Use of Quantitative Urinalysis in Monitoring Cocaine Use

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NEED FOR SENSITIVE MEASURES OF COCAINE USE

Cocaine use is a serious social and economic problem for which no solution currently exists. Considerable efforts have been expended to develop medications and other treatments for cocaine abuse, including clinical trials of a number of pharmacologic agents and behavioral approaches (Stitzer and Higgins 1995; Tutton and Crayton 1993). The primary goal of drug abuse treatment is to have patients decrease or stop their cocaine use. Because illicit drug use is a covert activity, it is usually measured indirectly through urine toxicology screens. Thus, urinalysis has become the primary outcome variable in most clinical trials of cocaine abuse treatments.

A major difficulty confronting drug abuse researchers is that appropriate pharmacological approaches to treatment are not clear. The exact basis for the rewarding effects of cocaine are not yet known, and although long-term neurochemical changes in cocaine abusers have been proposed, the exact nature of these changes have not been definitively identified (Cunningham et al. 1991; Johanson and Schuster 1995). Medications acting on different neurotransmitters (e.g., dopamine, serotonin, norepinephrine) through a variety of mechanisms (e.g., reuptake blockade, receptor antagonism, receptor agonism) have been evaluated (Tutton and Crayton 1993). The identification of medications with even partial efficacy could be valuable in guiding the direction of medication development activities. Therefore, the outcome measures used in the clinical trials in which experimental treatments are evaluated must be adequately sensitive to detect relatively small changes in cocaine use.

The most commonly used method for monitoring cocaine use in clinical trials is urinalysis. Typically, urine specimens are tested by qualitative immunoassays that detect benzoylecgonine (BE), the primary metabolite of cocaine. The standard cutoff concentration used in clinical trials to define positive and negative qualitative screens is 300 ng/mL of cocaine metabolite, the same requirement set in the Mandatory Guidelines for Federal Workplace Drug Testing

Programs (Department of Health and Human Services 1994). BE has a urinary excretion half-life of 6 to 8 hours (Ambre 1985) and can usually be detected in the urine for about 48 hours after cocaine administration (Saxon et al. 1988). The actual duration of detectability, however, is highly dependent on the amount of cocaine taken and individual rates of metabolism and excretion.

The persistence of cocaine metabolite in urine can lead to a phenomenon referred to as "carryover." Carryover occurs when a single episode of cocaine use results in multiple positive urine screens. This is particularly likely when specimens are collected frequently, at 48-hour intervals or less. When carryover occurs, it causes overestimation of the rate of cocaine use and, thus, may diminish the likelihood of detecting decreases in drug use in treatment studies. In addition, there is evidence to suggest that qualitative urinalysis is a relatively insensitive outcome measure. For example, significant decreases in self-reported cocaine use without concomitant significant decreases in rates of positive results from quantitative urinalysis has been found in a number of clinical trials (Covi et al. 1994; Kolar et al. 1992). Although the possibility of underreporting of cocaine use by cocaine users cannot be discounted (Magura et al. 1987; Sherman and Bigelow 1992), it is also possible that cocaine metabolite carryover obscures the true effects of treatment.

Another potential problem associated with urinalysis is the effect of fluid intake on BE concentration. Urine dilution can occur through normal variation in fluid consumption and excretion; however, deliberate dilution is known to occur, particularly when drug-positive urine specimens are linked to negative consequences. In fact, there are commercial products marketed for the purpose of defeating urine toxicology screen. Generally, the action of these products is based on urine dilution, encouraging the ingestion of large amounts of liquids. Unusually dilute specimens can be detected by measuring creatinine concentration and specific gravity. Guidelines recommended by the U.S. Department of Transportation for determination of abnormally dilute urine include a measurement of creatinine concentration of less than 20 mg/dL and a specific gravity of less than 1.003 (Goldberger et al. 1995).

Quantitative urinalysis may be a useful alternative to qualitative urinalysis as a primary outcome measure in clinical trials. This approach, coupled with creatinine concentrations, can be used to overcome problems of carryover and of urine dilution. Recently, the authors' laboratory examined BE and creatinine concentrations in

urine specimens collected in a clinical trial of a behavioral treatment for cocaine abusers (Silverman et al. 1995, 1996) to determine the usefulness of quantitative urine testing. Criteria for estimating whether cocaine use has occurred during the interval between urine specimen collections have been developed (see table 1). These new use criteria could aid in the identification of urine specimens that are positive due to carryover and might improve the sensitivity of urinalysis for detecting decreases in cocaine use. This chapter presents information on the new use criteria and the application of those criteria to representative patients from the clinical trial.

RULES FOR NEW USE CRITERIA

The new use criteria are based on assumptions about the pharmacokinetics of BE. As noted earlier, BE rapidly appears in urine after use, is excreted according to first-order kinetics, and has an average elimination half-life of 7.5 hours (Ambre 1985). Urine specimens that contain cocaine metabolite concentrations over 300 ng/mL, but that do not meet the new use criteria, are identified as positive specimens resulting from carryover from previous cocaine use. Urine specimens that contain cocaine metabolite concentrations less than 300 ng/mL and that do not meet the criteria were identified as negative. The new use criteria are summarized below.

TABLE 1. *Criteria for defining new use and carryover from quantitative urinalysis results.*

Assume new use if the sample meets any of the following criteria:

RULE 1 An increase in cocaine metabolite concentration to any value over 300 ng/mL compared to preceding urine specimen collected at interval of more than 48 hr

RULE 2A Concentration decreased to less than one-half of concentration in preceding urine specimen collected at interval of more than 48 hr

RULE 2B Concentration decreased to less than one-quarter of concentration in preceding urine specimen collected at interval of more than 48 hr

TABLE 1. *Criteria for defining new use and carryover from quantitative urinalysis results (continued).*

RULE 3 Cocaine metabolite is greater than 300 ng/mL in the first urine specimen

RULE 4 If the previous urine is missing (not collected), any urine specimen with cocaine metabolite greater than 300 ng/mL

RULE 5 Creatinine less than 20 mg/dL (does not have to be positive for cocaine metabolite and cocaine metabolite/creatinine ratio) is increased compared to that of previous specimen

Rule 1

Assume new cocaine use occurred for a patient when: (a) the concentration of cocaine metabolite in the newly collected specimen exceeds the cutoff concentration for a positive specimen (300 ng/mL), and (b) the previous specimen (collected more than 48 hours ago) was negative (less than 300 ng/mL). This rule accounts for the appearance of a positive specimen when previous specimens tested negative and assumes that a new appearance of BE in the urine must result from a new use of cocaine.

Rule 2A

Assume new cocaine use occurred for a patient when: (a) the concentration of cocaine metabolite in the newly collected specimen exceeds the cutoff concentration for a positive specimen (300 ng/mL), and (b) the concentration of cocaine metabolite in the newly collected specimen has not decreased by a factor of 2 (50 percent) below the concentration of the previous specimen (One-Half Rule).

Rule 2B

Assume new cocaine use occurred for a patient when: (a) the concentration of cocaine metabolite in the newly collected specimen exceeds the cutoff concentration for a positive specimen (300 ng/mL), and (b) the concentration of cocaine metabolite in the newly collected specimen has not decreased by a factor of 4 (75 percent) below the concentration of the previous specimen (One-Quarter Rule).

Rules 2A and 2B assume that urine BE should be decreased by at least 50 percent or 75 percent, respectively, if no use of cocaine has occurred since the previous urine specimen collection at least 48 hours earlier. Two different criteria are being evaluated because of uncertainty about the exact amount of decrease expected under the natural conditions that exist in outpatient treatment research with patients who self-administer large and varying amounts of cocaine. Based on pharmacokinetic considerations of the excretion half-life of BE determined under laboratory conditions, these criteria are quite liberal. In fact, when a second specimen is obtained 48 hours following a positive specimen, the concentration of cocaine metabolite should be diminished to less than 2 percent of the original starting concentration, assuming a half-life of 8 hours. If the cocaine metabolite half-life is as long as 12 hours, then the concentration in the second specimen should have diminished to less than 10 percent of the original concentration. These liberal criteria were chosen because significant variability in the pharmacokinetics of cocaine and other factors can occur among individuals. An increase in BE concentration would also be counted as a new use under either Rule 2A or Rule 2B by the same rationale as given in Rule 1.

Rules 3 and 4

Rules 3 and 4 were developed because of practical considerations in outpatient treatment trials. Rule 3—if the initial specimen is positive for cocaine metabolite, it is considered a new use. Rule 4—if a previous specimen is missing (not collected), the next collected specimen is considered a new use if it exceeds the cutoff concentration for a positive specimen (300 ng/mL). Rule 3 was adopted because of the lack of a previously collected comparison urine specimen for the first specimen collected in a trial. Rule 4 was needed because missed urine specimens are common in clinical trials. Under the conditions of the study in which these specimens were collected, a missed specimen would result in a 4- to 5-day interval between the previous specimen and the new specimen. As noted above for Rules 2A and 2B, it would be expected that the BE concentration would have decreased to below 300 ng/mL if no new cocaine use had occurred in that interval.

Rule 5

Assume new cocaine use occurred for a patient when: (a) a dilute urine specimen, i.e., creatinine less than 20 mg/dL (does not have to be positive for cocaine metabolite) is obtained, and (b) the cocaine

metabolite/creatinine ratio is greater than that of the previous specimen. This rule was developed for occasions when subjects attempt to subvert test results by ingestion of excess fluids.

URINE BENZOYLECGONINE AND CREATININE CONCENTRATIONS IN URINE SPECIMENS OF PATIENTS IN CLINICAL TRIALS

Urine specimens from a clinical trial were used to evaluate the potential utility of the new use criteria. Specimens had been collected three times per week for up to 17 weeks in methadone maintenance patients participating in a clinical trial of a behavioral treatment for cocaine abuse (Silverman et al. 1996). The behavioral treatment was based on an abstinence reinforcement model in which patients earned vouchers exchangeable for goods and services for each cocaine-negative urine specimen. Assays for the cocaine metabolite (BE) concentrations were performed with TDx® Cocaine Metabolite Assay reagents (TDx) (Abbott Laboratories, Abbott Park, IL) on a TDx instrument according to manufacturer's recommended procedures. The cross-reactivity of this assay for BE was 100 percent and less than 1 percent for cocaine, ecgonine methyl ester, and ecgonine. The lower limit of sensitivity of the assay for cocaine metabolite was 30 ng/mL. Specimens that contained concentrations of cocaine metabolite greater than 5,000 ng/mL were diluted with TDx reagent buffer and reanalyzed with the appropriate control samples. Creatinine measurements were performed by the Jaffe method with Boehringer Mannheim Diagnostic reagents on a Hitachi 704 analyzer (Boehringer Mannheim, Indianapolis, IN).

Visual inspection of graphs of urine BE concentrations from individual subjects suggested that most participants used cocaine intermittently, with cyclical patterns of high and low BE concentrations. BE concentrations from a representative subject are shown in figure 1 on a log scale. Concentrations greater than 300 ng/mL are indicated by circles, and concentrations less than 300 ng/mL are indicated by triangles. Horizontal lines indicate the cutoff for the qualitative testing (300 ng/mL) and the limit of detection for the assay (LOD; 30 ng/mL). This subject participated for a period of approximately 13 weeks, during which there were a total of 40 urine collections. The individual missed two urine collections, days 34 and 37, indicated by dashed lines on the figure. BE equivalent concentrations varied over a wide range, from below 30 to 86,700 ng/mL. Of the 38 specimens collected, 34 were considered positive (greater than 300 ng/mL), and 4 were negative (less than 300 ng/mL).

Application of the new use criteria to the urine BE concentrations identified 11 of the 34 (32 percent) positive urine specimens as possible cases of carryover by the One-Half Rule (Rule 2A), indicated on the figure as open circles. When the new use criteria were applied using the more stringent One-Quarter Rule (2B), two fewer specimens were identified as carryover, specimens 13 and 15. The new use criteria consistently identified as carryover those specimens in which there were substantial decreases in concentration compared to the prior specimen, but not to below the 300 ng/mL cutoff. Thus, these cases appear to be due to carryover rather than to a new use of cocaine between two consecutive urine specimen collections.

There were two samples, 35 and 38, that were identified as new uses via Rule 4, the Missing Specimen Rule. If the missing specimens (34 and 37) had been ignored, and the concentration compared to the next previous specimens (33 and 36), both specimens would have been identified as carryover positives by the One-Half Rule (2A), but as new uses by the One-Quarter Rule (2B). Given the circumstances (missed clinic visits) and the continued presence of BE at concentrations well above the 300 ng/mL level, these BE concentrations are very likely to be due to cocaine use that occurred after collections of specimens 34 and 37.

Rule 5 was designed to adjust for dilute urine specimens. Adulteration by dilution was relatively rare in the clinical trial in spite of the fact that subjects in the experimental group could earn vouchers for being cocaine abstinent and, thus, had a relatively strong incentive for having cocaine-negative specimens. No specimens with creatinine concentrations below the 20 mg/dL were found in the subject whose data are shown in figure 1; however, some cases of suspected urine dilution were found in other subjects. BE and creatinine concentrations for one such individual with multiple dilute urine specimens are shown in figure 2. This participant was among the group of subjects who could earn vouchers for cocaine- negative urine specimens. Drug use was monitored in urine specimens throughout the study. Test results had no programmed consequence in specimens 1 through 15; vouchers became available to subjects beginning with the 16th specimen. This subject had three urine specimens with creatinine concentrations at or below 20 mg/dL, the cutoff for dilute urine. Two of those specimens (22 and 23) coincided with BE concentrations below 300 ng/mL. The BE/creatinine ratios were increased relative to

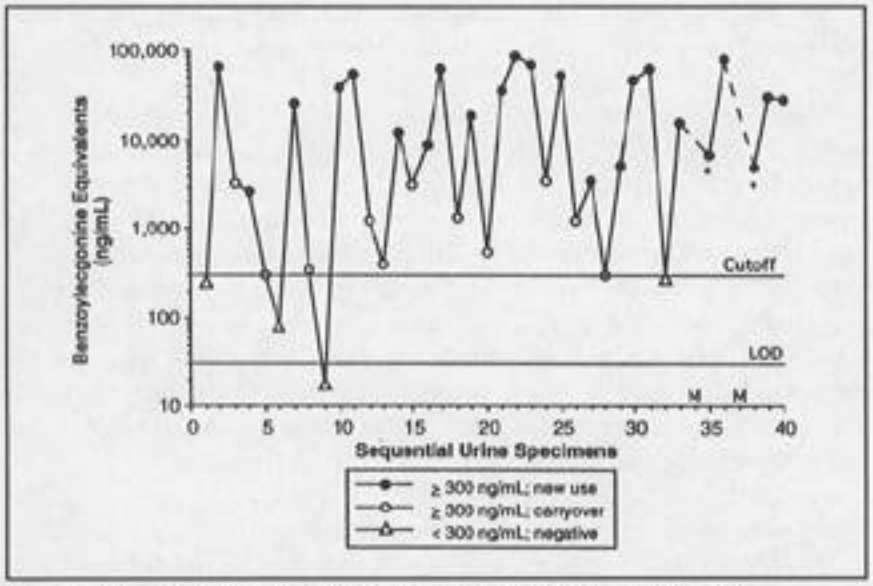

FIGURE 1. *Quantitative urinalysis results of sequential urine specimens of a subject in a cocaine abuse treatment clinical trial. M indicates missing specimens.*

the previous urine specimens and, thus, met the criteria as new uses as outlined in Rule 5. The suggestion that the subject used cocaine during this period is supported by the fact that five consecutive specimens (19 through 23) all contained BE concentrations around 200 ng/mL, below the 300 ng/mL cutoff but well above the limit of detection of the assay. Based on the known pharmacokinetic profile of excretion of cocaine and BE, it is extremely unlikely that BE concentrations would remain in the 200 ng/mL range over a period of several days without use. Data from other subjects indicate that when cocaine use is completely stopped, concentrations fall to below the limit of detection within several days.

CONCLUSION

There is growing interest in the use of quantitative urine testing in clinical trials. Changes in the pattern, frequency, and amount of use that are not apparent from qualitative urinalysis are discernible from quantitative urinalysis. Overestimation of drug use from carryover also can be avoided by the development of criteria (such as the new use

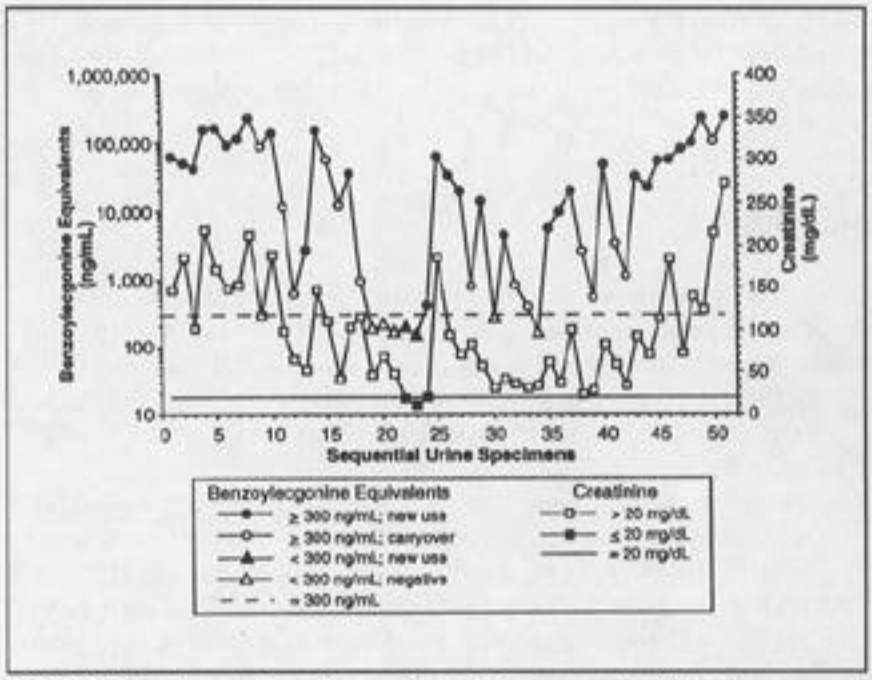

FIGURE 2. *Benzoylecgonine and creatinine concentrations in sequential urine specimens of a representative subject from a cocaine abuse treatment clinical trial.*

criteria described here) that are based on the pharmacokinetic profile of cocaine and its metabolites. These criteria can be applied objectively and consistently. However, quantitative urine testing is more expensive than qualitative testing, and urine drug/metabolite concentration can be affected by many variables such as the time between drug use and urine collection, fluid intake, and interindividual metabolic differences. For example, a urine specimen collected several days after self-administration of a large amount of drug could have the same drug/metabolite concen-tration as a specimen collected just after self-administration of a small amount of drug. Thus, the time of specimen collection could have greater impact on concentration than the total amount of drug used. Fluid intake is sometimes used by subjects to alter urine drug/metabolite concentration. As found in the present study, however, corrections can be made using a biological indicator such as creatinine to adjust for water consumption. Few clinical trials have been conducted with quantitative testing, though at least one study suggests that quantitative testing may be more sensitive to decreases in drug use than qualitative tests (Batki et al. 1993). McCarthy (1994) has also

reported on the utility of quantitative urine drug testing in the context of substance abuse treatment. Future studies will be needed to determine the true conditions under which quantitative analysis of drugs in urine is useful and cost effective.

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