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A Method for Delivery of Precise Doses of Smoked Cocaine-Base to Humans

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HATSUKAMI, D., R. KEENAN, M. CARROLL, E. COLON, D. GEISKE, B. WILSON AND M. HUBER. *A method for delivery of precise doses of smoked cocaine-base to humans.* PHARMACOL BIOCHEM BEHAV **36**(1) 1–7, 1990.—Despite increasing smoked cocaine-base use, there have been relatively few parametric studies in this area. The major reason for the limited number of studies is the lack of a simple procedure for the administration of precise doses of smoked cocaine-base to human volunteers. This paper describes a new method that allows for the delivery of precise doses of smoked cocaine-base. A complete description of the method and the precision of the administration procedure are presented. Furthermore, a study is described which was undertaken to determine: 1) the reproducibility of peak blood cocaine levels when the same dose of cocaine was given on two separate occasions; and 2) the dose-related effects on smoking topography, biochemical, physiological and subjective measures. Subjects (N = 5) were administered three doses of cocaine-base (10, 20 and 40 mg). Four subjects were given repeated doses of cocaine-base. Subjects were blind to the dose and in most cases randomly assigned to different doses. The results showed: 1) a significant correlation of peak whole blood cocaine concentrations among similar doses within subjects (r = .99); 2) no significant effects of dose on smoking topography; and 3) significant dose effects for whole blood cocaine concentrations, heart rate and systolic blood pressure.

Smoked cocaine-base Humans Physiological effects Subjective effects Crack

COCAINE use has become a significant concern over the past several years. The National Household survey conducted by the National Institute on Drug Abuse estimated that over 22 million individuals in the U.S. have used cocaine at least once in 1985 compared to 5.4 million in 1974. Six million reported current use in 1984 compared to 1.6 million in 1977 (12). There was a 75% increase in emergency room admissions related to cocaine use between 1981 and 1983 (7). More recently, cocaine use via the smoking route has gained prominence (5). The use of smoked cocaine among cocaine users has increased from 1% in 1977 to 18% in 1984. This route of administration has been of particular concern due to the immediacy of the effects and the lower costs of use.

Although basic experimental research with smoked cocaine-base would be important, a major limitation has been the technological difficulties related to administering precise doses of smoked cocaine. There have been only two studies of cocaine-base smoking in humans (8,9). In one of the human studies, subjects smoked cigarettes containing cocaine paste (8). This method of delivery did not allow for controlled doses of cocaine since individuals have different patterns of smoking topography. In addition, since there are other substances which are delivered to the subject during smoking besides cocaine, the effects cannot be solely attributed to cocaine. In the other study, the investigators examined the effects of 50 mg of cocaine-base smoked through a specially designed sealed glass pipe which was submerged in hot oil to volatilize the cocaine-base for smoking (9). The pipe was capped between puffs. Using this technique, only 32% of the cocaine was found to be inhaled. Furthermore, the cocaine was sublimated at such high temperatures, it is possible that the cocaine molecule was broken down to other unknown immeasurable substances (1). As a result of these procedural problems, both methods of smoked cocaine delivery may be limited in the replication of results, which would be essential in basic parametric studies. The present study was an attempt to develop a precise, reproducible method for administering controlled doses of cocaine-base to humans.

This research is presented in two parts. The first part describes the method for delivery of smoked cocaine-base and the precision of this method. The second part describes an experiment in which cocaine-base was administered to humans with this device to determine: 1) the replicability or reliability with which peak blood cocaine levels are obtained when the same dose of cocaine is administered on two separate occasions; 2) the effects of various doses of smoked cocaine-base on topography measures; and 3) the effects of different doses of smoked cocaine on whole blood cocaine concentrations, and physiological and subjective functioning.

PART I: METHOD AND ACCURACY OF SMOKED-COCAINE DELIVERY

METHOD OF DELIVERY OF SMOKED COCAINE

The description of the method used for delivery of cocaine-base to human volunteers and the simultaneous measurement of the puff

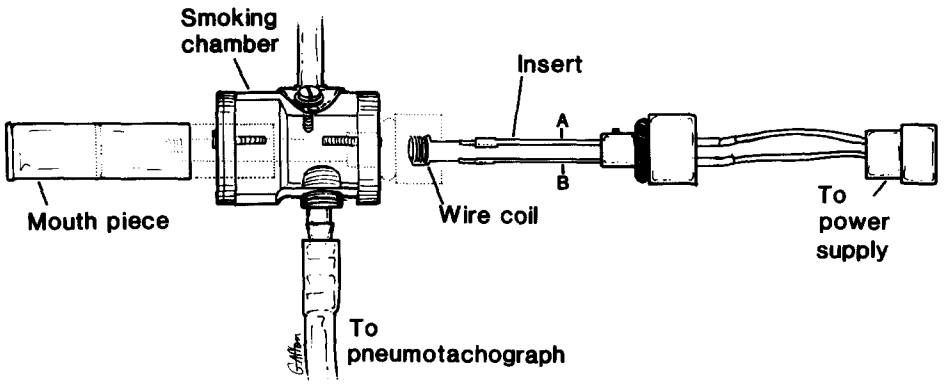

FIG. 1. This is a schematic drawing of the smoking device used to deliver cocaine-base to human volunteers.

and inhalation topography during smoking is discussed in three parts: 1) the preparation of the cocaine-base, 2) a description of the apparatus used for smoking, and 3) the administration of the proper dose of cocaine-base to the apparatus.

Cocaine Preparation

The following method was used (IND No. 29725) for the preparation and administration of cocaine-base to human volunteers. The cocaine was supplied by the Sigma Chemical Co., St. Louis, MO. Radiolabeled cocaine used for testing the apparatus was obtained from the National Institute on Drug Abuse (Research Triangle Institute, Research Triangle Park, NC). The following procedure was employed to liberate the cocaine-base from the hydrochloride salt.

Cocaine HCl (1 g) was combined with 30 ml of cold aqueous sodium carbonate solution (10% wt./vol.) in a mixing vessel. These ingredients were thoroughly mixed using a small stainless steel spatula. The pH of the mixture was measured using a standard pH meter. If the pH of the mixture was greater than 7.0, the mixing process was terminated. If the pH of the mixture tested in the acidic region (pH <7.0), the volume of the aqueous sodium carbonate solution in the mixture was increased until, with additional mixing, the pH of the mixture was measured as basic. The mixture was transferred from the mixing vessel to a vacuum-funnel filtering system. Finely textured filter paper was used for filtering. The mixture was washed several times using approximately 100 ml of cold deionized water. The filter paper with the collected cocaine-base was removed from the funnel, placed on a small watch glass and allowed to air dry for at least 24 hours. The theoretical yield is 88 percent. However, due to the loss of a small amount of cocaine-base that remains in the filter paper, a partial yield of 85 percent was obtained.

If commercially prepared cocaine-base was used rather than cocaine hydrochloride, one gram of cocaine is washed with cold water in the vacuum-funnel filtering system and then allowed to air dry on a watch glass.

Equipment

Smoking apparatus. The apparatus used for delivery of one puff of cocaine-base is shown in Fig. 1. It consists of a smoking chamber which has an insert on one end to which the cocaine is applied (the smoking insert), a replaceable glass mouthpiece used for puffing on the opposite end, and an air-flow opening on the bottom of the smoking chamber into which a brass hose barb is inserted. Plastic tubing (18 inches × ⅜ o.d.) connects the smoking chamber in series with a pneumotachographic device (Fleisch Model 00-7317; Dynasciences Incorporated; Blue Bell, PA) which is a differential pressure transducer sensitive to changes in air-flow through the smoking chamber. The output from the pneumotachograph is received and conditioned by a polygraphic instrument (Model R-511A; Beckman Scientific Products; Chicago, IL) which outputs its signal to an IBM microcomputer (Model PC-AT; Armonk, NY) via a 12-bit analog/digital converter (Labmaster series; Tecmar Computer Products; Chicago, IL) in the computer. This allows for continuous computer monitoring of air-flow through the smoking chamber. When a change in air-flow (consistent with puffing) is detected, the computer activates the power supply and heats the insert coil within one-half second after activation allowing the cocaine-base to be volatilized and inhaled under continuous air-flow conditions. This insures that the cocaine will be entrained by the air stream and delivered to the subject rather than deposited on the inside of the glass tube. Except for one modification, the calibration for puff volume and duration are similar to those performed using this system of measurement in past experiments with tobacco (6). This system was modified by changing the calibration volume range from 20, 40, 60 and 80 ml to 50, 500, 1000, 1500 and 2000 ml. A 2000 ml airtight syringe was used to achieve the 500 to 2000 ml calibration volumes.

Smoking insert. The purpose of the smoking insert is to allow for the deposition of crystallized cocaine-base onto the surface of a wire which can be heated so that the cocaine-base is volatilized for inhalation in proximity to the smoker's mouth. The wire coil does not become so hot that it pyrolizes the cocaine-base and yields inactive pyrolysis products (temperature less than 200 degrees centigrade).

The smoking insert is a machined plastic plug (see Fig. 1) which has two pieces of brass tubing (1/16 inch o.d. × 2¾ inches in length) running parallel through its base. At the widest end of the base, the brass tubes are flush with the plastic surface. At this end of the smoking insert, wires are inserted into each of the brass tubes (legs A and B) which lead to the power supply and are soldered into place. At the other end, a 5-inch 24-gauge nichrome wire coil is inserted and held in place using a Waldom "B" crimp. Since these metals cannot be soldered, this crimp is used so the brass tubes remain straight and make a suitable electrical connection. The insert coil is shaped by making a bend ¾ of an inch from one end of the wire (leg A). Next, the wire is tightly wrapped from that point backwards around a 3/16 inch o.d. metal rod so that there are seven turns in the coil. This leaves approximately one inch of straight wire (leg B) to be bent down and to parallel leg A. These are inserted approximately one-half inch into the respective legs A

and B of the brass tubing furthest away from the base and crimped. Longer wires with more loops (and surface area) may be employed for larger doses of smoked cocaine-base. A coil of approximately 0.5 cm is adequate for a dose of 20 mg; 1 cm was used for 40 mg.

Mouthpiece. The replaceable pyrex mouthpiece was designed to approximate the natural smoking pipe (see Fig. 1). A pyrex smoking pipe was obtained from a local paraphernalia shop and served as a model for our smoking apparatus. The dimensions are ⅝ inch o.d. × 2 inches in length. The mouth piece is removed and replaced with a clean mouthpiece between puffs.

Smoking chamber. The smoking chamber is a plastic cylinder which holds the smoking insert and mouthpiece in alignment while allowing for the continuous monitoring of air-flow through the cylinder (see Fig. 1). The mouthpiece is constructed for an airtight fit within the smoking chamber. The smoking insert is held in the chamber by a pin on the insert base which mates with a notch in the back plate of the smoking chamber. A rubber seal between the insert and smoking chamber is used to provide tension and an airtight seal. Turning the insert after insertion tightly locks the insert in place. Since the chamber is airtight at its junctions, any air that passes through the smoking chamber must pass through the pneumotachograph. This enables accurate puff topography measurement.

Power supply. The power supply consists of a AC-DC transformer (Stancor RT-204) configured for low output impedance. A computer-controlled reed relay in the primary coil circuit turns the transformer on and off whenever the computer senses a change in air flow through the smoking chamber. The secondary coil circuit of the transformer is connected to the smoking insert via a miniature 3-pin connector. A neon light is provided to indicate when the subject is puffing on the pipe.

The output of the secondary coil to the smoking insert is 5.5 volts. Since the insert resistance is approximately 0.7 ohms, an output current of 7.8 amperes with a corresponding power of 43 watts is achieved. It is necessary to adjust the output power to the insert so as to achieve quick volatilization of the cocaine-base. The time and/or power used for activation of the insert coil may be varied to achieve faster volatilization. Our heating times varied from 2 to 6 seconds depending upon the dose used. The wire is heated to temperatures of less than 200 degrees centigrade so that volatilization of the base can occur for inhalation. The heating of the insert coil is accomplished in approximately one-half second.

Administration of Cocaine-Base to the Insert

This method requires that the cocaine be crystallized on the wire coil of the insert. Small amounts of cocaine solution are dripped onto the coil and allowed to dry. A solution of cocaine-base dissolved in 95% ethanol (100 mg/ml). The ethanol evaporates rapidly depositing crystalline cocaine-base on the insert coil. To facilitate evaporation, the insert coil can be heated to approximately 65 degrees centigrade using a calibrated power supply. Since the volatilization point of cocaine-base is approximately 95 degrees centigrade, no cocaine-base should be lost during this facilitated drying phase.

The solution used to coat the insert coil is made by dissolving 2.5 g of the dry cocaine-base and bringing the volume up to 25 ml with 95 percent ethanol yielding a solution with a concentration of 100 mg of cocaine-base per ml of ethanol. This solution is stored in a 25 ml glass volumetric flask containing a rubber stopper. This allows for the solution to be withdrawn with a needle and syringe to limit the amount of evaporation which could increase the concentration of the mixture. Evaporation is further minimized by using a 25-gauge needle for repeated withdrawals of solution and by frequently replacing the stopper with a new one.

The initial dosing procedure called for delivery of 5 mg of cocaine-base to the insert coil for later smoking. A disposable one ml plastic tuberculin syringe was filled with 0.05 ml of cocaine-base solution; hence, 5 mg of cocaine was contained in the syringe (0.05 ml × 100 mg/ml = 5 mg). The needle of the syringe is then placed in proximity to the coil without touching it. The solution is dripped slowly from the syringe over the course of approximately 3 min. The insert coil is allowed to dry at room temperature for 24 hours. A rack that holds up to 10 inserts in a row is used for loading the coils. The insert is weighed before and 24 hours after delivery of the cocaine-base to validate the accuracy of application. This entire procedure for delivery and checking has been repeatedly tested for reliability.

ACCURACY OF THE COCAINE-BASE APPLICATION METHOD

Rationale

This experiment determined the accuracy of the method for delivery of cocaine-base to the insert coil, and measured the amount of cocaine remaining on the coil after heating. This was accomplished by using a known amount of tritiated cocaine-base and scintillation counting techniques. The experimental measurements were made in three phases to examine: 1) the amount of cocaine-base delivered to the insert using a single cocaine application, 2) the amount of cocaine delivered to the insert using multiple applications, and 3) the amount of cocaine-base left on the coil after heating.

Procedure

One hundred mg of tritiated cocaine-base was combined with 1.9 grams of nonradioactive cocaine-base prepared using the above method for transforming cocaine HCl to cocaine-base. This was dissolved in 95 percent ethanol and a final volume of 20 ml was obtained. The final molar concentration of 100 mg of cocaine-base per 1 ml of solution was achieved. Hence, a 0.05 ml delivery of cocaine-base solution yielded 5 mg of cocaine-base on the insert coil.

This experiment was performed in three phases. In the first phase, 0.05 ml and 0.10 ml of cocaine-base solution (5 mg and 10 mg, respectively) were delivered from a syringe to 20 ml glass scintillation counting vials. To this, 0.95 ml and 0.90 ml, respectively, of ethanol were added along with 9 ml of Aquasol (Beckman Products) scintillation counting fluid. The vials were tightly capped and labeled "A-5" or "A-10." Eight samples for each condition were made and set aside for later scintillation counting.

In the second phase, eight replicates of 0.05 ml (5 mg) and 0.10 ml (10 mg) of cocaine-base solution were delivered to insert coils. Then, the coils were allowed to dry for 24 hours. The 5 mg was administered in one application, while the 10 mg was administered in two 5 mg applications. At the end of the drying period, the insert coil was dipped into a scintillation counting vial containing 1 ml of 95 percent ethanol to remove the cocaine-base from the insert coil. Subsequently, 9 ml of scintillation counting fluid was added, the vials were tightly capped and labeled "B-5" or "B-10."

In the third phase, eight replicates of 5 mg and 10 mg of cocaine-base were delivered to the insert coils in the same manner as phase 2. At the end of the drying period, the insert coil was heated by the above method with manual controls to volatilize the cocaine-base from the coil. This was performed in a ventilated hood so that the smoke was drawn away from the coils. Finally, the insert coil was dipped into a scintillation counting vial containing 1 ml of 95 percent ethanol to remove any remaining cocaine-base from the insert wire. Scintillation counting fluid (9

TABLE 1

RELATIVE PROPORTION OF TRITIATED COCAINE-BASE DELIVERED TO THE VIALS FOR SCINTILLATION COUNTING

	A Mean (SE)	B Mean (SE)	C Mean (SE)
5 mg sequence	100.0 (3.5)	96.8 (1.2)	0.03 (0.01)
10 mg sequence	100.0 (1.3)	91.0* (1.2)	0.04 (0.01)

*The amount in vial B for the 10 mg sequence was significantly different from vial A ($t = -5.18$, $p<0.001$).

ml) was then added, the vial was tightly capped and labeled "C-5" or "C-10."

All sample vials contained the same volume of fluid. The number of scintillations were counted using a scintillation counter (Model LS 3801; Beckman Scientific Instruments; Chicago, IL). All samples were randomly positioned in the scintillation counter and each was counted for 1 min.

RESULTS

The results of this experiment are shown in Table 1. For the 5 mg sequence, no significant difference was observed between the amount of tritiated cocaine-base delivered directly to the vial (A) and that delivered to the smoking insert wire and then into the vial (B). The amount (mean ± SEM) of tritiated cocaine-base in the vials was (A) 100 percent (± 3.5) and (B) 96.8 percent (mean ± 1.2), respectively. The amount of tritiated cocaine-base in vial C (this represents the amount remaining on the insert coil after heating) was 0.03 percent (± 0.01).

For the 10 mg sequence, the amount of cocaine-base in the vials was (A) 100 percent (± 1.3) and (B) 91.0 percent (± 1.2), respectively. The amount of tritiated cocaine-base in vial C after heating was 0.04 percent (± 0.01). A statistically significant difference was observed ($t = -5.18$, $p<0.001$) between the amount of cocaine-base delivered directly to the vial (A) and that delivered to the smoking insert coil and then into the vial (B).

The data demonstrate that the single application technique allows for an accurate estimation of the amount of cocaine-base delivered to the insert coils. Also, multiple applications of 5 mg of cocaine-base appear to have an additive error effect which decreases the dose of cocaine-base delivered to the insert coil. However, until this is directly compared to a 10 mg application, the magnitude of the error effect cannot be determined. The results also show that virtually no cocaine-base was left on the wire after heating in either the 5 mg or 10 mg condition.

PART II: DOSE-RELATED EFFECTS OF SMOKED COCAINE-BASE

The purpose of this experiment was to determine: 1) the within subject reliability of peak blood cocaine levels when similar doses of cocaine are smoked on different occasions and 2) the dose-related effect of smoked-cocaine on behavioral (inhalation and puff volume), biochemical, physiological and subjective measures.

METHOD

Subjects

Subjects (N = 5) ages 19–30 were recruited for participation in the study from the Minneapolis-St. Paul metropolitan area by word of mouth. Interested persons were requested to contact the investigators by telephone during specified times. When these individuals called, they were screened for possible inclusion in the research project. The initial screening questionnaire included questions on demographic characteristics, health, cocaine and other drug use, and a brief mental health history. If the potential subject met the initial screening procedures, he was asked his name and invited to the Smoking Research Laboratory at the University of Minnesota for more extensive screening. During this screening, subjects were given detailed information on the research to be conducted. Informed consent was obtained from all the subjects prior to their participation in the study. They were then thoroughly interviewed for drug use and psychiatric history and given a complete physical examination, ECG, pulmonary function test, chest x-ray, urine analysis and a complete serology screen.

Subjects were included in the study if they met the following criteria: 1) males between the ages of 18 and 30; 2) history of cocaine use on the average of twice weekly over a six-month period (including the use of "crack" for at least once a month during the prior six months); 3) no history of suicidal attempt, major depressive disorder, bipolar disorder, schizophrenia, and generalized anxiety disorder; 4) no history of major medical illnesses; 5) current state of good health; 6) no pseudocholinesterase deficiency and nonreactive for HIV; and 7) not under the supervision of the legal system. Subjects were paid for participation.

Procedure

Subjects were run separately and asked to come into the laboratory between 9:00–9:30 a.m. They were required not to have used any drugs during the previous 24 hours. A urine drug analysis was performed and subjects were told that payment for the experiment was contingent on clean urines. (We are aware that some drugs will not have been metabolized within the 24-hour period.) Subjects were again reminded of the experimental procedures and shown the testing equipment. They were served a light breakfast at 10:00–10:30 a.m. Testing for baseline measures began at approximately 12:00 p.m. This time lag was instituted to insure that if the subjects had used cocaine before coming into the lab sufficient time had passed so that no cocaine was detected in their blood before the experimental administration of the cocaine. Between 9:00 a.m. and 11:30 a.m., subjects were free to read a newspaper, magazine or book, view a video film, or watch television. If subjects needed to use the restroom facilities, they were accompanied to insure that they would not use any cocaine at this time. At 11:30 a.m., subjects were connected to the heart rate monitor, skin temperature probe, and the inductive plethysmography (Respitrace System) used for inhalation volume and duration measurement (6). A 20-gauge intravenous catheter in combination with a heparin lock was put in the dorsum of the right arm at 12:00 p.m., and the 100 mm analogue scales which tap various subjective states was administered (3). They were asked to sit quietly for the next 10 minutes during which time baseline readings of heart rate, blood pressure, pupil size and skin temperature were obtained. A physician was present at this time in order to monitor the subjects' physical state during the administration of cocaine. At approximately 12:30 p.m., a 3 ml sample of blood was obtained using a standard 5 ml lavender-top vacutube that contained 0.35 ml of saturated sodium fluoride solution. The subjects were then asked to smoke a 10 mg dose of cocaine through the glass pipe. Blood samples were obtained at 1, 3, 5, 10, 15, 30 and 60 minutes after smoking cocaine. The 100 mm analogue scales were admin-

istered and blood pressure and pupil size were recorded at these times. Subjects had their ECG (lead II) and skin temperature continuously monitored throughout this period. Subjects remained in the laboratory until their heart rate and blood pressure returned to baseline values, and they were then escorted home. The subjects returned to the laboratory to be given subsequent doses of 20 and 40 mg. No adverse reactions were observed for these doses during any of these sessions. Repeated doses were given of 10, 20 or 40 mg in random order to some of the subjects. The subjects were blind to the doses of cocaine that were given as were the experimenters that were directly involved in taking measurements.

Whole blood cocaine analysis. Whole blood cocaine levels were obtained and analyzed using a standard protocol. Three ml of whole blood was drawn through a venous catheter into the lavender top (EDTA) venipuncture tube which had been prepared by adding 0.35 ml of saturated sodium fluoride solution. The whole blood was frozen at −70°C.

The blood analysis was performed by Medtox Laboratories, New Brighton, MN, a National Institute of Drug Abuse certified laboratory. The method of analysis utilized by Medtox involves gas chromatography with a nitrogen phosphorus detector using a capillary column (11). The sensitivity of the assay is 1 ng/ml. The reliability of the assay is 4.2 percent.

Heart rate. Heart rate was continuously monitored using an ECG coupler on the Beckman polygraph (Model R511A; Beckman Instruments; Chicago, IL) set at 25 mm/sec. Heart rate (beats/minutes) was determined by measuring a sequence of 10 RR-intervals using a standard ECG ruler after each measurement time. The average of these 10 measurements was then calculated as the heart rate.

Blood pressure. Blood pressure was measured manually using a hand-held sphygmomanometer.

Skin temperature. Skin temperature was continuously measured by affixing a probe (Yellow Springs Instrument Co., Model 408) to the dorsum of the nondominant hand with tape. The probe was calibrated to measure a range of temperatures from 29–37 degrees centrigrade. The signal from the probe was conditioned and recorded via a Beckman polygraphic instrument. Measurements were made at the appropriate intervals by measuring the amount of deflection of the pen on the recording chart. Calibrations were made before and after each session to ensure the accuracy of the measurements.

Pupil diameter. Pupil diameter was measured by direct confrontation using a hand-held paper scale used to estimate pupil sizes.

Self-report 100 mm Visual Analogue Scales (VAS). This questionnaire which was compiled from scales used in other studies (3) consisted of 10 lines, each 100 mm long. The lines are labeled "pleasantness," "high," "energy," "hungry," "sedated," "anxious," "stimulated," and "fatigue." Subjects indicated how they felt by placing a mark along each line labeled on one end as "not at all" and at the right side, "extremely."

Data Analysis

To determine the reliability of the cocaine dose administered to the subjects, Pearson correlation coefficients were computed for the peak blood cocaine concentrations within subjects for a given dose administered at two different sessions. To determine the effects of various doses on smoking topography, a repeated measures one-way analysis of variance was conducted for inhalation volume and duration. To determine the effects of various cocaine doses on blood cocaine concentrations and physiological and subjective functioning, a repeated measures two-way analyses of variance (Dose × Time) was undertaken. Missing values were replaced by the mean value of the measures of the remaining cases. The times examined for the measures were baseline and 3, 5, 10, 15, 30 and 60 minutes after smoking cocaine base. Main dose effects are reported to demonstrate the significant dose-related responses to cocaine. Interaction effects are reported to demonstrate significant Dose × Time effects. When a significant dose or interaction effect was obtained in any of the analyses, post hoc contrasts (*t*-tests) were computed. Statistical significance was defined as *p*-value less than or equal to 0.05.

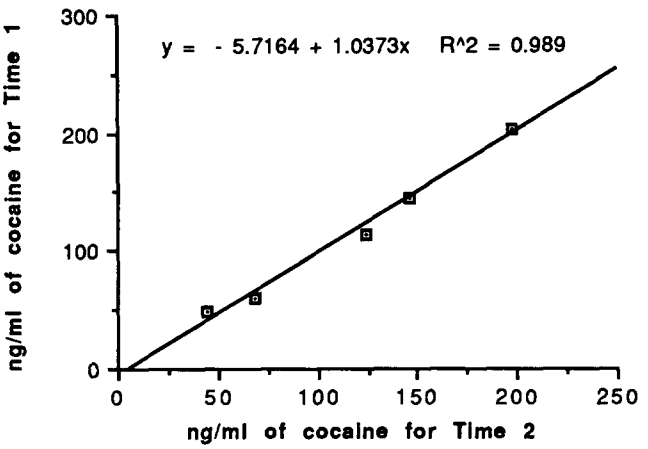

FIG. 2. The within subject correlation between peak whole blood cocaine concentrations from similar doses of cocaine-base given on two separate occasions (Time 1 and Time 2).

RESULTS

The subjects were 5 healthy males with experience with smoking cocaine-base. The mean ± S.D. age was 26.4 ± 3.1 (range = 21–28). The mean duration of cocaine use was 7.3 ± 4.8 years (range = 6 months–13 years); frequency of use was 3.4 ± 0.6 times/week (range 2.5–4 ×/week); and amount of cocaine/episode of use was 1000 mg ± 590 (range = 500–2000 mg). All subjects also used alcohol and/or marijuana on a regular basis.

Reliability of Doses

There were two subjects that received repeated doses of 20 mg cocaine base; one subject who received repeated doses of 10 mg; and one subject who received repeated doses of 10 mg and 40 mg. Subjects received these repeated doses at intervals from 1 to 314 days apart (mean = 95.2 days; S.D. = 131.0 days). The wide variability of intervening time periods was primarily due to extenuating circumstances (e.g., moves, nondrug related incarcerations). (Subjects were given repeated medical history and a brief physical exam if the testing times were greater than 3 months apart to ensure that they continued to meet criteria for inclusion into the study.) Figure 2 presents a within subjects correlation between the peak blood cocaine concentrations for similar doses obtained at two separate times. The correlation coefficient was r = .99 ($p<0.001$) demonstrating high reliability of blood cocaine concentrations within subjects. To further determine the precision of the dose administration, the inserts which held the cocaine were weighed after the cocaine was smoked. No cocaine remained on the inserts.

Dose-Related Effects of Smoked Cocaine-Base

Inhalation volume and duration. For inhalation volume, the

mean values are 1910 ml (±318 ml) for the 10 mg dose, 2466 ml (±347 ml) for the 20 mg dose, and 2451 ml (±538 ml) for the 40 mg dose. A one-way ANOVA across doses showed no statistically significant difference between these values. The mean values for inhalation duration are 10.5 seconds (±1.2) for the 10 mg dose, 11.6 seconds (±1.4) for the 20 mg dose, and 14.0 seconds (±0.9) for the 40 mg dose. No significant difference was observed across doses.

Cocaine blood levels, physiological and subjective effects. All subjects received all 3 doses. Although some subjects received repeated doses, only the first administration of each dose was selected for analysis. Three subjects received two different doses on the same day at intervals of at least 3 hours. All other subjects received subsequent doses at intervals from 1 day to 300 days apart (mean = 30.7 days; S.D. = 75.0 days). Figure 3 presents the data examining the relationship between dose and blood cocaine concentrations and significant physiological effects. There were significant effects of Dose for whole blood cocaine concentrations, $F(2,3) = 42.0$, $p<0.01$, for heart rate, $F(2,3) = 24.3$, $p = 0.01$, for systolic blood pressure, $F(2,3) = 14.4$, $p = 0.03$, and a near significant effect for diastolic blood pressure, $F(2,3) = 6.7$, $p = 0.08$. Post hoc analyses showed that significant differences existed between 10 versus 40 mg ($p<0.05$) for all these measures, and 20 versus 40 mg for all measures except heart rate ($p<0.05$). There were no significant differences for 10 versus 20 mg ($p>0.05$). There were no significant Dose × Time effects.

There were no significant effects for pupil size, skin temperature or subjective measures, although there was a near significant dose-related effect for "high," $F(2,3) = 6.64$, $p<0.08$.

DISCUSSION

The purpose of the first part of this paper was to report the method developed in our laboratory to deliver precise doses of smoked cocaine-base to human volunteers. Although the dose of cocaine delivered was small in comparison to the average amount used by our subjects per occasion of use, this method allows for precise dosing parameters on a per puff basis. Total cocaine-base intake can be modified by manipulating the number of puffs given.

The first experiment that was reported was designed to demonstrate that the single-application drip method of loading the insert coil with cocaine-base in ethanol was a reliable technique. It was shown that the amount of cocaine-base delivered to the insert coil does not differ significantly from the amount drawn into the syringe. Using multiple applications, however, does appear to significantly increase the error of the loading procedure. Consequently, the single application method allows one to load and handle the insert, optimally, only once in order to ready the device for smoking. Weighing the insert before and after loading, and after heating provides additional assurance that the appropriate dose will be given. Also, this experiment demonstrated that virtually no cocaine-base was left on the insert after heating.

The second part of this paper addressed whether this device produced reliable or reproducible results and dose-related effects. The results from these experiments showed clear evidence that the method that was developed to administer smoked cocaine-base is reliable. The extremely high correlation of the peak whole blood cocaine concentrations that was obtained from the same dose within subjects across sessions is even more striking given the fact that the doses were repeated from one day to several months apart.

The results also showed that during an ad lib puffing procedure, inhalation volume and duration did not vary as a function of dose. For future experiments, it appears that controlling the inhalation parameters would not be necessary to eliminate possible dose-related confounds resulting from topographical differences in smoking behavior for the administration of small doses of cocaine-base.

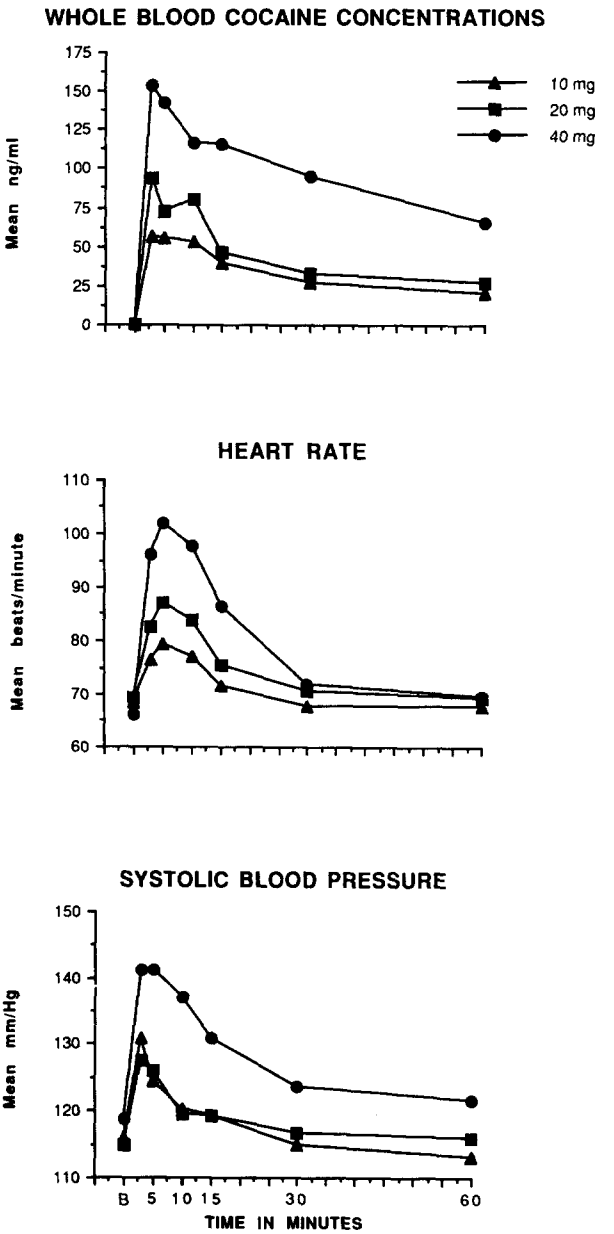

FIG. 3. Whole blood-cocaine concentrations and significant physiological functioning by cocaine dose (10, 20, 40 mg).

There were clear dose-related effects for blood cocaine concentrations and some of the physiological measures. These effects were primarily between 10 versus 40 mg and 20 versus 40 mg. These results indicate that future studies should use more discrepant doses. Unlike other studies, these results did not demonstrate any of the dose-related subjective effects previously found (2–4, 10). Perhaps this lack of effect was due to the extensive time periods that separated the testing.

There are several methodological problems associated with the human study. First, because this study was not undertaken while the subjects were on a controlled hospital unit, there was no control over potential confounding factors, such as drug use and other intervening variables. Furthermore, there was no consistency with regard to the time between doses. In spite of these potentially confounding factors, reliable and dose-related results were ob-

tained. Second, some of the subjects received another dose only 3 hr apart. Although the blood cocaine levels had returned to zero prior to the second dose, this blood level may not have reflected active site concentrations due to distribution delay and/or the effects of cocaine metabolites. Third, there was a procedural problem which may have broken the blind for the subjects. Earlier in the study, a longer heating time for higher doses was used to insure that all the cocaine would be inhaled. However, knowledge of dose would not have affected the dose-related plasma cocaine concentrations that were obtained. Fourth, ideally it would have been desirable to use a placebo to establish meaningful baseline measurements. However, currently there is no safe placebo that can be employed for smoked cocaine-base. Finally, the number of subjects in this study was small which may account for the large variability on some of the measures.

In summary, a precise method of administering smoked cocaine has been developed, and dose-related effects on the blood cocaine concentrations and physiological effects have been found. However, more studies need to be done which examine the bioavailability of this technique to deliver cocaine. As a result of developing this technology of smoked cocaine administration, future studies can be aimed at examining the effects of different pharmacological and behavioral interventions on this behavior.

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