Elimination of Cocaine and Metabolites in Plasma, Saliva, and Urine Following Repeated Oral Administration to Human Volunteers

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Abstract

Chronic administration of lipophilic drugs can result in accumulation and prolonged elimination during abstinence. It has been suggested that cocaine and/or metabolites can be detected in saliva and urine for an extended period following long-term, high-dose administration. The effects of chronic oral cocaine administration in healthy volunteer subjects with a history of cocaine abuse were investigated. Subjects were housed on a closed clinical ward and were administered oral cocaine in up to 16 daily sessions. In each session, volunteers received five equal doses of oral cocaine with 1 h between doses. Across sessions, cocaine was administered in ascending doses from an initial dose of 100 mg (500 mg/day) up to 400 mg (2 g/day), increasing by 25 mg/dose/session (125 mg/session). Participation in the study was terminated if cardiovascular safety parameters were exceeded. Plasma and saliva specimens were collected periodically during the dosing sessions and during the one-week withdrawal phase at the end of the study. All urine specimens were collected throughout the entire study. Specimens were analyzed for cocaine and metabolites by solid-phase extraction followed by gas chromatographic–mass spectrometric analysis in the SIM mode. The limit of detection for each analyte was approximately 1 ng/mL. The analytes measured included benzoylecgonine (BZE), ecgonine methyl ester, cocaine, benzoylnorecgonine, norcocaine, *m*- and *p*-hydroxycocaine, and *m*- and *p*-hydroxybenzoylecgonine. Noncompartmental analysis was employed for the determination of plasma and saliva pharmacokinetic parameters. Urinary elimination half-lives for cocaine and metabolites were determined by constructing ARE (amount remaining to be excreted) plots. Two phases of urinary elimination of cocaine and metabolites were observed. An initial elimination phase was observed during withdrawal that was similar to the elimination pattern observed after acute dosing. The mean ($N = 6$) plasma, saliva, and urine cocaine elimination half-lives were 1.5 ± 0.1 h, 1.2 ± 0.2 h, and 4.1 ± 0.9 h, respectively. For three subjects, the mean cocaine urinary elimination half-life for the terminal phase was 19.0 ± 4.2 h. There was some difficulty in determining if a terminal elimination phase for cocaine was present for the remaining three subjects because of interference by high concentrations of BZE. A terminal elimination phase was also observed for cocaine metabolites with half-life estimates ranging from 14.6 to 52.4 h. These terminal elimination half-lives greatly exceeded previous estimates from studies of acute cocaine administration. These data suggest that cocaine accumulates in the body with chronic use resulting in a prolonged terminal elimination phase for cocaine and metabolites.

Introduction

Repeated drug administration can result in accumulation in bodily tissues and extended elimination times upon cessation of use. Although cocaine has an extremely short half-life of approximately 1 h, accumulation in tissues could conceivably result in prolongation of effects, amelioration of withdrawal, and alteration of detection times. In an earlier study, Nayak et al. (1) compared cocaine disposition in acutely and chronically treated rats. Acutely treated rats received a single intravenous (IV) cocaine dose of 8 mg/kg or a single subcutaneous cocaine dose of 20 mg/kg. Chronically treated rats received subcutaneous injections of 20 mg/kg twice daily over a 23-day period. The authors found consistently higher levels of cocaine in the brain, fat, and other tissues from the chronically treated group compared to the acutely treated group. Moreover, cocaine concentrations were much greater in fat than in the other tissues of the chronically treated animals, and cocaine was detectable in fat from chronically treated animals for up to four weeks after the final cocaine injection.

Recent clinical studies with human volunteers suggested that prolonged excretion may occur with frequent or long-term cocaine use. Weiss and Gawin (2) analyzed urine specimens from long-term, high-dose cocaine abusers. The sub-

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jects in this study were three hospital patients who tested positive for cocaine by urinalysis at time of admission. Urine was screened periodically for cocaine metabolite by immunoassay, and the results were confirmed by gas chromatography–mass spectrometry (GC–MS). At a cutoff concentration of 300 ng/mL, urine detection times ranged from 10 to 22 days. The authors suggested that the prolonged excretion resulted from cocaine accumulation with subsequent changes in the rate of cocaine elimination. Unfortunately, there was no way of ensuring that additional drug use did not occur in that setting. Cone and Weddington (3) also reported an extended elimination phase for cocaine in saliva and urine. Subjects ($N = 6$) in this study were chronic cocaine users who sought treatment. They resided on a secured clinical research ward where saliva and urine specimens were collected periodically during cocaine withdrawal. Cocaine was detected in saliva for up to 10 days and in urine for up to 15 days with radioimmunoassay (sensitivity = 0.5 ng/mL). The mean saliva cocaine elimination half-life was estimated as 68.2 h. Although these studies suggested that chronic cocaine use can result in an extended elimination phase for cocaine and metabolites, there have been no controlled clinical studies to support these observations.

As a continuation of a previous study, the elimination pattern of cocaine and metabolites in plasma, saliva, and urine from six human subjects following repeated oral administration of cocaine was examined (4). Biological specimens were collected during the last daily dosing session and for 5–7 days during the withdrawal period. Specimens were analyzed for cocaine and metabolites by GC–MS. Elimination curves were evaluated by pharmacokinetic analyses for evidence of a prolonged phase for cocaine and/or metabolites.

Methods

Chemicals and materials

The following drug standards were obtained: cocaine hydrochloride (Mallinckrodt, St. Louis, MO); benzoylecgonine (BZE) tetrahydrate, norcocaine (NCOC), benzoylnorecgonine (BNE), *m*-hydroxycocaine (*m*-HOCOC), *p*-hydroxycocaine (*p*-HOCOC), *m*-hydroxybenzoylecgonine (*m*-HOBZE), and *p*-hydroxybenzoylecgonine (*p*-HOBZE) (Research Biochemicals International, Natick, MA); and ecgonine methyl ester (EME) HCl, [$^2H_3$]-cocaine HCl, [$^2H_3$]-BZE tetrahydrate, and [$^2H_3$]-EME HCl (Sigma Chemical Co., St. Louis, MO). Methanol, methylene chloride, 2-propanol, and acetonitrile were HPLC grade, and all other chemicals were reagent grade. *N,O-bis* (Trimethylsilyl)trifluoroacetamide (BSTFA) with 1% trimethylchlorosilane (TMCS) was purchased from Pierce Chemical Co. (Rockford, IL). Clean Screen® solid-phase extraction columns (ZSDAU020) were purchased from United Chemical Technologies (Bristol, PA).

Human research subjects

Subjects were healthy male cocaine users who reported a recent cocaine use history of at least six months in duration. Inclusion criteria included self-reported use of smoked or IV cocaine at least two times per week for the six weeks prior to admission. Recent cocaine use was confirmed by urinalysis prior to participation in the study. In addition, subjects were determined to be free from significant medical or psychiatric disturbance by physical examination, history, routine laboratory chemistries, and psychiatric assessment. All subjects provided written informed consent and were financially compensated for their participation. The protocol was approved by the Johns Hopkins Bayview Medical Center Institutional Review Board and the National Institute on Drug Abuse/Intramural Research Program Institutional Review Board. Subject characteristics are summarized in Table I.

Clinical protocol

Subjects resided on the closed clinical ward of the Johns Hopkins University Behavioral Pharmacology Research Unit (Baltimore, MD) for approximately 4–5 weeks. A daily urine drug screen was performed on all subjects to ensure abstinence from other drugs of abuse. The overall study consisted of four phases: a washout period, single dosing sessions, multiple dosing sessions, and a withdrawal period. The washout phase occurred immediately after admission to allow for the elimination of previously used illicit cocaine. Following the washout period, the single dosing sessions were conducted for the determination of oral cocaine bioavailability and pharmacokinetics. During these sessions, three single doses of cocaine were administered over a one-week period. Then, up to 16 daily (Monday–Friday) multiple-dosing sessions were conducted. Placebo was administered during 3 of the 16 multiple-dosing sessions to serve as a control condition. During each multiple-dosing session, five equal doses of oral cocaine hydrochloride or placebo were administered at 1-h intervals, beginning at 9:00 A.M. Subjects were instructed to complete breakfast 2 h prior to the start of the session. Cocaine capsules were double encapsulated and hand polished to avoid contamination of the oral cavity. Cocaine was administered in ascending doses, with

Table I. Subject Summary*

Subject I.D.	Age (years)	Weight range (kg) (admission/discharge)†	Drug use history	Final dosing session (mg)	Reason for early discharge
A	38	75.8/87.1	CA‡	5 x 400	N/A
B	42	89.4/91.6	CA/OP	4 x 300	Sys BP > 165
D	34	83.5/99.8	CA/OP	5 x 400	N/A
E	33	70.3/74.4	CA/OP	5 x 300	BP > 165/100
G	34	64.4/74.4	CA/OP	1 x 375	HR > 130
K	33	68.9/74.8	CA	3 x 275	sensory hallucinations

* All subjects were African-American males.
† Because most meals and snacks were unrestricted, some subjects gained a substantial amount of weight during the study.
‡ Abbreviations: CA, cannabis; OP, opiates; Sys, systolic; BP, blood pressure; HR, heart rate.

increments of 25 mg/dose across successive sessions, resulting in a total increase of 125 mg per session. The initial cocaine dose was 100 mg, and the maximum possible dose was 400 mg. Participation was terminated if designated cardiovascular safety parameters were exceeded: (1) if heart rate was > 130 or blood pressure was > 165/100 within 4 min preceding a dose; (2) if heart rate did not fall below 110 during period between doses; (3) if heart rate exceeded (220 – subject age) × 0.85 at any time; or (4) if blood pressure exceeded 180/120 for 4 or more min). The withdrawal phase commenced after the multiple-dosing sessions, either when the 16 sessions were completed or when cocaine dosing was terminated for safety reasons. The withdrawal phase was approximately one week in duration for most subjects and was incorporated into the protocol to provide data on the terminal elimination of cocaine and metabolites. The data in this report were collected during the final multiple dosing session and the withdrawal phase of this study. Additional details on the study design are available in a previous report (4).

Specimen collection and analysis

Plasma and saliva specimens were collected at designated timepoints. Specimen collection times (relative to the time of the first dose of the final session) for the final multiple dosing session and withdrawal phase were –15 min; +30 min; +1 h; +2 h; +3 h; +4 h; +5 h; +6 h; +7 h; +8 h; +12 h; +24 h; +36 h; +48 h; +72 h; +96 h; and +120 h. Every urine void was collected separately throughout the entire study.

Blood specimens (4 mL) were collected into heparinized vacutainer tubes containing 2% (w/v) sodium fluoride and acetic acid to increase cocaine stability. Blood specimens were centrifuged, and plasma was separated and immediately frozen at –30°C until time of analysis. Saliva specimens were collected by expectoration into a 50-mL polypropylene tube. Saliva flow was stimulated with a piece of citric-acid-based candy. Following collection, saliva was aliquoted into cryotubes and frozen at –30°C until analysis. Urine specimens were collected into 250-mL polypropylene bottles. Urine volume was measured, and the specimen was aliquoted into cryotubes and frozen at –30°C until analysis.

Plasma, saliva, and urine specimens were analyzed for cocaine and metabolites by a previously published procedure with modifications (5). Briefly, plasma specimens were mixed with internal standard solution and acidified with sodium acetate buffer (2M; pH 4.0). The specimen mixture was centrifuged (3000 rpm for 10 min) and the supernatant extracted by solid-phase extraction. Cocaine analytes were eluted with freshly prepared elution solvent (methylene chloride/2-propanol/ammonium hydroxide, 80:20:2, v/v/v). The eluent was evaporated under nitrogen in a 40°C water bath, and the residue was reconstituted in 20 µL acetonitrile. The samples were then transferred to autosampler vials and combined with 20 µL of derivatizing reagent (BSTFA with 1% TMCS). The vials were sealed and incubated at 80°C for 30 min. A 1-µL aliquot of the derivatized sample was injected in the splitless mode onto a Hewlett-Packard (Wilmington, DE) 5971 mass selective detector interfaced to a Hewlett-Packard 5890A GC with an autosampler (HP7673A). Separation was accomplished with an HP-1 fused-silica capillary column, and the MS was operated in the selected ion monitoring mode. Figure 1 displays SIM chromatograms of plasma, saliva, and urine samples from Subject K.

Duplicate matrix-matched calibration curves for each analyte were processed with each batch of specimens. Deuterated internal standards were used for quantitation: EME-d_3 for EME; cocaine-d_3 for cocaine, NCOC, *m*-HOCOC, and *p*-HOCOC; and BZE-d_3 for BZE, BNE, *m*-HOBZE, and *p*-HOBZE. Curves were constructed across the concentration range of 1.25 to 1000 ng/mL for cocaine, BZE, EME, BNE, NCOC, *m*-HOCOC, *m*-HOBZE, *p*-HOCOC, and *p*-HOBZE. The limit of detection for all analytes was approximately 1 ng/mL. Control samples containing all analytes at concentrations of 10, 100, and 500 ng/mL and a hydrolysis control containing cocaine at a concentration of 500 ng/mL were processed in duplicate with each assay. Accuracy of control measurements was within 20% for all analytes, and coefficients of variation were less than 10% across analytical runs.

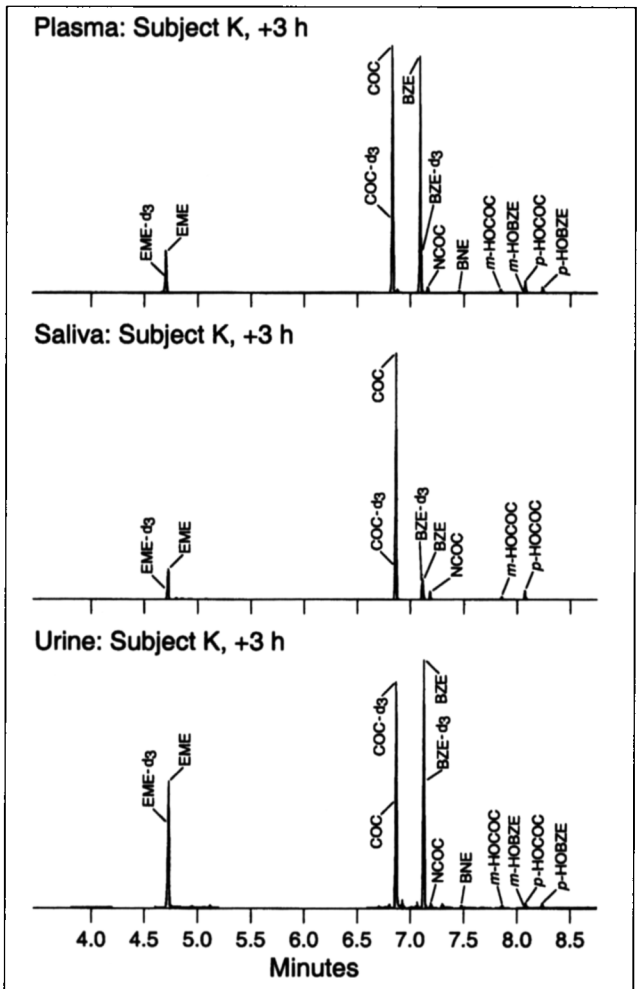

Figure 1. SIM chromatograms of plasma, saliva and urine samples from Subject K. Subject K received five oral doses of 300 mg of cocaine in the final session. All of the specimens were collected during the final dosing session. Collection time was 3 h after the initial cocaine dose was administered. Abbreviations: EME = ecgonine methyl ester; COC = cocaine; BZE = benzoylecgonine; NCOC = norcocaine; BNE = benzoylnorecgonine; *m*-HOCOC = *meta*-hydroxycocaine; *m*-HOBZE = *meta*-hydroxybenzoylecgonine; *p*-HOCOC = *para*-hydroxycocaine; *p*-HOBZE = *para*-hydroxybenzoylecgonine.

Pharmacokinetic analyses

Noncompartmental analysis was performed with WinNonlin Pro (Pharsight Corp., Mountain View, CA) for plasma and saliva AUC and half-life calculations. Urinary terminal elimination half-lives were estimated by constructing amount remaining to be excreted (ARE) plots (6).

Results

Subject participation

Two of the six subjects completed all 16 sessions without exceeding the designated safety parameters. Dosing was terminated prior to completion of all 16 sessions for the four remaining subjects for reasons including elevated cardiovascular measures and the occurrence of sensory hallucinations. The completion status of each subject is indicated in Table I. The total amount of oral cocaine administered to each subject during the final dosing session was as follows: A, 2000 mg; B, 1200 mg; D, 2000 mg; E, 1500 mg; G, 375 mg; and K, 825 mg.

Cocaine and metabolite profiles in plasma

A typical elimination profile of cocaine, BZE, and EME in plasma during the final dosing session and withdrawal phase (Subject B) is illustrated in Figure 2. The pharmacokinetic parameters for cocaine and metabolites in plasma are summarized in Table II. Carryover of cocaine from previous sessions was evident in some subjects, as small amounts of cocaine (< 10 ng/mL) were present in plasma prior to the first dose of the final session. Following oral administration, cocaine was detectable in plasma within 30 min and peak concentrations generally occurred within 2 h of the last dose. During the final dosing session, individual peak plasma cocaine concentrations ranged from 296 to 1351 ng/mL. The mean (N = 6) plasma cocaine elimination half-life was 1.5 h (range: 1.4–1.8).

A number of cocaine metabolites were present in plasma during the final dosing session. The relative amounts and peak concentration ranges of the most abundant metabolites in plasma were as follows: BZE (1810–5389 ng/mL) > EME (394–3073 ng/mL) > BNE (63–385 ng/mL) ~ *p*-HOBZE (94–336 ng/mL). Lesser amounts (< 150 ng/mL) of NCOC and *p*-HOCOC were detected in plasma. The relative abundances of cocaine and these metabolites in plasma are illustrated in Figure 3. A substantial amount of carryover from previous sessions was observed for plasma BZE concentrations. Typically, BZE was present prior to the start of dosing at concentrations greater than 500 ng/mL. Concentration-time profiles of BZE, BNE, and *p*-HOBZE were similar. The mean (N = 6) times of maximum concentration (T_{max}) for BZE, BNE, and *p*-HOBZE were 3 h (range: 2–5), 2.6 h (range: 2–5), and 3.5 h (range: 2–6), respectively. The mean (N = 6) T_{max} for EME was 2 h (range: 1–4).

The plasma elimination half-lives for BZE and BNE were similar, with mean (N = 6) values of 6.4 h (range: 5.4–7.6) and 7.0 h (range: 6.2–8.1), respectively. The plasma half-life of *p*-HOBZE was slightly shorter with a mean (N = 6) value of 5 h (range: 4.0–7.1). EME had a mean (N = 6) plasma half-life of 3.7 h (range: 2.7–5.6).

Cocaine and metabolite profiles in saliva

A saliva concentration-time profile during the final dosing session and withdrawal phase for Subject B is depicted in Figure 2. Saliva cocaine and metabolite data are summarized in Table III. Carryover from previous sessions resulted in the detection of small amounts of cocaine (< 20 ng/mL) in saliva prior to administration of the first dose of the final session. The peak saliva cocaine concentrations (range: 1978–13,822 ng/mL) were detected within 1 h of the last dose, with the exception of subject G, for whom peak concentration occurred 3 h after the last dose. Thereafter, saliva cocaine concentrations declined with a mean (N = 6) half-life of 1.2 h (range: 1.0–2.0).

Saliva BZE and EME concentrations were below 450 ng/mL in all subjects prior to the start of the final session. The metabolites most frequently detected in saliva were BZE, EME, NCOC, and *p*-HOCOC. Relative amounts of cocaine and these metabolites in saliva are illustrated in Figure 4A. The mean (N = 6) peak metabolite concentrations (nanograms per milliliter) were as follows: EME, 11,566 (range: 1313–22,197); BZE, 2980 (range: 926–5046); NCOC, 1013 (range: 139–1784); and *p*-HOCOC, 367 (range: 55–609). The mean (N = 6) time to peak saliva BZE concentration was 2 h after the last dose (range: 1–3 h).

The mean (N = 6) saliva elimination half-lives for BZE and EME were slightly longer compared to those observed for plasma, with values of 6.6 h (range: 4.8–9.2) and 4.3 h (range: 3.9–5.4), respectively. The mean (N = 6) saliva elimination

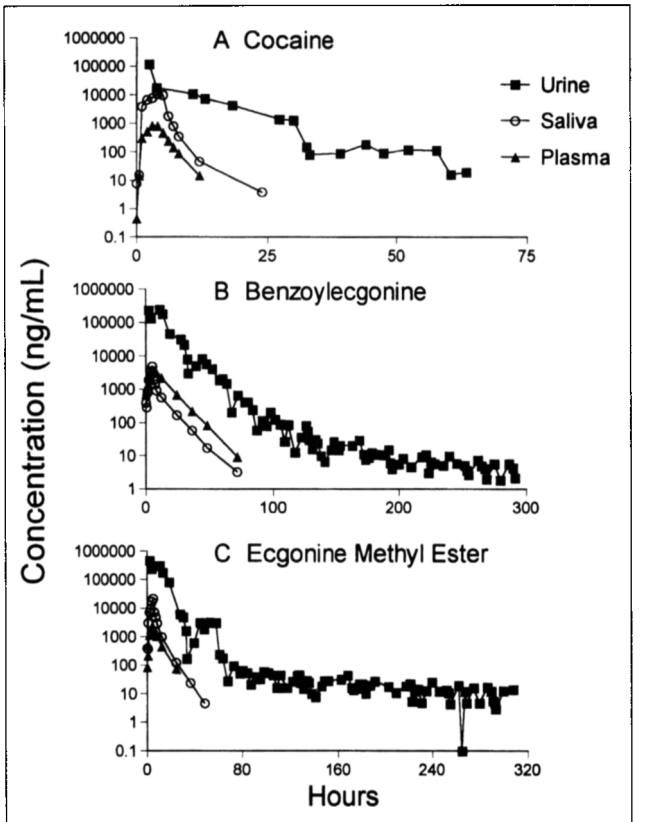

Figure 2. Plasma, saliva, and urine excretion profiles for cocaine and metabolites for Subject B. Subject B received four 300-mg doses of cocaine in the final dosing session. Time zero is the time at which the first dose was administered.

half-lives for NCOC (1.5 h, range: 1.1–2.0) and *p*-HOCOC (1.2 h, range: 1.0–1.3) were similar to cocaine.

Saliva/plasma (S/P) area under the curve (AUC) ratios

The abundances of cocaine and metabolites in saliva relative to plasma were evaluated by calculating S/P AUC ratios. Individual and mean S/P AUC ratios for cocaine, BZE and EME are displayed in Figure 4B. The mean ($N = 6$) cocaine S/P AUC ratio was 8.7 (range: 3.8–13.2). There was also a tendency for EME to concentrate in saliva relative to plasma, with a mean ($N = 6$) S/P AUC ratio of 3.7 (range: 2.3–5.1). In contrast to cocaine and EME, the S/P AUC ratio for BZE was less than unity in all subjects, with a mean value of 0.4 (range: 0.3–0.5). The minor cocaine metabolites, NCOC and *p*-HOCOC, were also detected in greater amounts in saliva than plasma. The mean ($N = 6$) S/P AUC ratios for NCOC and *p*-HOCOC were 10.3 (range: 5.6–13.6) and 6.1 (range: 2.4–10.8), respectively. S/P concentration ratios for each analyte (ranges: cocaine, 0.5–25.3; BZE, 0.1–1.4; EME, 0.6–10.8; NCOC, 0.7–22.7; and *p*-HOCOC, 0.8–15.7) indicated similar trends with respect to relative abundances of cocaine and metabolites in saliva and plasma. However, the S/P concentration ratios were variable over time, exhibiting a tendency to increase at time of peak concentration and then decrease to the values observed shortly after dosing.

Cocaine and metabolite profiles in urine

A urine concentration-time profile for Subject B during the final dosing session and withdrawal phase is illustrated in Figure 2. Urinary pharmacokinetic data for cocaine and metabolites are summarized in Table IV. Peak cocaine concentrations in urine generally occurred during (–2.1 h) or soon after (+0.3 h) the last dosing session. Subject G was an ex-

Table II. Individual and Mean Plasma Cocaine and Metabolite Profiles

Subject ID/ final dose (mg)	A 5 × 400	B 4 × 300	D 5 × 400	E 5 × 300	G 1 × 375	K 3 × 275	Mean	SEM
Cocaine								
C_{max}* (ng/mL)	1259	826	1256	653	296	1351	940	171
T_{max}† (h)	1	0	2	1	3	1	1.3	0.4
$T_{1/2}$ (h)	1.5	1.4	1.4	1.8	1.4	1.4	1.5	0.1
DT-10 (h)	8	9	8	8	8	10	8.5	0.3
DT-1 (h)	20	45	44	68	8	46	39	9
BZE								
C_{max} (ng/mL)	5389	3924	4420	3658	1810	3220	3737	491
T_{max}† (h)	2	2	3	3	5	3	3.0	0.5
$T_{1/2}$ (h)	5.4	7.6	7.4	6.0	6.0	5.9	6.4	0.4
DT-10 (h)	44	45	68	44	36	46	47	4
DT-1 (h)	92	69	116‡	68	36	118‡	83	13
EME								
C_{max} (ng/mL)	3073	2140	2272	1766	394	1231	1813	377
T_{max}† (h)	1	1	2	2	4	2	2.0	0.5
$T_{1/2}$ (h)	3.1	4.0	3.6	3.4	2.7	5.6	3.7	0.4
DT-10 (h)	20	21	20	20	12	46	23	5
DT-1 (h)	32	21	32	20	12	46	27	5
BNE								
C_{max} (ng/mL)	316	192	309	385	63	167	239	48
T_{max}† (h)	2	3	2	2	5	2	2.6	0.5
$T_{1/2}$ (h)	6.6	7.5	7.0	6.8	8.1	6.2	7.0	0.3
DT-10 (h)	32	33	32	32	12	22	27	3
DT-1 (h)	44	45	44	44	36	46	43	1
p-*HOBZE*								
C_{max} (ng/mL)	267	193	243	336	94	181	219	34
T_{max}† (h)	3	2	4	3	6	3	3.5	0.6
$T_{1/2}$ (h)	4.3	4.1	4.5	7.1	5.9	4.0	5.0	0.5
DT-10 (h)	20	9	32	20	12	10	17	4
DT-1 (h)	68	45	68	68	36	70	59	6

* Abbreviations: BZE, benzoylecgonine; EME, ecgonine methyl ester; BNE, benzoylnorecgonine; *p*-HOBZE, *p*-hydroxybenzoylecgonine; C_{max}, maximum concentration; T_{max}, apparent time of maximum concentration; $T_{1/2}$, elimination half-life; DT-10, detection time (time 0 = time of last dose) at a cutoff concentration of 10 ng/mL; DT-1, detection time (time 0 = time of last dose) at a cutoff concentration of 1 ng/mL.

† T_{max} is reported relative to the time of last dose (a negative T_{max} value resulted when peak concentration was reached prior to the last dose).

‡ Last specimen collected was positive.

ception, as his peak urinary cocaine concentration occurred 11.1 h after the last dose. In three subjects, the peak urinary cocaine concentrations occurred during the final dosing session, but prior to administration of the last dose. The T_{max} for the remaining three subjects ranged from 0.3 to 11.1 h. Peak cocaine concentrations ranged from 8 to 908 µg/mL with a mean of 253 µg/mL.

The pattern of cocaine elimination in urine appeared to be biphasic in 3 of 6 subjects. Both initial and terminal elimination half-lives were calculated for these subjects. The mean (N = 6) initial cocaine elimination half-life was 4.1 h (range: 0.8–7.3). The mean (N = 3) cocaine elimination half-life for the terminal elimination phase was 19.0 h (range: 13.5–27.4).

A variety of cocaine metabolites were detected in urine during and following the final dosing session. BZE, EME, BNE, and *p*-HOBZE were present at the highest concentrations. Smaller amounts of NCOC and *p*-HOCOC were also detected. A graph illustrating the relative abundances of cocaine and the most commonly detected metabolites is shown in Figure 5. Although they were normalized to the time of the last dose, the times of peak urinary concentration for cocaine metabolites were highly variable between subjects. The mean (N = 6) T_{max} values were 5.9 h (range: 1.0 to 11.1 h after last dose) for BZE, 3.4 h (range: 1.3 h prior to last dose to 8.8 h after last dose) for EME, 9.1 h (range: 0.6 h prior to last dose to 21.2 h after last dose) for BNE, and 4.5 h (range: 0.6 h prior to last dose to 11.1 h after last dose) for *p*-HOBZE.

Biphasic urinary excretion patterns were observed for cocaine metabolites in most subjects. This biphasic excretion pattern is exemplified for BZE and EME in Figure 2. The mean initial (N = 6) and terminal (N = 5 for BZE and *p*-HOBZE; N = 3 for BNE) half-lives were similar among BZE, BNE, and *p*-HOBZE, with respective values of 7.2 and 22.8 h for BZE, 7.7 and 21.7 h for BNE, and 8.4 and 19.0 h for *p*-HOBZE. The mean initial urinary elimination half-life of EME was 5.6 h (subject A had a single elimination phase half-life of 136.9 h and was excluded from the calculation). Terminal half-lives for EME were observed in five subjects, resulting in a mean (N = 5) terminal half-life of 32.8 h (range: 22.3–52.4).

Detection times

The detection times of cocaine and metabolites in plasma, saliva, and urine were evaluated at two cutoff concentrations, 10 ng/mL and 1 ng/mL. Individual and mean detection times are listed in Tables II–IV. Detection times were measured as the time between the last cocaine dose and the last positive specimen at the specified cutoff concentration. At their time of discharge, five subjects continued to test positive for cocaine and/or metabolites in urine at the 1-ng/mL cutoff concentration and three subjects continued to test positive at the 10-ng/mL cutoff concentration. These subjects are indicated in Table IV. The reported detection time values should be considered minimum urinary detection times, as final collection times for subjects who tested positive at discharge were included in the calculation of mean data. The mean (N = 6) minimum detection times of cocaine in urine were 71.9 h (range: 26.9–133.8) at a 10-ng/mL cutoff concentration and 84.1 h (range: 28.7–153.4) at a 1-ng/mL cutoff concentration. The mean (N = 6) minimum BZE urinary detection times at cutoff concentrations of 10 ng/mL and 1 ng/mL were 165.7 h (range: 112.5–218.1) and 177.6 h (range: 112.5–288.2), respectively. The mean (N = 6) minimum urinary detection times for EME, BNE, and *p*-HOBZE ranged from 129.1 to 174.6 h at a 10-ng/mL cutoff concentration and from 146.7 to 180.3 at a 1-ng/mL cutoff concentration.

The final plasma specimen collected from two subjects was positive for BZE at the 1-ng/mL cutoff concentration. The final plasma and/or saliva specimens collected from some subjects were positive for cocaine and/or metabolites at a 1-ng/mL cutoff concentration. These subjects are identified in Tables II and III. Given that the final collection times for these subjects were included in the calculation of mean detection time values, the reported saliva and plasma detection times for the 1-ng/mL cutoff concentration should be considered minimum detection times. The mean (N = 6) detection times for cocaine in plasma and saliva with a 10-ng/mL cutoff concentration were 9 h (range: 8–10) and 15 h (range: 8–22), respectively. Lowering the cutoff concentration to 1 ng/mL increased the mean (N = 6) plasma cocaine detection time to 39 h (range: 8–68) and the mean (N = 6) saliva cocaine detection time to 85 h (range: 45-118). BZE had the longest detection time in both matrices. The mean (N = 6) plasma detection times for BZE were 47 h (range: 36–68) using a 10-ng/mL cutoff concentration and 83 h (range: 36–118) using a 1-ng/mL cutoff concentration. The mean (N = 6) saliva detection times for BZE were 45 h (range: 34–68) using a 10-ng/mL cutoff concentration and 93 h (range: 44–118) using a 1-ng/mL cutoff concentration.

Discussion

Only a few investigators have evaluated the pharmacokinetics of orally administered cocaine and even less has been published about the pharmacokinetics of chronic cocaine administration. In the present study, peak plasma cocaine concentrations following multiple dosing sessions substantially exceeded those reported from previous studies of oral cocaine administration (7,8). Other studies of oral cocaine adminis-

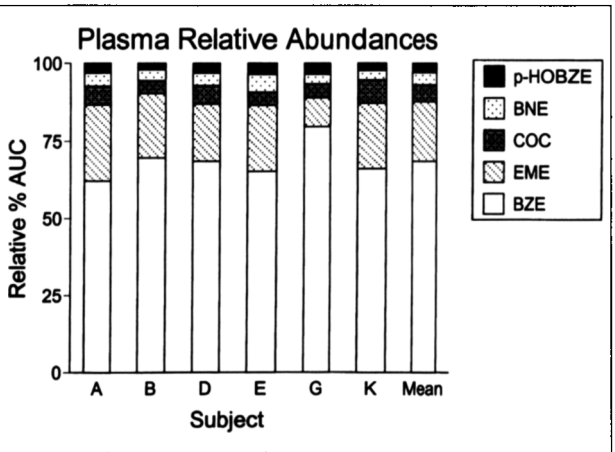

Figure 3. Relative area under the curve (AUC) values for cocaine and metabolites in plasma.

tration unfortunately did not include plasma metabolite concentrations (7,8). We reported earlier that repeated oral administration results in cocaine accumulation in plasma (4). Accumulation of cocaine from previous doses was apparent during some dosing sessions, resulting in the appearance of peak concentrations of cocaine and metabolites prior to the completion of the last dosing session.

The present study appears to be the first controlled dosing study to examine the disposition and elimination of cocaine during the withdrawal phase following chronic administration. Previous studies have examined the pharmacokinetics and pharmacodynamics of cocaine following acute administration by various routes. Intravenous cocaine administration resulted in individual cocaine plasma elimination half-lives ranging from 0.26 to 3.44 h (9–13). Similar cocaine half-life estimates of 0.55 to 4.79 h were obtained after intranasal cocaine administration (7,13). Single dose oral administration resulted in mean cocaine elimination half-lives of 0.9 h ($N = 4$) and 0.78 h ($N = 4$) (7,8). These previously reported values are in agreement with the mean ($N = 6$) plasma half-life of 1.5 h observed in the present study.

There are only limited data regarding cocaine metabolite

Table III. Individual and Mean Saliva Cocaine and Metabolite Profiles

Subject ID/ final dose (mg)	A 5 × 400	B 4 × 300	D 5 × 400	E 5 × 300	G 1 × 375	K 3 × 275	Mean	SEM
Cocaine								
C_{max}* (ng/mL)	7590	10922	13822	8844	1978	13395	9425	1794
T_{max}† (h)	–1	1	0	1	3	1	0.8	0.5
$T_{1/2}$ (h)	2.0	1.0	1.1	1.0	1.1	1.1	1.2	0.2
DT-10 (h)	8	9	20	20	8	22	15	3
DT-1 (h)	68	45	116‡	116‡	48	118‡	85	14
S/P AUC Ratio	5.4	11.9	10.7	13.2	3.8	7.1	8.7	1.6
BZE								
C_{max} (ng/mL)	2717	5046	3412	3726	926	2056	2980	582
T_{max}† (h)	2	2	2	2	3	1	2.0	0.3
$T_{1/2}$ (h)	4.8	7.8	9.2	6.6	6.5	4.9	6.6	0.7
DT-10 (h)	44	45	68	44	36	34	45	5
DT-1 (h)	44	117‡	92	92	96	118	93	11
S/P AUC Ratio	0.3	0.5	0.5	0.5	0.3	0.4	0.4	0.01
EME								
C_{max} (ng/mL)	10022	22197	14352	14741	1313	6771	11566	2952
T_{max}† (h)	2	2	2	2	3	1	2.0	0.3
$T_{1/2}$ (h)	4.1	4.1	5.4	3.9	4.0	4.1	4.3	0.2
DT-10 (h)	32	33	44	32	24	46	35	3
DT-1 (h)	44	93	116‡	92	96	118‡	93	11
S/P AUC Ratio	2.3	4.9	5.1	4.4	2.3	2.9	3.7	0.5
NCOC								
C_{max} (ng/mL)	809	945	1784	1737	139	662	1013	262
T_{max}† (h)	–1	1	3	1	3	1	1.3	0.6
$T_{1/2}$ (h)	2.0	1.4	2.0	1.2	1.1	1.4	1.5	0.2
DT-10 (h)	8	33	8	8	24	6	15	5
DT-1 (h)	20	45	68	44	36	94	51	11
S/P AUC Ratio	5.6	13.1	13.6	10.0	7.8	11.4	10.3	1.3
p-*HOCOC*								
C_{max} (ng/mL)	292	362	540	609	55	347	367	80
T_{max}† (h)	–1	1	2	2	3	1	1.3	0.6
$T_{1/2}$ (h)	1.3	1.3	1.2	1.0	1.1	1.3	1.2	0.1
DT-10 (h)	4	5	8	4	5	6	5	0.6
DT-1 (h)	4	21	8	20	8	22	14	3
S/P AUC Ratio	4.0	10.8	5.7	6.9	2.4	6.9	6.1	1.2

* Abbreviations: BZE, benzoylecgonine; EME, ecgonine methyl ester; BNE, benzoylnorecgonine; *p*-HOBZE, *p*-hydroxybenzoylecgonine; C_{max}, maximum concentration; T_{max}, apparent time of maximum concentration; $T_{1/2}$, elimination half-life; DT-10, detection time (time 0 = time of last dose) at a cutoff concentration of 10 ng/mL; DT-1, detection time (time 0 = time of last dose) at a cutoff concentration of 1 ng/mL; S/P AUC ratio = saliva/plasma area under the curve ratio.

† T_{max} is reported relative to the time of last dose (a negative T_{max} value resulted when peak concentration was reached prior to the last dose).

‡ Last specimen collected was positive.

plasma half-lives. Cone et al. (13) reported mean (N = 6) BZE elimination half-lives of 5.79 h following IV cocaine and 3.55 h after intranasal cocaine. The mean (N = 6) plasma elimination half-life for BZE in the current study was 6.4 h. Interestingly, plasma elimination half-lives for BNE and *p*-HOBZE were similar to that for BZE, with mean (N = 6) values of 7.0 h and 5.0 h, respectively. The mean (N = 6) plasma half-life for EME was somewhat shorter (3.7 h).

Cocaine disposition in saliva has been described in a number of previous studies. Thompson et al. (14) reported cocaine concentrations in plasma and saliva of two subjects after IV cocaine adminstration. In a single subject, the saliva/plasma cocaine concentration ratios ranged from 0.5 to 2.96 across three IV doses. Cone et al. (15) reported peak saliva cocaine concentrations of 237 to 1843 ng/mL after a 40-mg IV dose of cocaine. Jenkins et al. (12) also detected cocaine in saliva following IV cocaine administration. The peak cocaine concentrations ranged from 428 to 1927 ng/mL, and individual S/P concentration ratios ranged from 0.36 to 9.74. In the present study, much higher peak saliva cocaine concentrations were observed, ranging from 1978 to 13,822 ng/mL after repeated oral administration. The S/P cocaine concentration ratios observed in the present study (range: 0.5–25.3) also exceeded those reported by Jenkins et al. (12). It would seem likely that the concentrations measured in the present study are more representative of those concentrations achieved by regular cocaine users and that the previously reported values from single dose studies underestimate those concentrations.

The mean S/P AUC ratio for cocaine was 8.7. Although cocaine was administered by the oral route, it is unlikely that the high concentrations of cocaine were the result of oral contamination. Each dose of cocaine was carefully prepared in double capsules and polished to remove any residue. Consequently, cocaine transfer from plasma was likely to be the primary mechanism for entry into saliva.

BZE has been previously identified in saliva, but its kinetic profile has not been described. Schramm et al. (16) measured BZE concentrations in the serum and saliva of recent (within 24 h) cocaine users. Saliva BZE concentrations ranged from 8.8 to 1960 ng/mL. Serum BZE concentrations were an average of 2.5 times higher than saliva concentrations. Jenkins et al. (12) reported peak saliva BZE concentrations of 53–122 ng/mL after a single IV dose of cocaine. Corresponding peak plasma BZE concentrations ranged from 126 to 318 ng/mL. The peak saliva BZE concentrations in the present study ranged from 926 to 5046 ng/mL. Although the cocaine doses in the present study were much greater than those used in previous studies, the mean (N = 6) S/P AUC ratio for BZE was 0.4, which is consistent with earlier estimates.

Kato et al. (17) examined EME in saliva after IV administration. Cone et al. (18) also reported the presence of EME in saliva after IV, intranasal, and smoked administration, with the highest concentrations observed after intranasal administration. Jenkins et al. (12) identified EME and NCOC in saliva following IV and smoked cocaine administration. In the present study, EME, NCOC, and *p*-HOCOC were identified in saliva. The peak saliva EME concentrations ranged from 1313 to 22,197 ng/mL. Typically, greater amounts of EME were detected in saliva relative to plasma, with a mean (N = 6) S/P AUC ratio of 3.7. NCOC and *p*-HOCOC were also present in saliva at concentrations exceeding those in plasma. The mean (N = 6) S/P AUC ratios for NCOC and *p*-HOCOC were 10.3 and 6.1, respectively. The similar S/P ratios of cocaine, NCOC, and *p*-HOCOC could be the result of similar physico-chemical properties that influence their partitioning across membranes, that is, lipophilicity and pK_a constants. In addition, plasma protein binding characteristics could influence the saliva/plasma partitioning of these analytes.

Cone et al. (15) reported mean saliva cocaine elimination half-lives of 37.6 min and 31.8 min following IV administration of 15 mg and 40 mg cocaine, respectively. Jenkins et al. (12) calculated a mean half-life of 115 min after 44.8 mg of IV cocaine. In the present study, a mean (N = 6) cocaine elimination half-life of 1.2 h was found. A study reported by Cone et al. (3) measured cocaine elimination half-lives in saliva from chronic cocaine addicts during withdrawal. Following chronic use, saliva cocaine elimination half-life ranged from 21.6 h to 110.4 h. An extended half-life of this magnitude was not observed in the present study. However, the immunoassay employed to measure saliva cocaine concentrations in the previous study had a sensitivity somewhat higher than that employed in the present study. It is possible that extended

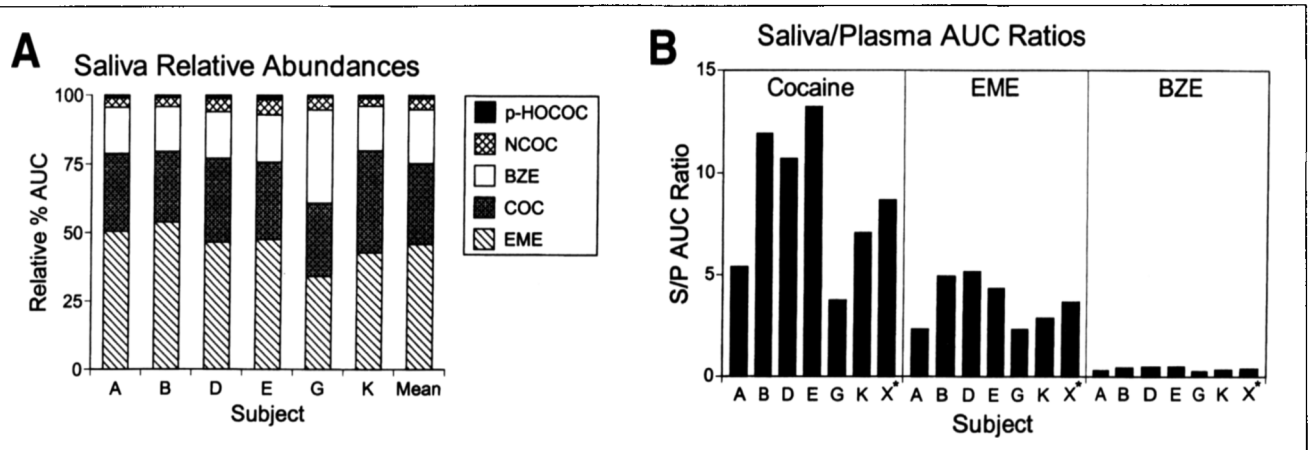

Figure 4. A, Relative area under the curve (AUC) values for cocaine and metabolites in saliva. B, Individual and mean saliva/plasma (S/P) AUC ratios for cocaine and metabolites. X*= mean.

elimination of cocaine could occur at extremely low concentrations and not be detectable by less sensitive assays.

In four subjects, BZE and EME saliva elimination half-lives were slightly longer than the corresponding plasma elimination half-lives. The mean (N = 6) BZE and EME half-lives in saliva were 6.6 h and 4.3 h, respectively, compared to mean (N = 6) plasma half-lives of 6.4 h for BZE and 3.7 h for EME. Saliva elimination half-lives for the minor metabolites NCOC and *p*-HOCOC were similar to saliva cocaine elimination half-lives, with mean (N = 6) values of 1.5 h for NCOC and 1.2 h for *p*-HOCOC compared to a mean (N = 6) cocaine half-life of 1.2 h.

Several researchers have investigated the urinary excretion profile of cocaine. Hamilton et al. (19) reported that BZE/cocaine concentration ratios in urine generally greatly exceeded unity. Inaba et al. (20) identified EME as a major urinary metabolite of cocaine, accounting for 32% to 49% of urinary metabolites after ingestion of a cocaine-containing solution. Ambre et al. (21) reported urinary elimination half-lives ranging from 4.8 to 5.5 h for BZE and 2.8 to 6.2 h for EME after intranasal and intravenous cocaine administration. Similar half-lives were obtained when Ambre (22) consolidated data from several studies to develop a pharmacokinetic profile for cocaine, BZE, and EME in urine. The urinary elimination half-lives calculated from this group of data were 1.5 h for cocaine,

Table IV. Individual and Mean Urine Cocaine and Metabolite Profiles

Subject ID/ final dose (mg)	A 5 × 400	B 4 × 300	D 5 × 400	E 5 × 300	G 1 × 375	K 3 × 275	Mean	SEM
Cocaine								
C_{max}* (µg/mL)	430	119	908	29	8	26	253	146
T_{max}† (h)	–1.3	–0.6	0.3	–2.1	11.1	1.4	1.5	2.0
$T_{1/2}$ A (h)	2.2	6.1	2.8	0.8	2.8	7.3	4.1	0.9
$T_{1/2}$ B (h)	13.5	–	16.2	–	–	27.4	19.0	4.2
DT-10 (h)	97.8	60.5	70.5	42	26.9	133.8	71.9	15.9
DT-1 (h)	112.5‡	60.5	107.5	42	28.7	153.4	84.1	19.6
BZE								
C_{max} (µg/mL)	365	245	890	151	115	320	348	115
T_{max}† (h)	3.0	7.8	4.9	1.0	11.1	7.7	5.9	1.5
$T_{1/2}$ A (h)	9 3	9.7	6.2	6.2	4.9	6.9	7.2	0.8
$T_{1/2}$ B (h)	–	34.5	15.0	20.0	23.4	21.3	22.8	3.2
DT-10 (h)	112.5‡	218.1	163.9‡	163.7	171.9‡	164.1	165.7	13.7
DT-1 (h)	112.5‡	288.2	163.9‡	163.7	171.9‡	165.3‡	177.6	23.8
EME								
C_{max} (µg/mL)	548	469	1093	214	72	202	433	151
T_{max}†(h)	–1.3	–0.6	4.9	1.0	8.8	7.7	3.4	1.8
$T_{1/2}$ A (h)	136.9	7.2	4.5	4.2	5.6	6.4	27.5	21.9
$T_{1/2}$ B (h)	–	52.4	22.3	29.1	32.0	28.2	32.8	5.2
DT-10 (h)	112.5‡	304.8‡	163.9‡	163.7	171.9‡	131.1	174.6	27.7
DT-1 (h)	112.5‡	304.8‡	163.9‡	163.7	171.9‡	165.3‡	180.3	26.4
BNE								
C_{max} (µg/mL)	107	65	55	29	15	19	48	14
T_{max}† (h)	3.0	–0.6	4.9	16.8	21.2	9.4	9.1	3.4
$T_{1/2}$ A (h)	9.6	10.2	5.4	6.3	3.8	11.1	7.7	1.2
$T_{1/2}$ B (h)	–	–	14.7	27.4	23.1	–	21.7	3.7
DT-10 (h)	112.5‡	124.0	136.0	162.7	141.5	97.7	129.1	9.3
DT-1 (h)	112.5‡	124.0	163.9‡	163.7	171.9‡	144.3	146.7	9.9
p-HOBZE								
C_{max} (µg/mL)	49	43	78	24	25	16	39	9
T_{max}† (h)	3.0	–0.6	4.9	1.0	11.1	7.7	4.5	1.8
$T_{1/2}$ A (h)	12.6	12.4	7.0	7.9	5.5	5.0	8.4	1.4
$T_{1/2}$ B (h)	—	20.5	14.6	17.6	23.6	18.7	19.0	1.5
DT-10 (h)	112.5‡	165.2	163.9	162.7	171.9‡	144.3	153.4	9.0
DT-1 (h)	112.5‡	177.8	163.9	163.7	171.9‡	158.3	158.0	9.5

* Abbreviations: BZE, benzoylecgonine; EME, ecgonine methyl ester; BNE, benzoylnorecgonine; *p*-HOBZE, *p*-hydroxybenzoylecgonine; C_{max}, maximum concentration; T_{max}, apparent time of maximum concentration; $T_{1/2}$ A, initial elimination half-life; $T_{1/2}$ B, secondary elimination half-life; DT-10, detection time (time 0 = time of last dose) at a cutoff concentration of 10 ng/mL; DT-1, detection time (time 0 = time of last dose) at a cutoff concentration of 1 ng/mL.

† T_{max} is reported relative to the time of last dose (a negative T_{max} value resulted when peak concentration was reached prior to the last dose).

‡ Last specimen collected was positive.

7.5 h for BZE, and 3.6 h for EME. The mean (N = 6) initial urinary elimination half-lives in the present study were 4.1 h for cocaine, 7.2 h for BZE, and 5.6 h for EME (range: 4.2–7.2) (N = 5, Subject A was excluded).

Substantial amounts of the minor metabolites BNE and *p*-HOBZE were detected in urine in this study. Oyler et al. (23) also detected high concentrations of these metabolites in urine collected from individuals in a cocaine treatment program. The authors reported relative analyte abundances in urine of BZE > EME > cocaine > BNE.

There have been two reports of prolonged urinary excretion of cocaine following chronic abuse (2,3). However, urinary elimination half-lives were not calculated for the individuals in these studies. In the present study, biphasic urinary excretion profiles were observed for cocaine and/or metabolites in most subjects. When a biphasic elimination pattern was observed, the half-life for the initial phase was generally comparable to previously reported values, and the half-life for the terminal phase was substantially longer. A biphasic urinary excretion profile for cocaine was observed in three subjects. The mean (N = 3) terminal elimination half-life for these subjects was 19.0 h (range: 13.5–27.4). For the three subjects that did not display a terminal phase, some difficulty was experienced in assaying cocaine concentrations accurately; thus, it is possible that a terminal phase was present for these subjects, but was obscured because of the limitations of the chromatographic system. In these subjects, BZE concentrations were extremely high (approximately 1500–24,000 ng/mL) at the time that cocaine concentrations were diminishing and approaching the assay LOD. This made it difficult to measure cocaine accurately in the presence of high concentrations of BZE. Consequently, it became difficult to determine if a second phase of cocaine elimination occurred in these three subjects.

Biphasic excretion of cocaine metabolites was also apparent in most subjects. The mean (N = 5) terminal phase half-life for BZE was 22.8 h (range: 15.0–34.5). EME was eliminated with a mean (N = 5) half-life of 32.8 h (range: 22.3–52.4) during the terminal elimination phase. Only Subject A did not display a biphasic elimination of EME. However, this subject had an extremely long initial half-life of 136.9 h for EME. Three subjects displayed biphasic excretion of BNE, resulting in a mean (N = 3) terminal half-life of 21.7 h (range: 14.7–27.4). Biphasic elimination of *p*-HOBZE was evident in five subjects. The mean (N = 5) secondary half-life for *p*-HOBZE was 19.0 h (range: 14.6–23.6).

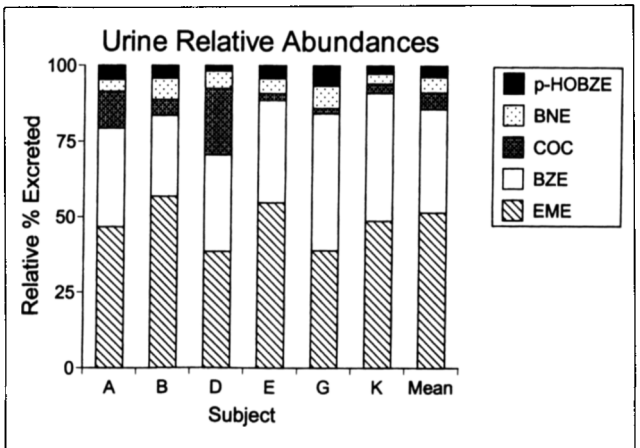

Figure 5. Relative amounts of cocaine and metabolites excreted in urine.

The biphasic urinary excretion profiles for cocaine and metabolites suggested that a second, long-term elimination phase occurred following repeated cocaine administration. This could have resulted from a slow release of cocaine that accumulated in the body as a result of chronic exposure. Cocaine is a lipophilic drug and likely accumulates in fatty tissues during chronic use. Cocaine has been detected in adipose tissue collected from a postmortem case of cocaine poisoning (24). Furthermore, cocaine was detected for an extended period in the adipose tissue of chronically treated rats (1). Although it is unlikely that the terminal excretion phases of the more polar metabolites BZE, BNE, and *p*-HOBZE resulted from their accumulation in the body, stored cocaine could be biotransformed to these metabolites, resulting in a secondary elimination phase for cocaine metabolites similar to that observed for cocaine. EME is the least polar metabolite and appears to be capable of efficiently crossing biological membranes, as was indicated by its accumulation in saliva. The terminal elimination phase for EME may be due to a combination of the metabolism of accumulated cocaine to EME as well as the accumulation and subsequent release of EME in fatty tissues.

Overall, this study demonstrated the utility of the oral route as a means of studying repeated cocaine dosing in humans. Pharmacokinetic parameters derived from plasma and saliva were generally comparable to those reported from acute dosing studies. The appearance of a longer secondary elimination phase for cocaine in 3 of 6 subjects and for cocaine metabolites in 5 of 6 subjects could be highly significant. This long-term terminal phase is likely a result of the release of accumulated body stores of cocaine. Although the concentrations of cocaine and metabolites during this protracted elimination phase are quite low, some pharmacological significance could be placed on this phenomenon.

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