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Intranasal cocaine in humans: acute tolerance, cardiovascular and subjective effects

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Abstract

Although recent research has focused on "crack" cocaine, the majority of the cocaine users in the United States insufflate ("snort") cocaine rather than smoke it. Furthermore, the intranasal route of administration is often the first way that many cocaine-dependent individuals used cocaine. Numerous studies have reported on the effects of repeated doses of smoked or intravenous cocaine, the relationship between cocaine plasma level and cocaine's effects, and the development of acute tolerance to smoked or intravenous cocaine. Significantly less information is available about similar effects of intranasal cocaine. The purpose of this study was to determine the dose-dependent effects of repeated intranasal cocaine in humans. Ten experienced male cocaine users were admitted to the hospital on two separate occasions for four days each, with a minimal two-week interval between admissions. During each admission, an intranasal cocaine (0.06, 0.34, 0.69, and 1.37 mg/kg) dose–response curve was determined during four laboratory sessions: Two administrations of the same cocaine dose occurred each session at 40-min intervals. Intranasal cocaine produced dose-related increases in ratings of "positive" drug effects, heart rate, and blood pressure. Plasma cocaine levels peaked following the second cocaine insufflation of each session, while metabolite levels increased during each session. Although the plasma cocaine level approximately doubled following the second cocaine administration, the ratings of positive drug effects, heart rate, and blood pressure did not increase after the second cocaine administration. These data demonstrate that, as observed with smoked and intravenous cocaine, acute within-session tolerance develops during repeated intranasal cocaine administration.

Keywords: Cocaine; Plasma levels; Subjective effects; Cardiovascular effects; BZE; EME; Tolerance; Humans

1. Introduction

Cocaine abuse remains a significant public health problem (Community Epidemiology Work Group, 2002). Although most recent laboratory studies have focused on "crack" cocaine, approximately two thirds of the 2 million current cocaine users in the United States do *not* use crack cocaine (SAMSHA, 2003). In addition, the most recent report of the CEWG (2002) indicated that powdered cocaine use was on the rise in Midwestern and Western states. While majority of cocaine-dependent individuals in treatment programs use cocaine via the smoked or intravenous route, many cocaine-dependent individuals have experience with intranasal cocaine (Foltin et al., 1996) and often started using cocaine via the intranasal route (Gorelick, 1992). Eighty percent of the heavy users of smoked cocaine who applied for research in our laboratory report that their first experiences with cocaine was by the intranasal route: Participants used intranasal cocaine for 4.0 ± 5.1 years (mean $\pm$ S.D.) before they first smoked cocaine. Because intranasal cocaine use may function as a gateway to the use of cocaine by other routes of administration with greater abuse potential, and because intranasal cocaine use may be common in young and neophyte users of cocaine, additional information about intranasal cocaine is relevant to understanding the life cycle of cocaine abuse.

Cocaine users typically abuse smoked and intravenous cocaine in bouts of repeated administration, or binges, which last from a few hours to several days (Gawin and Kleber, 1986). It is well established that the subjective and cardiovascular effects of single doses of smoked and intravenous cocaine dissipate more rapidly than would be

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expected, based upon its elimination half-life (Chow et al., 1985; Cone, 1995). This rapid diminution of the effects of cocaine may, in part, explain why cocaine is used in a binge pattern. Although users continue to "chase" the initial euphoric feeling, or "rush", that accompanies the first dose of the drug, they report that they are unable to achieve the initial positive mood state again within a single binge (Brower et al., 1986; Trinkoff et al., 1990). In laboratory settings, cocaine users show the greatest subjective and cardiovascular effects after the first or second smoked and intravenous cocaine dose, with subsequent doses maintaining, but not incrementing, the initial effect (e.g., Evans et al., 2002; Foltin and Haney, 2000; Hatsukami et al., 1994). These observations indicate that acute tolerance develops to the effects of cocaine. Acute tolerance, sometimes referred to as tachyphalaxis, is a decrease in the effectiveness of a drug within a single session that does not carryover to other sessions, which differs from other types of tolerance in which decreased effectiveness of a drug persists over time (Kalant et al., 1971).

In the first laboratory study on acute tolerance to cocaine, Fischman et al. (1985) demonstrated that the effects of a single intravenous dose of cocaine, when it was administered 1 h after the participants had received a single large dose (approximately 1.37 mg/kg) of intranasal cocaine, were significantly smaller compared with when they had received a tiny dose (approximately 0.06 mg/kg) of intranasal cocaine. An elegant demonstration of acute tolerance was presented by Ambre et al. (1988), who administered a single bolus dose of intravenous cocaine followed by a continuous cocaine infusion that maintained a stable cocaine venous plasma level: The subjective and cardiovascular effects of cocaine declined throughout the session (also, see Kumor et al., 1989). Both Evans et al. (1996) and Foltin and Fischman (1991) examined the response to a range of intravenous and smoked cocaine doses, given twice, within a laboratory session. The cardiovascular and behavioral effects of intravenous and smoked cocaine were significantly greater on the ascending than on the descending limb of the cocaine venous plasma concentration curve, demonstrating the development of acute tolerance (Kalant et al., 1971).

Although acute tolerance has been clearly demonstrated by comparing cocaine plasma concentration data to the cardiovascular and behavioral data for both intravenous and smoked cocaine, these relationships have not been as well studied following the administration of intranasal cocaine. Foltin et al. (1988) administered up to five intranasal 1.37 mg/kg doses of cocaine to three participants using a 45-min interdose interval: The heart rate and subjective effects plateaued after the first or second dose, indicating acute tolerance, but blood pressure continued to increase with subsequent doses. Ambre (1993), however, reanalyzed the data and concluded that acute tolerance, although incomplete, had developed to the pressor effects of cocaine. In a well-designed study, McCance-Katz et al. (1998b) administered four intranasal 1.0 mg/kg doses of cocaine to eight participants using a 30-min interdose interval. Heart rate and ratings of "high" were similar after the first and second cocaine administrations, although the cocaine plasma level approximately doubled after the second cocaine administration, i.e., acute tolerance. Interestingly, the heart rate and ratings of "high" did increase after the third or fourth cocaine administration.

The present study had two purposes: (1) extend the earlier studies on the effects of repeated administration of intranasal cocaine by providing a complete cocaine dose–response function, and (2) analyze the relationship between cocaine and metabolite venous plasma levels and the cardiovascular and subjective effects of cocaine. Because the peak effects of a single dose of intranasal cocaine occur 20 to 30 min after the dose is taken (Farre et al., 1993; Kouri et al., 2001; Oliveto et al., 1995), participants in the present study insufflated the same dose of cocaine twice, with a 40-min interval between doses.

2. Methods

2.1. Participants

Ten male research volunteers (six African-American, three Hispanic, one Caucasian), 25 to 44 years of age (mean 35.8 = years) and with an average of 12.1 ± 0.04 (mean $\pm$ S.D.) years of education, participated in this study. Seven of the participants smoked an average of 16 ± 3 tobacco cigarettes per day. The participants reported using cocaine for the past 17.9 ± 2.5 years, using cocaine 4.2 ± 0.4 days per week, and spending US\$260 $\pm$ 53 per week on crack cocaine (cocaine base cost about US\$30/g in the New York City area when these data were collected). One additional participant was enrolled in the protocol but left after the first inpatient phase for personal reasons. All the participants passed the medical evaluation prior to the study, and no one was receiving psychiatric treatment. Each signed a consent form, approved by the Institutional Review Boards of The College of Physicians and Surgeons of Columbia University and The New York State Psychiatric Institute, which described the study, outlined the possible risks, and indicated that cocaine would be administered.

2.2. Procedure

The participants were admitted to the Irving Center for Clinical Research in the Presbyterian Hospital for 4 to 7 days on two occasions, separated by approximately 2–3 weeks. Their private hospital rooms were equipped with a television, radio, and VCR; videotaped movies were provided to them. The rooms contained an air purification system, and the participants were free to smoke tobacco cigarettes in their rooms. Visitors were prohibited. The day following admission, volunteers participated in laboratory sessions twice/day for 2 days: The first session each day

began at 0900 h, and the second session each day began at 1500 h. The participants were discharged the morning following the second day of sessions. Because, as originally planned, a group of female cocaine users would complete the study at two menstrual cycle phases, the male participants also completed two sets of sessions. Recruitment difficulties prevented the completion of enough females for statistical comparisons to males, and their data were not included in this paper.

2.3. Experimental sessions

During the experimental sessions, the participants were seated in a reclining chair in front of a Macintosh computer and video monitor with a mouse manipulandum. An 18-gauge catheter (Quik-Cath, Travenol Laboratories, Deerfield, IL) was inserted in a subcutaneous vein on one arm: The intravenous line was available if needed. Electrocardiograms (ECGs) were monitored continuously with chest electrodes (MAC PC, Marquette Electronics, Milwaukee, WI), and heart rate (HR) and blood pressure (systolic, SP; diastolic, DP) were recorded every 2 min (Sentry II-Model 6100 automated vital signs monitor, NBS Medical, Costa Mesa, CA) beginning 20 min prior to cocaine administration. An Apple IIci computer located in an adjacent control room was used for automated data collection. The participants were monitored via a one-way mirror by a physician and research nurses located in the adjacent room, with whom they could communicate via an intercom system.

Each of the four laboratory sessions during each admission consisted of a 20-min resting baseline, followed by the insufflation of one cocaine dose (0.06, 0.34, 0.69, 1.37 mg/kg) at Time 0, and a second insufflation of the same dose at Time 40 min. Sessions continued for 110 min after the first dose was self-administered. Subjective-effects questionnaires were completed at baseline and at 4, 14, 34, 44, 54, 74, and 104 min. Because cocaine can cause behavioral and cardiovascular toxicity, the participants had the opportunity to refuse a dose at each trial, hence, that cocaine would not be given to the participant who did not want it at that time. No participant refused a dose. The dosing order and time of testing (a.m. vs. p.m.) were balanced across participants within each hospital stay and varied between the two times that each participant was in the hospital.

Cocaine hydrochloride was administered as 120 mg of white powder (cocaine and lactose), handed to the participants on a 50×50 cm mirror. The participants prepared four similar size lines of powder with a single-edged razor blade and insufflated the powder, two lines per nostril, within 60 s using a 7.5-cm straw (e.g., Foltin et al., 1988). Cocaine was not given if cardiovascular activity was above the criteria for safe drug administration (i.e., HR>130, DP>100, SP>165).

The subjective-effects questionnaire consisted of a series of 100-mm visual analog scales (VAS) anchored by *not at all* (0 mm) at one end and *extremely* (100 mm) at the other end. Eighteen of these VAS were labeled "I Feel..." "stimulated", "high", "anxious", "sedated", "depressed", "hungry", "friendly", "calm", "focused", "alert", "tired", "talkative", "self-confident", "social", "irritable", "confused", "good drug effect", and "bad drug effect". Four VAS were used to operationalize drug craving and were labeled "I want..." "cocaine", "heroin", "ethanol", and "nicotine". Three VAS were related specifically to the cocaine dose that the participant had just received and were labeled "The choice was of high quality", "The choice was potent", and "I liked the choice". A final question asked the participant "How much would you pay for the dose you just received", with a range of US$0–$25.

Venous blood was collected for the determination of cocaine and metabolite plasma levels at −20 min (before the first dose), 14 and 34 min after the first dose, and 14, 34, 64, 94, and 140 min after the second dose. Blood drawn 94 and 140 min after the second dose (session time 136, 180 min) was obtained in the participants' rooms. At each blood withdrawal, 6 cc of whole blood was placed in a glass centrifuge with a small amount of sodium fluoride. The bloods were then centrifuged, yielding 3 cc of plasma for the determination of cocaine, benzoylecgonine (BZE), and ecgonine methyl ester (EME) levels (Isenschmid et al., 1988; Cone, 1995).

2.4. Cocaine

Cocaine hydrochloride (provided by The National Institute on Drug Abuse) was weighed out by the Presbyterian Hospital Manufacturing Pharmacy to yield prepackaged doses of 0.06, 0.34, 0.69, and 1.37 mg/kg (rounded to the nearest 10 kg), with a maximal cocaine dose of 120 mg. The cocaine was combined with lactose to yield 120 mg of total powder. The 0.06-mg/kg dose, which, when insufflated, produces minimal cardiovascular and subjective effects but does produce a slight numbing of the nasal mucosa (Foltin et al., 1988; Javaid et al., 1978), served as an active placebo dose.

2.5. Data analysis

To reduce the number of dependent variables, a cluster analysis of previous cocaine data was performed. This analysis yielded five clusters of adjectives that are correlated with the changes in one item being predictive of the changes in the other items in the same cluster, but not predictive of changes in items in the other clusters (Evans et al., 2002). Each cluster is derived by taking the arithmetic average of the items in the cluster. *Bad drug effect* consists of seven items: anxious, bad drug effect, confused, depressed, irritable, sedated, and tired. *Self esteem* consists of five items: alert, focused, self-confident, social, and talkative. *Relaxed* consists of two items: calm and able to concentrate. *Good drug effect* consists of three items: good drug effect, high, and stimulated. *Cocaine rating* consists of three items: potency, quality, and liking.

Eight time points were used in the analyses of the subjective-effects measures: baseline, 4, 14, 34, 44, 54, 74, and 104 min. The corresponding time points were calculated for the cardiovascular measures by obtaining the mean of the data collected in 10-min bins beginning 2 min before each mood scale was started, e.g., −14 to −4 min, 2 to 12 min. The data for the entire study were compared using analyses of variance (ANOVA) with three within-participants factors: test (first and second hospital admission), dose (four levels), and time of measurement (eight levels). Helmhert orthogonal contrasts were accomplished following a significant dose effect: The 0.06 mg/kg dose was compared with the 0.34, 0.69, and 1.37 mg/kg doses; the 0.34 mg/kg dose was compared with the 0.69 and 1.37 mg/kg doses; and the 0.69 mg/kg dose was compared with the 1.37 mg/kg dose. Planned contrasts were used to compare the effects of the first to the second cocaine administration (34- vs. 54-min observation) for each of these measures. The planned contrasts were single degree of freedom comparisons that used the error term for the Dose × Time of Measurement interaction.

One of the second cocaine doses during one session was withheld due to elevated cardiovascular activity. Because this was the only dose out of the 160 total possible doses that was not given, the data from this session were still included in the analyses rather than excluding all of the data from this participant. Due to technical difficulties, the plasma samples were not obtained during one session for two participants. To not exclude the data from these two participants, the values from the same dosing condition during the other testing phase were used in the analysis; that is, results from the second 0.69 mg/kg session were also used for the first 0.69 mg/kg session for one participant, and results from the first 0.06 mg/kg session were also used for the second 0.06 mg/kg session for one participant. Thirteen additional plasma samples were not collected due to technical difficulties with blood drawing, such that, including the two missing sessions, 29 blood samples out of 640 were not collected, i.e., <5% plasma samples were missing. Because the pattern of the missing values was not related to cocaine dose or maintenance condition, i.e., data were missing at random (Little and Rubin, 1987), plausible estimates of the missing values were calculated using multiple imputation (Rubin and Schenker, 1991).

Cocaine plasma and metabolite levels were analyzed as described above, with the time of measurement factor using the times that blood was withdrawn (eight levels). Because of the single missing cocaine dose and the small amount of imputed blood data, the results were considered statistically significant at $P<.025$, using Huynh-Feldt adjustments to correct for possible violations of the sphericity assumption, where appropriate. Because there were no significant effects of test session (first vs. second hospital admission) and no significant differences between cocaine doses at baseline, only dose and time of measurement factors and their interaction will be described below.

3. Results

3.1. Plasma levels

As shown in Fig. 1, cocaine produced consistent increases in cocaine venous [$F(3,27)$, $P<.0001$] and BZE [$F(3,27)$, $P<.003$] plasma levels. The Helmhert comparisons indicated that the mean cocaine plasma levels were significantly increased with each larger cocaine dose

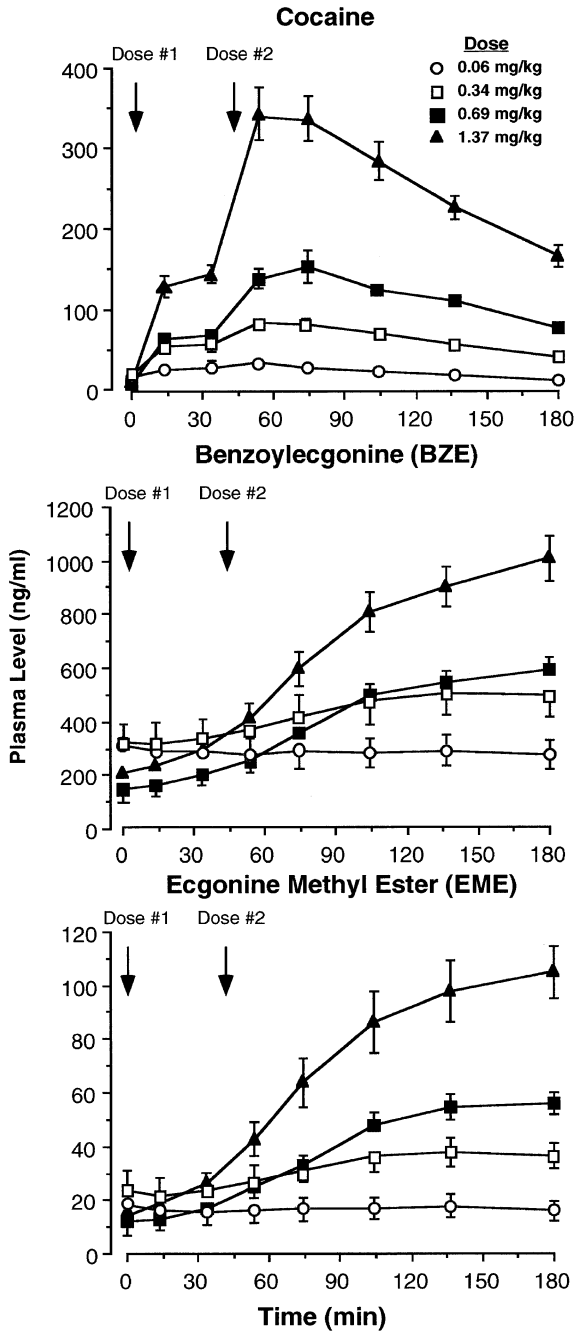

Fig. 1. Mean cocaine and metabolite venous plasma levels as a function of cocaine dose and time within session. The same dose of intranasal cocaine was administered at times 0 and 40 min, as indicated by the arrows. Error bars represent one S.E.M. Some error bars were omitted for clarity.

[$F(1,189)$, $P<.0001$, for all comparisons]. EME levels were significantly greater (1) after the three active doses, compared with the 0.06 mg/kg dose, and (2) after the 1.37 mg/kg dose, compared with the 0.69 mg/kg dose [$F(1,189)$, $P<.016$, for both comparisons]. By contrast, BZE levels did not vary across the active cocaine doses. There were significant Dose × Time Within Session interactions for all the measures [$F(21,189)$, $P<.0001$]. Cocaine plasma level significantly increased after the second 0.69 and 1.37 mg/kg dose [$F(1,189)$, $P<.0009$, for both doses], while BZE and EME plasma levels significantly increased only after the second 1.37 mg/kg dose [$F(1,189)$, $P<.01$, for both metabolites]. Peak cocaine plasma levels were observed at 54 min (14 min after the second dose), while BZE and EME levels increased throughout the session.

3.2. Cardiovascular effects of cocaine

As shown in the left panels of Fig. 2, cocaine produced dose-dependent increases in HR, DP, and SP [$F(3,27)$, $P<.0001$, for all measures]. The Helmhert comparisons indicated that the mean HR, DP, and SP were significantly

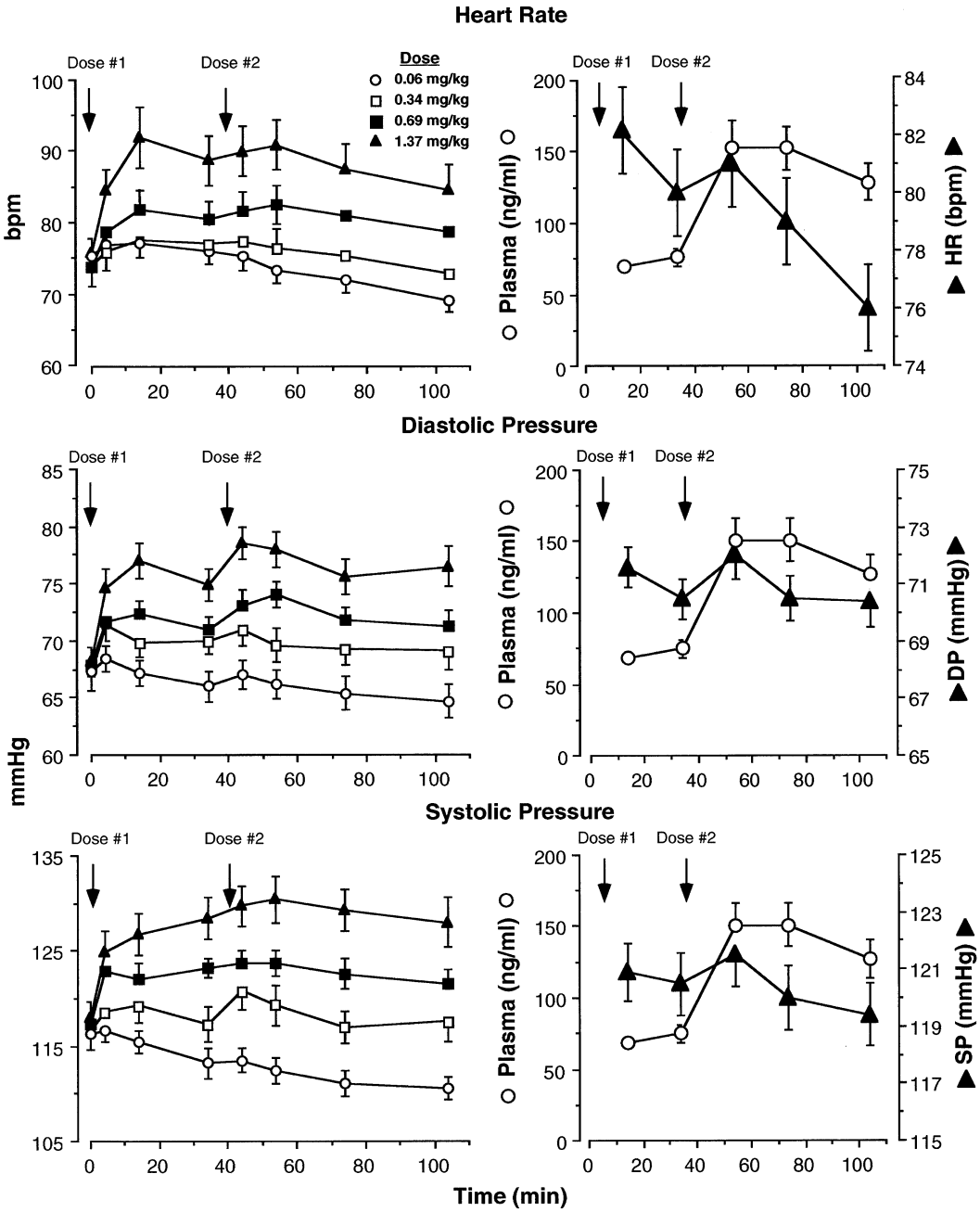

Fig. 2. Left panels: mean HR, DP, and SP as a function of cocaine dose and time within session. Right panels: mean cocaine venous plasma levels, collapsed across cocaine dose, and mean cardiovascular activity, collapsed across dose, as a function of time within session. See Fig. 1 for details.

increased with each larger cocaine dose [$F(1,189)$, $P < .009$, for all comparisons]. There were significant Dose × Time Within Session interactions for all measures [$F(21,189)$, $P < .0001$]. Although cardiovascular activity increased after the first administration of each of the three active doses, the second administration of a cocaine dose, for the most part, did not increase cardiovascular activity above levels seen following the first cocaine administration: Only DP significantly increased only after the second 1.37 mg/kg dose [$F(1,189)$, $P < .003$].

The right panels of Fig. 2 portray the relationship between the mean cocaine plasma level, averaged across all cocaine doses, and the mean cardiovascular response to cocaine, also averaged across all cocaine doses. The mean cocaine plasma level after the second cocaine administration was about twice of that observed after the first cocaine administration. Clearly, the mean HR, DP, and SP did not increase after the second cocaine administration. The mean HR decreased across the session, while DP and SP remained stable throughout the session.

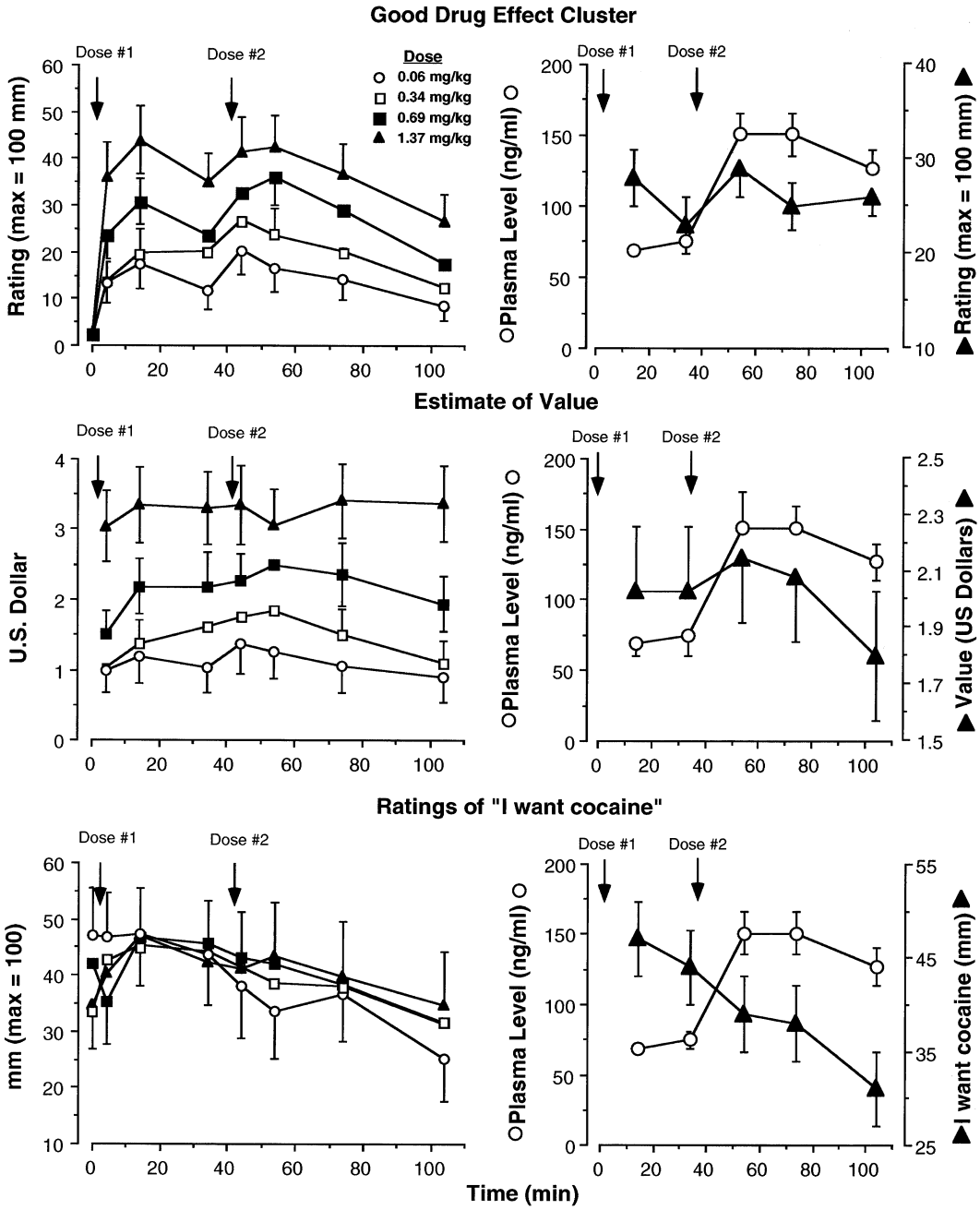

Fig. 3. Left panels. Mean scores on the good drug effect cluster, estimates of cocaine value, and ratings of "I want cocaine" as a function of cocaine dose and time within session. Right panels. Mean cocaine venous plasma levels, collapsed across cocaine dose, and mean subjective-effects measures, collapsed across dose, as a function of time within session. See Fig. 1 for details.

3.3. Subjective effects of cocaine

Cocaine produced dose-dependent increases in the scores on the good drug effect [$F(3,27)$, $P < .0002$; upper left panel of Fig. 3] and the cocaine rating clusters [$F(3,27)$, $P < .0003$; data not shown], without affecting the scores on the bad drug effect, self-esteem, or relaxed clusters. Because the results for the good drug effect and the cocaine rating clusters were parallel, only the data obtained for the good drug effect cluster will be described in detail. The Helmhert comparisons indicated that the mean scores on the good drug effect cluster were significantly increased with each larger cocaine dose [$F(1,189)$, $P < .025$, for all comparisons]. There was no significant Dose × Time Within Session interaction, and the second administration of a cocaine dose failed to increase the scores on the good drug effect cluster. Thus, although cocaine plasma levels increased after the second 0.69 and 1.37 mg/kg dose, as shown in the right panels, the subjective effects of cocaine did not increase in accordance with increasing cocaine plasma levels.

As shown in the left middle panel of Fig. 3, cocaine produced dose-dependent increases in the estimates of the value of the cocaine dose [$F(3,27)$, $P < .0001$]. The Helmhert comparisons indicated that the mean estimated value was significantly increased with each larger cocaine dose [$F(1,189)$, $P < .013$, for all comparisons]. Although there was a significant Dose × Time Within Session interaction [$F(21,189)$, $P < .001$], as observed with the good drug effect cluster, the second administration of a cocaine dose failed to increase the estimates of value above those scores observed following the first administration of that dose. As shown in the left bottom panel of Fig. 3, cocaine did not affect the ratings of "I want cocaine". There was a significant effect of time within session, however, such that the ratings of "I want cocaine" decreased at the end of the session, regardless of cocaine dose [$F(7,63)$, $P < .016$].

The right panels of Fig. 3 portray the relationship between the mean cocaine plasma level, averaged across all cocaine doses, and the mean behavioral response to cocaine, also averaged across all cocaine doses. The subjective response to cocaine did not increase after the second cocaine administration despite the increasing cocaine plasma levels. The mean scores on the good drug effect cluster and the estimates of dose value remained stable throughout the session, while the mean ratings of "I want cocaine" decreased across the session.

4. Discussion

The results of the present study are the first to demonstrate the development of acute tolerance to a range of intranasal cocaine doses. The first administration of intranasal cocaine produced dose-dependent increases in subjective and cardiovascular measures of cocaine's effects, but the second administration of intranasal cocaine, 40 min later, which significantly increased cocaine and metabolite venous plasma levels, did not increase the effects of cocaine. Plasma cocaine levels after the first 1.37 mg/kg dose were similar with those reported in the same time frame following the administration of 1.00 mg/kg doses of intranasal cocaine (Farre et al., 1993; McCance-Katz et al., 1998a,b; but see Farre et al., 1997 for higher levels). Thus, the observed plasma levels were in the expected range and time frame observed following a single cocaine administration (Wilkinson et al., 1980).

The effects of the first cocaine administration replicate those reported for intranasal cocaine in many other studies (e.g., Farren et al., 2000; Lukas et al., 2001). Surprisingly, the maximal increase in the positive drug effect cluster (40 mm), as well as the estimates of value (US$3) of the 1.37 mg/kg dose, was similar with those observed after the participants smoked 25 mg of cocaine under similar circumstances (Foltin et al., 2003). Furthermore, the maximal cardiovascular effects (15 bpm, 10–20 mm Hg increase) of the 1.37 mg/kg dose were similar with those observed after the participants smoked 50 mg of cocaine (the largest cocaine dose used in the laboratory) under similar circumstances (Foltin et al., 2003). Thus, intranasal cocaine produced significant behavioral effects in the range observed after intermediate to large doses of smoked and intravenous cocaine (Hatsukami et al., 1994; Walsh et al., 1996). However, as is well established, the onset of the peak effect was slower for intranasal cocaine (Johanson and Fischman, 1989).

Although behaviorally significant, comparing across studies suggests that heavy users of cocaine have a smaller response to intranasal cocaine (Kosten et al., 1996; McCance-Katz et al., 1998a; Oliveto et al., 1995; Winther et al., 2000) than light or occasional cocaine users do (Higgins et al., 1990; Kouri et al., 2001; Lukas et al.,1996, 2001; but see Farre et al., 1993). Clearly, to better understand the possible differences between light and heavy cocaine users in their response to intranasal cocaine, it will be necessary to test groups of light and heavy cocaine users in the same laboratory under the same conditions.

The design of this study was based on that used by Foltin and Fischman (1991) and Evans et al. (1996), which examined tolerance development to two administrations of the same dose of smoked and intravenous cocaine. In those studies, the second cocaine administration approximately doubled the mean cocaine venous plasma concentrations without incrementing the cardiovascular and subjective effects of the first cocaine administration. The present results extend this pattern of results to cocaine given by the intranasal route (also, see McCance-Katz et al., 1998b). Acute tolerance has also been reported to develop to the cardiovascular effects of volatilized cocaine when given repeatedly to rats (Lichtman et al., 1995). In addition, Tella et al. (1999) has demonstrated that rats who self-administer cocaine develop tolerance across sessions to the cardiovas-

cular effects of cocaine and also show within-session acute tolerance to the cardiovascular effects of cocaine. Finally, acute tolerance has also been reported to develop to the subjective, but not cardiovascular, effects of a single dose of D-amphetamine in humans (Brauer et al., 1996), indicating that acute tolerance is commonly observed to the effects of stimulants, regardless of the route of administration.

The graphs show that the effects of cocaine and cocaine venous plasma level increase in the same direction after the first dose, but further increases in plasma level following the second dose are not related to further increases in the effects of cocaine. Unfortunately, because the session observations ended before cocaine venous plasma levels significantly declined, it was not possible to graph both the ascending and descending limbs of the plasma concentration curves. Because cocaine venous plasma levels nearly doubled after the second cocaine administration, without an increase in effect, a smaller effect of cocaine would have been observed on the descending limb of the plasma concentration curve, i.e., hysteresis, if later observations had been obtained. Cocaine metabolite levels increased across the session, with maximal levels observed at the end. This pattern did not correspond with that for the cardiovascular and subjective effects of cocaine, indicating that the metabolites have little behavioral influence. In an imaging study that examined brain metabolism, Volkow et al. (1998) reported that a single dose of intravenous methylphenidate decreased brain metabolism, while repeated doses of intravenous methylphenidate increased brain metabolism. Thus, changes in brain metabolism may play a role in producing the greater hysteresis observed following multiple cocaine administrations compared with a single cocaine administration.

There are several weaknesses in the current study. To limit the study length, two sessions were accomplished each day. The time interval between sessions was too short to allow the complete elimination of cocaine metabolites and precluded obtaining sufficient plasma levels on the descending limb of concentration curves. Although the use of a balanced dosing order across participants within each admission and different dosing orders for each participant between admissions limited the influence of residual plasma levels, pharmacokinetic parameters could not be accurately estimated using this design. In addition, long-term heavy users of cocaine participated in this study, which was designed to obtain data relevant to participants in the early stages of cocaine use. We selected applicants with lighter cocaine use and recent intranasal experience, but all were long-term cocaine users. Despite this behavioral history, the cocaine doses used were behaviorally active and liked by the participants.

One of the enigmas of cocaine abuse is, for the most part, cocaine users self-administer cocaine using repeated-dose patterns and intervals that are most likely to induce acute tolerance, thereby reducing cocaine's effects. Furthermore, when sober, cocaine abusers can perfectly describe the phenomena. The results of the present study demonstrate that acute tolerance develops to the effects of intranasal cocaine when taken in a repeated-dose pattern. It is likely that users experience this phenomena even when they are novitiates to cocaine use and snorting cocaine. Thus, the pattern of cocaine repeated-dose self-administration and tolerance development within a binge develops early in the cycle of cocaine abuse. It is interesting to speculate that because this acute tolerance is so dramatic, users initially escalate the size of the doses taken and then move on to smoked cocaine, in an effort to experience the positive effects of cocaine. The results highlight the need for further controlled studies comparing the effects of cocaine in light or novice cocaine users to the effects in heavy or long-term cocaine abusers so that a better understanding can be obtained of the long-term neurochemical and biological changes that occur with repeated cocaine use, which may play a role in making cocaine abuse so recalcitrant to treatment.

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