Effect of Repeated Cocaine Administration on Detection Times in Oral Fluid and Urine

Rebecca Jufer
Office of the Chief Medical Examiner, Baltimore, Maryland

Sharon L. Walsh
Johns Hopkins University School of Medicine, Baltimore, Maryland

Edward J. Cone* and **Angela Sampson-Cone**
ConeChem Research, Severna Park, Maryland

Abstract

Detection times reported for single-dose studies may not predict detection times following repeated cocaine dosing. Although repeated cocaine administration can result in drug accumulation and extended excretion time, there is a paucity of data from controlled dosing studies with repeated drug administration. We compared detection times for cocaine and benzoylecgonine (BZE) in oral fluid and BZE in urine following single and repeated cocaine dosing. Two groups of cocaine-experienced subjects participated in these studies. The single-dose group received cocaine by intravenous, intranasal, and smoked administration. The repeated dose group received daily escalating oral cocaine doses culminating in a total of 1250–2000 mg. Oral fluid and urine specimens following the last dosing were analyzed by gas chromatography–mass spectrometry. Detection times were determined as the time to the last positive specimen. The effect of repeated dosing was to extend oral fluid detection times for cocaine approximately fourfold and BZE detection times sevenfold, whereas urine BZE detection times were extended twofold. Because cocaine abusers frequently self-administer higher and repeated doses, we conclude that the short detection times observed in single-dose studies underestimate the utility of oral fluid for detection of cocaine abuse in realistic settings.

Introduction

The detection time of a drug or metabolite in a biological specimen is a useful concept when interpreting drug tests. Detection times are generally determined in drug administration studies performed with a small number of individuals who are housed in a closed setting without access to alternative sources of the drug. The usual protocol involves collection of specimens prior to and periodically following administration of the drug. Most frequently, detection times are determined in studies in which a single drug dose is administered. Analyses of specimens at a specified cutoff concentration provide information on individual excretion times. The average across subjects is frequently reported as the "detection time". Numerous factors are known to influence detection times, and these factors must be taken into consideration when interpreting drug tests. In particular, detection times are dependent upon specimen characteristics, assay sensitivity and specificity, cutoff concentration, individual rates of metabolism and excretion, drug dosage, and frequency of drug administration.

Although detection times often serve as useful guides in interpretation of drug tests, some caution is needed because of inherent limitations on detection times based on single-dose studies. Frequent drug administration can result in accumulation of drug and metabolites in body tissues and extended excretion time. Elimination kinetics based on single-dose studies may not reveal slower excretion phases because of assay sensitivity. Hence, detection times based on single-dose studies may not be truly representative of frequent drug users. For example, heavy cannabis users may excrete cannabinoid metabolites in urine for days to weeks (1), whereas the detection time for single use is approximately 2–3 days (2). Unfortunately, there is a paucity of data on drug detection times following repeated use, particularly from controlled-dosing studies in which outside access to drug is denied. Repeated-dosing studies under controlled conditions are exceedingly difficult and expensive to perform. Consequently, our major source of information on detection times is limited primarily to single-dose studies. It remains unclear how repeated dosing alters or prolongs detection times.

The goal of the current study was to compare detection times for cocaine and its major metabolite, benzoylecgonine

* Author to correspondence should be addressed: Edward J. Cone, ConeChem Research, LLC, 441 Fairtree Drive, Severna Park, MD 21146. E-mail: Edward.cone@comcast.net.

(BZE), in a single-dose group to a repeated-dose group. Oral fluid and urine specimens were collected from six individuals in each group and analyzed by gas chromatography–mass spectrometry (GC–MS).

Methods

Single-dose cocaine study

The participants were six healthy adult males who provided written informed consent and were paid for their participation. All subjects had a history of intravenous and smoked cocaine use. Subjects participated in four experimental sessions in which cocaine or placebo was administered in a randomized, crossover design. Each session was separated by a minimum of three days. The design of the study and detailed procedures have been described (3). Four cocaine/placebo (partial) combinations were administered as follows: 1. 25 mg cocaine hydrochloride (intravenous, IV), 32 mg lactose (intranasal, IN); 2. 32 mg cocaine hydrochloride (IN), saline (IV); 3. 42 mg cocaine base (smoked, SM), saline (IV), 32 mg lactose (IN); and 4. saline (IV), 32 mg lactose (IN). No placebo was included for the SM route.

Urine specimens were collected before and after each drug administration (ad libitum) for a minimum of three days. The volume was measured and an aliquot was frozen at –30°C for subsequent analysis. Oral fluid specimens were collected in polypropylene tubes under stimulated conditions (citric acid-sour candy). The time needed for oral fluid collection ranged from 3 to 5 min. Collection times included a baseline specimen (zero time) and periodically through 12 h. Specimens were frozen immediately after collection at –30°C for subsequent analysis.

Repeated-dose cocaine study

The participants were six healthy male cocaine users (average age = 34.2 years, range 30–40 years) who reported a recent cocaine history of at least six months in duration. The subjects reported using cocaine an average of 10.8 days over the last two weeks prior to their participation and an estimated amount of cocaine used per day of 1.1 g (range 0.1–2.5 g). Inclusion criteria included self-reported use of smoked or intravenous cocaine at least two times per week for the six weeks prior to admission. Recent cocaine use was confirmed by urinalysis prior to participation. Subjects resided for the entire period on a closed research ward for approximately 4–5 weeks. A daily urine 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, repeated dosing sessions, and a withdrawal period. During the repeated dosing period, up to 16 daily sessions were conducted. During each daily repeated dosing session, five equal doses of oral cocaine hydrochloride or placebo (administered twice during repeated dosing) were administered at 1-h intervals, beginning at 9:00 a.m. Cocaine capsules were double encapsulated and hand polished to avoid contamination of oral fluid. Cocaine was administered in ascending doses, with increments of 25 mg/dose across successive sessions, resulting in a total increase on a daily basis of 125 mg. The initial cocaine dose was 100 mg, and the maximum possible single dose was 400 mg (2000 mg/day). Participation was terminated if the following 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 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. Two subjects reached the maximum dose of 2000 mg/day without exceeding safety parameters; three subjects exceeded cardiovascular limits at doses ranging from 1500 to 1875 mg/day. One subject experienced sensory hallucinations at 1375 mg/day and dosing was terminated. The withdrawal phase commenced immediately after the last repeated dosing session, either when the 16 sessions were completed or when safety parameters were exceeded. The maximum tolerated daily cocaine dosing for the six subjects ranged from 1250 mg to 2000 mg.

Table I. Mean Detection Times (Last Positive) by GC–MS for Cocaine and BZE* in Oral Fluid and Urine Following Single and Repeated Dosing

Total Cocaine Dose, Route	N	Oral Fluid Cocaine (cutoff = 8)	Oral Fluid BZE (cutoff = 8)	Urine BZE (cutoff = 150)	Urine BZE (cutoff = 100)
Single dose 25 mg, IV					
Mean	6	4.67	6.67	41.32	47.43
SEM		0.61	1.91	3.78	3.37
Range		3.0–6.0	0–12.0	31.0–53.9	31.0–53.9
Single dose 32 mg IN					
Mean	6	6.33	8.67	42.88	48.46
SEM		1.20	1.52	4.21	3.80
Range		4.0–12.0	4.0–12.0	32.5–59.4	36.3–62.7
Single dose 42 mg, SM					
Mean	5	4.10	5.02	39.88	44.22
SEM		1.02	2.14	4.28	4.38
Range		1.5–6.0	0.1–12.0	26.7–50.3	33.5–54.0
Single dose					
Overall mean	5–6	5.03	6.78	41.36	46.70
Mean SEM		0.95	1.85	4.09	3.85
Mean range		2.8–8.0	1.4–12.0	30.1–54.5	33.6–56.9
Repeated doses 375–2000 mg, OR					
Mean	6	21.33	50.00	93.73	104.63
SEM		5.99	4.82	7.14	8.72
Range		8.0–48.0	36.0–72.0	72.2–122.2	74.8–141.2

* Abbreviations: BZE, benzoylecgonine; IV, intravenous; IN, intranasal; SM, smoked; and OR, oral.

Details of the study design have been published (4).

Urine specimens were collected ad libitum during the withdrawal phase for up to 120 h, but some subjects remained longer and urine continued to be collected. The volume was measured and an aliquot was frozen at –30°C for subsequent analysis. Oral fluid specimens were collected in polypropylene tubes under stimulated conditions (citric acid-sour candy) for up to 120 h during the cocaine cessation period. Specimens were frozen immediately after collection at –30°C for subsequent analysis.

Specimen analyses

Oral fluid and urine specimens were analyzed for cocaine and BZE by GC–MS according to a published procedure (5). The limits of detection for cocaine and BZE were approximately 1 ng/mL. Cutoff concentrations for cocaine and BZE in oral fluid were administratively set at 8 ng/mL according to proposed DHHS guidelines (6). Cutoff concentrations for BZE in urine specimens were set at 150 ng/mL and 100 ng/mL according to current DHHS guidelines (7) and to proposed DHHS guidelines (6).

Results and Discussion

Following single-dose cocaine administration by the intravenous, intranasal, and smoked routes, cocaine and BZE appeared and declined rapidly in oral fluid with average detection times (last positive, cutoff concentration = 8 ng/mL) of 4.7, 6.3, and 4.1 h (overall average = 5.0 h) for cocaine and 6.7, 8.7, and 5.0 h (overall average = 6.8 h) for BZE, respectively (Table I). BZE was detectable in urine at the DHHS cutoff concentration (150 ng/mL) for 41.3, 42.9, and 39.9 h, respectively (overall average = 41.4 h). Lowering the urine cutoff concentration to the new proposed DHHS cutoff concentration (100 ng/mL) extended detection times to 47.4, 48.5, and 44.2 h, respectively (overall average = 46.7 h).

In the chronic cocaine study, detection times in oral fluid and urine were substantially increased. Cocaine was administered by the oral route in five equal daily doses and increased on a daily basis by 125 mg to a maximum of 2000 mg/day. Detection time data were collected during cocaine cessation at the end of the study. Although oral cocaine administration is not common amongst abusers, this route of administration was chosen because of the medical risks inherently associated with cocaine administration by faster parenteral routes of administration. Following repeated oral cocaine dosing, average cocaine and BZE detection times in oral fluid were 21.2 and 50.0 h, respectively. BZE was detectable in urine at the DHHS cutoff concentration (150 ng/mL) for 93.7 h. Extended detection times for BZE in the urine of chronic cocaine users have also been reported by Preston et al. (8). They reported a mean detection time (time of last positive; TDx; cutoff = 300 ng/mL) of 81 ± 34 h, based on self-report after last use of cocaine.

In the present study, lowering the urine cutoff concentration to the new proposed DHHS cutoff concentration (100 ng/mL) extended the detection time to 104.6 h. Individual excretion patterns for cocaine and BZE are shown in Figure 1 (oral fluid) and Figure 2 (urine).

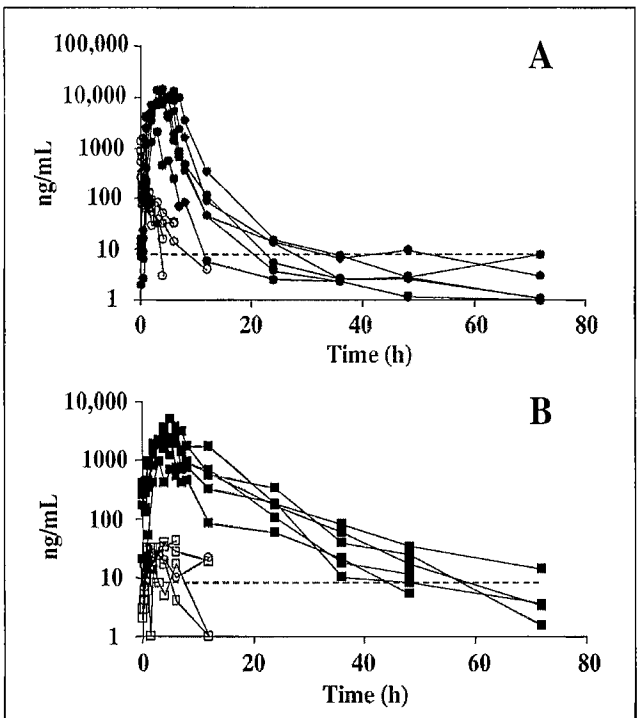

Figure 1. Individual patterns of excretion of cocaine (A) and BZE (B) in oral fluid following a single intravenous cocaine dose (open symbols) and repeated cocaine doses (filled symbols). The dotted lines indicate the recommended DHHS cutoff concentration (8 ng/mL) for each analyte.

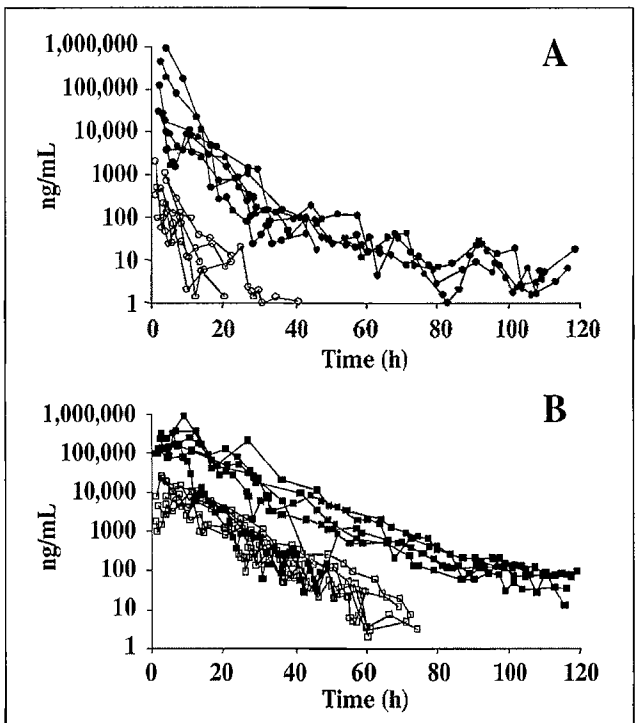

Figure 2. Individual patterns of excretion of cocaine (A) and BZE (B) in urine following a single cocaine dose (open symbols) and repeated cocaine doses (filled symbols). The dotted line indicates the recommended DHHS cutoff concentration (150 ng/mL) for BZE.

A comparison of average detection times for cocaine and BZE in oral fluid and BZE in urine following single and repeated cocaine dosing is shown in Figure 3. It is interesting to note that the effect of repeated dosing extended average oral fluid detection times for cocaine by a factor of approximately 4 and for BZE by a factor of 7, whereas urine BZE detection times (at both cutoff concentrations) were only extended by a factor of 2. The enhancement of oral fluid detection times in comparison with urine following repeated dosing is likely related to differences in disposition and excretion kinetics of cocaine and BZE. Cocaine is a lipophilic compound that can be stored in bodily tissues to a greater extent than the more water-soluble metabolite, BZE, following repeated dosing. In an earlier study, Cone and Weddington (9) provided evidence of prolonged excretion of cocaine in oral fluid specimens collected from heavy cocaine users during abstinence and postulated that cocaine can be accumulated in bodily tissues and excreted in low concentration over long periods of time. Also, as shown in this study, there appears to be important differences in the disposition and excretion of cocaine and BZE. Cocaine displays a rapid initial elimination phase followed by a slower phase (biexponential) in both oral fluid and urine. It is likely that the slower elimination phase for cocaine represents release from tissues. In contrast, BZE appears to be eliminated monoexponentially. These kinetic differences between cocaine and BZE are illustrated in Figure 4 for one of the repeated cocaine dosing subjects in the current study. Thus, repeated cocaine dosing results in drug accumulation and prolonged release of cocaine. Apparently, the prolongation of cocaine excretion increases BZE concentrations sufficiently to extend the detection time of BZE in oral fluid as well. Although urine BZE detection times are also extended by accumulation, the apparent first order elimination of BZE limits the effect on BZE's detection time in urine.

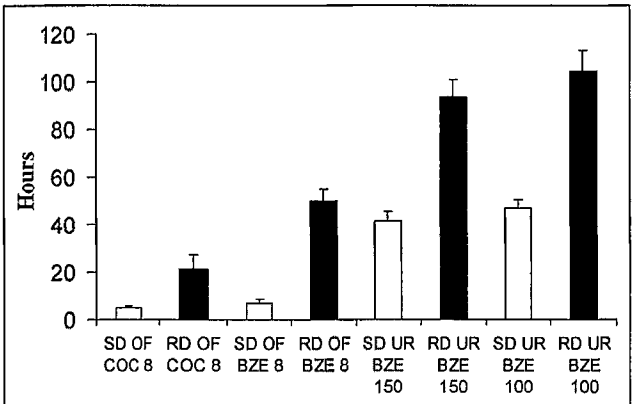

Figure 3. Mean detection times (last positive) by GC–MS for cocaine and BZE in oral fluid and urine following single and repeated dosing. Single dose detection times are depicted in open bars and repeated doses detection times are depicted in filled bars. Cutoff concentrations are shown on the *x*-axis. Error bars represent the standard error of the mean. Abbreviations: SD, single dose; RD, repeated doses; OF, oral fluid; UR, urine; COC, cocaine; and BZE, benzoylecgonine.

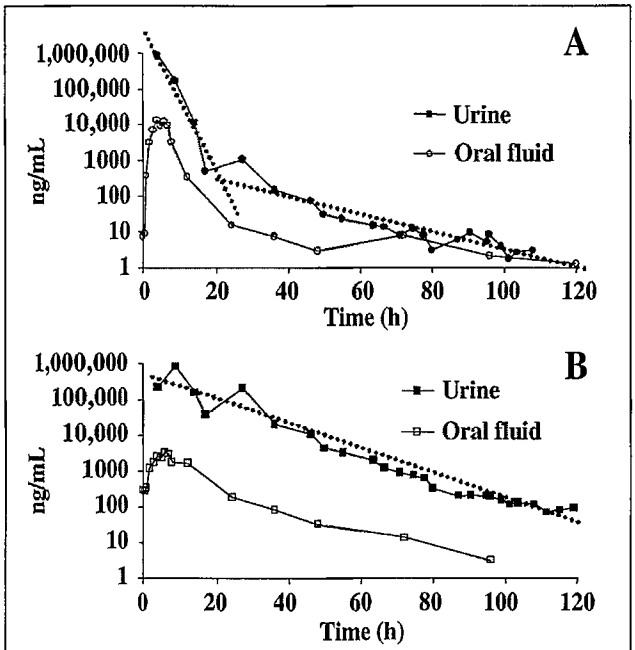

Figure 4. An individual's excretion pattern of cocaine (A) and BZE (B) in oral fluid and urine following repeated cocaine doses. The dotted lines illustrate the bi-phasic nature of excretion of cocaine in urine as compared to first order elimination of BZE.

It is well known that cocaine abusers frequently self-administer multiple doses over the course of a day. As shown in this study, repeated dosing clearly leads to prolonged detection times for cocaine and BZE in oral fluid and urine, but oral fluid detection times are affected more so than urine. This differential effect on oral fluid's detection time compared to urine may provide some explanation of the success of oral fluid testing for cocaine use. In a study of more than 77,000 oral fluid tests for cocaine use, Cone et al. (10) reported a 1.12% positive prevalence rate (confirmed positives) for BZE as compared to a 0.69% positive prevalence rate in urine specimens collected from a similar population (Quest Diagnostics' Drug Testing Index). The higher detection rate for BZE in oral fluid compared to urine would be surprising if oral fluid BZE detection times were considerably shorter than for urine, as found in single dosing studies. Although additional factors (such as direct observation of oral fluid collection but not for urine collection) may have contributed to the success of oral fluid as compared to urine, it is likely that extended detection times for cocaine and BZE in oral fluid following repeated cocaine use also contributed to its success.

The observation of extended oral fluid detection times following repeated cocaine dosing may also be applicable to other drugs. Repeated dosing is also known to be common for abusers of other psychoactive drugs. Detection times based on single-dose studies are likely to underestimate the utility of oral fluid tests.

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