Pharmacokinetics of Cocaine: Considerations When Assessing Cocaine Use by Urinalysis

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INTRODUCTION

Changes in a patient's patterns of cocaine use are generally considered an important outcome measure of treatment efficacy. Other treatment outcome measures are important as well, but if a treatment does not stop or significantly decrease the intensity of a cocaine addict's cocaine use, many would question the treatment's efficacy. Examination of a patient's urine for evidence of cocaine or cocaine metabolites is an objective index of cocaine use. Like many biochemical measures useful in medical practice, urinalysis to measure cocaine or its metabolites, although relatively simple and straightforward from an analytic standpoint, is subject to misinterpretation and erroneous conclusions if the underlying biological principles are not properly considered.

This chapter considers selected aspects of cocaine clinical pharmacology, particularly cocaine pharmacokinetics as it applies to the use of urinalysis to measure treatment outcome in cocaine addiction treatment trials. The focus will be on examination and assessment of urine, though cocaine and its metabolites are also measurable in other biological media—hair, sweat, saliva and, of course, blood. Saliva, hair, and sweat offer advantages in terms of accessibility but have not been sufficiently studied to fully understand the biodisposition and kinetics of cocaine. At this time, there are insufficient data to make proper quantitative interpretations. Consideration of future use of hair and saliva assays to measure cocaine use and discussion of assay procedures in general are included elsewhere in this volume.

The pharmacokinetics and metabolism of cocaine make for easy monitoring of illicit cocaine use in most clinical situations. Typical patterns of use result in substantial levels of cocaine and metabolites in urine. A variety of immuno- and chromatographic assays make quantitative urine measures relatively easy compared to other drugs of abuse. Cocaine is taken by a variety of routes. In the United States,

cocaine is most commonly smoked or snuffed, but it is also used intravenously, particularly by individuals likely to enter treatment research programs. Some kinetic considerations are route dependent. Smoking in particular has special attributes (Jones 1990).

PHARMACOKINETICS AND METABOLISM

Cocaine hydrochloride, a crystalline salt, is commonly snuffed or injected. Cocaine base (crack) is the form usually smoked because the base is more volatile, vaporizing at a lower temperature, in contrast to cocaine hydrochloride, which decomposes before it volatizes when heated. Cocaine is a weak base with a pKa of 8.6. In its basic form in blood and smoke, cocaine crosses cell membranes quickly and efficiently. Like nicotine in tobacco smoke, cocaine, when it reaches the small airways and alveoli of the lung, is rapidly absorbed into the blood. Although cocaine's pulmonary kinetics are not as well studied as nicotine, rapid absorption of cocaine through the lungs, presumably because of the large surface area of the alveoli and small airways, probably accounts for the appeal of that route of administration.

The rate and the relative amount of cocaine entering systemic circulation depend greatly on the route of administration. Figure 1 illustrates differences in time of peak plasma levels of cocaine when approximately equipotent doses were administered to the same 10 volunteer subjects by different routes. Absorption from nasal mucosa when snuffed and absorption from mouth and the gastrointestinal tract when taken orally are similar and much slower than after smoking or after intravenous (IV) administration (Jeffcoat et al. 1989; Jones 1990). Peak plasma levels occur on average about 60 minutes after nasal or oral intake; though, like many attributes of cocaine kinetics, individual variability is great, ranging from 30 to 120 minutes in different individuals. An individual's kinetics vary between laboratory sessions as well. Oral and nasal bioavailability are both about 30 to 40 percent, though variability is greater by the oral route.

Like nicotine in cigarette tobacco, cocaine has smoked bioavailability of between 10 and 20 percent, more commonly the lower amount with typical smoking devices. When cocaine is smoked, the relatively low and variable bioavailability is a consideration if attempts are made to infer cocaine dose consumed by examination of only urine concentrations.

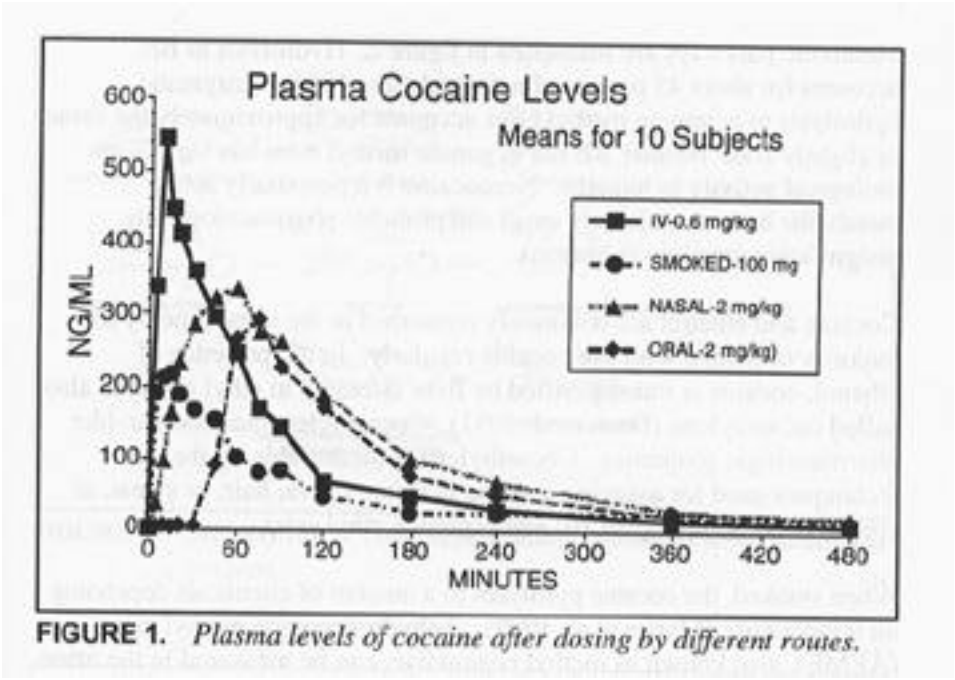

FIGURE 1. *Plasma levels of cocaine after dosing by different routes.*

A patient may report buying and putting considerable cocaine in a pipe and smoking it, report experiencing intense effects, and yet show less benzoylecgonine (BE) in urine assays than an IV or nasal user (Jones 1990).

Peak venous blood concentrations and, by inference, peak arterial blood levels after self-administered doses of cocaine vary enormously. Not only do cocaine doses vary but, with IV administration, rate of injection is as important a determinant of peak cocaine levels in blood as is total dose. Cocaine doses commonly range from 0.2 to 3 or 4 mg/kg, depending on route. Peak plasma levels can range from 50 to 2,000 ng/mL or greater, depending on route and rate of injection. Peak arterial blood levels of cocaine should be several times higher than venous levels when cocaine is smoked or taken intravenously (Chiou 1989).

Cocaine, after intake, is widely distributed through body tissues. Volume of distribution usually ranges between 1.5 to 2 L/kg (Ambre et al. 1988; Jeffcoat et al. 1989). Cocaine is rapidly metabolized. Major metabolic pathways are by enzymatic hydrolysis to BE or ecgonine methyl ester, then to ecgonine (Ambre et al. 1988). About 1 to 5 percent of a cocaine dose is excreted unchanged in urine. Cocaine is rapidly cleared from plasma, but variably, at 20 to 30 mL/min/kg. Elimination half-life of cocaine is similarly variable,

averaging 1 to 1.5 hours. BE elimination half-life is 6 to 8 hours. Ecgonine methyl ester half-life is 3 to 8 hours.
Metabolic pathways are illustrated in figure 2. Hydrolysis to BE accounts for about 45 percent of a dose (Ambre 1985). Enzymatic hydrolysis to ecgonine methyl ester accounts for approximately the same or slightly less. Neither BE nor ecgonine methyl ester has significant biological activity in humans. Norcocaine is a potentially active metabolite but occurs in only small and probably pharmacologically insignificant amounts in humans.

Cocaine and ethanol are commonly consumed at the same time by the majority of people who use cocaine regularly. In the presence of ethanol, cocaine is transesterified by liver esterases to ethyl cocaine, also called cocaethylene (Dean et al. 1991). Cocaethylene has cocaine-like pharmacologic properties. Cocaethylene is measurable by the same techniques used for assaying cocaine in urine, saliva, hair, or sweat, as are the ethyl homologs of BE and ecgonine ethyl ester.

When smoked, the cocaine pyrolyzes to a number of chemicals depending on temperature (Martin et al. 1989). Anhydroecgonine methyl ester (AEME), also known as methyl ecgonidine, can be measured in the urine of people who have smoked relatively small amounts of cocaine (Jacob et al. 1990). AEME does not appear in the urine after injection or snuffing. Thus, if treatment-related changes in typical route of use are of interest as a treatment outcome measure, it might be possible to objectively measure by urinalysis a patient's shifts from or to cocaine smoking. Thus, in principle, even typical routes of use and concurrent use of alcohol can be measured. The human pharmacology of AEME has not been studied, but in animals it is pharmacologically active.

BE is the commonly assayed metabolite for monitoring treatment outcome. With most commercially available assays, BE can be detected in urine for 3 to 4 days after last cocaine use. The detection duration obviously depends on the amount of cocaine used in the recent past, on the definition of the cutoff value required before reporting the presence of BE, and on assay sensitivity.

ROUTE OF ADMINISTRATION

Route of administration can also determine amount of cocaine entering the body and thus the amount of BE in urine. Figure 3 shows mean plasma

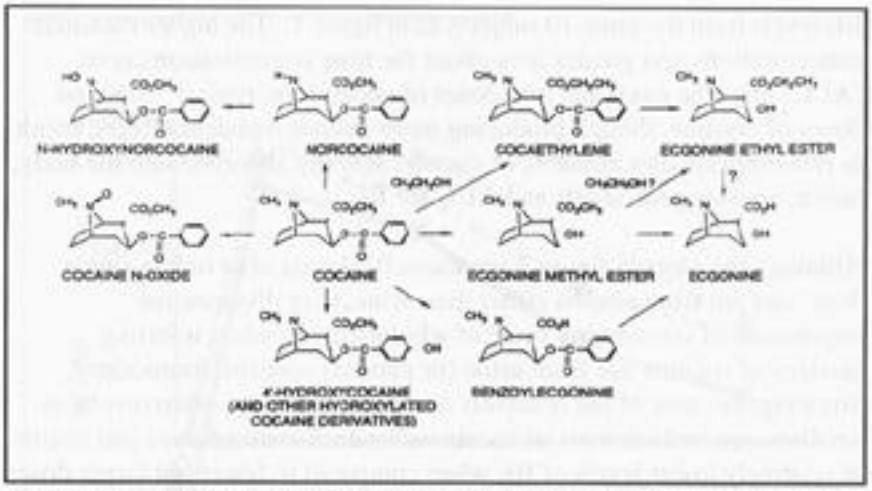

FIGURE 2. *Metabolism of cocaine, including pathways when ethanol is present.*

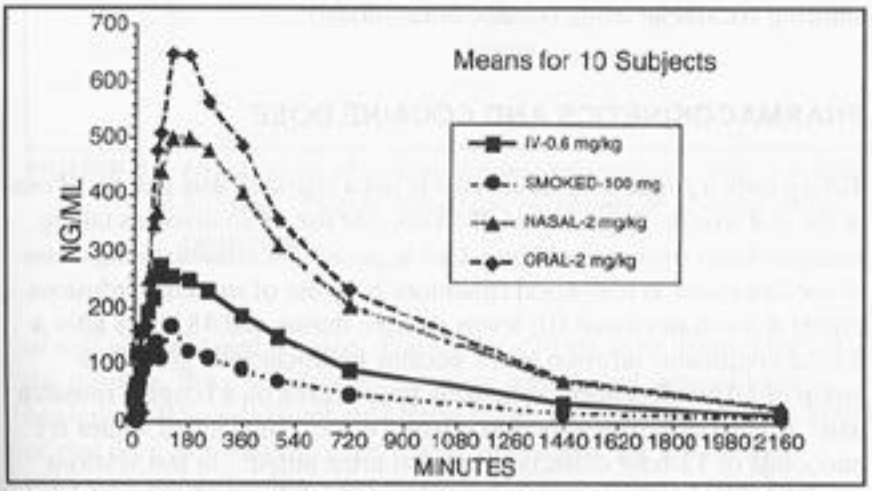

FIGURE 3. *Plasma levels of benzoylecgonine after dosing by different routes.*

BE levels from the same 10 subjects as in figure 1. The higher maximum concentrations and greater area under the time concentration curve (AUC) after the nasal and oral doses of cocaine are typical. Smoked doses of cocaine, though producing more intense transient effects, result in relatively smaller amounts of cocaine actually absorbed into the body; hence, smaller peak levels and AUC for BE.

Although the plots in figure 3 represent BE levels after only a single dose, and are from plasma rather than urine, they illustrate the importance of considering route of administration when inferring patterns of cocaine use from urine (or plasma) concentrations alone. Smoking, because of the relatively low bioavailability, often results in smaller absorbed amounts of cocaine after each smoked dose and results in relatively lower levels of BE when compared to fewer but larger doses of nasal cocaine or IV doses of cocaine. Of course, increased numbers of smoked doses over whatever time is being considered could change this pattern, but the principle holds; other things being equal, a cocaine smoker may have relatively lower levels of BE in urine than someone snuffing cocaine or using cocaine intravenously.

PHARMACOKINETICS AND COCAINE DOSE

Taking only a single dose of cocaine is not a characteristic pattern of use in the real world. A session of illicit cocaine use often involves taking multiple doses over many hours. One approach for administering doses of cocaine closer to real-world conditions is by use of sustained infusions. Figure 4 illustrates mean BE levels in urine during and 48 hours after a 4-hour continuous infusion of IV cocaine hydrochloride given to a group of 10 nondependent volunteers hospitalized on a hospital research unit. All had extensive experience with IV use. The plotted values are midpoints of 12-hour collections of total urine output. In test sessions spaced 2 days apart, subjects received over the 4-hour infusion total cocaine doses of 105 mg, 210 mg, 420 mg, and a placebo infusion. The cocaine doses were administered as 0.3, 0.6, and 1.2 mg/kg loading doses followed by constant rate infusions at a rate calculated to equal previously determined clearance.

The 420 mg dose was judged by all 10 subjects as very high and close to exceeding what they could comfortably tolerate during a typical session

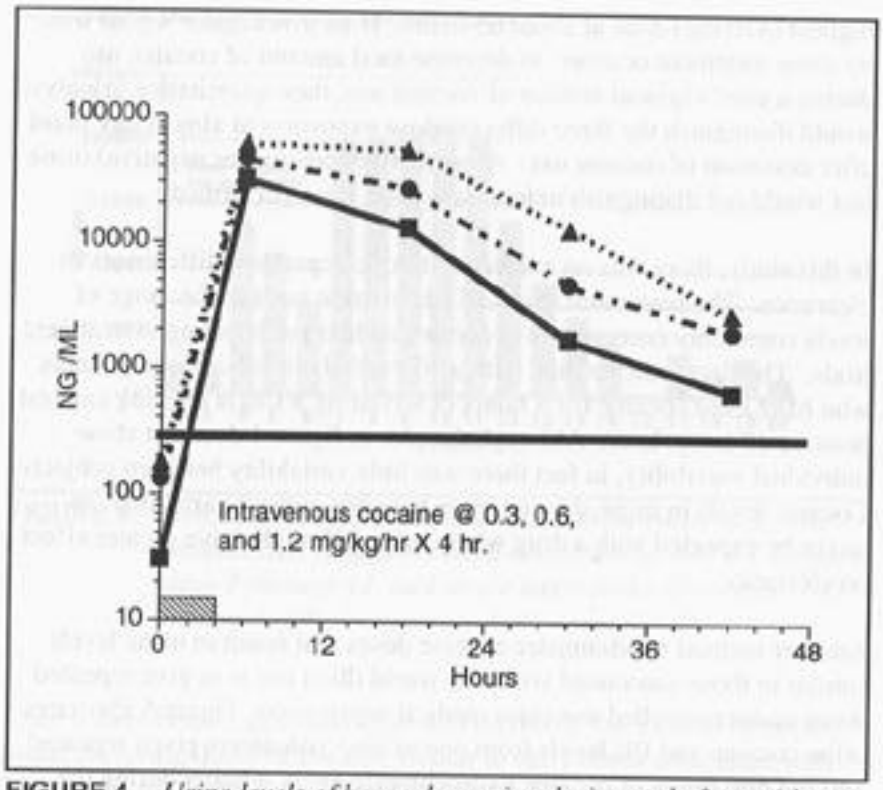

FIGURE 4. *Urine levels of benzoylecgonine during and after a 4-hour infusion. Plotted values are midpoints of 12-hour urine collections.*

of self-administered cocaine. During the 420 mg dose, toward the end of the infusion, three subjects became very restless and showed hints of beginning delusional thinking. None of the subjects described the effects of that dose as a pleasant experience. In contrast, the lowest dose (105 mg) was judged by most subjects as less than they would have liked. The effects were described as less than typically experienced during a session of self-administered use.

Each of the doses was significantly different in effects and in BE AUCs and plasma concentrations during the log linear phase of clearance. However, if a 300 ng/mL cutoff criteria was used for determining positive or negative urines, the three very different doses would appear equal at 48 hours, i.e., all urines were still positive. By a least square fit for the log linear phase, the lowest dose would have become negative at about 49 hours, the medium (210 mg) dose at about 60 hours, and the highest (420 mg) dose at about 65 hours. If an investigator's goal was, by some treatment or other, to decrease total amount of cocaine use during a user's typical session of cocaine

use, then quantitative urinalysis would distinguish the three different dose exposures at almost any point after cessation of cocaine use. A qualitative (positive or negative) urine test would not distinguish unless daily tests were performed.

In this study, there was no evidence of dose-dependent differences in clearance. The maximum levels of BE in urine were in the range of levels commonly encountered in cocaine addicts participating in treatment trials. The data indicate that, with a 300 ng/mL cutoff criteria, patients who have used cocaine for 4 hours or so during a single evening can test positive 60 hours later. Although the plot in figure 4 does not show individual variability, in fact there was little variability between subjects. Cocaine levels in urine showed more between-subject variability, as might be expected with a drug where urine pH might have greater effect on clearance.

Another method to administer cocaine doses that result in urine levels similar to those associated with real-world illicit use is to give repeated doses under controlled and close medical supervision. Figure 5 illustrates urine cocaine and BE levels from one of nine volunteers given repeated 140 mg oral doses of cocaine hydrochloride every 4 hours during the period beginning on day 7 and ending on day 11. Twenty-four hour urine collections began on the first day of admission to the University of California General Clinical Research Center and continued each day, 0800 to 0800, until discharge on day 21. The kinetics of the oral cocaine doses approximated nasal doses. While on this 840 mg/day dose schedule, urine levels of BE were approximately 100,000 ng/mL; levels not unlike the BE concentrations measured in the urine of some cocaine addicts in treatment trials. Cocaine levels in urine during the period of repeated oral doses were about 3,000 ng/mL and also in the range observed in cocaine addicts in treatment.

When the oral doses of cocaine were replaced by placebo capsules late in the afternoon of day 11, the 24-hour urine BE concentrations decreased over the next 3 days. Noteworthy in this typical patient was that by the third day after cocaine administration stopped, by criteria commonly used in treatment trials (a 300 ng/mL cutoff), the patient would probably have tested negative for BE with a urine sample containing 180 ng/mL.

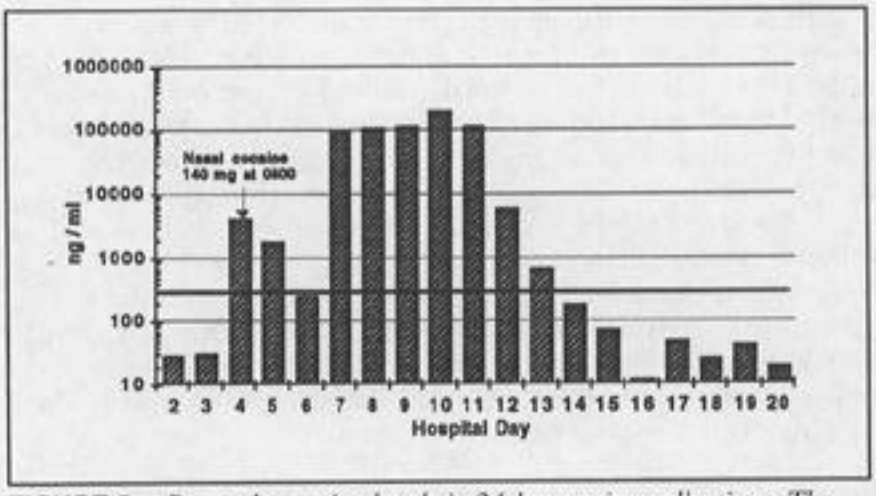

FIGURE 5. *Benzoylecgonine levels in 24-hour urine collections. The hospitalized subject received oral cocaine, 840 mg daily, on days 7 through 11, and single nasal doses of cocaine, 140 mg, on day 4.*

Only 3 days before, this individual was markedly intoxicated by cocaine while receiving doses of cocaine similar to daily doses associated with binge-type use behaviors. If a quantitative assay was used, in this instance gas chromatography with mass spectrography with cutoff of 10 ng/mL, the patient had measurable BE 9 days after the last dose of cocaine. The increase in BE levels on day 4 resulted from a single 140 mg nasal dose of cocaine. That single dose produced very modest effects and also was followed by a negative urine 2 days later, if a 300 ng/mL cutoff criteria was applied. The point is, using nonquantitative urine criteria there was only 1-day difference in changing from positive to negative after a single, pharmacologically trivial dose of nasal cocaine as compared to the urine change after cocaine doses that produced a period of sustained and pharmacologically intense effects.

HOW MUCH BENZOYLECGONINE IS IN AN ADDICT'S URINE?

After becoming aware of typical urine levels of BE after cocaine administration in conditions that partially mimic the real world of cocaine use, as illustrated in figure 4 or figure 5, it seemed important to determine what urine concentrations might be in typical cocaine addicts participating in treatment trials. Curiously, no one had

bothered to measure actual concentrations of BE in urine despite the enormous amount of money and time spent on nonquantitative urine assays in treatment trials. It was well known that patients arriving in emergency rooms with cocaine-related medical complications not uncommonly had urine BE levels over 100,000 ng/mL, but nothing was known about actual levels in typical cocaine addicts in treatment programs (Batki et al. 1993). Gas chromatographic quantitative assays of urines from cocaine addicts in treatment trials showed that urine BE levels above 10,000 ng/mL were common and 22,562 ng/mL was the median value for a group of 16 patients just entering treatment. Patients with urine levels of 100,000 ng/mL or more were not unusual. Occasional patients with urine BE levels as high as 300,000 ng/mL did not report any noteworthy acute toxicity or unusual cocaine-related events.

The pharmacokinetic data on cocaine and BE levels in urine collected in the author's research laboratory experiments with nonaddict, cocaine-using volunteers are remarkably congruent with the real-world urine levels in a cocaine treatment clinic. In light of typical urine BE levels of 10,000 to 100,000 ng/mL, routine application of a 300 ng cutoff to define positive or negative (or clean or dirty) urines may be a little shortsighted and holds cocaine treatment trials to a higher standard for determining a clinically significant change than is commonly applied in other medical treatments. For example, consider a patient who had been using cocaine almost every day and enters a treatment trial with urine levels of about 100,000 ng/mL of BE. The patient would test positive for urine BE. After 8 weeks' treatment if the patient was still using some cocaine almost every day but taking much smaller doses, and if the patient had levels of 310 ng/mL at the time of testing, the urine still would be reported as positive if judged by binary criteria and the patient might be termed a treatment failure despite a 99.7 percent decrease in the amount of cocaine used. Most treatments in medicine that change maladaptive behavior or symptoms by 99.7 percent would be considered successful.

SPECULATIONS ABOUT HISTORY AND RATIONALES

One argument for the binary urine assessment strategy is that quantitative urinalysis is more time-consuming and more costly. However, considering the total cost of a typical, well-designed Phase II clinical treatment trial and the hidden costs of falsely accepting a treatment that later turns out to be less useful, the true cost differences

may not be as great as assumed. Worse yet, consider missing significant decreases in amount of cocaine use in a treatment trials and thus falsely and prematurely rejecting a promising treatment. In medical practice, it is rare for a quantitative biochemical test, particularly one that may be important in clinical decisionmaking, to be judged on a simplistic binary positive or negative report. Drug abuse research almost stands alone in using such data as an outcome measure.

Perhaps the original justification for the use of binary assessments was a common treatment goal in addiction treatment research: achieving total abstinence. However, if an acceptable treatment goal is fewer occasions of cocaine use or use of a lower dose or a more acceptable route on each occasion of use, then consideration of the pharmacokinetics of cocaine becomes important when using urinalysis to measure treatment outcome.

Until recently, most cocaine addiction treatment trials used the same urinalysis methods and the same rationale when interpreting urinalysis results as were developed for detecting or following illicit cocaine use in the workplace or for clinical monitoring, mainly to make therapeutic decisions regarding illicit drug use in opiate addiction treatment programs. The assays generally were immunoassays for BE. Because of concerns about cross-reactivity and resulting false-positive reports, a common practice was to specify a 300 ng concentration cutoff for BE. Any sample with a BE concentration below 300 ng/mL was reported negative or a clean urine. A sample with BE concentration above 300 ng/mL was reported a positive sample (or a dirty urine).

Selection of the 300 ng/mL cutoff did not involve any formal consideration of cocaine's pharmacokinetics. In fact, when currently popular cutoffs were established, there were no data on typical BE levels in the urine of cocaine users entering treatment trials. The 300 ng/mL cutoff was largely determined by committee, with considerable input from marketing and legal advisers, as a compromise to minimize false-positives and limit, to an acceptable number, false-negatives in workplace testing programs. Given the goals of typical workplace testing programs (zero tolerance for any cocaine use), absolute or upper levels of BE in a urine sample were irrelevant. Whatever workplace sanctions imposed as a consequence of urine test results were the same at 325 ng/mL as at 100,000 ng/mL levels. To apply the same logic when establishing an appropriate cutoff in a clinical trial may be inappropriate.

CONCLUSIONS

Of what practical value is information on cocaine kinetics for someone designing or evaluating a treatment trial outcome and considering urinalysis data? Patients participating in treatment trials might typically enter with concentrations of 100,000 or 200,000 ng/mL of BE in their urine. How long BE would be measurable after complete abstinence, of course, depends on assay sensitivity or the selection of cutoff criteria. With commonly available gas-chromatographic assays, sensitivities of 10 to 100 ng/mL are not unreasonable. A patient might have measurable BE in urine 5 days after last use if an assay sensitive to 10 ng/mL is used. If the clinician chooses to or has to discard some of the potentially available quantitative data and instead applies some higher cutoff (200, 300, 400 ng/mL), then obviously the window of urine positivity following complete abstinence narrows considerably.

BE concentration in urine is a dose-dependent quantitative measure of systemic cocaine dose actually delivered. In contrast, addict self-reports of money spent on cocaine or reports of days cocaine was used are subject to greater error due to bioavailability considerations, memory impairment related to cocaine-induced delirium, unreliable underestimation or overestimation, or deliberate lying. Cocaine dose differences as small as 100 mg are distinguishable (see figure 4). With daily urine measures, even the taking of a single 140 mg nasal dose is detectable for 1 or 2 days after use. With frequent enough urine sampling, changes in urine BE levels accurately reflect very small changes in dose patterns, assuming some measure of the usual pattern of dosing. Since frequency and amount of cocaine use per time unit are interrelated, BE assays will never completely distinguish dose frequency from dose amount. However, for estimates of the amounts of cocaine used over a 24-hour period, the pharmacokinetic data indicate that reliable estimates of dose are possible.

How the pharmacokinetic information might best be applied depends greatly on treatment goals. If total abstinence is the treatment goal, then whatever the assay, whether semiquantitative or quantitative, a very low cutoff used to define the urine as negative is most desirable. A 300 ng/mL cutoff may be too high if abstinence is the treatment goal. If urine samples are obtained only two or three times a week, and the patients are other than regular daily users, episodes of cocaine use will be missed if a 300 ng/mL cutoff criteria is applied. If a

treatment goal is to significantly decrease cocaine use in terms of typical dose used or frequency of dosing, then quantitative urine BE assays obtained as frequently as possible would be the ideal continuous variable to measure that aspect of outcome. How frequently urines can be obtained depends on the clinical setting and research budget. The best advice would be to obtain urine samples as frequently as possible—daily if possible. Any frequency of urine sampling less than daily will tend to underestimate the frequency of use and typical dose used over days or weeks.

An individual addict's cocaine taking is a behavior as complicated as any other behavior. A single snapshot or sample of a behavior at any point in time cannot give an accurate representation of complicated behavioral patterns over the previous few days or week. A urine sample every day is probably more than is necessary to track small changes in cocaine-using behavior. However, even a cursory consideration of cocaine pharmacokinetics suggests a single weekly urine sample is not enough and even every-other-day sampling will miss small fluctuations. Measurement of BE levels in urine offers an objective, quantitative, biological measure of treatment outcome; to some extent clinical researchers can get from it what they are able to afford.

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