

Cocaine and Metabolite Elimination Patterns in Chronic Cocaine Users During Cessation: Plasma and Saliva Analysis

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Abstract

Several reports suggest a prolonged elimination of cocaine and metabolites after chronic use compared with single or occasional use. This study was designed to measure the half-lives of cocaine in plasma and saliva of individuals who consumed cocaine on a frequent basis. The disposition and elimination patterns of cocaine and metabolites in the body fluids of chronic high-dose cocaine users during acute cessation of use were investigated. Plasma and saliva specimens were collected over a 12-h period during cessation and analyzed by gas chromatography–mass spectrometry. Pharmacokinetic parameters were derived by noncompartmental analysis of plasma and saliva data. Results indicated a cocaine terminal $T_{1/2}$ of 3.8 h in plasma and 7.9 h in saliva. The terminal $T_{1/2}$ of benzoylecgonine was 6.6 h in plasma and 9.2 h in saliva. Compared with prior studies of acute low-dose cocaine administration, these findings suggest that cocaine's half-life is longer in active street users than in occasional users though the half-life of its main metabolite benzoylecgonine remains similar (as do cocaine saliva-to-plasma ratios). Thus, regular use of cocaine appears to alter the disposition and elimination of cocaine when compared to single or occasional use.

Introduction

Cocaine remains a commonly reported illicit drug in most cities' emergency departments and accounts for a considerable proportion (20% or more) of total emergency department drug mentions in the United States (1). Fatal overdoses from cocaine occur, but fortunately, humans have efficient metabolic and excretory pathways to detoxify large doses. Several studies have reported a rapid (35–90 min) elimination half-life when cocaine is administered as a single, low dose in an experimental setting

(2–5). Cocaine was shown to be converted to the principal metabolites, benzoylecgonine (BE) and ecgonine methyl ester (EME), in human research subjects. BE was excreted according to first-order kinetics with an average elimination half-life of 7.5 h (2).

The elimination of cocaine and its metabolites may, however, be more protracted after long-term, high-dose cocaine abuse. A three-patient case report and a small-scale study, both using enzyme-multiplied immunoassay technique (EMIT) (cutoff concentration = 300 ng/mL), reported prolonged presence of BE in urine (more than 120 h) (6,7). Further, a highly sensitive and specific gas chromatography–mass spectrometry (GC–MS) assay (limit of detection, 0.5 ng/mL) confirmed the presence of unmetabolized cocaine through the first 24 h of collection in saliva and for the first 4–5 days in urine of subjects who reported using 1–10 g (street quantities) per week for 1–10 years (8). More recently, in analyses of urine from cocaine-using methadone-maintenance patients, cocaine (> 25 ng/mL, GC–MS) was found to be present in one-third of all specimens and approximately half of all specimens positive for BE (> 300 ng/mL, EMIT) (9). This proportion of cocaine- to BE-positive specimens was higher than one would expect based on the 7- to 15-fold difference between the published half-lives of cocaine and BE.

Taken together these reports suggest that the prolonged presence of cocaine and metabolites in these clinically obtained samples reflects a longer half-life and window of detection in "street" cocaine users than previously reported from acute dosing studies performed in the laboratory setting. Such a possibility has also been suggested by an earlier finding of dose-dependent changes in cocaine pharmacokinetic parameters (10). However, the prolonged half-life following high doses of cocaine has not been clearly demonstrated. In fact, little work on the kinetics of chronic administration of cocaine in doses that are commonly self-administered by cocaine users in their own environments (referred to in the rest of this paper as "street" cocaine users) has been reported.

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Previous studies of controlled administration in our and other laboratories have evaluated the kinetics of low to moderate doses of cocaine by various (intranasal, intravenous, and smoked) routes (11–14). In light of cocaine's known toxicity (15–18), clear safety and ethical constraints limit the types of cocaine administration studies that can be conducted. Therefore, we designed a study to measure the half-lives of cocaine in plasma and saliva of street cocaine users by investigating the disposition and elimination patterns of cocaine and metabolites in body fluids of street cocaine users during acute cessation (in the absence of drug administration). In addition to blood, mixed "saliva" samples were also obtained. Mixed saliva is composed of all the secretions in the mouth, that is, saliva (the fluid produced by salivary glands), crevicular fluids, and mucus, and may also contain cellular debris and particles present during collections. Plasma and mixed saliva cocaine and metabolite concentrations, as well as kinetic analyses, were obtained because of the growing interest in saliva as a convenient and non-invasive alternative biological matrix for monitoring drug use.

Methods

Participants

Participants were individuals between the ages of 18 and 65 with evidence of recent high-dose cocaine use by self-report and urine test. Only subjects with good venous access and no evidence of anemia were included. Prior to participation, subjects underwent screening procedures including a complete physical and psychological examination. For the duration of the study, participants resided on a closed ward, under close supervision. This study was approved by the National Institute on Drug Abuse, Intramural Research Program Institutional Review Board. Subjects provided written informed consent and were paid for their participation.

Study procedures

Participants reported to the laboratory at approximately 8:30 AM. The experimental session lasted for 12 h, after which participants were housed on the closed inpatient ward for 4–14 days for continued urine collections. No drugs or medications were administered during the study. Meals, noncaffeinated beverages, and water were freely available to subjects during the session, and recreational activities (television, reading material, and games) were provided.

An intravenous catheter was inserted into the forearm upon the participant's arrival at the research unit. Blood (15 mL) and mixed-saliva (4 mL) specimens were obtained periodically for up to 12 h at the following time points: 15, 30, 45, 60, 75, 90, 120, 240, 360, 480, and 720 min. Additional measures were collected but not reported here; these included urine specimens, pupil diameter, vital signs, and subjective effects.

Specimen collection and analysis

Whole-blood specimens were collected in vacutainer tubes containing sodium fluoride (25 μ L per mL of whole blood) and acetic acid (25 μ L/mL of whole blood); specimens were centrifuged and plasma removed. Participants placed citric-

acid-containing candy into their mouths to facilitate saliva production. Mixed-saliva specimens were then collected untreated in polypropylene tubes. Both plasma and mixed saliva were frozen and stored at -20°C .

Prior to extraction, both plasma and mixed saliva samples (1 mL) were treated with internal standards, diluted with acetate buffer (pH 4), and centrifuged for 5 min. SPE columns were conditioned with methanol (2×2 mL), water (2×2 mL), and acetate buffer (1 mL, pH 4.0). Vacuum was removed prior to addition of the acetate buffer to prevent column drying. Samples were added to the wet columns. Samples were eluted through the SPE columns, and the columns were washed with water (2×1 mL), 0.1N HCl (1×1.25 mL) and methanol (2×1 mL). The columns were dried for 5 min and eluted with 3×2 mL of freshly prepared elution solvent (methylene chloride/2-propanol/ammonium hydroxide, 80:20:2, v/v/v). Column flow-rate was controlled at 1–2 mL/min during processing. The eluate was collected and evaporated to dryness, and the residue was reconstituted with 20 μ L of acetonitrile and transferred to an autosampler vial. *N,O*-bis(Trimethylsilyl) trifluoroacetamide (BSTFA, 20 μ L containing 1% TMCS) was added, and the mixture was heated at 60°C for 30 min. An aliquot (1 μ L) of the derivatized extract was analyzed by GC-MS, according to previously published methods (19,20). The limits of detection and quantitation for all analytes were approximately 1 and 1.5 ng/mL, respectively, in both plasma and mixed saliva.

Chemicals and materials

Compounds for preparation of standards were obtained: cocaine (Mallinckrodt, St. Louis, MO); BE, *m*-hydroxycocaine (*m*-OH-COC), *p*-hydroxycocaine (*p*-OH-COC), benzoylecgonine (BNE), norcocaine (NCOC), *m*-hydroxybenzoylecgonine (*m*-OH-BE), and *p*-hydroxybenzoylecgonine (*p*-OH-BE) (Research Biochemical International, Natick, MA); cocaethylene (CE) and norcocaethylene (Research Triangle Institute, Research Triangle Park, NC); EME, [$^2\text{H}_3$]-cocaine, [$^2\text{H}_3$]-BE, and [$^2\text{H}_3$]-EME (Sigma Chemical, St. Louis, MO); *o*-hydroxycocaine and *o*-hydroxybenzoyl ester HCl (Elsolby Laboratories, Inc., Oxford, MS); and anhydroecgonine methyl ester (AEME) and ecgonine ethyl ester (EEE) (Dr. A. Allen, NIDA, Baltimore, MD). Methanol, methylene chloride, 2-propanol, and acetonitrile were purchased from J.T. Baker (Phillipsburg, NJ). BSTFA with 1% trimethylchlorosilane (TMCS) was purchased from Pierce Chemical (Rockford, IL). Solid-phase extraction columns (Clean Thru ZC DAU020; 200 mg-10 mL) were purchased from United Chemical Technologies (Bristol, PA).

Pharmacokinetic and data analyses

Pharmacokinetic parameters were derived by noncompartmental analysis (WinNonlin, Scientific Consulting, Apex, NC) of plasma and mixed saliva data. Uniform weighting for all data points was utilized throughout the analysis. The terminal elimination phase (λ_z) was selected for each data set as the final log-linear portion of the curve (3–6 terminal data points). All kinetic parameters were derived from "predicted" data as a result of regression analysis.

To examine how pharmacokinetic parameters were related to self-reported patterns of cocaine use, Pearson correlation coefficients were calculated between each of four self-report

Table I. Subject Characteristics and Self-Reported Drug Use

Subject	Gender	Age	Weight (kg)	Self-reported Cocaine Use*			All other drugs reported by code†
				Grams per day of use	Time since last use (h)	Days used in last 14	
A	M‡	38	68.6	2.5	3	14	e, m
B	M	30	68.1	1.3	2.5	13	e, m, f, p
C	M	36	83.5	0.5	36	11	e, m, h
D	M	30	68.3	1.0	15	8	e
E	M	34	81.9	1.0	7	10	e, m, h
F	F	42	59.0	1.0	NR	1	e, m, h, t, f, p
G	F	40	68.6	0.5	13	10	e, m, h, f
H	F	41	47.2	0.5	13	8	e, h, m, f, a
I	M	39	101.7	0.8	NR	14	e, h, m, t, f
J	M	31	89.0	2.0	15	12	e, h, m
K	M	33	55.8	0.1	NR	10	e, h, m
L	F	39	52.2	1.0	39	9	e, h, m, t, f
M	F	38	56.8	0.5	15	12	e, m
N	F	38	90.8	1.3	6	11	e, h, m
O	M	37	63.6	1.0	15	12	e, h, m, t
P	M	38	70.1	1.0	15	10	e, h, m
Q	M	31	69.0	1.0	NR	6	e, h, o, m, t, a, b, f
R	M	39	69.0	2.0	15	7	e, m, o, f
S	F	40	105.3	2.5	15	13	e, m, a, f, p, i, d
T	M	39	71.7	0.5	63	7	e, h, m

* Cocaine was used by the smoked route by all subjects.

† Drug codes: a = amphetamines, b = barbituates, d = anti-depressants, e = alcohol, f = hallucinogens, h = heroin, i = inhalants, m = marijuana, o = opiates, p = PCP, t = tranquilizers.

‡ Abbreviations: M, male; F, female; NR, not reported.

variables (days of recent cocaine use, typical amount used, time since last use, and years of use) and initial plasma concentrations of cocaine, BE, and EME. For these analyses, all variables were first log ($x + .001$) transformed to reduce departures from normality. No correction was used for multiple tests of significance (12 in all); thus, significant correlations should be interpreted with caution.

Results

Twenty individuals participated in the study; demographic and drug use histories are summarized in Table I. Participants reported substantial histories of cocaine use with 7.8 ± 4.9 years (mean $\pm$ SD) duration of cocaine use and recent cocaine consumption of 0.12–2.5 g. All reported using cocaine by the smoked route. The reported time of last use ranged from 2.5 to 63 h.

Plasma

Cocaine was detected in plasma from 12 of 20 subjects with an initial mean $\pm$ SD concentration (in the first blood collection) of 22.5 ± 46.5 ng/mL (range 1.7–162.2) (Table II). BE was detected in plasma from all 20 participants, with an initial mean $\pm$ SD concentration of $371.8 \pm$

Table II. Initial Concentrations of Analytes at Admission in Plasma of Individual Participants*

Subject	COC†	BE	EME	m-OH-BE	p-OH-BE	BNE	NCOC	EEE	CE	m-OH-COC	p-OH-COC	AEME
B	162.2	1715.5	289.8	15.8	84.7	86.7	10	0	0	5.7	5.4	7.6
E	55.8	1597.4	65.3	0	0	127.6	0	0	0	0	0	0
M	6.7	725.1	25.4	9.7	9.9	35.4	0	0	0	0	0	0
D	6.0	592.0	37.9	1.8	5.2	11.7	0	0	0	0	0	0
N	13.6	515.4	44.1	7.4	7.0	13.0	0	6.7	7.1	0	0	0
G	10.1	453.2	20.9	9.3	2.8	7.1	2.0	0	4.0	2.6	0	0
K	3.2	337.4	22.2	4.9	6.8	12.6	0	0	0	0	0	0
J	1.9	286.1	12.1	3.6	3.0	9.0	0	0	0	0	0	0
S	0	284.5	9.0	0	1.5	5.7	0	0	0	0	0	0
R	2.6	156.7	13.0	0	2.2	5.1	0	0	0	0	0	0
C	2.2	149.9	13.0	1.8	1.4	2.7	0	0	0	0	0	0
O	0	146.9	11.6	1.8	0	3.5	0	0	0	0	0	0
H	1.7	144.9	10.2	4.2	3.0	5.3	0	0	0	0	0	0
A	0	89.6	4.3	1.9	1.1	2.0	0	0	0	0	0	0
I	0	74.6	0	0	0	0	0	0	0	0	0	0
L	4.5	67.2	3.8	0	0	3.3	0	0	0	0	0	0
P	0	49.0	4.3	0	0	0	0	0	0	0	0	0
F	0	31.4	0	0	0	0	0	0	0	0	0	0
Q	0	11.2	0	0	0	0	0	0	0	0	0	0
T	0	8.3	0	0	0	0	0	0	0	0	0	0

* Concentrations are reported in nanograms per milliliter. Subjects are reported in order of descending BE concentration.

† Abbreviations: COC, cocaine; BE, benzoyllecgonine; EME, ecgonine methyl ester; m-OH-BE, m-hydroxybenzoyllecgonine; p-OH-BE, p-hydroxybenzoyllecgonine; BNE, benzoylnorecgonine; NCOC, norcocaine; EEE, ecgonine ethyl ester; CE, cocaethylene; m-OH-COC, m-hydroxycocaine; p-OH-COC, p-hydroxycocaine; and AEME, anhydroecgonine methyl ester.

484.7 ng/mL (range 8.3–1715.5). BE was always found in higher concentrations than all other analytes (Table II) and, in four subjects (Subjects F, I, Q, T), was the only metabolite found. EME was detected in plasma from 16 subjects, with mean admission concentrations of 36.7 ± 69.5 ng/mL (3.8–289.8). Across specimens taken at all time points ($n = 260$), EME was detected at concentrations ranging from 0 to 28.9% of BE concentrations, with a mean (SD) of 4.8% (4.5). Considering only specimens positive for EME ($n = 185$), the range was 2.0 to 28.9% with a mean (SD) of 6.8% (3.9). Other metabolites, which were detected in fewer subjects, included BNE, *m*-OH-COC, *p*-OH-COC, *m*-OH-BE, *p*-OH-BE, CE, NCOC, and AEME, a cocaine pyrolysis product and marker for smoked cocaine (21,22). Although various profiles of metabolites were found, a general trend was that a greater number of metabolites was found in subjects with higher concentrations of BE.

The time-courses of analyte concentrations are illustrated for one subject (B) in Figure 1. Subject B had the highest concentrations of cocaine and BE upon admission and also had the largest number of metabolites detected in plasma. This participant also reported the most recent cocaine use (2.5 h, dose 1.3 g). Cocaine, BE, EME, BNE, *m*-OH-BE, and *p*-OH-BE were detectable through the last measure. AEME was found in trace amounts, consistent with the reported smoked route of self-administration. EME was noted to exceed cocaine concentrations across the entire measurement time. In addition, BNE and *p*-OH-BE exceeded cocaine concentrations 2 h after the beginning of the session, and *m*-OH-BE exceeded cocaine concentrations 6 h later.

Plasma cocaine, BE, and EME concentration-time curves for each individual participant are displayed in Figure 2. Elimination profiles of these three main analytes show similar trends across subjects with BE highest, and cocaine concentrations lowest or undetectable. Where cocaine and BE were

both present, cocaine concentrations decreased more rapidly than BE, which is consistent with the kinetic profiles of these two metabolites. A consistent trend also was noted in that EME concentrations exceeded cocaine concentrations when both were measurable; EME was measurable in four subjects when cocaine was absent (A, O, P, and S).

To evaluate the relationships between drug use and the presence of drug in plasma, comparisons were made between admission cocaine, BE, and EME concentrations and self-reported grams used per day, time since last use of cocaine, number of days used of the last 14, and years of cocaine use. There were no significant correlations between cocaine concentration and any of the self-report measures. Significant or near-significant correlations were found between BE concentration and time since last use ($r = -0.623$; $p = 0.010$) and number of days used in the last 14 ($r = 0.435$; $p = 0.055$) and between EME concentration and time since last use ($r = -0.638$; $p = 0.008$) and number of days used in the last 14 ($r = 0.531$; $p = 0.016$). Concentrations of BE and EME did not correlate significantly with typical amount used or with years of use.

Saliva

Figure 3 illustrates mixed saliva time-curve concentrations of cocaine, BE, and EME (for comparison with the plasma data in Figure 2). Upon mixed saliva collection at admission, 10 subjects were positive for cocaine, 14 for BE, and 8 for EME. The only additional analyte found in mixed saliva was AEME. Mean ($\pm$ SD) admission concentrations (in positive specimens) were as follows: cocaine 31.1 ± 49.5 ng/mL (range 5.1–170.7); BE 54.2 ± 45.3 ng/mL (3.8–144.4); and EME 69.1 ± 111.9 ng/mL (5.1–337.0). BE was present in the highest concentration in most participants though this pattern was less consistent than in plasma. A few participants (M, N) had higher cocaine than BE concentrations at some time points, while other subjects (D, K) had similar concentrations of BE and cocaine. Relative concentrations of EME varied across individuals, and EME was never present in the absence of BE or cocaine.

The differences between plasma and mixed saliva concentrations can be observed by comparing Figures 2 and 3. Cocaine remained detectable in the plasma of six subjects (B, E, M, N, G, H) and in the mixed saliva of seven subjects (E, M, D, N, G, K, H) for the entire 12-h monitoring period; five subjects (E, M, N, G, H) had cocaine detectable in both mixed saliva and plasma for the entire 12-h monitoring period. Cocaine concentrations were generally higher in mixed saliva than in plasma, except in subjects E, G, and L. BE concentrations in plasma were consistently higher than in mixed saliva. Concentrations of EME tended to be similar in plasma and mixed saliva. Where analytes were detected in both matrices, mean $\pm$ SD admission saliva-to-plasma (S/P) ratios were cocaine 2.41 ± 1.97 (range 0.50 to 5.93); BE 0.18 ± 0.21 (0.03 to 0.85); and EME 0.99 ± 0.34 (0.78 to 1.48).

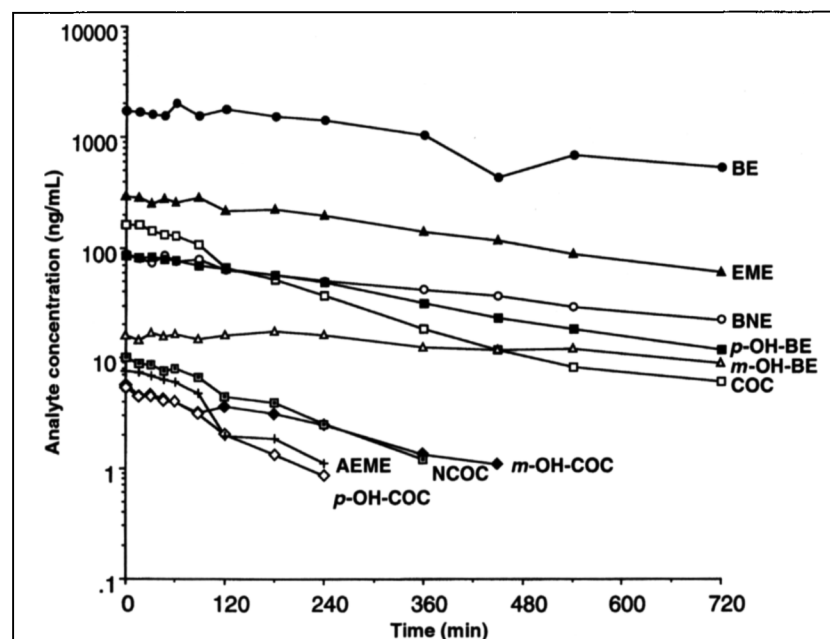


Figure 1. Time courses of cocaine and metabolite concentrations in plasma of a selected subject (B). Concentrations were determined by GC-MS. Analytes are indicated at the end of each time course line.

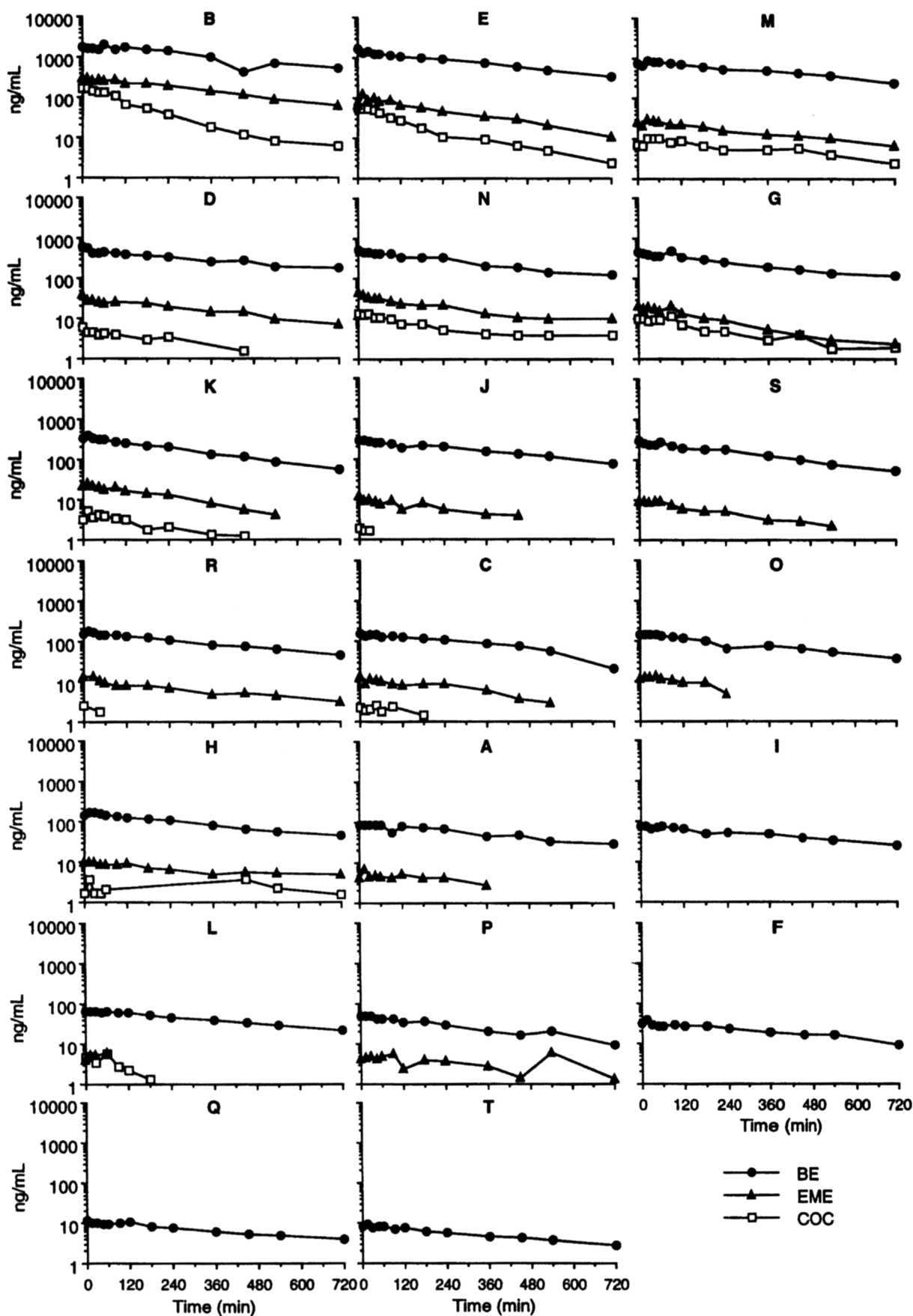


Figure 2. Time courses of cocaine, BE, and EME concentrations in plasma of individual subjects. Concentrations were determined by GC-MS.

Elimination kinetics

Noncompartmental kinetic analysis was performed on the terminal linear portion of the plasma and mixed saliva concentration-time curves (Table III). Concentrations of cocaine and all metabolites declined rapidly over the 12-h period. Many of the analytes were either not detected or declined below the limits of detection too quickly for pharmacokinetic analysis. Therefore, the numbers of subjects included in the pharmacokinetic analyses varied. Cocaine, BE, EME, *m*-OH-BE, *p*-OH-BE, and BNE were in greatest abundance in plasma (9–20 subjects); only cocaine, BE, and EME were in sufficient abundance in mixed saliva for pharmacokinetic analysis (6–11 subjects). An occasional subject had sufficient concentrations

of additional analytes for analysis (1–2 subjects).

Half-lives and mean residence times (average time for all drug to reside in the body; MRTs) of cocaine, BE, and EME were generally longer for mixed saliva versus plasma. Plasma half-lives and MRTs for cocaine, BE, and EME were 3.8 and 5.7 h, 6.6 and 9.6 h, and 5.5 and 7.7 h, respectively. In comparison, mixed saliva half-lives and MRTs for cocaine, BE, and EME were 7.9 and 11.9 h, 9.2 and 12.5 h, and 10.0 and 13.9 h, respectively. Generally, cocaine and metabolites having an intact carboxy-alkyl group ($-\text{COOCH}_3$ or $-\text{COOCH}_2\text{CH}_3$), including EME, NCOC, EEE, CE, *m*-OH-COC, and *p*-OH-COC, displayed shorter half-lives and MRTs than those metabolites in which this bond had been cleaved by hydrolysis.

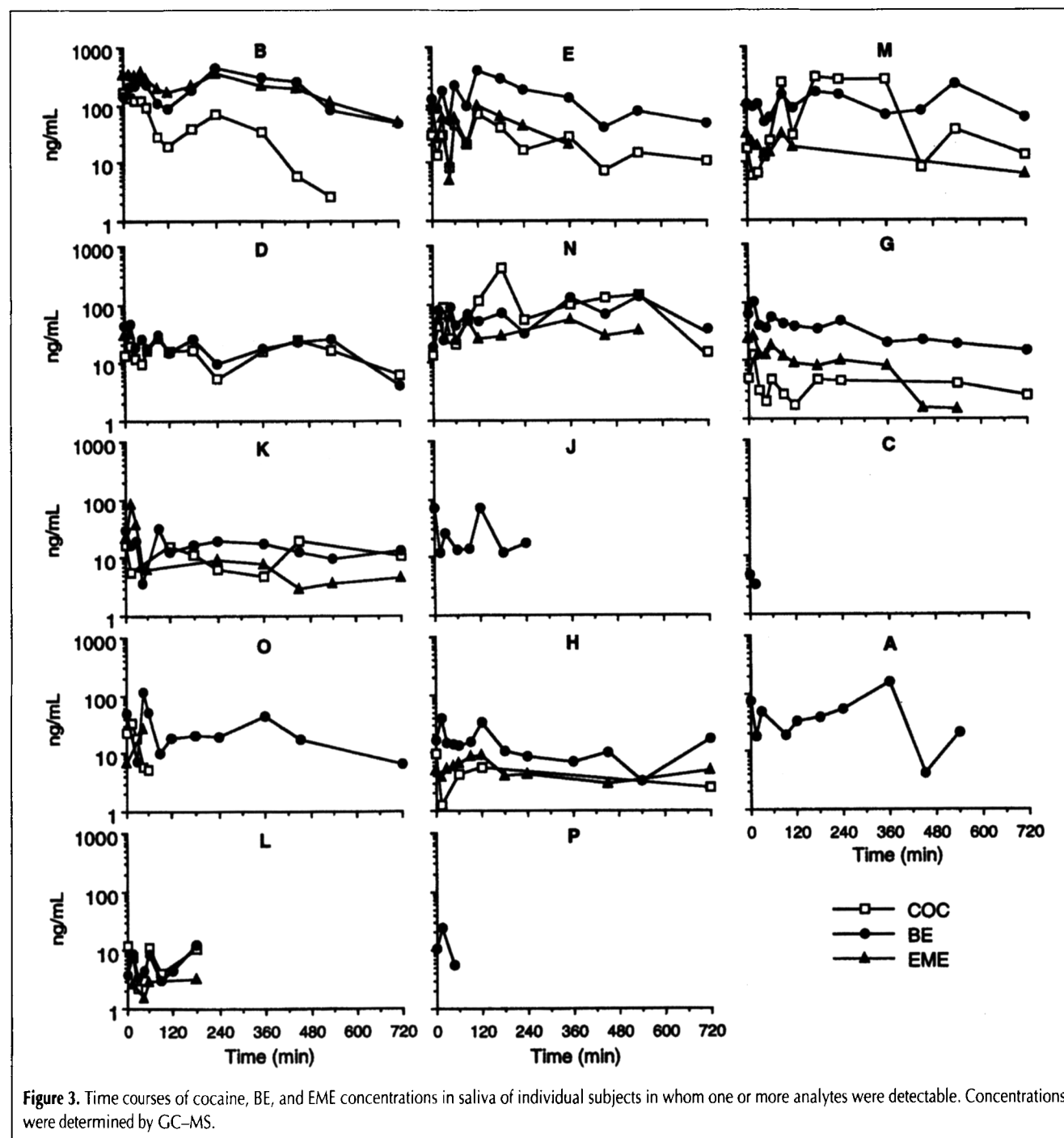


Figure 3. Time courses of cocaine, BE, and EME concentrations in saliva of individual subjects in whom one or more analytes were detectable. Concentrations were determined by GC-MS.

Discussion

Although the subject population consisted of individuals who self-reported regular use of cocaine, only 12 out of 20 were positive for cocaine in plasma on admission to the study. However, all subjects had measurable concentrations of BE, an indication that relatively recent cocaine use had occurred. The detectability of plasma cocaine is presumed to be the result of a combination of analytical and pharmacological factors that include assay sensitivity, dose, and recency and frequency of use. In our sample, self-reported measures of the latter three variables did not distinguish subjects in whom cocaine was or was not detected. For example, 11 subjects who had detectable cocaine in their plasma reported a median of 13 h (range 2.5–39) since last use of cocaine; five subjects without detectable cocaine reported a median of 15 h (range 3–63) since last use. (Data on last use were missing for four subjects.) Similarly, the 12 subjects who had detectable cocaine in their plasma usually reported using a median of 1 g of cocaine (range 0.12–2) per use in the last 14 days; the 8 subjects without detectable cocaine also reported using a median of 1 g of cocaine (range 0.5–2.5) per use in the last 14 days. Median number of days of use in the last 14 days was 10 days (range 7–13) in the 12 subjects with detectable plasma cocaine and 11

days (range 6–14) in the 8 subjects without detectable plasma cocaine. Significant correlations were found between BE and EME concentration on admission and time since last use and number of days used in last 14; these were in the expected direction of higher concentrations with more recent use and more days of recent use. No correlations were found between cocaine concentration and any self-report measure. A likely reason that EME and BE may correlate better with self-report measures than cocaine does is their longer half-lives.

The amount of cocaine measured in subjects during cocaine cessation was within the range of those concentrations reported following single administrations of cocaine in laboratory studies, whereas concentrations of BE and EME were somewhat higher in the present study. The concentrations of plasma cocaine measured on admission in 12 subjects in the present study ranged from 2 to 162 ng/mL. EME concentrations were consistently less than BE and greater than cocaine concentrations. BE and EME ranged from 67 to 1716 ng/mL and from 4 to 290 ng/mL, respectively, in subjects with detectable plasma cocaine. It should be borne in mind that these plasma specimens were collected up to 15 h after the last reported use of cocaine. Based on earlier studies of acute administration, such high concentrations would not be expected. For example, after intravenous administration of 20.5 mg cocaine, plasma cocaine and BE concentrations peaked at approximately 200 and 600 ng/mL, respectively(5).

After intravenous administration of 32 mg cocaine HCl, mean plasma cocaine concentrations declined from 308 ± 32 ng/mL (at 5 min) to 49 ± 10 ng/mL (at 120 min) (23). Similarly, after intravenous administration of 25 mg cocaine HCl in six subjects, plasma cocaine peaked at 102 to 348 ng/mL; by 12 h, the concentrations ranged from 0 to 22 ng/mL (11). In these same six subjects, peak BE concentrations ranged from 56 to 170 ng/mL, and EME was detectable in only one subject. Considered in relation to these earlier findings, the present results suggest accumulation of cocaine metabolites with repeated administration. This suggestion is supported by a study in which cocaine was administered orally five times daily in doses increasing from 500 mg/day to 2000 mg/day (24). Peak cocaine concentrations greater than 1000 ng/mL were found. Relative peak concentrations of cocaine and metabolites were BE > EME > cocaine > BNE = *p*-OH-BE > NCOC > *p*-OH-COC > *m*-OH-BE > *m*-OH-COC, similar to the order found in Subject B (Figure 1) the present study.

The half-life of cocaine in our street cocaine users was longer than that previously reported in acute administration studies, 3.8 h compared to approximately 1.25 to 1.5 h, whereas the half-life of BE was similar to an earlier report (2). The plasma half-life of 5.5 h for EME calculated from our street cocaine users is longer than the value of 3.6 h reported earlier by Ambre (2). Other studies have found even shorter half-lives

Table III. Elimination Kinetics of Cocaine and Metabolites in Plasma and Saliva*

	<i>n</i>	Plasma				<i>n</i>	Saliva			
		<i>T</i> _{1/2} (h)	MRT (h)	AUC (ng·h/mL)	No. of points		<i>T</i> _{1/2} (h)	MRT (h)	AUC (ng·h/mL)	No. of points
COC*	11	3.8 (0.5)	5.7 (0.8)	93.6 (41.0)	8.5 (1.2)	9	7.9 (3.1)	11.9 (4.3)	517.6 (195.9)	6.3 (1.3)
BE	20	6.6 (0.3)	9.6 (0.4)	3213.2 (893.1)	12.5 (0.2)	11	9.2 (2.2)	12.5 (2.8)	1131.9 (407.6)	8.2 (1.6)
EME	11	5.5 (0.5)	7.7 (0.8)	300.1 (148.1)	10.6 (0.9)	6	10.0 (3.5)	13.9 (5.0)	801.7 (480.7)	10.7 (0.7)
<i>m</i> -OH-BE	9	12.7 (3.3)	18.0 (4.3)	75.2 (12.9)	8.7 (1.1)					
<i>p</i> -OH-BE	11	8.2 (2.2)	11.5 (2.9)	97.1 (43.9)	6.9 (1.4)					
BNE	15	7.0 (0.8)	10.2 (1.2)	161.8 (54.7)	9.7 (0.7)					
NCOC	2	1.3 (1.0)	1.9 (1.3)	16.0 (19.2)	8.0 (4.8)					
EEE	1	4.6	6.6	41.7	12.5					
CE	2	3.5 (0.1)	4.9 (0.2)	27.8 (9.0)	10.5 (1.5)					
<i>m</i> -OH-COC	1	3.6	5.0	25.7	10.0					
<i>p</i> -OH-COC	1	1.4	2.0	12.1	7.0					
AEME	1	1.3	1.8	16.6	9.0					

* Values show mean (SEM); *n* = number of subjects fitted in the estimate of the pharmacokinetic parameter; *T*_{1/2} = terminal half life; AUC = Area Under the Curve; MRT = Mean Residence Time; Mean No. of Points = mean number of plasma or saliva specimens used to generate the values for each analyte. No SEM is listed where *n* = 1.

† Abbreviations: COC, cocaine; BE, benzoylecgonine; EME, ecgonine methyl ester; *m*-OH-BE, *m*-hydroxybenzoylecgonine; *p*-OH-BE, *p*-hydroxybenzoylecgonine; BNE, benzoynorecgonine; NCOC, norcocaine; EEE, ecgonine ethyl ester; CE, cocaethylene; *m*-OH-COC, *m*-hydroxycocaine; *p*-OH-COC, *p*-hydroxycocaine; AEME, anhydroecgonine methyl ester.

for cocaine (3,12). Several biological mechanisms might potentially account for the longer half-life detected in these street cocaine users, including accumulation of cocaine in tissues and saturation of enzymatic pathways. Accumulation of cocaine in tissues could increase the apparent terminal half-life of cocaine if redistribution were relatively rapid. Differences in the disposition and metabolism of cocaine may occur following chronic dosing compared to acute single-dose administration. Saturation of key enzymes could lead to shunting to alternate enzymatic pathways. Cocaine is known to be metabolized by several enzyme systems (esterases and cytochrome P-450 systems) found in the blood and liver (25–28). Normal concentrations of endogenous enzymes could be saturated by a high bolus dose of cocaine or by multiple self-administrations in chronic users. Saturation of plasma butyrylcholinesterase has been reported (29). Although the present study does not provide supportive evidence for a specific mechanism, it does support the clinical finding that detection times for cocaine and metabolites are longer in street cocaine users than those suggested by laboratory pharmacokinetic studies (6–9).

The fact that cocaine's but not BE's half-life was prolonged is likely because cocaine is eliminated substantially more quickly than BE. Thus, cocaine's conversion to BE is not a rate-limiting step and should not impact the half-life or elimination of BE. These results suggest that chronic cocaine use does not significantly extend the elimination time for the principal metabolite BE but does extend the elimination time for the parent compound. Thus, our findings do not lead to any recommendations to revise decisions based on results from assays used for detection of cocaine metabolites in treatment and other programs, even if obtained from chronic high-dose cocaine users.

Three analytes—cocaine, BE, and EME—were detectable in the mixed saliva of most participants. Their relative concentrations in saliva were distinct from, and more variable than, their relative concentrations in plasma. In plasma, the concentration of BE was consistently higher than that of either EME or cocaine; in saliva, none of the analytes was consistently highest, though BE was most often detected. Cocaine saliva concentrations were on average 2.4-fold higher than those found in plasma, although individual subjects showed widely variable patterns. BE saliva concentrations were approximately one-fifth those in plasma, and EME concentrations in saliva and plasma were approximately equivalent; however, as with cocaine, there was substantial intersubject variability. Although the half-lives of cocaine, BE, and EME were all longer in saliva than in plasma, they were generally detected in fewer subjects and for shorter periods of time in saliva than in plasma. These findings may have implications for the utility of saliva to monitor cocaine use. Acute-administration studies have consistently reported higher concentrations of cocaine in saliva than in plasma, with similar individual variability (12,13,30). S/P cocaine concentration ratios reported here are comparable to those reported from studies of acute administration (11). The ranges of S/P ratios may reflect fluctuations in saliva pH (which increases with saliva flow rate).

One limitation of this study is that the exact cocaine use histories of these street users are not known. Although there

were significant correlations between self-reported use and some concentration data, the accuracy of the self-reported drug use is questionable. A study is currently underway to test individuals in whom a more documented history of cocaine use is available. Another limitation is the limited number of subjects and data points for some of the minor metabolites.

Overall, the present study documented a cocaine terminal $T_{1/2}$ of 3.8 h in plasma and 7.9 h in mixed saliva. The terminal $T_{1/2}$ of BE was 6.6 h in plasma and 9.2 h in saliva. These findings suggest a longer cocaine half-life and similar BE half-life in street users than reported in most studies based on acute low-dose cocaine administration. In contrast to its longer $T_{1/2}$, cocaine S/P ratios were comparable to those reported from studies of acute administration. Thus, regular use of cocaine appears to alter the disposition and elimination of cocaine when compared to single or occasional use.

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