-administer drugs of abuse. To date, this has only been demonstrated for ethanol, and it is the scientific basis of driving under the influence laws.

The need for understanding the relationship between plasma drug concentrations and pharmacological or toxic effects is important for many reasons, including understanding mechanisms of drug action and in treatment of overdose cases. In addition, understanding the relationship between drug concentrations and effects may facilitate the development of new pharmacotherapies for the treatment of drug addiction.

Cocaine use is extensive in our society, with 1.5 million people currently using cocaine according to the United States (U.S.) 1999 National Household Survey on Drug Abuse (2). The last decade has seen a shift in the preferred route of illicit cocaine self-administration from the snorting route to the smoking route (3). A study conducted in Brazil by Dunn and Laranjeira (4) between January 1996 and October 1997 evaluated transitions in the route of cocaine administration of 294 cocaine users. Although 87% of the study population reported beginning use of cocaine by snorting, by the end of the study, 74% had changed their preferred route of administration with 68% transitioning to the smoked route. The increase in popu-
larity of the smoked route may be due to the increase in purity of street drugs with the advent of crack cocaine. In addition, smoking permits the user to avoid the use of needles. If problems of bioavailability can be overcome, smoking is an effective route of drug administration because drug is delivered rapidly to the brain (5).

Given the high prevalence of smoked cocaine, the present study was designed to evaluate the relationship between plasma cocaine concentrations and pharmacological effects in volunteer subjects. Cocaine base was administered by the smoked route utilizing a computer-controlled drug delivery system (6). Cocaine was delivered as a single puff, with minimal cocaine pyrolysis and no loss due to sidestream smoke. Concentrations of cocaine in plasma were compared to physiological, subjective, and performance measures collected at similar times following drug administration.

Methods

Chemicals and materials

Cocaine hydrochloride (HCl) for human use was obtained from Mallinckrodt (St. Louis, MO), and cocaine base was prepared from cocaine HCl by treatment with sodium bicarbonate. Cocaine HCl was also obtained from Mallinckrodt for use as a standard in gas chromatographic-mass spectrometric (GC-MS) analysis. All solvents were reagent grade.

Cocaine smoking device

Smoked doses of cocaine base were administered with a computer (IBM, model PC-AT, Armonk, NY)-assisted smoking device. This device was developed and initially used in clinical cocaine studies by Hatsukami et al. (6) and consisted of a smoking insert, mouthpiece, smoking chamber, and power supply. The smoking insert was constructed of a nichrome wire coil, the ends of which were inserted into two brass rods. The rods were maintained in parallel alignment with a machine plastic plug. A replaceable Pyrex mouthpiece was placed over the coil, and an air-tight seal was made between the coil and mouthpiece with a smoking chamber. Rubber seals on the interior surface of the chamber and the base of the smoking insert ensured an air-tight seal. The base of the plastic plug was attached to a power supply that consisted of an AC/DC transformer configured for low output impedance. The transformer was configured so that the coil would be heated up to 200°C. The smoking chamber was connected to a differential pressure transducer and pneumotachograph sensitive to changes in air flow. A solution of cocaine was applied to the wire coil and allowed to air dry. The subject inhaled deeply, and on command, inhaled with their lips making a tight seal on the mouthpiece. The inhalation resulted in a change in air flow in the smoking chamber. This was detected by the pneumotachograph and signaled to the transformer via a computer-controlled relay circuit. The transformer then heated the coil, and the cocaine was volatilized and inhaled by the subject in a single puff. The subject was required to hold the inhalation for a minimum of 15 s.

Cocaine doses and efficiency of the smoking device

Cocaine doses were prepared by applying cocaine solutions to a pre-weighed nichrome wire coil. The cocaine solution consisted of 100 mg/mL cocaine base in 95% ethanol. The solution was applied to the coil with a Hamilton syringe; a maximum volume of 50 µL was applied at one time. The coil was air dried overnight to permit solvent evaporation and reweighed prior to additional loading and also prior to dosing. Coils were required to weigh ± 20% of dose to be acceptable for use. The efficiency of the smoking device for the delivery of cocaine base was determined in a series of experiments in which cocaine was volatilized in the device and the volatilized products were collected in a cold trap (dry ice/acetone). The power supply of the smoking device was manually triggered and the resulting vapor was condensed in the cold trap under constant air flow conditions. The condensate was analyzed by GC–MS and consisted of approximately 94% cocaine and 6% of the pyrolysis product, anhydroecgonine methyl ester (AEME) (7).

Subjects

This study was performed under the U.S. federal guidelines for the protection of human subjects (45 CFR 46) and was approved by the Institutional Review Board of the Johns Hopkins Bayview Medical Center (Baltimore, MD). Seven volunteers were recruited from the Baltimore-Washington metropolitan area. The subjects underwent physical and psychiatric evaluation prior to admission to the study. This evaluation included a complete medical history including drug use, psychiatric evaluation, physical examination, electrocardiogram, blood chemistry, hematological assessments, and urine drug testing. Inclusion criteria included (1) no DSM-III-R psychiatric diagnoses (other than substance abuse); (2) no current physical dependence on drugs or alcohol (excluding nicotine or caffeine); (3) no blood donations in the three months prior to admission; and (4) use of cocaine by the smoked route at least once per week for three months prior to the study. Seven male subjects, aged 27–39 years (mean = 33 years), with heights ranging from 1.70 to 1.85 m, and who weighed between 61.2 and 83.4 kg, fulfilled the inclusion criteria and participated in the study. The age of first reported cocaine use for these subjects ranged 14 and 23 years old, with intravenous or snorting as routes of drug administration pre-dating cocaine use by the smoked route by 4–17 years. During the 30 days prior to the pre-admission interview, subjects reported using cocaine 2–7 times weekly. All seven subjects were polydrug users, and in the past had self-administered licit and illicit substances including nicotine, ethanol, marijuana, heroin, morphine, benzodiazepines, barbiturates, phencyclidine, and amphetamine. Although they were polydrug users, cocaine was their primary illicit drug of abuse.

Subjects resided on the clinical research unit for approximately 4–6 weeks. Continuous nursing support was provided, and a physician was present or on call 24 h per day. Prior to admission and periodically throughout the study, urine drug testing was performed to ensure compliance with study and clinical ward guidelines. The urine samples were analyzed by immunoassay (Emit® II reagents, Syva Co., San Jose, CA) for
amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine metabolite, opiates, and phencyclidine. Subjects were required to test negative for all drugs prior to the start of the study. All subjects provided written informed consent and were financially compensated for their participation.

Dosing schedule
This was a double-blind study. Each subject received placebo and three active smoked doses of cocaine (10, 20, and 40 mg of cocaine base). For safety, the cocaine doses were administered in an ascending dose design. The placebo dose was interspersed randomly between ascending doses. Each experimental session was separated by a minimum of 48 h.

Dependent parameters
**Physiological measures.** A continuous electrocardiogram (ECG) was obtained 15 min prior and for 30 min after drug administration utilizing a MAC®VU (Marquette Electronics, Inc., Hanover, MD). Thereafter, an ECG was obtained at selected times for 4 h post drug. Other physiological measures were monitored with a Dinamap® TM vital signs monitor (model no. 1846SX, Critikon Inc., Tampa, FL) and were collected 15 min prior to dosing and then periodically after cocaine administration (2, 5, 10, 15, 30, 60, 120, and 240 min). Measures included systolic and diastolic blood pressure and heart rate. Pupil diameter was obtained with a modified Polaroid® camera (Polaroid Corp., Cambridge, MA).

**Behavioral and performance measures.** Behavioral measures were collected periodically during each experimental session (−15, 2, 5, 10, 15, 30, 60, 120, and 240 min). Behavioral questionnaires and performance tasks were presented with a Dell personal computer (model 333PW). The “Feel Drug” and “Drug Liking” scales of the Single Dose Questionnaire (SDQ) (8,9) were administered to detect transient changes in mood and subjective state. In addition, subscales of the Addiction Research Center Inventory (ARCI) (10) were administered as follows: morphine-benzedrine group (MBG), which evaluates a drug's euphoriant properties; pentobarbital-chlorpromazine-alcohol group (PCAG), which reflects sedation and intoxication; and the lysergic acid diethylamide scale (LSD), which reflects dysphoria and feelings of paranoia and fear (11). The Profile of Mood States (POMS) questionnaire was also administered to assess transient changes in mood (12). In addition, a visual analogue scale (VAS) was presented to the subjects prior to and after dosing. The subjects rated their responses on a scale of 0–100 to the question “Do you feel any good drug effects?”

Two performance tasks were obtained prior to smoking and periodically after cocaine administration (−15, 30, 60, 120, and 240 min), namely the Digit Symbol Substitution Task (DSST) and the Reaction Time Task (RCT) (13). The DSST consisted of a series of geometric patterns presented on the computer screen that the subject was required to duplicate using the keyboard. The patterns appeared for a period of 1.5 min per trial. Data were collected according to total number of patterns attempted, total correct, and percent correct. The RCT consisted of a black square image shown every 2 s on the computer screen for a period of 2.5 min per trial. When the image appeared in the upper field, the subject was required to press a hand-held button. When the image appeared in the lower field the subject was instructed to refrain from pressing the button. The mean lag time between the appearance of the image and correct response (milliseconds), standard deviation, and between the appearance of the image and incorrect response, and standard deviation, were calculated for each trial.

**Experimental cocaine sessions**
Prior to the first experimental session, subjects received training on the computer tasks in order to familiarize themselves with the questions and keyboard use. At the beginning of an experimental session, an intravenous catheter was inserted in the antecubital vein in the non-dominant forearm for blood withdrawal. Nursing personnel prepared subjects for each session and were present throughout. A physician was present prior to dosing and for at least 20 min after drug administration. For dosing, subjects were instructed to exhale, place their lips over the mouthpiece to form a seal, and then inhale deeply. This triggered the smoking device, which immediately volatilized cocaine base for inhalation. Blood samples were collected 15 min prior to dosing and at 2, 5, 10, 15, 30, 60, 120, and 240 min after cocaine administration.

**Collection and analysis of plasma samples**
Whole blood samples (3–4 mL) were collected in green top Vacutainer® tubes containing 75 µL of saturated sodium fluoride and 75 µL of 10% acetic acid. Blood specimens were stored in ice prior to separation by centrifugation (3000 rpm for 10 min). Plasma samples were transferred into polypropylene cryotubes and frozen at −30°C until analysis. Plasma samples were analyzed for cocaine by solid-phase extraction (SPE) followed by GC–MS analysis in the selected ion monitoring mode, according to a previously published procedure (14). Standard curves were constructed in a concentration range of 6.25–500 ng/mL and the limit of detection for cocaine was 1 ng/mL. Coefficients of variation for cocaine at 100 ng/mL were 2–3%. The assay was linear over the concentration range of 3.1 to 1000 ng/mL. Control samples were assayed in each run, including a 500 ng/mL cocaine control utilized to monitor the hydrolysis of cocaine during extraction and GC–MS analysis. Hydrolysis of cocaine during the SPE-GC-MS procedure was approximately 5%.

**Data analysis**
Differences in physiological, subjective and performance measures were analyzed by a repeated measures two-way ANOVA. Huynh-Feldt p values were utilized to determine significance. Dose effects were reported to indicate significant dose related responses to cocaine and interaction effects were reported to show significant dose x time product effects (7). Tukey’s post hoc analyses were conducted when a significant dose effect was observed. Statistical significance was defined as a p value less than or equal to 0.05. The correlation between dependent measures, expressed as mean change from baseline, and mean plasma cocaine concentrations over time was determined by linear regression analysis.
Results

Smoked cocaine produced increases in blood pressure, heart rate, pupil diameter, behavioral measures and performance measures. Significant changes by dose, time, and interaction (dose × time) effects were observed for plasma cocaine concentrations, systolic blood pressure, heart rate, “Feel” drug scores on the SDQ, and “Good” drug response on the Visual Analogue Scales. Significant changes by time and interaction, but not dose, were observed for diastolic blood pressure and drug “Liking” response on the SDQ. Post hoc analysis indicated significant differences in peak plasma cocaine concentrations between placebo and each active dose and also between each active dose. Significant dose differences were also found in systolic blood pressure between placebo and the 20- and 40-mg doses, between the 40- and 10-mg doses, and between the 40- and 20-mg doses. Increases in heart rate were significant between placebo and each active dose and between active doses, except there was no significant difference in heart rate increases between the 20- and 40-mg doses. The subjective measures of drug effect, “feel” and “good”, showed significant differences in scores between the active doses and placebo.

No significant dose, time, or interaction effects were observed for the PCAG, MBG, and LSD subscales of the ARCI, the Tension/Anxiety, Vigor, or Total Mood Disturbance subscales of the POMS or the DSST and RCT performance measures.

Discussion of results will emphasize mean data and the highest dose administered, 40 mg cocaine. This dose was considered the dose most representative of real-life “street” doses. Any deviation or differences in effects or general trends between this dose and the 10- and 20-mg cocaine doses are noted in the text. Graphical analysis of data from the 40-mg cocaine dose provided correlation coefficients of mean data. Although correlation coefficients of individual subject data obviously differed from mean data, differences did not affect trends or the interpretation of the results.

Correlation of plasma cocaine concentrations with physiological effects

Plasma cocaine concentrations rose rapidly and were detected in the first blood samples at 2 min after smoked cocaine. Mean concentrations (± SD) of cocaine (N = 7) in plasma at 2 min after smoking 10 mg, 20 mg, and 40 mg of cocaine base were 32.6 ng/mL ± 30.1 ng/mL, 113.7 ng/mL ± 93.6 ng/mL, and 153.0 ng/mL ± 107.5 ng/mL, respectively (Figure 1). Mean peak concentrations were achieved at 5 min (N = 4, at 2 min in one subject and 10 min in 2 subjects) after the low dose, and at 2 min after the 20 mg (N = 4; 5 min, N = 1; 10 min, N = 1; and 15 min, N = 1) and 40 mg (N = 4; 5 min, N = 3; 10 min, N = 1) doses. Mean peak plasma cocaine concentrations were 45.5 ng/mL ± 25.1 ng/mL, 122.5 ng/mL ± 84.8 ng/mL, and 160.8 ng/mL ± 99.1 ng/mL, after the 10-, 20-, and 40-mg doses, respectively. Mean peak plasma cocaine concentrations for the 3 doses differ from the mean concentration at 2 min, even though the mean time to peak for the 20- and 40-mg doses was 2 min because of differences in the individual time to achieve peak plasma levels.

Physiological measures also changed rapidly after cocaine administration. Increases in pupil diameter were detected at 2 min and peak increased occurred between 2 and 10 min across doses. Mean (N = 7) peak changes from baseline were 0.9 ± 0.6 mm, 0.8 ± 0.4 mm, 1.0 ± 0.7 mm, and 1.7 ± 0.5 mm after placebo, 10, 20, and 40 mg cocaine base, respectively. Baseline was defined as the pre-drug value for each parameter, obtained 15 min prior to dosing.

Figure 2 illustrates the relationship between mean plasma cocaine concentrations and mean changes in physiological effects after smoking 40 mg cocaine base. Mean peak plasma cocaine concentrations occurred at 2 min whereas peak changes in pupil diameter occurred at 5 min with only slight evidence of hysteresis occurring between 2 and 10 min. Thereafter, pupils returned to baseline levels in a linear manner with declining plasma cocaine concentrations over a period of 15–60 min. Linear regression between changes in pupil diameter and mean plasma cocaine concentrations provided a correlation coefficient (r²) of 0.857 (p < 0.001).

Increases in systolic blood pressure were also observed at the 2 min measure after smoked cocaine. Mean peak increases above baseline of 23.9 ± 12.0 mm Hg, 30.1 ± 19.9 mm Hg, and 31.6 ± 16.1 mm Hg occurred at 2 min after the 10-, 20-, and 40-mg doses, respectively. Figure 2B illustrates the relationship between mean changes from baseline in systolic blood pressure and mean plasma cocaine concentrations after smoking 40 mg cocaine base (N = 7). There was no evidence of hysteresis between peak cocaine concentrations and maximal response. Thereafter, systolic blood pressure approached baseline levels in a linear manner with declining plasma cocaine concentrations. After approximately 60 min, systolic blood pressure fell below baseline levels as plasma cocaine concentrations continued to decline. Linear regression analysis between systolic blood pressure and plasma cocaine concentrations after the 40-mg dose provided a correlation coefficient (r²) of 0.908 (p < 0.001). Diastolic blood pressure increased slightly after cocaine administration in a similar manner to systolic blood pressure changes. Mean peak increases occurred at 2 min after the three active doses. There was no delay between maximal physiological response and peak plasma cocaine concentra-

\[ 	ext{Figure 1. Mean plasma cocaine concentrations (N = 7) after smoking 10, 20, and 40 mg cocaine base.} \]
tions after the 40-mg dose (Figure 2C). Thereafter, diastolic blood pressure declined in a linear manner with declining cocaine concentrations for 30 min. After approximately 15 min, diastolic pressure declined below baseline while plasma cocaine concentrations continued to diminish. Linear regression between mean changes in diastolic blood pressure and mean plasma cocaine concentrations after the 40-mg dose provided a correlation coefficient (r²) of 0.953 (p < 0.001).

Increases in heart rate were also observed early after cocaine administration, with mean peak increases occurring at 5 min, 2 min, and 10 min for the 10-, 20-, and 40-mg doses, respectively. For these doses, the mean peak heart rate increased above baseline levels by 12.3 ± 8.2 beats per minute (bpm), 21.9 ± 10.3 bpm, and 27.3 ± 9.0 bpm, respectively. Figure 2D illustrates the relationship between mean heart rate changes and mean plasma cocaine concentrations after smoking 40 mg cocaine base. Maximal heart rate responses occurred at 10 min and were delayed with respect to peak plasma cocaine concentrations. Thereafter, heart rate decreased in a linear manner with declining plasma cocaine concentrations. Heart rate returned to baseline levels between 30 and 60 min and continued to decline in an apparent rebound effect. This effect appeared to plateau after 120 min when the mean plasma cocaine concentration was 23 ng/mL. This apparent rebound effect was also observed at the lower doses. At 120 min, the mean plasma cocaine concentrations were 3 and 14 ng/mL after 10 and 20 mg cocaine base, respectively. Linear regression between mean heart rate changes and mean plasma cocaine concentrations after the 40-mg dose provided a correlation coefficient (r²) of 0.855 (p < 0.005).

Correlation of plasma cocaine concentrations with subjective effects

"Feel Drug" responses were maximal at 2 min after cocaine smoking for the 10-, 20-, and 40-mg doses. The maximal response was maintained for at least 5 min for all three active doses. Figure 3A illustrates the relationship between mean changes in "feel drug" scores with mean plasma cocaine concentrations after the 40-mg cocaine dose. The maximal response at 2 min persisted briefly while plasma cocaine con-
After 10 min, the response appeared to decline more rapidly than plasma cocaine concentrations. The scores returned to baseline levels at 30 min when the mean plasma cocaine concentration was 69 ng/mL. Linear regression analysis between mean changes in “feel” drug scores and mean plasma cocaine concentrations after the 40 mg cocaine dose provided a correlation coefficient ($r^2$) of 0.792 ($p < 0.005$).

Drug “liking” scores showed maximal response 2 min after cocaine administration for all active doses. Figure 3B illustrates the relationship between mean changes in “liking” scores with mean plasma cocaine concentrations after smoking 40-rag cocaine base. Maximal response scores were maintained until 10 min after dosing for all doses and thereafter, declined rapidly in a similar manner to that observed with “feel” drug scores. After the 40-mg cocaine dose, mean plasma cocaine concentrations declined from 120 ng/mL to 91 ng/mL from 5 to 15 min post drug but mean change from baseline “liking”, scores appeared to decline more rapidly. Scores returned to baseline after 30 min when the mean plasma cocaine concentration was 69 ng/mL. A slight rebound effect was observed at 60 min after the 40-mg dose. This effect was not apparent at the low doses and was considered insignificant. Linear regression between mean changes in drug “liking” scores and mean plasma cocaine concentrations after the 40-mg cocaine dose provided a correlation coefficient ($r^2$) of 0.815 ($p < 0.005$).

Mean maximal response to the VAS scale question “Do you feel any good drug effect?” was achieved at 5 min after the 10 and 20-mg doses and at 2 min after the 40-mg dose. Mean ($\pm$ SD) peak changes from baseline were 44.3 $\pm$ 31.3 mm, 56.0 $\pm$ 28.0 mm, and 53.1 $\pm$ 28.1 mm after 10, 20, and 40 mg cocaine base, respectively. Figure 3C illustrates the relationship between mean changes in “good” drug effects and mean plasma cocaine concentrations after smoking 40 mg cocaine base. Maximal “good” drug effects were achieved concurrently with peak plasma cocaine concentrations after this dose. Thereafter, “good” drug effects declined linearly with cocaine con-
Correlation of plasma cocaine concentrations with performance

The DSST was administered to assess changes in psychomotor performance after cocaine administration. Data were collected for the total number of patterns attempted, total correct and percent correct. None of these measures showed significant dose, time or interaction effects. Figure 4A illustrates the relationship between mean changes from baseline in the number of patterns attempted and mean plasma cocaine concentrations after smoking 40 mg cocaine base. The first measure at 15 min was the maximal response obtained. This occurred at a time when the mean plasma cocaine concentration was 91 ng/mL. Initial increases at 15 min for this measure were observed for all doses including placebo. As Figure 4A illustrates, this effect was short-lived, with performance declining towards baseline levels with decreasing plasma cocaine concentrations. Changes from baseline in performance declined linearly with decreasing plasma cocaine concentrations for 60 min. Then changes in performance remained at a minimum below the baseline as the plasma cocaine concentration continued to fall. At 240 min after smoking 40 mg cocaine base, the number of patterns attempted on the DSST returned to baseline levels. Linear regression analysis between mean changes in the number of patterns attempted and mean plasma cocaine concentrations provided a correlation coefficient ($r^2$) of 0.673, which was not significant.

No significant dose, time, or interaction effects were observed with the reaction time task. The relationship between the mean change from baseline in average lag time for correct responses with the RCT and the mean plasma cocaine concentration after smoking 40 mg cocaine base is shown in Figure 4B. With this performance measure there was a slight delay to maximal response. The maximal performance response occurred at the second measure at 30 min. The lag time decreased only observed at the 40-mg dose and not with the lower doses or placebo. After 30 min, the average lag time for correct responses increased linearly with declining plasma cocaine concentrations until 120 min after cocaine administration. Linear regression between mean change in lag time for correct responses and mean plasma cocaine concentrations provided a correlation coefficient ($r^2$) of 0.551 which was not significant.

Comparison between plasma cocaine concentrations and effects across doses

Pharmacological effects of cocaine may be compared at different times after cocaine administration when the plasma levels are similar in order to determine the usefulness of drug concentrations in predicting effects. In the current study this is possible only at a few times after dosing because mean cocaine concentrations did not overlap over the three doses (Figure 1). The mean plasma cocaine concentration at 15 min after the 20-mg dose was 68 ng/mL. A mean plasma cocaine concentration of 69 ng/mL was achieved after the 40-mg dose at 30 min. Comparison of the physiological and subjective effects at these times showed that at a similar plasma concent-

![Figure 4](https://academic.oup.com/jat/article-abstract/26/7/382/708885)
tration the effects at these time points differed. The trend was in the same direction, but the magnitude of the effect was equal or greater at 5 min than at 15 min (e.g., the mean change from baseline in systolic blood pressure was 14 mm Hg at 15 min after 20 mg but only 2 mm Hg at 30 min after 40 mg). Changes in pupil diameter were equal. Mean changes from baseline in drug liking scores were lower (0.1) at 30 min after the 40-mg dose than at 15 min after the 20-mg dose (0.4).

Similarly, the mean plasma cocaine concentration at 5 min after the 20-mg dose was 84 ng/mL. A mean plasma cocaine concentration of 91 ng/mL was achieved after the 40-mg dose at 15 min. Comparison of the physiological and subjective effects at these times showed that, at a similar plasma concentration, the absolute effects at these time points differed. The trend was in the same direction, but the magnitude of the effect was equal or greater at 5 min than at 15 min (e.g., the mean change from baseline in systolic blood pressure was 16 mm Hg at 5 min after 20 mg and 14 mm Hg at 15 min after 40 mg cocaine). Changes in pupil diameter were equal. Mean changes from baseline in drug liking scores were lower (0.4) at 15 min after the 40-mg dose than at 5 min after the 20-mg dose (1.9).

In order to obtain a clearer picture of the possibility of the development of acute tolerance, a similar plasma concentration of cocaine early after dosing at 10 mg may be compared with that achieved late after dosing with 40 mg. For example, the mean plasma cocaine concentration at 5 min after the 10-mg dose was 38 ng/mL. A mean plasma cocaine concentration of 39 ng/mL was achieved after the 40-mg dose at 60 min. Comparison of the physiological and subjective effects at these times showed that, at a similar plasma concentration, the effects at these time points differed. The magnitude of the effect was equal or greater at 5 min than at 60 min. For example, the mean change from baseline in systolic blood pressure was 15 mm Hg at 5 min after 10 mg and less than baseline at 60 min after 40 mg. The mean increase in pupil diameter at the low dose was 0.7 mm Hg and 0.4 mm Hg after the 40-mg cocaine dose. Mean changes from baseline in drug liking scores were lower (0.3) at 60 min after the 40-mg dose than at 5 min after the 10-mg dose (1.0).

Comparison across doses may also be evaluated by considering the relationship between plasma cocaine concentration and cocaine effects at a single time point. At 2 min, the mean plasma cocaine concentrations were 32.6, 113.7, and 153.0 ng/mL after the 10-, 20-, and 40-mg doses, respectively. At this time point, the mean increase in heart rate was 6, 19, and 21 bpm, respectively. Similarly, the mean change in systolic blood pressure was 20, 27, and 23 mm Hg after the 10-, 20-, and 40-mg doses, respectively. The mean change in pupil diameter was 0.7, 0.7, and 1.4 mm, respectively, and the mean change in drug liking scores was 1.0, 1.9, and 2, after the 10-, 20-, and 40-mg doses. Measures of good drug effect were higher after the 40-mg dose at 2 min, with mean changes of 28, 48, and 53 mm VAS scales after the 10-, 20-, and 40-mg doses. Diastolic blood pressure measures did not follow this trend with a lower mean change observed at the highest dose (7, 9, and 5, respectively, at 2 min after 10, 20, and 40 mg smoked cocaine).

### Discussion

Several clinical studies have described the pharmacological effects in humans after smoking cocaine base. Perez-Reyes et al. (15) compared the effects of smoking 50 mg of free base cocaine to the intravenous administration of 20 mg cocaine HCl in six subjects. Individuals reported greater feelings of “high” and experienced larger increases in heart rate and systolic blood pressure after smoking compared with the intravenous route. Foltin and Fischman (16) also compared the physiological and subjective effects of smoked and intravenously administered cocaine. Ten volunteers were administered doses of 16 mg and 32 mg cocaine HCl intravenously and 25 mg and 50 mg cocaine base smoked in a modified corn-cob pipe. Smoked and intravenously administered cocaine produced similar increases in heart rate and blood pressure at similar cocaine venous plasma concentrations. However, subjective ratings of “liking” and “high” were greater at similar plasma levels after smoked cocaine than after intravenously administered cocaine. Cone (17) also found that behavioral measures of “good” drug effect and “liking” were higher after smoking than after intravenous administration. Physiological changes were approximately equal at equivalent plasma cocaine concentrations. In addition, Foltin and Fischman (18) demonstrated that given the choice between matched doses of smoked and intravenous cocaine, subjects most often chose the smoked dose. These studies demonstrated that smoking produces many of the effects similar to intravenous administration, namely, a rapid rise in blood cocaine levels and concomitant increases of equal or greater magnitude in subjective, physiological, and behavioral effects, but without the negative sequelae associated with needle use. However, there are few published reports describing the empirical relationship between cocaine blood concentrations with measures of drug effect. The relationship between cocaine concentrations in blood and pharmacological effects is undoubtedly complex. Immediately after dosing, blood concentrations are high and tissue concentrations (effector sites) are low, whereas later in the postabsorptive stage, tissue concentrations may be higher than blood concentrations. When maximal pharmacological response is observed later than peak plasma concentrations in a counter-clockwise manner (counter-clockwise hysteresis), this is considered to be suggestive of an early distribution phase in which there is a lag between blood concentrations and effect due to drug being transported through tissues to the effect compartment. Alternatively, if maximal pharmacological effect is observed before peak drug concentrations are achieved (clockwise hysteresis) this suggests development of acute tolerance to the effects of the drug. Javaid et al. (19) reported that heart rate changed at a faster rate than plasma cocaine levels after administration of cocaine to human subjects. Jones (20) reported a clockwise hysteresis between subjective intoxication levels and plasma cocaine concentrations in 10 subjects after smoking 100 mg cocaine base. The effect of cocaine concentrations on intoxication was less on the descending limb of the hysteresis plot compared to the ascending limb. In addition, maximal subjective response occurred while plasma cocaine concentrations were still rising, with submaximal responses recorded at peak
cocaïne concentrations. In the present study, there was no delay, and therefore, little evidence of hysteresis between maximal subjective response and peak plasma cocaine concentrations. Differences between the observed results may be due to the methods of cocaine delivery. In the study by Jones (20), subjects were permitted to take one or two inhalations spaced 1 min apart, beginning 45 s after 100 mg cocaine base was dropped into an electrically heated flask. This relatively incremental mode of drug delivery likely produced a delay in the time to peak plasma cocaine concentrations. In contrast, in the present study the entire dose was delivered within a few seconds of inhalation.

Foltin and Fischman (16) used linear regression analysis to describe the effects of cocaine concentrations on subjective measures of drug effect. Ten subjects smoked the same dose (25 or 50 mg) of cocaine base twice with a 14-min interval between doses. They suggested that acute tolerance developed to the effects of cocaine on subjective ratings of “stimulated” and “high” measured with Visual Analogue scales. They also determined that the relationship between venous plasma cocaine levels and the MBG, PCAG, and LSD subscales of the ARCI was similar throughout the experimental session. Therefore, there appeared to be a lack of acute tolerance to the effects of cocaine with these measures. However, they reported that predicted changes in scores on the MBG subscale at 60 and 90 min after the first dose were less than those predicted 4 min after the first dose. In the current study, scores on the MBG subscale were maximal at the first timepoint and decreased to baseline levels within 60 min. It is important to note that in the current study the ARCI was first administered 30 min post drug. Therefore, the time of maximal response may have been missed. This is supported by the work of Foltin and Fischman (18) who found no statistically significant effects of dose on any scale of the ARCI, in agreement with the current study, but did observe a significant change in MBG scores from baseline at 4 min after the high smoked dose (50 mg cocaine base).

In a study by Evans et al. (21), cocaine was administered to subjects by the smoked and intravenous routes and arterial and venous plasma cocaine concentrations determined. Arterial cocaine concentrations were substantially higher than venous cocaine concentrations with the former reaching peak concentrations within 15 s of drug administration by both routes. These authors observed a mean time to peak venous plasma cocaine concentrations of 4 min after smoking 25 or 50 mg cocaine base, as “crack”, compared with a mean time to peak concentration of 2 min after smoking 20 or 40 mg cocaine base in the current study. This difference was most likely due to differences in drug delivery by the smoking route between the two studies. In the study of Evans et al. (21) “crack” was placed in a modified corn-cob pipe and the subject was instructed to exhale. The pipe was placed in the subject’s mouth, and a nurse lit the cocaine with a pipe lighter. The subject inhaled deeply for 10 s, paused for 5 s and then exhaled. The end of drug administration, time 0, was considered to be at the end of the exhalation. In the current study, the subject triggered the smoking device which vaporized the cocaine base. Triggering of the device and completion of drug administration was achieved within 3 s, resulting in a bolus of drug administered to the subject. Peak plasma cocaine concentrations cannot be realistically compared between the two studies since, Evans et al. (21) did not determine how much of each dose was actually delivered to the subject by measuring losses due to thermal degradation, condensation within the pipe stem, and losses in sidestream smoke. Therefore, differences in delivery of cocaine by the smoked route to the subjects in these studies likely accounts for the differences in time to peak cocaine concentrations.

Evans et al. (21) observed maximal increases in systolic and diastolic blood pressure at 30 s or 1 min after smoked cocaine but peak plasma cocaine concentrations occurred at 4 min. Again, the difference in results compared with the present study may be explained by examining the method of drug delivery and the time of the first measurement of physiological parameters; for example, Evans et al. (21) measured systolic blood pressure using invasive monitoring and therefore, were able to acquire multiple measures immediately after drug administration. In the present study the first blood pressure reading was acquired 2 min after dosing. The present study observed no delay between maximal physiological response and mean peak plasma cocaine concentrations for systolic and diastolic blood pressure after smoking. Further, there appeared to be a linear relationship between mean plasma cocaine concentrations and mean changes in systolic and diastolic blood pressure for 30 min after smoking 40 mg cocaine base. After 30 min, systolic and diastolic blood pressure continued to decrease below baseline levels in an apparent rebound effect. Only a slight delay in maximal physiological response was observed for increases in pupil diameter and heart rate after smoking cocaine. The slight delay between maximal response of the physiological effect and peak plasma cocaine concentrations, indicative of a counter-clockwise hysteresis, suggested a brief initial distribution phase in which cocaine concentrations in the central compartment were not equilibrated with concentrations in the effect compartment. After reaching maximal physiological response, changes in pupil diameter and heart rate declined linearly with decreasing plasma cocaine concentrations from 15 to 60 min. A slight rebound effect, as described here previously, was also observed with changes in heart rate after approximately 60 min. In the study of Evans et al. (21), the maximum heart rate was observed at the end of cocaine administration with a transient decrease at 0.25 min followed by a rebound at 2 min (50-mg dose, N = 8). These investigators concluded there was no evidence of hysteresis after smoked cocaine. The explanation offered for the transient decrease in heart rate was a Valsalva maneuver in response to the inhalation process.

An understanding of the possible mechanisms responsible for the observed cardiovascular effects is complicated by the many actions of cocaine. It has both local anesthetic and sympathomimetic effects, in addition to blocking the uptake of norepinephrine, dopamine, and serotonin (22). Increases in blood pressure and heart rate after cocaine administration are produced by increased central sympathetic outflow to the cutaneous circulation and the heart producing peripheral vasoconstriction and tachycardia (23). The blocking of norepinephrine reuptake at adrenergic nerve endings results in
increased blood levels of catecholamines, which produce increased adrenergic impulses. These responses may be attenuated by treatment with the combined alpha and beta adrenergic blocker, labetalol (24). In the current study, maximal increases in blood pressure occurred without delay, whereas there appeared to be a delay in the maximal heart rate response following cocaine smoking. This may be due to the rate of response of different receptors because pressor responses are considered to be mediated by $\alpha_1$ adrenoceptors and tachycardic effects by $\beta_1$ adrenoceptors (25). A delay was also observed in the time to achieve maximal pupillary dilatation following cocaine smoking. The mydriatic effect of cocaine appears to be due to contraction of the radial muscle of the iris mediated by $\alpha_2$ adrenergic receptors (25).

The brief to non-existent delay between maximal subjective responses and peak plasma cocaine concentrations may be a result of the rapidity of cocaine delivery to effector sites in the brain by the smoking route or due to a bolus of drug reaching the brain. Benowitz (26) estimated that it takes approximately 11 s from the start of a puff for nicotine to reach the brain from the lungs and an additional 8 s to distribute throughout the brain. Nicotine is a weak base with a $pK_a$ and lipid solubility similar to cocaine. Therefore, cocaine should demonstrate comparable absorption characteristics to nicotine. As a result, cocaine smoking likely delivers a bolus of active drug to the reward centers of the brain within seconds of inhalation. Behavioral and reinforcing effects are considered to be mediated via dopaminergic processes rather than adrenergic processes (22). This would suggest that the behavioral and cardiovascular effects of cocaine are controlled by different pharmacological mechanisms (22). Schindler et al. (21) investigated this possibility utilizing calcium channel antagonists as pretreatment drugs. The compounds tested in squirrel monkeys were effective antagonists of the pressor effects of cocaine but failed to antagonize cocaine induced tachycardia (22). Further, none of the antagonists altered schedule-controlled food-reinforced behavior or cocaine self-administration. The rebound effect noticed with some measures suggested that a compensatory mechanism was triggered. However, this has not been reported in previous studies of cocaine smoking and warrants further investigation.

Performance on the DSST and RCT, measured as the number of patterns attempted and the lag time for correct responses, respectively, increased after the high cocaine dose. However, increases in performance were not statistically significant. This agrees with the work of Johnson et al. (27) who assessed the effects of intravenously administered cocaine on cardiovascular function, learning, and performance in eight cocaine addicts in a double-blind randomized crossover study. These investigators reported that IV doses of 0.325 and 0.650 mg/kg were associated with increased attention as measured by an increase in the number of correct responses on the Rapid Visual Information Processing Task, but the trend towards decreased reaction time was not statistically significant. The authors also observed a small but statistically insignificant improvement in learning on the DSST.

In the current study, on the DSST, there was no delay between maximal response as determined by the number of patterns attempted and peak plasma cocaine concentration. However, there was a delay observed between maximal decreases in lag time for correct responses on the RCT and peak plasma cocaine concentrations. Mean change from baseline declined linearly with decreasing plasma cocaine concentrations from 15 to 60 min with the DSST and from 30 to 120 min with the RCT after the 40-mg dose. A slight rebound effect was noted between 60 and 120 min on the DSST. No rebound effect was observed with the average lag time of correct responses on the RCT performance task. The apparent increase in performance observed with the DSST and RCT performance measures may have been due to increased visuo-motor coordination. This suggests that altered neuromuscular mechanisms could be involved.

Comparison of physiological and behavioral effects at different times after dosing, when plasma cocaine concentrations were similar, suggested the development of acute tolerance, since the magnitude of the effects were greater at the earlier timepoint. However, effects were not equal, for example, differences in pupil diameter appeared to be less than differences observed with other parameters such as behavioral and cardiovascular measures of drug effect. This finding, together with the observation that measures of drug effect returned to baseline in the presence of detectable levels of cocaine, suggests that plasma cocaine concentrations cannot be used to accurately predict the magnitude of the pharmacological effect of cocaine.

In summary, this study investigated the empirical relationships between plasma cocaine concentrations and pharmacological effects after cocaine smoking. Several physiological and subjective measures of drug effect appeared to be linearly correlated with plasma cocaine concentrations. Cardiovascular and subjective responses declined more rapidly than cocaine concentrations. Return to near baseline levels in the presence of 50–100 ng/mL cocaine in plasma has important implications in the interpretation of cocaine blood concentrations. This finding suggests that there may be a “threshold” concentration of cocaine in blood necessary for production of pharmacological effects.

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