THE PHARMACOKINETIC DETERMINANTS OF THE FREQUENCY AND PATTERN OF INTRAVENOUS COCAINE SELF-ADMINISTRATION IN RATS BY PHARMACOKINETIC MODELING

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ABSTRACT:

We investigated the pharmacokinetic determinants of the frequency of intravenous cocaine self-administration in 2.5-h sessions. Two groups of rats were implanted with dual catheters that permitted cocaine infusion and blood sampling via the femoral and jugular vein catheters, respectively. Half of the animals in each group self-administered one of the two cocaine unit doses (0.5 and 1 mg/kg/infusion) by pressing a lever under a continuous schedule of reinforcement. To monitor serum cocaine concentrations, the remaining animals received concurrent, response-independent infusions whenever the matched animals self-administered cocaine infusions. Multiple concentration-time data in two successive self-administrations were determined to monitor the extent of fluctuation in concentrations by pharmacokinetic modeling. Behavioral analyses revealed the higher unit dose (1 mg/kg) resulted in less frequent cocaine self-administration, and a longer interinfusion interval, whereas the total doses were similar for the two groups (24.5–27.0 mg/kg/2.5 h). Cocaine decayed biexponentially. Both the values of clearance and terminal elimination rate constant for the self-administration paradigm were significantly greater than those after the bolus cocaine dosing series (0.5 and 1 mg/kg, separated by 3 days). The regularity in cocaine self-administration produced relatively stable serum cocaine concentrations that oscillated between maximum (C_{max}) and minimum (C_{min}) values regardless of dose size and interinfusion interval. Although the C_{max} for the 1-mg/kg unit dose (1.47 μg/ml) was significantly higher than that for the 0.5-mg/kg dose (0.82 μg/ml), the C_{min} values between the groups approximated each other (0.28, and 0.34 μg/ml, respectively). Hence, the C_{min} is the determinant of the initiation of the next drug-taking behavior.

Intravenous cocaine self-administration was first demonstrated in rats in 1968 (Pickens and Thompson, 1968). In that study, rats implanted with i.v. cannulas were placed in operant chambers where each lever-press response (i.e., fixed ratio 1 schedule) produced an infusion of a fixed dose of cocaine (e.g., 1 mg/kg/infusion). The resulting self-infusion behavior was viewed as an example of operant conditioning, in which the drug infusion served as a reinforcer for responses leading to its presentation. The results indicated that the number of infusions varied inversely in an almost linear manner with the size of the unit dose. That is, as the unit dose was increased, the number of infusions decreased and the interinfusion interval increased. As a result, the total self-administered drug dose remained relatively similar across different unit doses. The inverse relationship between the frequency of drug self-administration and unit dose also has been shown in studies of cocaine and other drugs of abuse (e.g., morphine, amphetamine) by using various schedules of reinforcement in mice (David et al., 2001), rats (Carroll et al., 1981; Caine et al., 1999), monkeys (Goldberg et al., 1971; Wilson et al., 1971), and humans (Foltin and Fischman, 1992; Dudish et al., 1996).

It has been hypothesized that in self-administration sessions, animals compensate for changes in drug unit dose by adjusting response rates to maintain a constant blood level over time (Wilson et al., 1971). Indeed, blood concentrations of dextro and levo isomers of amphetamine determined immediately after a drug infusion in rats were found to be similar across a range of unit doses (0.25–1 mg/kg/injection) in drug self-administration behavior (Yokel and Pickens, 1974). These results suggested that the initiation of stimulant drug administration occurs when blood drug concentration falls below a minimum level (Yokel and Pickens, 1976). However, plasma β-phenylethylamine concentrations (Cone et al., 1978) determined immediately before and after a drug infusion in dogs were different between the two unit doses (3 and 6 mg/kg/infusion). Due to a lack of complete concentration-time profiles for the self-administration sessions in the two studies, the inconsistent conclusions are likely to occur.

Accordingly, the aim of this study was to investigate the pharmacokinetic (PK) determinants of the rate of intravenous cocaine self-administration in rats by applying PK principles developed by pharmacokineticists in therapeutics for multiple dosing. That is, cocaine concentration-time profiles (CTPs) for multiple dosing in the linear range can be predicted after a drug’s PK parameters have been characterized (Gibaldi and Perrier, 1982). The regularity in frequency

1 Abbreviations used are: PK, pharmacokinetics; CTP, concentration-time profile; PD, pharmacodynamics; AIC, Akaike’s information criterion; CL, clearance; V_c, volume of distribution in the central compartment; MRT, mean residence time; AUC, area under the curve; ANOVA, analysis of variance.
of cocaine self-administration can be treated as a special case of multiple-dose regimen. Cocaine concentration is expected to increase and then decrease after each self-administration, whereas the extent of this fluctuation mainly depends upon PK parameters, dose size, and dosing interval as described in our previous study for oral cocaine in a cumulative dose regimen (Lau et al., 2000). It is of interest to characterize whether or how the PK of cocaine after self-administering high doses of cocaine differed from that after an acute dose regimen, thereby facilitating delineation of the determinant of the initiation of the next drug-taking behavior.

Materials and Methods

Animals. Sixteen male, adult, albino, virus-free rats of the Sprague-Dawley strain from Harlan Bioproducts for Science (Indianapolis, IN) with a mean, initial body weight of 381 g (range 378–387 g) were housed individually in a temperature-regulated room with a daily cycle of illumination from 7:00 AM to 7:00 PM. Body weights were reduced to 80% of free-feeding levels by limiting daily food rations over a 2-week period as described previously (Lau et al., 1999), and held at these weights for the duration of the experiment. The food-limited regimen was chosen to facilitate comparison of PK parameters to those determined in our previous studies (Lau et al., 2000; Sun and Lau, 2001a). Water was continuously available in the living cages. Experiments were conducted in accordance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publication 85-23, revised 1996).

Drug. Cocaine HCl (mol wt. 339.8) was obtained from the Research Triangle Institute (Research Triangle Park, NC) through the National Institute on Drug Abuse. The drug was dissolved in sterilized 0.9% NaCl. For i.v. bolus administration, cocaine solution was administered in a volume of 1 ml/kg of body weight and delivered in 30 s. To ensure drug solution was completely administered, 0.3 ml of 0.9% saline was delivered in 30 s to wash out the catheter. For i.v. cocaine self-administration sessions, two concentrations, 1.5 and 3.0 mg/ml, were prepared daily to give unit doses of 0.5 and 1 mg/kg, respectively. Each infusion of cocaine was delivered in a 0.117-ml volume at a rate of 1.17 ml/min over 6 s by using a syringe infusion pump (Razel Scientific Instruments Inc., Stamford, CT) equipped with a 20-ml syringe (BD Biosciences, Franklin Lakes, NJ). All cocaine doses were expressed in terms of salt and were corrected to base (mol wt. 303.4) for calculation of PK parameters.

Catheterization. Right jugular and femoral vein cannulation was performed under sterile conditions and has been described previously (Sun and Lau, 2001a). The jugular vein catheters were made of polyethylene tubing (PE 50; 0.58-mm i.d. x 0.97-mm o.d.; BD Biosciences, Parsippany, NJ) attached to silicone tubing (0.51-mm i.d. x 0.94-mm o.d.; Silastic; Dow Corning, Midland, MI). The femoral vein catheters were made of Renathane tubing (0.64-mm i.d. x 1.02-mm o.d.; Braintree Scientific, Inc., Braintree, MA). The proximal end of the Silastic catheter or the Renathane catheter was inserted into the vein. The distal ends of the catheters were externalized subcutaneously and connected to two metal outlets of a plastic pedestal (Value Plastics, Inc., Fort Collins, CO) cemented to the skull. The dual catheters accommodate the administration of drug solution via the femoral vein catheter and blood sampling via the jugular vein catheter to avoid contamination of the blood samples with dosing solution. The animals were allowed to recover from catheterization for at least 5 days before drug administration. The catheter was flushed with 0.9% saline containing 50 units of heparin per milliliter and was sealed with fishing line (0.6 mm) when not in use.

Apparatus. Each operant chamber (30 x 33 x 27 cm) had side and back panels of aluminum, a front panel of Plexiglas, and a stainless steel grid floor. A response lever (MED Associates, Georgia, VT) was mounted on the right side panel, 4 cm from the grid floor and a small stimulus light (4 W) was located 3 cm above the response lever. Two Chicago Miniature Lamp house lights (28 V, 0.1 amp, Allied Electronics, Inc., Parsippany, NJ) were mounted inside each chamber to provide illumination. The rat’s cannula was connected to a drug delivery leash (MED Associates) attached to a swivel (Instech Laboratories, Plymouth Meeting, PA) mounted above the chamber. Tygon tubing connected the top of the swivel to an infusion pump. Each chamber was enclosed in a light- and sound-attenuating box (104 x 76 x 60 cm; MED Associates). A fan provided ventilation and masking noise for each chamber. An IBM compatible computer with interface control cards (MED Associates) was used for session programming and data were collected using QuickBasic (Microsoft Corp., Redmond, WA).

Procedures for i.v. Cocaine Self-Administration. After animals’ body weights had been stabilized, two i.v. bolus doses of cocaine (0.5 and 1.0 mg/kg) separated by 3 days were administered for characterization of PK parameters of cocaine. Serial blood samples (100 μl) were obtained via jugular vein catheters for determination of cocaine concentrations. An equal volume of sterilized 0.9% NaCl solution was administered to maintain a constant blood volume after each blood sampling. Rats were then divided into two groups (n = 8) in terms of the unit dose of cocaine infusions. Groups 1 (s1-s8) and 2 (t1-t8) received 0.5 and 1 mg/kg/infusion, respectively. Half of the animals in each group (n = 4; s1-s4 and t1-t4) were allowed to self-administer cocaine via indwelling jugular catheters under a fixed ratio 1 schedule of cocaine presentation (i.e., the rat had to press the lever once to receive the cocaine injection) in 2.5-h sessions. No limits were imposed on the number of infusions allowed per session. Daily self-administration sessions commenced after two training sessions. Each rat was weighed and then connected to the catheter. The start of the self-administration session was signaled by the illumination of house lights. Activation of the lever produced an audible click of a microswitch and initiation of cocaine infusion (i.e., 6 s) throughout which the stimulus light flashed at a constant rate. Each infusion was immediately followed by a 30-s time-out period signaled by retraction of the response lever and turning off of the stimulus cue light. Extension of the response lever indicated the next period of access to cocaine. Animals were returned to home cages after each daily session.

Data Analysis. Because the number of self-administration sessions conducted (range 5–10 days) differed among animals due to the variation in catheter lives, behavioral analyses were performed only for the first five sessions. The interdosing intervals (150 min/number of infusions) and total cocaine doses self-administered (unit dose x number of infusions) were calculated for each individual rat and averaged for all subjects under the same conditions.

Blood Sampling during Self-Administration Sessions. The remaining animals from the two groups (n = 4; s5-s8 and t5-t8) received response-independent infusions of the same dose simultaneous with the infusion of the matched self-administering animals for monitoring serum cocaine concentrations. These yoked rats were placed in Plexiglas chambers located adjacent to the operant chambers. The between-subject design in the PK and PD studies was used to prevent any effect of blood sampling on the ongoing behavior, as was done in our previous studies (Lau et al., 1999; Sun and Lau, 2000). Each yoked animal in the PK study experienced the same drug infusions as those of the matched self-administering animal, so that the PK profile of the former reflected that of the latter. To accurately determine the fluctuation of cocaine concentrations between two successive cocaine infusions, serial blood samples (usually 4–6 samples) were obtained at a rate adjusted by each rat’s interinfusion intervals (i.e., groups 1 and 2, 3.5 and 6.2 min/infusion, respectively; see below). Namely, sampling started immediately after a cocaine infusion and continued after the following infusion with each sampling separated by 1 to 2 min. To avoid dilution of the blood samples due to the short intersampling times, an equal volume of sterilized 0.9% NaCl solution was not administered during this period. Because only 10 blood samples (100 μl/sample) can be drawn in a day for rats, the cycle of blood sampling was repeated once more in the later part of the session, 59 min apart (range 31–109 min). The first blood sampling was conducted during the second self-administration session, and thereafter, every 3 days if the catheters remained patent. Hence, total blood sampling sessions for the two groups were three, two, and one for two (t2, t6; and t4, t8), five (s1, s5; s2, s6; s3, s7; s4; s8; and t3, t7), and one (t1, t5) pair of animals, respectively. For self-administering animals, two blood samples were taken immediately after sessions for verifying cocaine concentrations.

Blood samples were immediately centrifuged; serum samples were stored frozen and analyzed within a week. Previously, we found that in vivo rat serum cocaine samples were stable for at least a month without the presence of sodium fluoride, a cholinesterase inhibitor (Lau et al., 1990); thus, sodium fluoride was not used in the present study.

Determination of Cocaine by High-Performance Liquid Chromatography. Serum levels of cocaine were determined by a fluorometric high-perfor-
mance liquid chromatography method developed in our laboratory for micro-samples with a detection limit of 0.5 ng/ml (Sun et al., 2000).

PK Analysis. The compartmental module of the SAAM II software system (SAAM Institute, 1997) was used for PK analyses as described previously by using naïve pooled data (Lau et al., 1999, 2000; Sun and Lau, 2001a). Model parameters were estimated by visual examination and numerical optimization using Akaike’s information criterion (AIC) as the objective function (Akaike, 1974) to evaluate model order and to perform model discrimination. During model formulation, different weights [e.g., 1/(0.1)2], were used, where y is the predicted concentration. The best fit was achieved with the weight of 1/(0.1)2.

Serum cocaine CTPs after i.v. bolus (0.5 and 1 mg/kg) were described by an open two-compartment model, with elimination from the central compartment. The compartmental model parameters, the volume of distribution of the central compartment (V1,0), and the rate constants for drug transfer between compartments and for elimination (k12,b, k12,sa, and k10,sa) are used to calculate the pharmacokinetic parameters in the equation C = A e−kt + Be−pt, by using standard formulas (Gabrielsson and Weiner, 1997), where the terms A and B are the extrapolated zero intercepts, and α₁ and β₁ are the slopes representing the apparent first order distribution and elimination rate constants, respectively. The subscript b denotes bolus. The PK parameters, namely, clearance (CL1,0), volume of distribution at steady state (V1,0), and mean residence time (MRT1,0), were calculated using standard noncompartmental methodology. The area under the CTP from time 0 to infinity (AUC) for cocaine was obtained from the SAAM II software system.

The time points of each self-administration were recorded throughout each rat’s session for the use of the simulation mode of the SAAM II software system. That is, by applying PK principles for a drug exhibiting linear kinetics under both acute and multiple-dose regimens (Gibaldi and Perrier, 1982), cocaine CTPs for self-administration can be simulated from the PK estimates for the acute bolus administration (Table 1, top) if both the dose size (0.5 or 1 mg/kg) and the time of each self-administration are known. However, the simulated CTPs did not describe the observed CTPs obtained from the yoked animals (Fig. 4), indicating that cocaine disposition after cocaine self-administration differed from that of acute bolus administration. Accordingly, the PK parameters for serum cocaine CTPs after i.v. self-administration sessions were estimated using separate PK parameters for volume of distribution (V1,0), and the elimination rate constant (k10,sa) from those of bolus administration. However, the intercompartmental rate constants (k12,sa and k12,b) were fixed for each animal at the respective values for the bolus dosing (see Results). The subscript sa denotes self-administration. The observed concentration-time profiles for self-administration sessions for each rat were fitted simultaneously. Because cocaine infusions were stable after the 15-min time point (Figs. 1D and 2), the maximum (Cmax) and minimum (Cmin) cocaine concentrations for each self-administering animal were calculated from the predicted values for the sessions that blood samples were taken.

Statistical Analysis. Two-way analyses of variance (ANOVA) with one factor (time or session for PK and PD experiments) were used to analyze between-group (PD or PK) differences. Repeated measures two-way ANOVAs were used to compare within-group differences in CTPs between the two bolus doses. One-way repeated measures ANOVAs were used for the within-group comparisons in PK (rate constants) and PD (15-min time blocks or session) profiles. Post hoc analyses were performed as appropriate using Newman-Keuls tests. Paired t-tests were used to analyze within-group differences in PK parameters (e.g., V₁,₀, rate constants), whereas t-tests were used to examine between-group PK and PD parameter differences (e.g., V₁,₀, k₁₀,₀, the number of responses, interinfusion intervals, cocaine doses, Cmax, and Cmin). A significance level of P < 0.05 was used for all statistical analyses. All analyses were conducted using SigmaStat (SPSS, Inc., Chicago, IL).

Results

After the two training sessions of cocaine self-administration, the number of responses was stable across the five consecutive sessions within a group (P > 0.05), whereas the responding for group 1 (0.5 mg/kg/infusion) was significantly greater than that for group 2 (1 mg/kg/infusion; P < 0.001; Fig. 1A). Accordingly, the interinfusion intervals for group 2 were significantly longer than those for group 1.

### Table 1

Mean PK and PD parameters (± S.E.) for cocaine after bolus and self-administration dosing regimes in rats

<table>
<thead>
<tr>
<th>Subscript b and sa denote bolus and self-administration, respectively.</th>
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<tr>
<td><strong>PK parameters</strong></td>
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<tr>
<td><strong>Bolus administration</strong></td>
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<tr>
<td>V₁,₀,b (l/kg)</td>
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<tr>
<td>V₁,₀,sa (l/kg)</td>
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<td>CL₁,₀ (l/h/kg)</td>
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<td>MRT₁,₀ (min)</td>
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<td>k₁₀,b (min⁻¹)</td>
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<td>α₁ (min⁻¹)</td>
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<tr>
<td>t₁/₂,₀,b (min)</td>
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<td>β₁ (min⁻¹)</td>
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<tr>
<td>t₁/₂,₀,sa (min)</td>
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<tr>
<td>AUC₀→∞,₀,b (µg · min/ml)</td>
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<td>AUC₀→∞,₀,sa (µg · min/ml)</td>
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<td>AIC</td>
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| **Self-administration**                                     |
| V₁,₀,sa (l/kg)     | 1.3 ± 0.07     | 1.25 ± 0.08 |
| k₁₀,sa (min⁻¹)     | 0.03 ± 0.02    | 0.04 ± 0.02 |
| k₁₂,sa (min⁻¹)     | 0.040 ± 0.009  | 0.034 ± 0.006|
| CL₁,₀ (l/h/kg)     | 16.7 ± 2.4     | 11.3 ± 1.1  |
| α₁ (min⁻¹)         | 0.28 ± 0.03    | 0.22 ± 0.03 |
| t₁/₂,₀,sa (min)    | 2.5 ± 0.2      | 3.2 ± 0.4   |
| β₁ (min⁻¹)         | 0.046 ± 0.007  | 0.030 ± 0.004|
| t₁/₂,₀,sa (min)    | 15.7 ± 2.5     | 23.7 ± 2.5  |
| AUC₀→∞,₀,sa (µg · min/ml) | 72.6 ± 10.7 | 125.7 ± 9.6 |
| AIC                | -1.23 ± 0.58   | -0.81 ± 0.57|

| **PD parameters**                                           |
| Number of responses                                         |
| 43.7 ± 1.3                                                  | 24.5 ± 0.6   |

| Interinfusion intervals (min)                                |
| 3.5 ± 0.1                                                   | 6.2 ± 0.1   |

| Total doses (mg/kg)                                         |
| 24.5 ± 0.8                                                 | 27.0 ± 0.6  |

| Cmax (µg/ml)                                                |
| 0.82 ± 0.08                                                | 1.47 ± 0.05 |

| Cmin (µg/ml)                                                |
| 0.28 ± 0.06                                                | 0.34 ± 0.05 |

FIG. 1. For the five consecutive cocaine self-administration sessions in groups 1 (0.5 mg/kg/infusion; s1-s4) and 2 (1 mg/kg/infusion; t1-t4), the mean (S.E.) daily values of number of responses (A), interinfusion intervals (B), cocaine doses (C), and number of responses in 15-min blocks (D) are presented.
Although the overall doses for group 2 were significantly greater than those for group 1 (P < 0.05; Fig. 1C), post hoc comparisons revealed that for each daily session, cocaine doses did not differ between the two groups (P > 0.05). Figure 1D shows the mean total responses plotted against 15-min time blocks to show the rate and pattern of cocaine self-administration within a session for the two groups. The numbers of responses for the first 15-min time block were significantly greater than those for the successive blocks in each group (P < 0.001), and the values after the first 15-min time block were found to be similar within each group (P > 0.05). However, the number of responses across the session for group 1 was significantly greater than that for group 2 (P < 0.001). Figure 2 shows that a stable cocaine self-administration behavior in terms of the rate and pattern of cocaine infusions was established rapidly for the five daily sessions as indicated by the results from two rats, one from each group (s1 and t1).

The mean serum cocaine CTPs for rats assigned to self-administered (filled symbols) and yoked (open symbols) cocaine infusion groups are shown in Fig. 3, A and B. Although serum cocaine CTPs were dose-related within a group (P < 0.05), the profiles for the yoked group approximated those of the self-administered group for the two bolus doses (P > 0.05). Hence, the PK parameters were estimated simultaneously for each pair of matched animals. The mean PK estimates for four pairs of matched animals in each group are shown in Table 1 (top). Cocaine decayed biexponentially after i.v. bolus administration, with a distribution half-life (t1/2,d) of 5.8 to 6.8 min, and a terminal half-life (t1/2,sa) of 31.1 to 38.0 min. One set of PK parameters accounted for the two cocaine doses, indicating that the PK of cocaine was not dose-dependent in the dose range used (0.5–1.0 mg/kg) irrespective of groups. The coefficient of variation values for the model parameters (Vc,sa, k10,sa, and k12,sa) for group 1 were 7.9, 11.3, 22.0, and 14.2%, respectively, and for group 2 were 1, 9.4, 17.7, and 13.8%, respectively. Figure 3, C to F, shows that the predicted (lines) CTPs described the observed data (symbols) well for each pair of matched animal from both groups.

During model formulation, we examined whether the PK parameters of bolus administration described adequately the serum cocaine CTPs for the self-administration sessions. The simulated CTPs for both groups overestimated grossly the measured serum cocaine CTPs during and after the self-administration sessions as shown in the representative profiles, one from each group (Fig. 4, A and B). In particular, the values of Cmin were inflated. Because the interinfusion intervals for both groups were t1/2,b (Table 1), a one-compartment PK model was explored. The monoexponential decay described the CTPs of self-administration sessions adequately well as judged by visual examination of the plots and AIC values (1.22 and 0.67 for groups 1 and 2, respectively). However, both the Vc,sa (i.e., 1.16 and 1.18 l/kg for groups 1 and 2, respectively) and the t1/2,sa (0.693/k10,sa) values (i.e., 2.9 and 4.7 min for groups 1 and 2, respectively) were smaller compared with those after bolus administration. Based on the finding that cocaine exhibited biexponential decay under an i.v. constant infusion dose regimen (Sun and Lau, 2001b), we excluded the one-compartmental model, because absorption, distribution, metabolism, and elimination are ongoing processes. However, this exercise...
Group 1 (0.5 mg/kg/infusion)

- s2
- s6
- Predicted

Group 2 (1.0 mg/kg/infusion)

- t2
- t6
- Predicted

Fig. 4. Predicted (lines) and measured serum CTPs for two representative pairs of matched animals, one from each group: group 1 (s2 and s6; 0.5 mg/kg/infusion) (A) and group 2 (t2 and t6; 1 mg/kg/infusion) (B).

Serum cocaine CTPs were predicted from the PK estimates of cocaine after bolus administration by inputting the dosing regimens of the self-administering rats (i.e., the unit dose, and the times of self-injections). Open and filled symbols are the measured concentrations obtained from the yoked rats during sessions and from the self-administering rats after the sessions, respectively.

Serum cocaine CTPs were predicted from the PK estimates of cocaine after bolus administration by inputting the dosing regimens of the self-administering rats (i.e., the unit dose, and the times of self-injections). Open and filled symbols are the measured concentrations obtained from the yoked rats during sessions and from the self-administering rats after the sessions, respectively.

Table 1 (middle) shows that \( V_{c,sa} \) and \( t_{1/2,sa} \) differed significantly from those after the bolus administration for both groups, whereas the values of \( V_{c,sa} \) did not differ between those of group 2 (\( P > 0.05 \)). Specifically, the values of \( V_{c,sa} \) and \( t_{1/2,sa} \) for the self-administration sessions were about half of those for the bolus doses (\( P < 0.01 - 0.0005 \)). Consequently, \( CL_{sa} \) was about 2 times greater than \( CL_{b} \) (\( P < 0.05 \)), indicating that the parameters of \( V_{c} \), \( t_{1/2} \), and \( t_{1/2} \) exhibited nonlinear characteristics after repeated cocaine self-administrations. The coefficient of variation values for the model parameters \( (V_{c,sa} \) and \( k_{10,sa} \)) for group 1 were 6.22 and 7.8%, respectively, and for group 2 were 8.1 and 12.7%, respectively. Figure 5, A to H, shows serum cocaine CTPs for the two groups predicted from the PK parameter values that were estimated from the observed CTPs of yoked animals by inputting the dosing regimens for the corresponding self-administering animals (i.e., dose size and the times of self-injections). It is apparent that the predicted CTPs (solid lines) described the observed profiles adequately (open symbols) irrespective of the individual differences in pattern of self-administration (Fig. 5). Furthermore, serum cocaine concentrations determined from the self-administering animals after the session (filled symbols) were accounted for by the predicted profiles. Taken together, the unit dose of cocaine governed the rate of cocaine self-administration, which in turn determined the extent of fluctuations in serum cocaine concentration from \( C_{min} \) to \( C_{max} \) values.

Table 1 (bottom) shows the overall mean PD estimates for the five self-administration sessions. Although the number of responses for group 1 was significantly greater than group 2 (\( P < 0.001 \)), the total dose administered did not differ between the two groups (\( P > 0.05 \)). Furthermore, although the \( C_{max} \) for group 2 was significantly greater (\( P < 0.0001 \)) than that for group 1, \( C_{min} \) values did not differ between the two groups (\( P > 0.05 \)). This indicates that \( C_{min} \) is the determinant of the initiation of the next episode of drug-taking behavior, coinciding with the results that the interinfusion interval for group 2 was much longer than that for group 1 (\( P < 0.0005 \)).

Discussion

Animals will self-administer most of the drugs (e.g., cocaine) that humans abuse (Griffiths et al., 1980). Hence, the cocaine self-administration paradigm is widely used in animal research as a model of drug abuse, and studies of such behavior are thought to have relevance for the analysis and treatment of cocaine abuse in humans (Witkin, 1994; LeSage et al., 1999). Our behavioral analyses revealed the higher unit dose (1 mg/kg) resulted in less frequent cocaine self-administration (Fig. 2A), and a longer interinfusion interval (Fig. 2B), whereas the total doses were similar for the two groups (Fig. 2C). The inverse relation between the frequency of self-injection and unit dose corresponded to the finding reported by other investigators (Goldberg et al., 1971; Wilson et al., 1971; Carroll et al., 1981; Caine et al., 1999). To the best of our knowledge, however, this is the first study that describes the complete cocaine CTPs for self-administration sessions by PK modeling, thereby facilitating the investigation of the PK determinants for drug-taking behavior.

The reinforcing effects of cocaine are mediated by increases in extracellular dopamine concentrations resulting from the blocking of the dopamine reuptake into presynaptic terminals (Sershen et al., 1982; Ritz et al., 1987). Numerous studies have used an in vivo microdialysis procedure in the brain to determine either dopamine (Pettit and Justice, 1989, 1991) or concurrent dopamine and cocaine concentrations (Hemby et al., 1997) under self-administration paradigms. Simulated dopamine and concurrent dopamine and cocaine concentrations with biexponential decay in the nucleus accumbens fluctuated phasically from \( C_{max} \) to \( C_{min} \) values (Pettit and Justice, 1989; Wise et al., 1995). Hence, the pattern of dopamine and cocaine CTPs in the brain is similar to that in plasma for drugs under multiple-dose regimens. This is expected, as serum cocaine concentrations correlated with those in the brain (Lau et al., 1991; Hedaya and Pan, 1997).

Regularity in cocaine self-administration occurred about 15 min after sessions commenced, after which serum cocaine concentrations oscillated between relatively stable \( C_{max} \) and \( C_{min} \) values regardless of dose size or interinfusion intervals, as shown in the CTPs (Fig. 5). Although the \( C_{max} \) for group 2 was about two times greater than that for group 1 (Table 1, bottom), the \( C_{min} \) did not differ between the two groups, demonstrating that \( C_{min} \) is the determinant of initiation of the next drug-taking behavior. It is known that about 90% of a steady-state drug concentration \( (C_{ss}) \) will be reached within approximately four half-lives after multiple dosing (Gibaldi and Perrier, 1982). Therefore, the values of \( C_{max} \) and \( C_{min} \) reported herein (Table 1, bottom) are not those of \( C_{ss,max} \) and \( C_{ss,min} \), which should be calculated at approximately 63 to 95 min based on cocaine’s \( t_{1/2} \) values for the two groups. Rather, the \( C_{min} \) is self-regulated by each animal, and it takes about 15 min to reach a desired stable \( C_{max} \), as indicated by the irregularly high numbers of responses that occur after the start of cocaine self-administration.

It has been suggested that animals responded for the subsequent
injections only when the drug level reached a constant, critical level irrespective of the unit drug dose presented in drug self-administration sessions (Yokel and Pickens, 1976). This was based on simulated body amphetamine levels by using a published $t_{1/2}$ value and a standard multiple-dosing formula. However, in that study, as a separate experiment, single blood amphetamine concentrations, determined immediately after a self-injection, appeared to remain monotonic with no fluctuation. To monitor the fluctuation accurately, more detailed CTPs of successive self-injections must be obtained, which is a difficult task due to the limited sample size and the short catheter lives. Because the interinfusion intervals were relatively stable across the session, we concentrated on taking the maximal number of blood samples possible in two successive self-injections from the matched yoked rats, so that blood sampling had no effect on the ongoing self-administration behavior. This is feasible because of the minimal between-subject variability in serum CTPs for each pair of animals after bolus administration (Fig. 3, C and D). Furthermore, the predicted CTPs for the yoked rats accounted for the concentration-time data obtained after the sessions with the self-administering rats (Fig. 5), corresponding to the finding that cocaine concentrations in the nucleus accumbens were not different between self-administering and yoked rats (Hemby et al., 1997).

**Fig. 5.** Predicted (lines) and measured serum cocaine CTPs for representative self-administration sessions: group 1 (s1-s8; 0.5 mg/kg/infusion) (A-D) and group 2 (t1-t8; 1 mg/kg/infusion) (E-H).

Serum cocaine CTPs were predicted from the PK parameters estimated from the observed CTPs of yoked rats by inputting the dosing regimens of the corresponding self-administering rats (i.e., the unit dose and the times of self-injections). Open and filled symbols are the measured concentrations obtained from the yoked rats during sessions and from the self-administering rats after sessions, respectively.
Cocaine exhibited linear kinetics after i.v. bolus administration (0.5–5 mg/kg) in rats (Booze et al., 1997; Hedaya and Pan, 1997; Lau et al., 1999; Mets et al., 1999). Because the PK estimates of i.v. cocaine bolus administration for both groups reported here approximated those described previously for rats under the same food-limited regimen (Lau et al., 1999, 2000; Sun and Lau, 2001a), linear kinetics can be assumed here (Table 1). However, CL and $t_{1/2,\beta}$ of cocaine under acute i.v. dose regimens (1–5 mg/kg) decreased with dose in dogs and humans (Barnett et al., 1981; Parker et al., 1998).

Under the infusion paradigms, the disposition of cocaine exhibited different characteristics. A significant increase in $CL_{ci}$ (ci denotes constant infusion) for cocaine was found under constant i.v. infusion for 2 h (4.9–9.8 mg/kg) compared with that after bolus administration in rats (Sun and Lau, 2001b). This is consistent with the results presented here after rats self-administered a total dose of 24.5 to 27 mg/kg. Furthermore, the values of $CL_{sa}$ and $CL_{sn}$ approximated those of $CL_{ci}$ and $CL_{sa}$ in the above-mentioned study. This indicated that within a dose regimen CL was not dose-dependent but regimen-dependent. Cocaine is known to significantly increase heart rate, blood pressure, and blood flow (Fraker et al., 1990), which in turn may change the elimination ability in a dose-related manner. In our two infusion studies that change may yield a greater CL after large doses of cocaine were administered. Simulation revealed that the intercompartment rate constants produced no apparent CTP changes even when their values were 10 times greater or smaller than those shown in Table 1, whereas the parameters of $V_{a,sa}$ and $k_{1,0,sa}$ produced profound upward or downward shifts in CTPs (Fig. 4, A and B). The decrease in $V_{a,sa}$ values cannot be explained by the increase in blood volume that resulted from cocaine self-infusions; otherwise, the values would be greater. Therefore, the PK estimates of bolus dosing could not describe the observed CTPs during and after self-administration sessions, especially for the $C_{\text{min}}$ values (Fig. 4). This might at least, in part, explain why different calculated $C_{\text{min}}$ values of $\beta$-phenethylamine were observed in dogs after the animals self-administered three unit doses when linear kinetics was assumed (Cone et al., 1978).

Although the effects of cocaine on the cardiovascular system (Resnick et al., 1977; Kloner et al., 1992) may account for the increase in $CL_{sa}$ compared with $CL_{sn}$, other as yet unknown factors cannot be excluded. Further studies are needed to determine the mechanism(s) involved in the change in elimination ability for the constant infusion and self-administration dosing regimes. Although either monoexponential or biexponential decay can equally describe the CTPs under cocaine self-administration as described under Results, the biexponential decay is the model of choice based on the notion that disposition is a continuous process, as shown in the biexponential decay after cessation of constant cocaine infusions for 2 h (Sun and Lau, 2001b). Furthermore, Fig. 6 shows that the initial disappearance of cocaine also exhibits the tendency of biexponential decay after 60- and 90-min self-administration sessions (0.5–mg/kg/infusion dose).

In summary, this study provided direct evidence that the $C_{\text{ma}}$ is the determinant for initiation of the next drug-taking behavior after describing the complete CTPs for the two unit cocaine doses by PK modeling. The disposition of cocaine after self-administered high doses differed from that after acute dose administration. The methodology described here can be used to investigate whether and how the PK of cocaine plays a role in pharmacotherapies to aid in the treatment of cocaine abuse. Recently, PK intervention was investigated as a possible method in which catalytic antibodies promote rapid degradation of cocaine into its metabolites, thereby blocking its reinforcing effects in animals (Baird et al., 2000). To successfully assess the effectiveness of this intervention, it is useful to compare the

**PK parameters for cocaine self-administration before and after implementing the intervention.**

**References**


