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Subjective Response During Continuous Infusion of Cocaine

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KUMOR, K. M., M. A. SHERER, J. GOMEZ, E. CONE AND J. H. JAFFE. *Subjective response during continuous infusion of cocaine*. PHARMACOL BIOCHEM BEHAV 33(2) 443–452, 1989.—The relationship between the subjective effects induced by IV cocaine injection(s) and cocaine plasma concentrations is complex and difficult to interpret. We designed a study in which bolus loading doses of cocaine followed by 4-hr placebo infusions were compared with the same bolus loading doses of cocaine followed by 4-hr infusions of cocaine calculated to maintain the peak plasma concentrations produced by the bolus. Seven cocaine-using volunteers were successfully studied using a randomized double-blind design, in which self- and observer-rating scales were used to measure drug effects. After the cocaine bolus loading doses, scores for most subjective measures remained elevated when the bolus was followed by a cocaine infusion. In contrast, the subjective responses returned to baseline when the bolus was followed by a placebo infusion. However, self-estimates of the intensity of the cocaine "rush" were not altered by the presence of active cocaine infusions and returned rapidly to baseline.

Cocaine Rush Tolerance Human subjective effects Continuous infusions

ANIMAL experiments have demonstrated that administering cocaine can induce either tolerance or sensitization to the effects of this central stimulant (6, 11, 36, 42, 43, 48, 49, 52, 61, 62). Sensitization or tolerance to physiologic, behavioral and psychiatric effects of cocaine have also been suggested to be important factors in the human response to this drug (10, 13, 16, 27). Over the past decade the pharmacologic effects of cocaine have been examined in several controlled studies with human volunteers. In one study, Fischman *et al.* (13) compared the subjective and cardiovascular effects of intravenous cocaine following pretreatment with intranasal doses of cocaine. In another, Javaid *et al.* (27) compared the relative rates of decline of plasma cocaine concentrations and drug effects following a single intravenous dose. Both of these studies relied on comparisons of drug concentrations and drug effects following acute doses of cocaine; both suggested the development of acute tolerance or tachyphylaxis to the examined effects. Such analyses, however, are complicated by the short action of cocaine, which results in rapid changes in both the plasma concentrations (2, 9, 28, 37) and the pharmacologic effects of the drug (13, 37, 46, 49). In addition, it is difficult to isolate pharmacological effects from conditioned euphoria and/or anxiety which may be present at the time of drug administration (8).

We studied the development of tolerance or sensitization to the subjective and physiological effects of cocaine by administering an intravenous loading dose of cocaine followed by an intravenous (IV) cocaine infusion over a period of 4 hours. With this method it is theoretically possible to achieve and maintain constant plasma concentrations of the drug for the duration of the infusion (30, 35, 38).

This method, which minimizes the confounds of changing drug concentrations and drug distribution inherent in single dose studies, allows detailed examination of drug effects including more direct measurement of short-term tolerance. In addition, this method may be useful in separating conditioned and anticipatory drug responses from unconditioned pharmacologic responses. This is achieved by extending the period of peak cocaine plasma concentration beyond the time when these anticipatory responses are usually present.

Paranoid feelings and behavior and toxic psychosis are observed only after repeated or very large doses of cocaine (10, 34, 41, 47, 50, 60). While there have been a number of studies on the effects of single doses of cocaine in man (7, 15, 18–20, 27, 46, 55–57), there have been few studies of the effects of repeated administrations of cocaine (13, 17, 40). The study to be described was designed to produce pharmacologically-active plasma cocaine concentrations for a substantially longer period than single dose administrations, thus permitting a different approach to the study of acute tolerance as well as some observations on the effects of longer periods of cocaine exposure.

METHOD

Subject Population

Ten male volunteers, aged 21–35 years, with a history of recent

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intravenous cocaine use, participated in the study and seven out of the ten completed the study and fulfilled the criteria for inclusion of their data in the analysis. The study was approved by the IRB and all subjects signed an approved consent form. Subjects were searched on admission to our closed research ward and random urine drug screens were carried out during the study period to assure that subjects were exposed only to those substances experimentally administered. All subjects reported using IV cocaine within 14 days of admission, with the exception of one subject, a poly drug user, whose last use was within 2 months. The seven subjects included in the final data analysis had used cocaine between 3 to 10 days out of the previous 14 days prior to admission.

Following admission to the ward, subjects were evaluated with a computerized version of the Diagnostic Interview Schedules which yielded DSM-III diagnoses. In addition, subjects were evaluated by a board certified psychiatrist. None of the subjects were found to meet DSM-III criteria for current axis one disorders other than substance abuse. The presence of DSM-III axis two diagnoses did not exclude subjects from participation in the study. Three subjects met criteria for antisocial personality and another three had features of this diagnosis.

The 8 subjects who participated in the study are best described as poly drug abusers. All were users of cocaine; all but one denied impairment on cocaine and, therefore, did not meet criteria for cocaine abuse. Using DSM-III criteria 5 of 8 met criteria for dependence on at least one drug other than nicotine. Except for 2 subjects whose alcoholism was rated as current within the past 6 months, all diagnoses were lifetime, rather than current diagnoses. The dependence diagnoses were as follows: opioids (2), alcohol (3) (2 within past 6 months), cannabis (4), barbituates (2), amphetamines (2). Subjects were observed on the ward for at least 5 days and often considerably longer, prior to the start of the study described here. None of them exhibited signs of withdrawal from drug use as detected by a nursing staff experienced in making formal observations of drug withdrawal.

Screening and Dose Calculations

Subjects underwent a detailed medical evaluation which was supervised by a cardiologist. Subjects were screened for unusual sensitivity to cocaine using an ascending series of single, once daily, intravenous bolus cocaine doses of 20, 40, 60 and, for some individuals, 80 mg over a period of 3 to 5 days. During this screening, cardiac function was monitored with EKG. Two subjects of the original ten were rejected for further study with this procedure, one because of elevated pulse and blood pressure observed just prior to drug injection, and another because of premature nodal contractions following the first 20 mg dose of cocaine. Before and following one of the cocaine doses given as part of subject sensitivity screening, 10 plasma samples were obtained over a 4-hour period. These samples were collected in the presence of sodium fluoride to prevent hydrolysis of cocaine, chilled and the plasma removed and frozen until analyzed for cocaine by gas-liquid chromatography with a nitrogen-sensitive detector. The sensitivity of the assay was 5 ng/ml. Within-assay variability was 9.7% (N = 4) and between-assay variability was 8.8% (n = 31) (54). Plasma concentrations were then fit with a one or two compartment nonlinear mamillary model and the kinetic constants calculated using the PCNONLIN program (Metzler, C. M. and Weiner, D. L., Statistical Consultants, Inc., 462 E. High St., Lexington, KY 40508). All subject data were best fit with a one compartment model. This permitted the use of a constant infusion (instead of the exponentially declining infusion rate) to maintain a plateau concentration in two-compartment kinetic systems (30,58). The kinetic constants for each individual subject were used to calculate the infusion dose necessary to maintain the theoretical peak plasma cocaine concentration after the 40 mg and after the 60 mg or 80 mg IV loading doses. Therefore, in the double-blind phase of the experiment, each subject was administered a cocaine solution, the concentration of which was determined by his personal kinetic constants. The infusion was administered using an IVAC pressure pump and the rate of infusion was constant (50 ml/hr) for all subjects over the 4-hour period.

Drug Conditions and Environment

Each subject received each of five different dose conditions in a double-blind randomized noncounterbalanced design. These conditions included: a 40 mg loading dose of cocaine followed by either cocaine or placebo infusion (low cocaine-cocaine infusion; low cocaine-placebo infusion), a 60 mg (6 subjects) or 80 mg (2 subjects) loading dose of cocaine followed by either cocaine or placebo infusion (high cocaine-cocaine infusion; high cocaine-placebo infusion), and a placebo loading dose followed by a placebo infusion (placebo-placebo infusion).

Subjects were studied no more frequently than every 48 hours. The studies were conducted in a quiet, noise-insulated room, with one or two nurses and a physician in attendance. The physician in attendance rotated between K.K. and M.S. and each subject was assigned one of the nurses as the observer throughout that subject's study. The nurse observers participating in the study refrained from talking with each other or initiating conversation with the subjects and provided a supportive but nondirective milieu in their interactions with subjects. The observers were blind to the conditions of the study but were aware of the general study design, that is, they knew a placebo day was included in the design and that on some days a cocaine continuous infusion would be given and on others a placebo infusion would be given.

Guidelines were provided for interruptions of the study in the event of excessive autonomic activation. On each study day, following an overnight fast and while at bed rest, subjects had an indwelling IV heparin lock catheter inserted into a vein in each arm; one for drug administration, the other for blood sampling. Sixty to ninety minutes later subjects received an IV dose of cocaine (or placebo) which was administered manually as a bolus over a 2–5-second period. Immediately following this, the catheter was flushed with heparinized saline and the infusion was started using an IVAC pressure pump which infused cocaine (or placebo) into the indwelling catheter via a needle inserted into the heparin lock. The drug infusion lasted for four hours, after which the intravenous line was removed from the catheter. Subjects were kept at bedrest during the first 30 minutes of the study. Limited ambulation was allowed thereafter, but subjects were not permitted to engage in exercise.

Four plasma samples were obtained at strategic times during the infusions to determine the degree to which the achieved levels met the definition of steady state. These times, 12, 20, 60 and 240 minutes during the infusion, were arranged according to the rule of geometric spacing for optimum sampling for multiexponential modeling curves with small adjustments to suit the collection of other data (33).

Scales and Schedules

Several self-rating scales were used to measure the feelings and mood states of subjects before, during and after the doses of cocaine. Scales from the Addiction Research Center Inventory included the Morphine Benzedrine Group Scale (MBG-maximum score 16), the Pentobarbital, Chlorpromazine, Alcohol Group

TABLE 1

COMPARISON OF MEAN SUBJECTIVE MEASURES SCORES OVER 7.5 HOURS (N=7)

Measure	Placebo/ Placebo	Low Cocaine- Placebo	Low Cocaine- Cocaine	High Cocaine- Placebo	High Cocaine- Cocaine	lsd	p
Rush (analog)	0.002	0.084†	0.411†	0.133*	0.322*	0.182	1.9×10^{-2}
Rush (graph)	0.003	0.203	0.209	0.271	0.342	0.205	2.9×10^{-2}
Good	0.198	0.529†	1.618†	0.442*	1.827*	0.958	4.0×10^{-3}
Anxious	0.180	0.736	1.716	0.687*	2.742*	1.171	1.1×10^{-3}
Energetic	0.329	1.051	1.856	0.976*	2.667*	1.278	9.8×10^{-3}
Tired	1.353	0.931	0.707	0.929	0.644	—	NS
Irritable	0.287	0.644	0.644	0.467	0.727	—	NS
Feel Drug	1.182	1.324†	1.744†‡	1.311*	2.158*‡	0.378	8.4×10^{-5}
MBG	4.800	6.400	8.000	5.867*	9.067*	2.262	1.7×10^{-3}
LSD	2.267	3.333†	4.533†	3.200*	4.800*	1.069	5.5×10^{-3}
Obs. Effect	0.147	0.240	0.800	0.320*	1.053*	0.414	4.0×10^{-4}
Obs. Signs	0.0	0.085	0.273	0.052*	0.347*	0.267	5.1×10^{-2}
Obs. Liking	0.018	0.292	0.667	0.360*	0.867*	0.480	1.3×10^{-2}

The mean subjective measure score over 7.5 hours is the mean of the time-weighted means of each subject's study score for the day (area under response-time curve/450 minutes) for seven subjects. Five conditions are presented with least significant differences (lsd) between any two conditions and associated p value for F distribution of ANOVA. Symbols (*†‡) denote some interesting pairs of data (but not all) that are different from each other at a p value less than 0.05. (Differences of drug conditions from placebo/placebo are not marked however.) The individual symbols are listed after each of the two data values that are statistically different from one another.

Scale (PCAG-maximum score 16), and the LSD Group Scale (LSD-maximum score 14) (24). These scales were used to assess, respectively, feelings of euphoria, sleepiness and tired feelings, and dysphoric, distorted sensations. The four-point, Feel the Drug interval scale assessed the intensity of drug effects (31). The St. Mary's Sleep Questionnaire, a self-report measure, was used to assess the quantity, quality, and pattern of sleep following study days (12).

We also used a series of interval scales to provide additional measures of sensations commonly reported as effects of cocaine. Among areas probed by these interval scales are self-rated feelings of "good," "bad," "energetic," "tired," "irritable," "restless" or "uncomfortable," "sad," "happy," "relaxed," and "anxious." Included among these was one scale labeled as "rush." These items were selected following a perusal of the literature and interviews with intravenous cocaine users. All the cocaine-sensitive interval scale (CSI) items were subjected to pilot testing in between 3–5 cocaine users (different from study subjects) using doses of 10 to 80 mg of intravenous cocaine prior to the double-blind cross-over experiment described here. The scales were scored only as face value measures and no effort was made to remove redundant or covariant dimensions of the scales. The CSI scales were presented to the subject on a computer display terminal as a horizontal line labeled from 0–9 at evenly spaced intervals. Subjects selected the desired rating by use of the computer number pad.

Despite previous descriptive efforts, "rush" does not have an accepted operational definition (1,49). We sought to use a standard procedure in order to measure this feeling state. Information gathered from interviews with 20 intravenous cocaine users indicated that while there was variation in the adjectives used to describe this feeling state, all intravenous and free base cocaine users described a sensation that generally did not occur with intranasal use. The sensation which the users referred to as "rush" or "thrill" was experienced immediately after injection and was typically portrayed as very desirable, although the language used was variable. Prior to participation in the experiment, all subjects confirmed their experience of this "rush" during the dose screening portion of the study. During the experiment subjects were instructed that the "rush" item referred to the first intensely pleasurable experience after injections. They were also aware that they might receive "blanks" or small doses of cocaine.

No other instructions were given. Since the experimental design involved a steady-state infusion of cocaine, the duration of the feeling of rush was of particular interest. Therefore, we took care not to convey to our subjects any expectations about the duration of the "rush." Some subjects expressed a hope that cocaine infusions would extend rush. They were neither encouraged nor discouraged about these expectations, but were told that part of the purpose of the experiment was to find out how cocaine made people feel under different dosing conditions.

In addition to the horizontal CSI scale for measuring "rush," the sensation, "rush," was also assessed by allowing the subjects to rate themselves on a computerized bar graph. Subjects adjusted a cursor on the ordinate for "rush" intensity, causing a thick line on the computer monitor to be generated parallel to the ordinate. After each rating, the curser automatically shifted to the next point on the abscissa. At the next timepoint for self-rating, the subject was able to view his previous response(s), and then adjust the cursor to correspond to his current rating of the intensity of "rush." Thus, the subjects developed and responded to a histogram-like graph of "rush" (graphic rush). In this histogram of intensity versus time the ordinate measuring intensity was labeled as a 100-point scale, the abscissa was labeled "time."

In addition to the various techniques for self-rating, the nurse observer rated the subject using existing ARCI Observer scales (21). The ARCI subject "Liking" scale requires the observers to rate the subjects' liking for the drug on a four-point scale by rating any behavior, facial expression and volunteered comments (0 = Not at all, 1 = Slight, 2 = Moderate, 3 = A lot, 4 = An awful lot). The ARCI Observer "Effects" scale used the same four-point scale to measure the intensity of the drug effect. The ARCI Observers "Signs" scales is a checklist that in addition to opioid-specific items included several items that are commonly

reported after cocaine administration such as, "high," "nervousness," "need to talk" and "increased drive." The scales were all administered and scored as previously described (21). All observers were trained and tested by experienced ARC personnel in the administration of the observer scales. Observers were instructed not to examine subjects' self-ratings or initiate conversations with subjects. However, the observers could see the rushgraph scale from many positions in the room and were in some cases responsible for recording vital signs. In keeping with long standing procedures at the Addiction Research Center, volunteered comments could be used in rating drug effects (21). Observers were instructed to consider subjects' usual behavior as a baseline and not to hesitate to give their opinion of the drug response, even though it might differ from that of a subject (21). Observer ratings, therefore, are not entirely independent of subjects' verbal behavior and self-ratings and, in this case, despite the experimental design, cannot be described as truly double-blind since the cardiovascular effects of cocaine are not subtle.

The CSI scales, Graphic "Rush" and Feel Drug scales were administered at −30, +3, +10, +15, +60, +120, +180, +270, +330, +390, and +450 minutes from the bolus loading dose, which was given at approximately 9 a.m. Because of time limitations during the first minutes after bolus administration,the observer scales and the ARCI subscales were completed on a somewhat different schedule of −30, +3, +60, +120, +180, +270, +330, +390 and +450 minutes after the bolus loading dose. The St. Mary's Sleep Questionnaire was completed by subjects on awakening after vital signs on the mornings before and after the experimental study days. In addition to the EKG monitoring mentioned above, physiologic responses to cocaine were measured; these are the subject of another report (32).

Analysis

The time-weighted mean measurement of the scores on each subjective scale (CSI and ARCI) was calculated for each individual person for each condition using the trapezoidal rule. This resulted in areas under the response-time curve (score × time in minutes). For the purposes of more meaningful exposition this number was then divided by time to yield a time-weighted mean measurement with units reflecting the average score on that scale during the entire experimental (450 minutes) session (Table 1). For statistical purposes, the raw areas under the curve for each scale for individal subjects on each study day were subjected to analysis of variance for repeated measures (conditions by subjects matrix). A Fisher's *t*-test for protected comparisons was used as the post hoc test for the comparisons when the initial F ratio for the ANOVA was <0.05 (29). Analysis of variance and Fisher's *t*-test were also used to compare the five drug conditions at various points in time after drug administration and cessation. We calculated linear correlations among selected scale scores and the natural logarithm of the plasma concentration, producing correlation matrices with covariances for all combinations of data sets in the group. Individual subject data were used in the correlation calculations and the natural logarithm of the plasma concentrations were used because the logarithm of the plasma concentration correlated better than the plasma concentration with all rating scale scores. Standard single variable linear regressions were used to examine the slopes of scores as a function of time. The analysis of significance and magnitude of the slope are the criteria used to determine the presence or absence of tolerance and its clinical importance.

Steady State

The operational definition of steady-state plasma concentrations for a given subject and study day was a pattern of cocaine plasma concentrations in which none of the measured plasma concentrations during a particular cocaine infusion differed from the mean concentration for that day by more than 25%. This degree of variability was approximately 2.5 times the mean assay variability (coefficient of variation) or the 99% confidence interval.

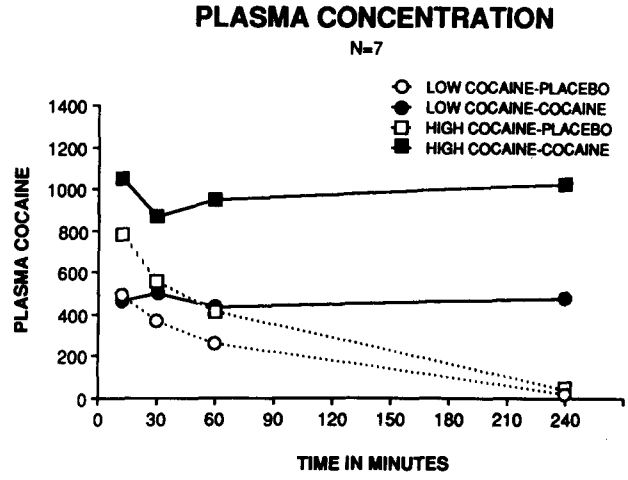

FIG. 1. Cocaine plasma concentrations (ng/ml) during the first 240 minutes after beginning infusions. Cocaine infusions (placebo or active) were administered between 0–240 minutes, then discontinued. The placebo/placebo concentration is not graphed as plasma levels were uniformly zero.

RESULTS

Plasma Concentrations and Doses of Cocaine

The cocaine plasma concentrations at 12, 20, 60, and 240 minutes after the bolus-loading doses of cocaine followed by cocaine infusions (cocaine/active) revealed that steady-state drug concentrations, as defined here, were obtained by 12 minutes for both the low cocaine-cocaine infusion and the high cocaine-cocaine infusion conditions in seven of the eight subjects who completed the study (Fig. 1). Plasma levels from the 8th subject did not meet criteria for steady state because his plasma concentrations tended to increase over time and he exceeded our definition of steady state. All data from this subject were excluded from analyses on subjective effects and mean plasma levels.

Cocaine plasma concentrations for the seven subjects who met our criteria for steady state are presented in Fig. 1. When the bolus-loading doses of cocaine were followed by placebo infusions (low cocaine-placebo infusion; high cocaine-placebo infusion) plasma cocaine concentrations declined exponentially as expected. No cocaine was found in the plasma on days on which a placebo bolus loading dose was followed by placebo infusion. Mean steady-state cocaine concentrations for individual subjects during the low cocaine-cocaine infusion varied from 276 ng/ml to 668 ng/ml; cocaine dosage for the infusion varied from 25 to 43 mg/hr. Mean steady-state cocaine concentrations for individual subjects during the high cocaine-cocaine infusion varied from 497 ng/ml to 1419 ng/ml for the six subjects who received the 60 mg dose; cocaine dosage for the infusion varied from 37 to 65 mg/hr.

Subjective Effects

ARCI scales. Following all cocaine bolus-loading doses, there

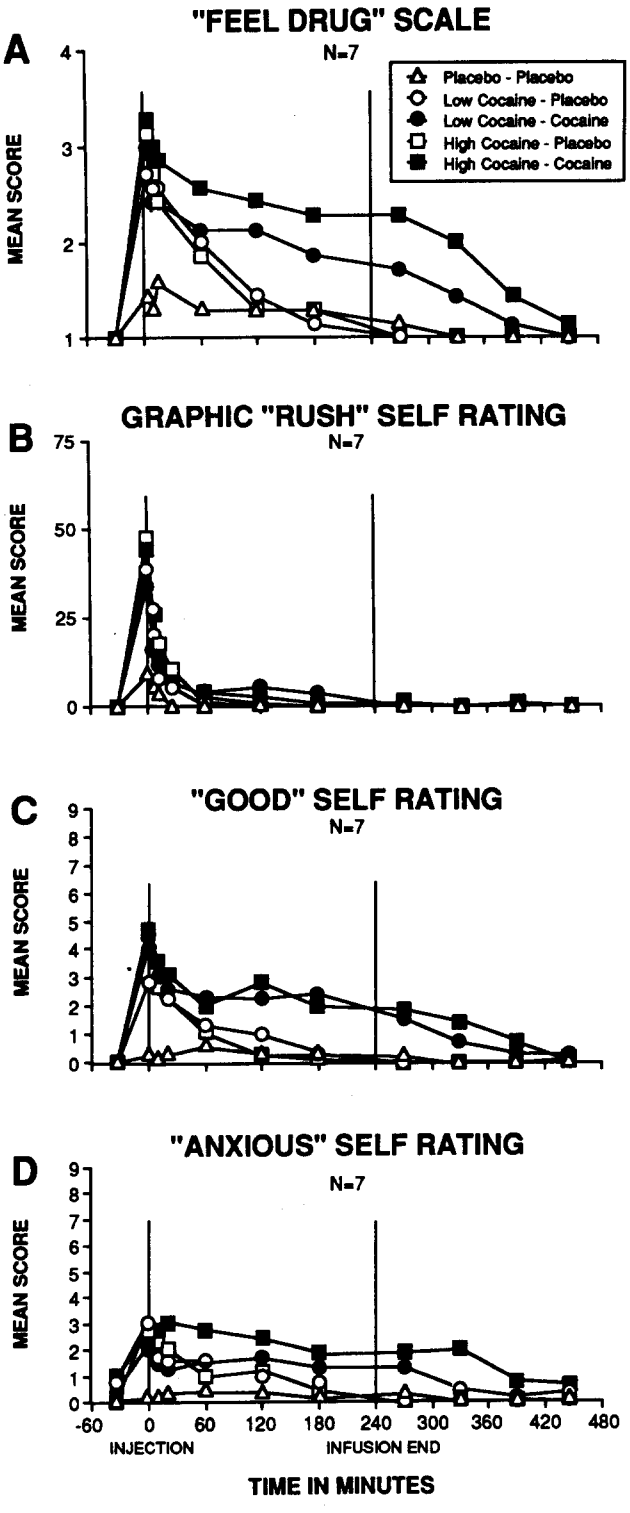

FIG. 2. Mean scores for four self-rating scales. Cocaine infusions (placebo or active) were administered between 0–240 minutes, then discontinued. Bolus loading doses were given at zero time.

were robust increases on the LSD, MBG and "Feel Drug" scales by the time of the first measures at 3 minutes (Fig. 2A). When the bolus-loading dose of cocaine (either high or low dose) was followed by a placebo infusion these increases returned to baseline over a 90- to 180-minute period. When the cocaine bolus- (either high or low) loading dose was followed by an active cocaine infusion (cocaine/active) the increases measured at three minutes were followed by a decline, then a stabilization of ratings at modestly lower values than those observed at 3 minutes. On these scales the scores for the active infusion conditions were statistically different from the conditions in which the same bolus loading doses were followed by placebo infusions (low cocaine-placebo infusion; high cocaine-placebo infusion; Table 1). Although the "Feel the Drug" and MBG scales scores during the active infusion conditions (low cocaine-cocaine; high cocaine-cocaine) remained elevated, they exhibited a slight downward slope that was statistically significant for the Feel Drug (slope -0.18/hr; $p<0.05$) but not MBG scale (Table 2).

CSI and graphic scales. Observed peak responses on the graphic scale for cocaine "rush" for both the high cocaine-cocaine infusion and high cocaine-placebo infusion were significantly higher than the low cocaine-cocaine infusion. When we compared the two high bolus-loading dose conditions to the low cocaine-placebo infusion, the responses were greater and in the same direction, although they did not meet the criterion for statistical significance ($p=0.07$). On both the CSI items and graphic measure of "rush" there were nearly identical returns to baseline levels during the cocaine infusion conditions (low cocaine-cocaine infusion; high cocaine-cocaine infusion) and the two cocaine/placebo infusion conditions (low cocaine-placebo infusion; high cocaine-placebo infusion) (Fig. 2B). During all conditions, feelings of "rush" were no longer statistically detectable by 30 minutes, and infusions of cocaine did not prolong this effect. A small difference between the two methods of measuring "rush" was apparent in that a minor "tailing" (a slower decrease in the intensity of score over time) was seen on the CSI item measure of "rush" in which subjects could not view their previous responses as they could with the graphic "rush" procedure.

In contrast to ratings of "rush," which returned promptly toward baseline whether or not a cocaine infusion was given, CSI item scores of "good," "energetic" and "anxious" feelings remained elevated during both cocaine/cocaine infusion conditions (high cocaine-cocaine infusion, low cocaine-cocaine infusion), but not when bolus-loading doses of cocaine were followed by placebo infusions (Fig. 2C and D). Similar to the results of the Single Dose Questionnaire and Feel Drug items scores, there were statistically significant differences between the scores for these three items when cocaine infusions followed the loading dose as compared to an inactive infusion following a loading dose (Table 1). During the conditions when cocaine boluses were followed by cocaine-active infusions, these subjective effects remained elevated for the entire period of the cocaine infusion after steady state was demonstrated. Analysis of slope revealed no increases or decreases ($p>0.05$) over the four-hour period except for the "anxious" scores during the high cocaine-cocaine infusion which had a slight but significantly negative slope (-0.04 units/hr) (Table 2). When bolus-loading doses of cocaine were followed by placebo infusions, CSI item scores returned to baseline levels over a period of about 2 hours (Fig. 2). Some CSI ratings were less sensitive to the effects of cocaine (i.e., generally subjects did not score them as different from baseline conditions). Thus, under all drug conditions, there were no significant differences among the mean scores on the self-ratings of irritability, bad feelings, happiness, relaxation, sadness, restlessness or discomfort.

Observer ratings. The time-weighted mean observer rating scores for drug "Liking and drug "Effects" were significantly higher when the bolus-loading doses of cocaine were followed by cocaine infusions than when cocaine was followed by placebo infusions (high cocaine-cocaine infusions vs. high cocaine-placebo infusions and low cocaine-cocaine vs. low cocaine-placebo

TABLE 2

REGRESSION SLOPES OF MEAN RESPONSES DURING STEADY-STATE INFUSION
N = 7

Measure	Slope (per hr)	MAX/Baseline score	Cocaine Infusion	Inclusive Period (hr)	*p* Value of Slope
Rush (analog)	−0.25	9/0	Low	0.25–3	N.S.
	−0.36	9/0	High	0.25–3	<0.05
Rush (graph)	−0.41	20/0	Low	0.33–3	N.S.
	+1.38	20/0	High	0.33–3	N.S.
Good	−0.39	9/0	Low	0.25–3	N.S.
	−0.25	9/0.14	High	0.25–3	N.S.
Anxious	+0.006	9/0.43	Low	0.25–3	N.S.
	−0.04	9/1	High	0.25–3	<0.05
Energetic	+0.03	9/0.43	Low	0.25–3	N.S.
	+0.03	9/0.43	High	0.25–3	N.S.
Feel Drug	−0.18	4/1	Low	0.25–3	<0.05
	−0.18	4/1	High	0.25–3	<0.05
MBG	−0.57	16/5.4	Low	0.33–3	N.S.
	−0.33	16/5.3	High	0.33–3	N.S.
LSD	+0.09	14/2.4	Low	0.33–3	N.S.
	−0.98	14/2.3	High	0.33–3	<0.05
Obs Eff	−0.04	4/0.42	Low	0.33–3	N.S.
	−0.05	4/0.14	High	0.33–3	N.S.

Slopes from linear regressions of scale scores versus time between 12–240 minutes after cocaine loading dose for cocaine active (low and high) continuous infusions. MAX is the maximum score for the particular scale. Baseline score is the mean of the seven subjects at baseline for the condition listed. Inclusion period denotes period of time over which regression was performed.

infusions). The increases were evident by the time of the initial observation at 3 minutes. These ratings correlated very well with the self-rating scores of the subjects. The 4-point interval drug "Effects" scale asks the observer to rate the magnitude of the drug effect on the subject. This is comparable to the "Feel Drug" scale in which subjects rate the magnitude of the drug effects on themselves. The "Effects" scale showed that drug effect persisted during the cocaine-cocaine infusion conditions (slope NS) (Tables 1 and 2). The observer "Liking" 4-point scale similarly reflected the results of the self rated "good" feelings of the subjects although with less sensitivity (slope NS). The observer "Signs" ratings, although developed primarily for use on opiate studies, did demonstrate a statistically significant difference between the high cocaine-cocaine infusion and the high cocaine-placebo infusion conditions although with diminished sensitivity (Table 1).

We examined the correlations between the natural logarithm of the individual cocaine plasma concentrations and the raw self-rating scores during all conditions in which cocaine was administered. Thus, cocaine plasma concentrations at 12, 20, 60 and 240 minutes were compared with CSI items and Feel Drug scale scores at the nearest time points of 10, 15, 60 and 180 minutes. On the ARCI scales plasma concentrations at 12, 60, and 240 minutes were compared with the nearest items measurements at 3, 60, and 240 minutes.

The logarithm of the plasma cocaine concentrations were significantly correlated with scores on self-rated "anxious," "energetic" and "good" CSI items, and the Feel Drug scale and LSD and MBG ARCI rating scales (Table 3). For these scales, correlations ranged from .39 to .58. Compared to these high correlations, the logarithm of the cocaine plasma concentrations correlated less well with measures of "rush" because of the rapid dissipation of "rush" occurring during active infusions of cocaine. The logarithm of the plasma concentrations of cocaine correlated with the scale responses better than the plasma concentrations. This is often the case for drug-related responses.

The St. Mary's Sleep Questionnaire was given daily during the study. Subjects used the questionnaire in the morning to rate their previous night's sleep. No significant differences among the drug conditions were found for sleep patterns on the night following cocaine administration as compared to the previous night's sleep. Furthermore, no patterns emerged suggestive of a change in sleep as a function of time living on the ward or cumulative exposure to cocaine.

We also examined the possibility of two potential confounds to our results: the possibility of 1) intersubject variability in response to self-report and observer ratings and 2) ordering effects resulting from less than perfect random assignment to experimental conditions. ANOVA of scores on observer scales showed that some subjects had consistently high or low scores relative to other subjects across all conditions, i.e., there were significant interindividual differences. Scores on all self-rating scales (other than the graphic "rush") also showed significant interindividual differences. Despite these differences in magnitude, the subjects' ratings were consistent in the direction and temporal patterns of their responses. In a second analysis, we looked for ordering effects that might have arisen from our use of a randomized design. Using paired *t*-tests, we compared the scores of subjects on each scale (measured at 3 and 10 minutes) for the first vs. the second exposure to the low bolus loading dose conditions (low cocaine-cocaine infusion and low cocaine-placebo infusion pooled and segregated according to order of exposure). We also compared at these time points the scores on all scales for each subject for first vs. the second exposure to the high bolus loading dose conditions (high cocaine-cocaine infusion; high cocaine-placebo infusion). No differences were noted. It is necessary to point out, however, that subjects received several cocaine doses during the screening

TABLE 3A

CORRELATION MATRIX OF INDIVIDUAL DATA FOR SELECTED MEASURES*
4 DATA PAIRS × 4 STUDY DAYS

	Plasma Cocaine (ln)	Rush (Analog)	Rush (Graphic)	Anxious	Energetic	Good	Feel Drug
Plasma Cocaine (ln)	1.00	.37	.32	.41	.39	.51	.52
Rush (Analog)	.37	1.00	.80	.23	.33	.64	.46
Rush (Graphic)	.32	.80	1.00	.10	.16	.57	.45
Anxious	.41	.23	.10	1.00	.82	.57	.60
Energetic	.39	.33	.16	.82	1.00	.62	.56
Good	.51	.64	.57	.57	.62	1.00	.82
Feel Drug	.52	.46	.45	.60	.56	.82	1.00

*Correlation coefficients >.16 are significant at $p<0.05$ level.

Correlations among CSI and "Feel the Drug" individual scale scores and the logarithm of the plasma cocaine concentrations. Four data pairs were obtained by pairing the 12-, 20-, 60- and 240-minute plasma cocaine concentrations with the 10-, 15-, 60-, 180-minute scale scores (nearest measurements).

TABLE 3B

CORRELATION MATRIX OF INDIVIDUAL DATA FOR SELECTED MEASURES†
3 DATA PAIRS × 4 STUDY DAYS

	Plasma Cocaine (ln)	LSD	MBG
Plasma Cocaine (ln)	1.00	.52	.58
LSD	.52	1.00	.45
MBG	.58	.45	1.00

†Correlation coefficients >.2 are significant at $p<0.05$ level.

Correlations among ARCI Scale scores and the logarithm of the plasma cocaine concentrations. The data pairs were obtained by pairing the 12-, 60- and 240-minute plasma cocaine concentrations with the 3-, 60- and 240-minute scale scores (nearest measures). The 20-minute concentration had no appropriate pair.

for drug sensitivity which preceded the actual study, and thus it is possible that the initial research exposure differed from subsequent exposure.

DISCUSSION

Drug infusions which produce plateau plasma levels are useful tools for the study of time-dependent functions because the interpretation of the dynamics of observed responses is simplified. Theoretically, once steady-state plasma concentrations are achieved and maintained, drug concentrations in other tissues or compartments are also maintained (22). This allows the separation of dynamic events such as acute tolerance to drug effects from decreasing drug effects due to drug distribution and elimination and permits a more direct calculation of the rate of development of acute tolerance or sensitization. Furthermore, this technique which maximizes drug exposure per unit time (area under the drug concentration time curve) has been shown to speed the development of tolerance to some receptor-mediated drug effects (59). Our definition of steady state employs the 99% confidence limits for the coefficient of variation of the drug assay in order to assess deviations from steady state. The pattern of plasma/cocaine variations that we observed appeared to be random and thus resulted in basically flat mean cocaine plasma concentrations during cocaine infusions.

While this study was designed as a double-blind cross-over study, it could not overcome the limitations inherent in all studies of potent psychoactive substances. It is unlikely that truly blind self-ratings or observer ratings can be maintained when the drug effects are robust. Recognizing these limitations, we believe that it is still possible to draw the three main inferences we have drawn from the data presented here are: 1) Infusions of cocaine which produced plateau plasma levels of cocaine between 12 and 240 minutes (cocaine/active) also maintained increased scores for most subjective scales which, in turn, correlated with the plasma levels during all drug conditions. 2) For several of the subjective (and the observer rating) scales, the slopes of the scores as a function of time (between 12 minutes and 240 minutes) were not significant. Thus, for these measures, acute tolerance could not be detected as statistically significant. The Feel Drug scale, a scale measuring the total drug subjective experience, was an exception. Scores on this scale for both the low- and high-cocaine infusion conditions diminished with time. 3) Ratings of rush during the cocaine/active conditions did not differ from drug "rush" scores obtained during the cocaine/inactive conditions (low cocaine-placebo; high cocaine-placebo infusions). This suggests the presence of acute tolerance or the existence of a refractory period for this phenomenon.

We believe that differences between "rush" and other subjective effects of cocaine are important. Many clinicians believe that cocaine "rush" is a powerful reinforcer of drug-taking behavior (1,49). Phenomenological descriptions of cocaine "rush" are found in the drug literature (49,51). Spotts and Shontz have

reported detailed interviews with cocaine addicts.These addicts distinguished between rush and other cocaine-induced euphoric feelings and reported that the desire to experience "rush" determined their preference for intravenous cocaine abuse over intranasal administration and their binging behavior (51). We have drawn the same conclusions from our interviews with our volunteer subjects.

Our subjects' reports may have been influenced by the instructions they were given, i.e., to rate the first intense pleasurable feeling after the injection as "rush." These instructions, however, were based on the shared perception of "rush" reported to us by every subject in our earliest contacts with them. Instructions may have guaranteed that "rush," when reported, would be reported soon after the injection. However, since we were careful to avoid any implication about the way in which the experimental procedures would influence the *duration* of "rush" we believe that the instructions did not influence the subjects' estimates of "rush" intensity as a function of time. Since some subjects expressed the hope that "rush" would be prolonged and we had no hypothesis nor particular interest about the effect of maintained blood levels on "rush" duration, we are inclined to accept the current findings as reflecting what the subjects experienced rather than a communication that was influenced by a desire to please the investigators.

The pharmacologic mechanisms of cocaine-induced "rush" are unexplored. The relative independence of "rush" from the cocaine plasma concentration during steady state could result from a physiologic refractory period. Alternatively, the response of "rush" may be related specifically to rapid increases in cocaine brain concentrations. Under such circumstances, steady plateau concentrations of cocaine would not prolong the effect. Another possibility is that rather than "rush" being dependent primarily on the rate of increase it depends on absolute brain concentrations. It is likely that the intravenous bolus dose makes its first circuit or pass through the blood stream with relatively little dilution before the distribution phase. It is possible, therefore, that the initial very high concentrations of cocaine present before distribution are necessary for the induction of "rush." This principle of dilution pharmacodynamics has been well described and forms the basis for the measurement of cardiac output (4). Furthermore, there is evidence from animal experiments that brain levels of cocaine minutes after intravenous administration are much higher than plasma levels (26, 39, 45).

Direct comparison of our results with those of other investigators is complicated by important differences in study designs. We gave the cocaine injections (prior to the infusions of cocaine or placebo) as boluses in order to simulate the self-administration of the IV drug user and we included early measurements of the drug response at 3 and 10 minutes postinjection because the sensation of "rush" peaks quickly after IV injection. Other studies have injected cocaine over one minute (13, 17, 27), have not stated the injection period (9), or have commenced subjective measures at 10–15 minutes (13,17). Despite these design differences, the results of our measures of "rush" appear to be in substantive agreement with previous studies which reported some degree of acute tolerance to the pleasurable effects of acutely administered cocaine (13, 20, 27). However, previous studies did not attempt to quantify "rush" as distinct from other pleasurable cocaine-induced sensations and it is probable that "rush" was a component of other scales such as "high."

Apart from two categories of subjective effects ("rush" and "Feel the Drug") we did not observe statistically significant declines in the drug effects with time. If a substantial degree of acute tolerance develops to the subjective effects of cocaine, then the expectation is that during a steady-state infusion the subjective effects would decline and the rate of tolerance development could be measured. Chow and Javaid and their co-workers described a more rapid rate of decline of the physiologic and subjective effects as compared to the decline in plasma cocaine concentrations following single doses of cocaine (9,27). Additionally, Fischman and co-workers reported a diminution in subjective and heart rate responses to IV cocaine one hour after pretreatment with an intranasal dose of cocaine 96 mg as compared to pretreatment with 4 mg of cocaine (13). These investigators hypothesized the existence of either acute tolerance to the subjective and physiologic responses of cocaine or a homeostatic dampening of pharmacologic responses. However, we were unable to confirm this model with a steady-state experiment for any measure except Rush scale scores and the Feel and Drug scale scores which itself reflects rush in large measure.

We have reported in a separate publication the results of our observations of the behavior of the volunteers described in this current report (50). In that work we related that the subjects did not self-report suspicious or paranoid feelings, yet they behaved in a fashion strongly suggestive of a state of mistrust or suspiciousness. The subjective effects in the current report appear to be independent of the suspicious behavior we observed. For example, we observed subjects to be discussing their own death and recording their own blood pressures overtly stating they mistrusted the nurses' recordings at the same time they reported good or euphoric feelings. The good and euphoric feelings also were coincident with self-reported anxious feelings and elevations in the LSD scale scores. Although this is a puzzling result, it is consistent with a report of intravenous amphetamine administration in which psychosis and elation were noted to coexist (5).

It is possible that conditioned responses such as fearful anticipation or conditioned euphoria could also have contributed to the findings of Chow *et al.* and Javaid *et al.* (9,27). We have studied the responses of cocaine users receiving placebo injections in our studies. We find that significant conditioned responses do exist (8). These conditioned responses peak early and wane faster than the cocaine-induced effects and may cause a more rapid decline of the observed response than expected from analysis of the cocaine plasma concentrations alone. This is supported by the fact that in our study observers monitoring the ECG saw increases in the pulse rate immediately prior to drug injections.

In the study of Fischman *et al.*, the dimunition of cocaine's effect attributed to tolerance was expressed as a decrease in the percent of baseline of the response observed after a pretreatment with an intranasal dose of cocaine. Alternatively, this effect could be accounted for by the presence of higher cocaine concentrations after pretreatment with 96 mg cocaine than after the 4 mg cocaine pretreatment (13). Since the pharmacologic responses of drugs typically describes a sigmoidal dose-response curve, the percent change in response is smaller as the asymptote is approached (23). Conceivably, some of the decrease seen after intranasal cocaine pretreatment could be due to differences in the positions on the dose-response curve rather than tolerance. Alternatively, some of the observed diminution may result from the inclusion of "rush" which appears to exhibit a refractory period as a component of the "high" scale or could be due to a habituation to the conditions of the experiment at the second dose. However, differences in experimental design preclude any complete resolution of the discrepancies between these experiments.

The relatively steady cocaine plasma concentrations achieved by 12 minutes after initiation of cocaine/active infusions allow examination of complex subjective sensations. However, interpretation of the data during the first 12 minutes is more difficult because it is assumed that, for at least a portion of this period, drug distribution takes place. We did not sample earlier than 12 minutes because of the limits on blood volume withdrawal and recognition that it takes a finite though short time (probably in the range of 5–10 minutes) to complete distribution of the initial bolus.

In the first 12 minutes an interesting phenomenon was observed during the cocaine/active infusion conditions (low and high cocaine bolus-cocaine infusions). An early transient peak on the scores of several self-rating scales (Feel Drug, "good," "anxious") occurred at 2–5 minutes after injection (Fig. 2A, C, D). The peak declined into the plateau of responses at a somewhat lower level which was then maintained by the steady-state cocaine plasma concentrations after 12 minutes. This same pattern was observed in the heart rate and blood pressure responses which are the subjects of another report (32). In contrast, when the cocaine bolus was followed by the placebo infusion, the subjective scores and physiological measures exhibited a typical, smooth exponential decline. It is possible that high early cocaine brain concentrations prior to the steady-state cocaine plasma concentration at 12 minutes are the cause of these early peaks in subjective and physiological responses superimposed on the pharmacologic response. It is also possible that the early peaks may in some measure be due to a cocaine-induced conditioned response. The presence of conditioned responses to cocaine have been proposed in both human (8) and animal investigations (3, 25, 44).

Two observations lend credibility to this interpretation. First, the aforementioned observation that the heart rate increases substantially immediately prior to drug injections. Secondly, during the first 12 minutes after injection, transient peaks were observed in the responses to placebo bolus followed by placebo infusions. These responses were similar in duration and magnitude to the duration and magnitude of the peak or overshoot *above* the plateau maintained by the cocaine/active infusions. However, without both brain concentrations and frequent cocaine plasma concentrations during the early minutes of the experiment, we can only speculate.

The steady-state cocaine infusion design permits the detection and separation of some factors that together constitute the cocaine drug response. With this design we have found evidence that several subjective responses after cocaine correlate with the cocaine plasma concentrations. In addition, during the period of relatively steady (plateau) cocaine concentrations between 12 and 240 minutes, we found no compelling evidence of acute tolerance for these subjective measures.

However, the lack of evidence for acute tolerance does not rule out the presence of tolerance or sensitization to the effects of the drug taking place over longer periods than examined in this experiment. Our subjects were current cocaine users and it is likely that they are tolerant to the effects of cocaine as compared to a naive population.

The rating patterns of drug "rush" differed from other subjective responses. Drug "rush" was unaffected by maintained cocaine plasma concentrations while still dose responsive. Thus, this feeling state shows partial independence of drug plasma concentration and either acute tolerance or a refractory period. We believe that drug rush is a distinct feeling state and may be a critical variable that under real-world conditions is a determinant of the pattern and frequency of intravenous cocaine self-administration.

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