Is Quantitative Urinalysis More Sensitive?*

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Outcome measures for assessing clinical efficacy of cocaine addiction pharmacotherapy should reliably and accurately reflect the benefits of the treatment. A core battery of outcome measures has been proposed by the Food and Drug Administration (FDA) and used by investigators for such trials. These measures include: (1) cocaine use by urinalysis, self-report, or both; (2) retention in treatment; (3) patient self-assessment; and (4) physician global assessment. Currently, urinalysis is the only generally accepted surrogate biological marker for objectively monitoring cocaine intake.

Cocaine is eliminated from the body primarily by metabolism and has an elimination half-life of approximately 1 to 1.5 hours (Cook et al. 1985; Jones 1984). Benzoylecgonine (BE) is a major metabolite of cocaine. Approximately 30 to 50 percent of the dose of cocaine is excreted in the urine as BE, whereas only 2 to 3 percent is excreted in the urine as unchanged cocaine (Ambre 1985; Cook et al. 1985; Hamilton et al. 1977). The elimination half-life for BE of 7 hours is much longer than that for cocaine; BE can be detected in the urine for 2 days or longer after a single dose of cocaine (Reid et al. 1995). Therefore, BE is the most commonly screened target for assessment of cocaine use. In general, urinary BE concentrations are highly variable and depend on dose and route of administration, pharmacokinetics for each individual, urine volume, and factors such as disease state and drug interactions that may affect the pharmacokinetics.

Qualitative urinalysis has been widely employed for detecting illicit drug use in the workplace (Hawks and Chiang 1986). Immunoassays such as radioimmunoassay (RIA), enzyme immunoassay (EIA), and fluorescence polarization immunoassay (FPIA) are the most commonly used methods for detecting BE in the urine. A BE concentration of 300 ng/mL has been typically established as the cutoff point. Any concentration below the

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level of 300 ng/mL is considered a negative sample (a clean urine), any sample that has a BE concentration above 300 ng/mL is a positive sample (a dirty urine). This approach provides binary data (clean or dirty).

Recently, there has been increased interest in the use of quantitative urinalysis as an outcome measure in clinical trials. Instead of urine samples being assessed in a binary fashion, data can be evaluated quantitatively to assess an increase or reduction in urinary BE concentrations. Batki and colleagues (1993), studying the effect of fluoxetine on cocaine use, showed that qualitative urinalysis did not reveal a statistically significant difference between the treatment and control groups, whereas quantitative urinalysis did.

Chromatography assays such as gas chromatography/mass spectrometry (GC/MS) provide a precise estimate of BE concentration. However, the high cost of these assays could limit their utility in clinical trials where a large number of urine samples are collected. Immunoassay methods, such as FPIA and EIA, can provide a quantitative estimate of urinary BE concentrations (Crosby et al. 1991). The quantitative immunoassay is inexpensive compared with the chromatographic method, although it is still more costly than qualitative urinalysis. The recent development of quantitative techniques for automated mass screening using immunoassays has made this approach feasible for use in clinical trials (Foltz et al., this volume).

This study uses simulated BE data from a set of simple clinical models to evaluate whether quantitative urinalysis is a more sensitive measure of the reduction in frequency or amount of cocaine use than is qualitative urinalysis. The model defined a treatment effect as a 60 percent reduction in cocaine use—either in daily amount or weekly frequency (at the same daily amount). A 60 percent reduction in cocaine use was considered to be clinically significant (Tai 1993). In addition, comparison was made of urine sampling schemes of three times per week and once per week for assessing treatment outcomes.

METHODS

Pharmacokinetic Model

Cocaine disposition can be described by a one-compartment model as depicted in figure 1 (Ambre 1985). The pharmacokinetic parameters

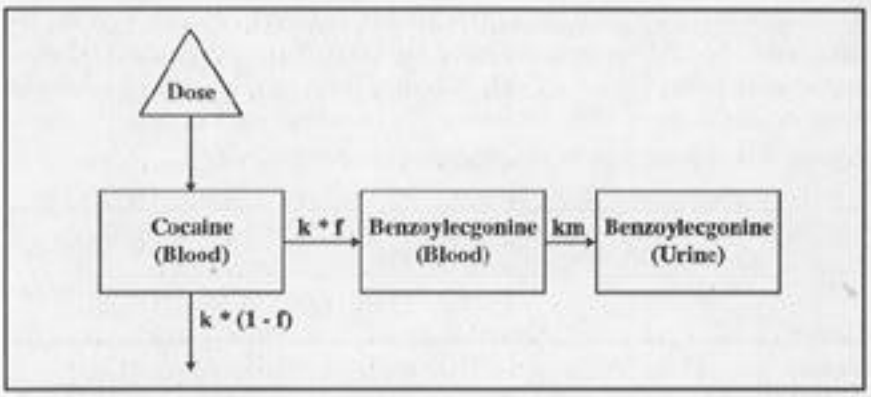

FIGURE 1. *Pharmacokinetic model for cocaine disposition.*

KEY: k = overall elimination rate constant for cocaine
f = fraction of cocaine dose metabolized to benzoylecgonine
k*f = rate constant for the formation of benzoylecgonine
km = urinary excretion rate constant for benzoylecgonine
k* (1 - f) = rate constant for the elimination of cocaine by routes other than metabolism to benzoylecgonine

used in this simulation were obtained from a clinical pharmacokinetic study involving 10 subjects (Jones 1992). The averages of the overall elimination rate constant for cocaine (k), the urinary excretion rate constant for BE (km), and the fraction of cocaine dose metabolized to BE (f) were 0.44 hr^{-1}, 0.097 hr^{-1}, and 30 percent, respectively, and the standard deviations were 0.074 hr^{-1}, 0.020 hr^{-1}, and 7.2 percent, respectively. The parameters of k and km are in good agreement with those reported by Ambre (1985) and the parameter f is in good agreement with recent reports of f values equal to 0.22 and 0.36 by Ambre and colleagues (1988) and Jeffcoat and colleagues (1989), respectively. The individual subjects' pharmaco-kinetic parameters for the simulation were randomly generated, assuming normal distribution, so that the mean and standard deviation of the simulated group parameters matched those calculated from the clinical pharmacokinetic study.

Assumptions

The model assumed that there were no intrasubject variations in pharmacokinetic parameters or in urine volumes and that self-administration was by the intravenous (IV) route. The urine flow rate was taken as 1 mL/min (0.06 L/hr). Urinary BE concentrations were calculated for a 9:00 a.m. sample for Monday, Wednesday, and

Friday. Self-dosing times were randomly assigned from 6:00 a.m. to 12 midnight throughout the study. The following equation was used to describe the urinary BE concentrations at time *t* (see the Appendix):

$$(BE)t=\frac{(k*f*dose)*(km*e^{-(k*t)}*(e^{k}-e^{(-k)})-k*e^{-(km*t)}*(e^{km}-e^{(-km)}))}{k*(km-k)*(0.06*2)}$$

Simulation

Three groups of urinary BE concentrations were simulated to mimic a 12-week clinical study. Each group consisted of data from a simulation with a sample size of 30 where the IV dose of 200 mg/day was given for 7 days a week before the treatment period. Group A served as a control or placebo group and groups B and C were treatment groups. In group B, it was assumed that treatment resulted in a reduction in the daily amount of cocaine use with no change in the frequency. In group C, it was assumed that treatment resulted in a reduction in the weekly frequency of use with no change in the daily amount. A treatment effect (reduced cocaine use) was assumed to start during week 2 and continue through week 5, after which no further reduction would occur through week 12. The extent of the daily dose reduction for group B was assumed to be linear and at a rate of 15 percent per week; this reduction was equivalent to a 1 day/week reduction for group C. Overall, this treatment assumption resulted in an approximately 60 percent decrease in cocaine use for both groups. The specific weekdays of cocaine use from weeks 2 to 12 were assigned randomly for group C. Table 1 presents these dosing assumptions.

Statistical Analysis

Because a 60 percent reduction in cocaine use was considered to be clinically significant, it was necessary to establish statistically that this degree of reduction could be detected in urine. The approach taken was to assume a reduction in four increments of 15 percent each over 4 weeks to achieve the 60 percent level and to analyze the simulated urine concentrations at each increment to be sure that the reduction could be detected at or before the 60 percent point. A simple *t* test was used to test the difference between each treatment group (group B or group C) and

TABLE 1. *Assumed daily cocaine consumption as altered by treatment.*

Weeks	1	2	3	4	5 to 12
Control (A)					
Daily dose (mg)	200	200	200	200	200
Frequency (days/week)	7	7	7	7	7
Treatment effects					
% Reduction of weekly dose	0	15	30	45	60
Reduction in daily amount (B)					
Daily dose (mg)	200	170	140	110	80
Frequency (days/week)	7	7	7	7	7
Reduction in frequency (C)					
Daily dose (mg)	200	200	200	200	200
Frequency (days/week)	7	6	5	4	3

the placebo group (group A) in the quantitative urinalysis scenario for each week. A chi-square test was used to test the difference between each treatment group and the placebo group in the qualitative urinalysis scenario for each week.

RESULTS

Comparison of Simulated Data and Clinical Data

Urine BE concentration simulated for a representative of group C is presented in figure 2. The variability of the BE concentrations is seen to increase significantly when the frequency of cocaine use decreased starting in week 3. When cocaine use was reduced to 3 days per week (weeks 5 to 12), the BE concentration fell below the cutoff concentration in several samples but rebounded to concentrations three orders of magnitude higher in the subsequent samples. These results are similar to the large variations reported in clinical studies (Batki et al. 1994; Crosby et al. 1991).

Table 2 presents a comparison of the BE data generated from the simulation model with the baseline data for 50 cocaine abusers who were methadone patients participating in a clinical trial to evaluate fluoxetine

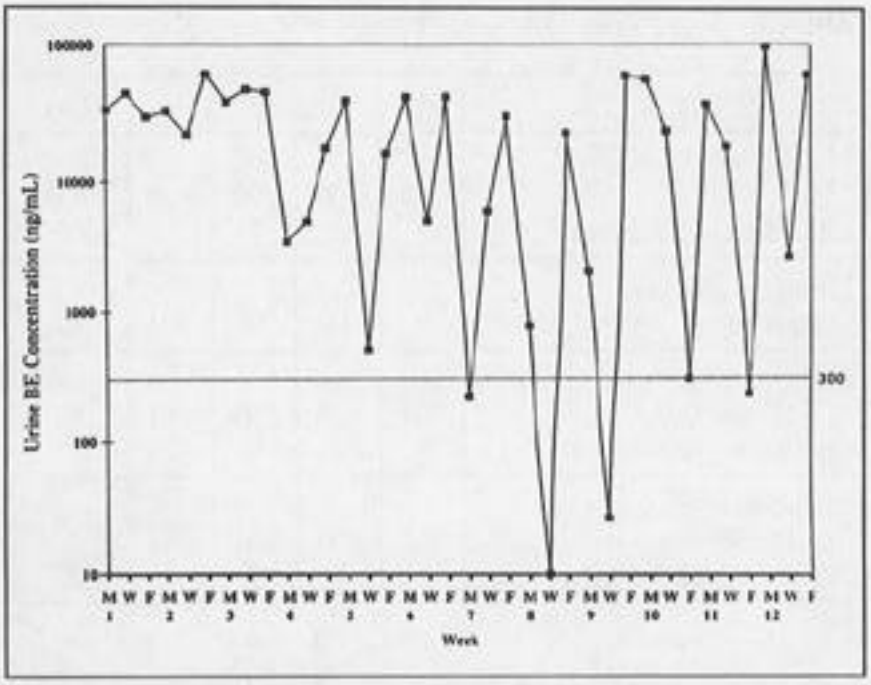

FIGURE 2. *Urine benzoylecgonine concentrations simulated for a representative of group C.*

for treating cocaine addiction (Batki et al. 1994). The cocaine usage pattern, based on self-reports by the 50 subjects before the trial started, showed an average frequency of cocaine use of 4.8 days/week. BE urine concentrations were simulated for two 50-subject groups using the proposed pharmacokinetic model, but with different dosage regimens. An IV usage pattern of 200 mg/day, 7 days/week was assumed for the first group (as in the placebo group A of the comparison simulations). The second group was assumed to ascribe to the same weekly usage pattern as reported for the clinical trial but at an IV dose of 600 mg/day.

There was a wide distribution of BE concentrations for the clinical data, with most subjects tending toward high BE concentrations between 10,000 and 1,000,000 ng/mL. The distribution of BE for group A (control) was very narrow (10,001 to 100,000 ng/mL). When a frequency of use the same as that for the clinical data was assumed and the daily dose increased to 600 mg, the BE distribution for these simulated data was similar to the clinical data.

TABLE 2. *Urinary benzoylecgonine concentrations for simulated and clinical data (sample size = 50).*

Urine BE concentrations (ng/mL)	0-300	301-1,000	1,001-10,000	10,001-100,000	100,001-1,000,000
Clinical data*	4	5	7	19	15
Simulated data based on 200 mg daily use	0	0	4	46	0
Simulated data based on 600 mg and Batki's self-report pattern	4	1	7	25	13

KEY: * = Clinical data provided by Batki et al. (1994) with the following frequency of use pattern from self-report.

Days/week of cocaine use	0	1	2	3	4	5	6	7
# of subjects	1	3	3	7	7	6	6	17

The mean and standard deviation of the clinical data (86,000Å118,000 ng/mL) was much larger than for the simulated control group (32,000 Å 16,000 ng/mL) but closer to those for the simulated data (74,000Å78,000 ng/mL) using a larger dose and the same usage pattern of the clinical data. The coefficient of variation for the clinical data (137 percent) was slightly larger than that for the simulated data (105 percent) in the second case. This variance might be expected because the subjects in the clinical trial would likely use various amounts of cocaine and routes of administration. The similar mean and similar pattern of BE distribution for the simulated and clinical data support the assumption that the pharmacokinetic model is valid.

Quantitative Urinalysis

Table 3 presents the weekly group mean and the standard error for urinary BE concentrations for a urine sampling schedule of three times

TABLE 3. *Weekly group mean for urine benzoylecgonine concentration simulated for three times per week sampling.*

Week	Control Group (A)	Reduction in Daily Amount (B)	Reduction in Frequency (C)
1	31,984 (2165)*	32,079 (2031)	29,738 (2238)
2	26,944 (2180)	28,832 (1844)	29,596 (1924)
3	29,510 (2477)	25,620 (1739)	25,193 (3004)
4	30,514 (2051)	18,002** (1095)	21,346** (2161)
5	37,342 (2719)	14,199** (957)	16,131** (1914)
6	34,592 (2850)	13,691** (1186)	11,308** (1157)
7	37,633 (3199)	13,134** (883)	15,092** (1828)
8	33,783 (2062)	13,970** (1408)	15,666** (2479)
9	31,944 (2371)	14,622** (1153)	20,373** (2309)
10	35,121 (2756)	14,360** (954)	12,649** (1722)
11	30,753 (2313)	12,614** (983)	15,071** (2144)
12	30,591 (2458)	11,704** (796)	17,320** (2004)

KEY: * = Standard error; ** = significantly different from group A, $p < 0.05$.

per week. The simulated BE values for each week were determined as the mean of the BE concentrations on Monday, Wednesday, and Friday for the week. A statistically significant difference ($p < 0.05$) was shown between the control group and the treatment groups in week 4 when a 45 percent reduction in the weekly dose was reached—in daily amount of cocaine used (group B) or in frequency of use (from 7 days to 4 days per week, group C). The weekly mean for BE concentrations was similar for groups B and C. The standard errors for group C were about twice those for group B when the reduction in

the weekly dose reached 30 percent (at week 3). This reduction is a result of the large fluctuation resulting from the variations in the interval between dosing and sampling.

Table 4 presents the weekly data for urinary BE concentrations for a sampling schedule of once a week. The Monday samples were used. The weekly means for group B were similar to those for group C, whereas the standard errors for group B were smaller than those for group C. A statistically significant difference could be detected between either treatment group (group B or group C) and the control group (group A) when there was a 60 percent reduction in the weekly dose (week 5). The statistical difference was observed for every week from weeks 5 to 12 of group B. However, group C failed to show a statistical difference for weeks 9 and 12 even though the reduction had occurred from week 5 on as a result of the large variability for the BE data for group C.

When the data for the two sampling schedules (one time and three times per week) were compared, the means for each corresponding group were similar, but the standard errors for one time per week sampling were much larger than those for the three times per week sampling (figures 3 and 4). A further reduction in cocaine use of 15 percent (from 45 percent to 60 percent or fourth week to fifth in the figures) was required to detect the statistical difference for the one time per week sampling because of the large variations of the weekly BE concentrations associated with one time per week sampling. The weekly mean of three samples would smooth out these variations. The reduction in daily amount of cocaine use curve (figure 3) had a smoother curve than the reduction in frequency curve (figure 4) after week 5.

Qualitative Urinalysis

Figure 5 presents the weekly percentage of positive (dirty) urine samples for the three times per week urine collection schedule using the “majority rule” analysis. This analysis, widely used in clinic trials, assumes the weekly urine is dirty if at least two of the three samples for the week are positive. Group A (control) and group B (reduction in amount) always presented 100 percent positive samples with no significant difference (chi-square test) between them. However, a significant difference was observed between groups C and A for 5 of the 8 weeks when the

TABLE 4. *Weekly group mean for urine benzoylecgonine concentration simulated for once a week sampling.*

Week	Control Group (A)	Reduction in Daily Amount (B)	Reduction in Frequency (C)
1	33,814 (3162)*	37,674 (3745)	29,566 (3404)
2	28,414 (4325)	31,753 (3012)	32,373 (2872)
3	33,231 (4438)	29,613 (3014)	28,256 (4785)
4	31,204 (3910)	21,684 (1985)	24,525 (3587)
5	37,768 (5637)	16,929** (1758)	19,684** (3560)
6	36,626 (4967)	13,569** (1729)	8946** (2277)
7	31,270 (4013)	13,692** (1334)	10,183** (2432)
8	32,969 (3725)	15,738** (2103)	14,460** (4004)
9	32,440 (4293)	15,419** (1996)	23,818 (4061)
10	36,516 (4391)	17,931** (1723)	9755** (2313)
11	27,696 (2684)	13,566** (1581)	16,307** (2907)
12	27,805 (2904)	9432** (867)	18,766 (4057)

KEY: * = Standard error; ** = significant different from group A, $p < 0.05$.

frequency of use of group C was reduced to three times per week (weeks 5 to 12).

Because groups A and B presented 100 percent positive samples all the times, neither a thrice-weekly nor a once-weekly sampling schedule for

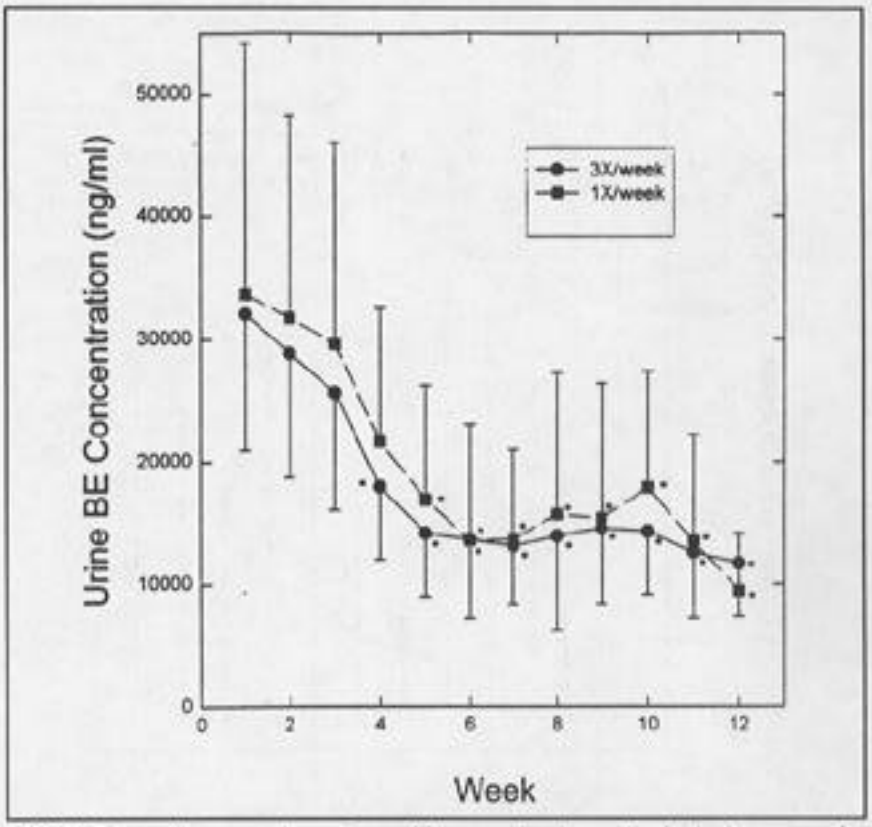

FIGURE 3. *A comparison of weekly quantitative urinalysis (mean and standard error) simulated between three times per week versus one time per week sampling for reduction in daily amount group (group B).*

KEY: * = Significantly different from control group, $p < 0.05$.

qualitative urinalysis could detect the difference in the amount of daily dose between these two groups.

Figure 6 compares the percentage of positive (dirty) urine samples for group A and group C using (1) the one time a week sampling schedule, (2) the three times per week schedule using the majority rule analysis, and (3) the three times per week schedule using the actual percentage of positive urine samples. Group A presented 100 percent positive urines at all times. For group C, the data using the majority rule for the three times

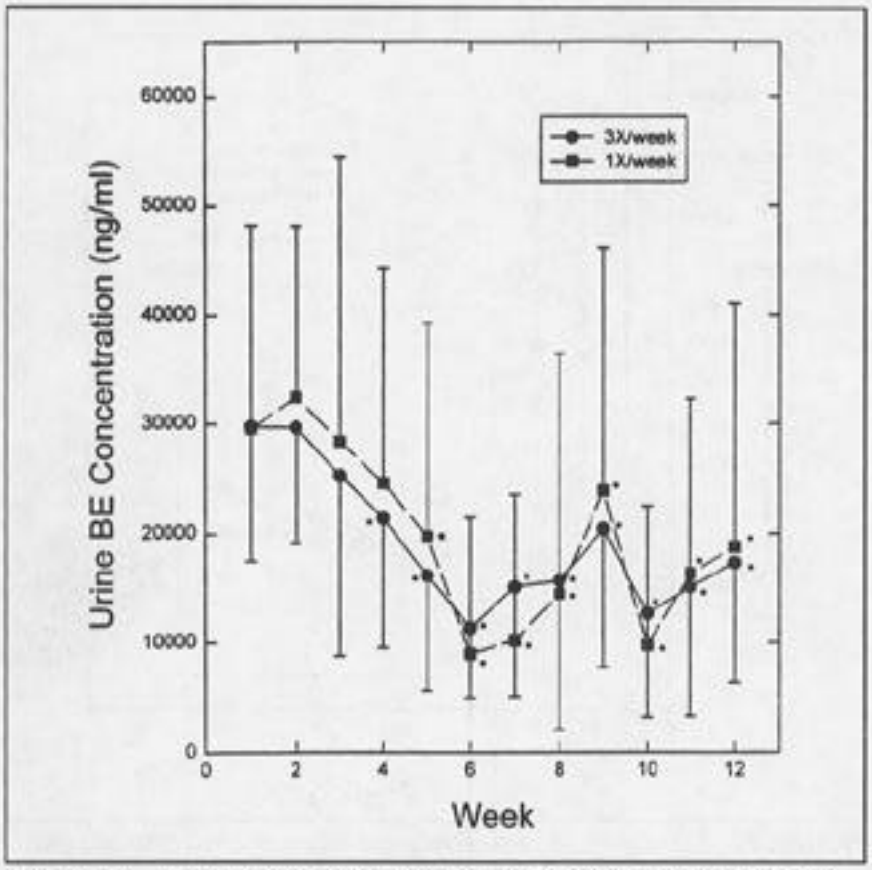

FIGURE 4. *A comparison of weekly simulated quantitative urinalysis (mean and standard error) between three times a week versus one time per week sampling for reduction in frequency group (group C).*

KEY: * = Significantly different from control group, $p < 0.05$.

per week schedule always gave the highest estimates for the percentage of positive urines, higher than did the actual percentage of positive samples. The one time per week sampling could give either higher or lower estimates than the actual percentage of dirty urines. When the frequency of use was reduced to three times per week (week 5), a significant difference was detected between the treatment (group C) and control (group A) groups for all the remaining 8 weeks using the actual data for three times per week sampling. Group C differed significantly from

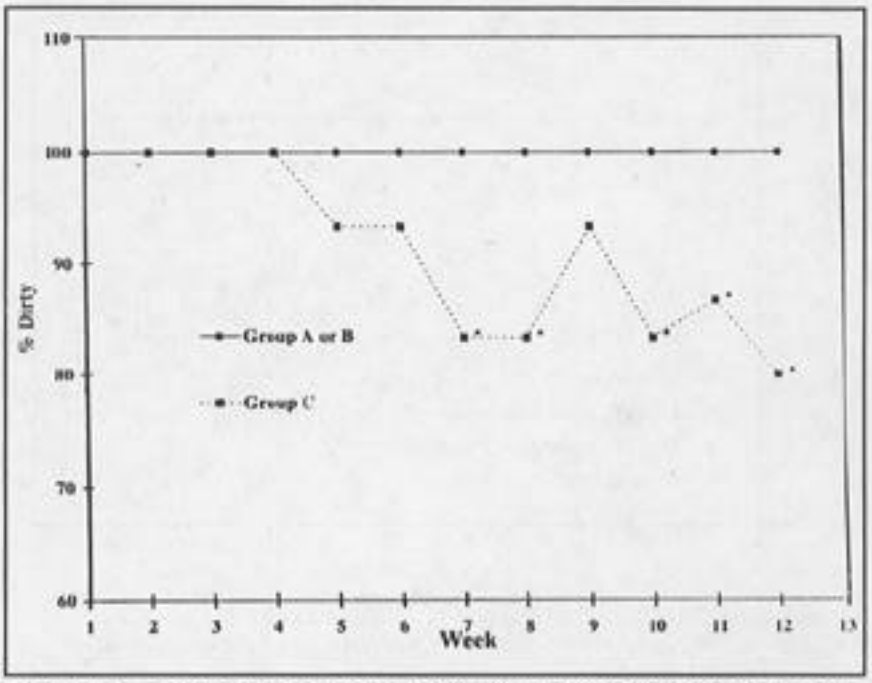

FIGURE 5. *Weekly percentage of dirty urine simulated for three times per week sampling schedule.*

KEY: * = Significantly different from group A, $p < 0.05$.

group A in 6 of 8 weeks when one time per week sampling was simulated. This difference was reduced to 5 of 8 weeks when the majority rule analysis was used for the three times per week schedule.

DISCUSSION

Urinary data in general are not a very sensitive marker for the assessment of cocaine use and vary widely because of the differences in the amount of cocaine used, the frequency of use, the route of administration (intranasal, oral, or smoking), the urine volume (urine flow rate), sampling times, and factors such as disease state and concomitant medications. In addition, there are intraindividual differences in these parameters from day to day. It is difficult to use urine data to estimate the frequency and amount of cocaine use. Depending on the frequency of urine sampling and the pattern of cocaine use (daily versus binge use), a

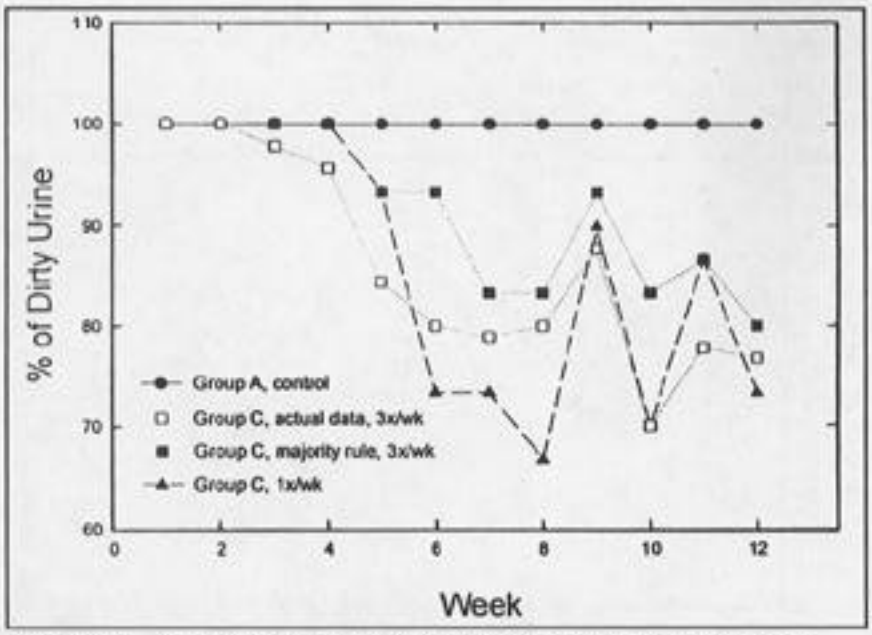

FIGURE 6. *A comparison of weekly percentage of dirty urine data simulated between three times per week versus. One time per week sampling schedule.*

KEY: * = Significantly different from group A, $p < 0.05$.

negative urine sample may not indicate a lack of cocaine use, and a positive urine sample may reflect the carryover effects of an episode several days before sampling.

Cocaine is usually administered by an intranasal, IV, or smoked route of administration. The absorption is different for the different routes of administration, which results in different urinary excretion profiles after a single dose (Cook et al. 1985; Jeffcoat et al. 1989; Jones 1984; Jones, this volume). Intranasal absorption is slow and the bioavailability is approximately 40 to 80 percent. Smoking provides a rapid absorption but low bioavailability (approximately 20 to 45 percent). The pharmaco-kinetic profile for smoking is similar to that for IV administration, but a much larger dose is required to achieve the same plasma and urine concentrations. Because of the wide range of street doses a subject may have used as well as the uncertainty of when the dose was taken, similar urinary BE concentrations were observed for cocaine addicts following different routes of administration. Because the IV dose provides a simple pharmacokinetic model, it was

chosen for the simulation. A dose of 200 mg was used because the pharmacokinetic parameters were derived from a clinical pharmacokinetics study using this dose. In addition, the urinary BE after this dose can be detected (using the 300 ng/mL cutoff) for 2 to 3 days, which is consistent with the report that the detection window for BE is 1 to 2 days after a regular cocaine dose.

These simulated data were based on a simple clinical situation with an ideal homogeneous patient population with the same usage pattern, dose, and route of administration. The only variables were the dosing times and individual pharmacokinetic parameters. In actual clinical settings, urinary BE concentrations are more variable, as noted in the Results section in which a coefficient of variation calculated for actual clinical data (137 percent) was much larger than that for the two simulated cases (105 percent and 50 percent). Because the number of subjects required to detect a specified reduction in cocaine use depends on the variability of the BE concentrations, a sample size of 30 for each group would be too small to detect any difference between the treatment and the control groups in actual clinical situations. Based on the BE concentrations in the clinical data of Batki and colleagues (1993), the number of subjects required to detect a 60 percent reduction in cocaine use at a significance level of 0.05 and with a power of 80 percent would be 90 subjects per group. If a power of 95 percent is required, the number of subjects would have to increase to 140 per group. It should be noted that these estimates of group size are based on this single clinical data set (that of Batki et al.)—the only one available to the authors.

Two hypothetical situations were used to compare the treatment effects: a change in daily amount of use and a change in frequency of use. All the individuals were assumed to be equally affected by the treatment. In an actual situation, the treatment group would be a mixture of subjects, some of whom would manifest a reduction in amount used, some in frequency, and others showing no change in habits. The magnitude of the individual reductions and the time required to reach and maintain those concentrations would be expected to be variable across subjects and to further complicate the detection of treatment outcome. For instance, if a treatment has a significant effect on a small segment of the group leading perhaps to cessation of use, an analysis based on the average across the group might not be able to detect any significant difference from the control group, but an obvious subgroup might emerge if the analysis includes an assessment of consecutive negative urine days or weeks.

For this simulation, qualitative urinalysis could not detect a reduction in the amount of daily dose for daily users but could detect a reduction in the frequency of cocaine use from 7 to 3 days per week. Urinary BE concentration depends on dose, route of administration, pharmacokinetics, and sampling time. If a large dose is used and the frequency of use is reduced from daily to every other day on those days (e.g., Sunday, Tuesday, and Thursday) preceding the sampling days (rather than randomly assigned), it is possible for the subjects to have positive results all the time. If a homogenous group of heavy daily cocaine users participates in the clinical trial, qualitative urinalysis is less likely to show a statistically significant decrease even though there is a reduction of cocaine use from 7 to 3 times per week (every other day). On the other hand, if the cocaine dose is lower or the cocaine use less frequent, negative results may occur even if there is less than a 60 percent reduction of frequency of cocaine use. In clinical situations, there will be a heterogeneous population and it is likely that statistically significant results can be detected by qualitative analysis if enough subjects are used. Quantitative urinalysis would be more powerful than qualitative urinalysis in clinical trials for detecting reductions in both frequency and in amount.

From the clinical aspect, a period of sustained abstinence, not the reduction of drug amount, might be the most acceptable therapeutic goal. If the efficacy criterion is to demonstrate an increase in the number of days of abstinence, then the only acceptable therapeutic goal is a reduction in frequency, not in daily dose; qualitative urinalysis as the outcome measure would probably be able to meet this goal and quantitative urinalysis would provide only a limited advantage. On the other hand, a reduction in dose only and not frequency would appear to require quantitative analysis.

Currently, the most popular sampling schemes for urine collection are either three times per week (Monday, Wednesday, and Friday) or once a week. This simulation indicates that a three times per week schedule is more powerful than a one time per week schedule in detecting a treatment effect using quantitative urinalysis data. This indication is in agreement with the report by Cone and Dickerson (1992) that the most efficient testing schedule for judging the outcome for a cocaine medication trial would be three times per week.

For qualitative urinalysis, a one time per week sampling schedule could underestimate or overestimate the positive samples compared with the actual data for the three times per week schedule. Because a conservative approach is generally taken for the assessment of

clinical efficacy, a three times per week schedule would seem preferable, even though the majority rule approach always provides an artificially higher estimate of percentage positive samples. The use of actual data, which is not commonly practiced in clinical trials, appears to be advantageous and its utility in clinical trials should be considered.

CONCLUSION

A simple simulation model was used to study the advantages and the limitations of quantitative versus qualitative urinalysis for daily cocaine abusers with an assumed reduction of cocaine use up to 60 percent. In addition, one time per week versus three times per week urine sampling schedules for the assessment of treatment outcomes were compared. The following general conclusions can be made based on this simplified model of simulation:

- Qualitative urinalysis using a cutoff concentration of 300 ng/mL is capable of statistically detecting a reduction in frequency of daily cocaine use, although it is less powerful than that from the quantitative analysis. Qualitative analysis cannot detect significant differences in reduction in the daily amount of use.

- Quantitative urinalysis is capable of detecting reductions both in frequency and amount of cocaine use. Quantitative urinalysis is more sensitive in detecting a reduction in the daily amount than a reduction in the frequency when the reduction is greater than 30 percent.

For quantitative urinalysis, a three times per week urine collection schedule provides more statistical power than does a one time per week collection.

For qualitative urinalysis, the majority rule analysis for a three times per week schedule provides a higher estimate of percentage positive samples than is actually the case. The one time per week schedule could give either higher or lower estimated percentage positive samples. Sampling and analysis of three times per week sampling would seem to be the preferable approach.

Finally, it is abundantly clear from this exercise that an increasing database of actual quantitative clinical urine values will greatly enhance the potential for developing more realistic simulations,

which in turn will enhance the design and analysis of outcome data in future clinical trials.

REFERENCES

Ambre, J.J. The urinary excretion of cocaine and metabolites in humans: A kinetic analysis of published data. *J Anal Toxicol* 9:241-245, 1985.

Ambre, J.J.; Ruo, T.I.; Nelson, J.; and Belknap, S. Urinary excretion of cocaine, benzoylecgonine, and ecgonine methyl ester in humans. *J Anal Toxicol* 12:301-306, 1988.

Batki, S.L.; Manfredi, L.B.; Jacob, P.; and Jones, R.T. Fluoxetine for cocaine dependence in methadone maintenance: Quantitative plasma and urine cocaine/benzoylecgonine concentrations. *J Clin Psychopharmacol* 13:243-250, 1993.

Batki, S.L; Washburn, A.; Manfredi, L.; Murphy, J.; Herbst, M.D.; Delucchi, K.; Jones, T.; Nanda, P.; Jacob, P., III; and Jones, R.T. Fluoxetine in primary and secondary cocaine dependence: Outcomes using quantitative benzoylecgonine concentration. In: Harris, L.S., ed. *Problems of Drug Dependence, 1993: Proceedings of the 55th Annual Scientific Meeting, The College on Problems of Drug Dependence, Inc.* National Institute on Drug Abuse Research Monograph 141. DHHS Pub. No. (ADM)94-3749. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1994. p. 140.

Cone, E.J., and Dickerson, S.L. Efficacy of urinalysis in monitoring heroin and cocaine abuse patterns: Implications in clinical trials for treatment of drug dependence. In: Jain, R.B., ed. *Statistical Issues in Clinical Trials for Treatment of Opiate Dependence.* National Institute on Drug Abuse Research Monograph 128. DHHS Pub. No. (ADM)92-1947. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1992. pp. 46-57.

Cook, C.E.; Jeffcoat, A.R.; and Perez-Reyes, M., Pharmacokinetic studies of cocaine and phencyclidine in man. In: Barnett, G., and Chiang, C.N., eds. *Pharmacokinetics and Pharmacodynamics of Psychoactive Drugs.* Foster City, CA: Biomedical Publications, 1985. pp. 48-74.

Crosby, R.D.; Halikas, J.A.; and Bowers, L.D. Quantitative cocaine urine testing in clinical research settings. *Ann Clin Psychiatry* 3:243-249, 1991.

Gilbaldi, M., and Perrier, D. *Pharmacokinetics.* New York: Marcel Dekker, 1982.

Hamilton, H.E.; Wallace, L.E.; Shimek, E.L., Jr.; Land, P.; Harris, S.C.; and Christenson, J.G. Cocaine and benzoylecgonine excretion in humans. *J Forensic Sci* 22:697-707, 1977.

Hawks, R.L., and Chiang, C.N., eds. *Urine Testing for Drugs of Abuse.* National Institute on Drug Abuse Research Monograph 73. DHHS Pub. No. (ADM)87-1481. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1986.

Jeffcoat, A.R.; Perez-Reyes, M.; Hill, J.M.; Sadler, B.M.; and Cook, E. Cocaine disposition in human after intravenous injection, nasal insufflation or smoking. *Drug Metab Dispos* 17:153-159, 1989.

Jones, R.T. Cocaine: The pharmacology of cocaine. In: Grabowski, G., ed. *Pharmacology Effects and Treatment of Abuse.* National Institute on Drug Abuse Research Monograph 50. DHHS Pub. No. (ADM)84-1326. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1984. pp. 34-53.

Jones, R.T. National Institute on Drug Abuse contract report no. 271-87-8123, 1992.

Reid, K.; Peters, J.E.; Chou, J.; Borg, L.; and Kreek, M.J. Quantitative measurement of benzoylecgonine as a marker for relapse to cocaine abuse. In: Harris, L.S., ed. *Problems of Drug Dependence, 1994: Proceedings of the 56th Annual Scientific Meeting of the College on Problems of Drug Dependence, Inc.* Vol. II. National Institute on Drug Abuse Research Monograph 153. NIH Pub. No. (ADM)95-3883. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1995. p. 331.

Tai, B. *Clinical Decision Network of Cocaine Addiction Pharmacotherapy: Summary Report.* National Institute on Drug Abuse, 1993.

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APPENDIX

The cumulative amount (M) of benzoylecgonine (BE) excreted in the urine until time *t* is described by the equation (1.48) of Gibaldi and Perrier (1982). The following for M is obtained by rearranging the equation.

$$M=(k*f*dose)*(km*(l-e^{-k*t})-k*(l-e^{-km*t})) \ / \ k*(km-k) \qquad (1)$$

Assuming the urine is collected during t_1 and t_2, t is defined as the midtime between t_1 and t_2. In this simulation, 9 a.m. is assumed to be the midtime (*t*) and the collection period is assumed to be 2 hours.

$$t_2 - t_1 = 2 \qquad (2)$$
$$t_2 = t + 1 \qquad (3)$$
$$t_1 = t - 1 \qquad (4)$$

The cumulative amount of BE excreted in the two consecutive sampling times, t_1 and t_2, is given by:

$$M(t_2)=(k*f*dose)*(km*(l-e^{-k*(t+l)})-k*(l-e^{-km*(t+l)})) \ / \ k*(km-k) \qquad (5)$$

and

$$M(t_2)=(k*f*dose)*(km*(l-e^{-k*(t+l)})-k*(l-e^{-km*(t+l)})) \ / \ k*(km-k) \qquad (6)$$

Amount of BE excreted for the mid-time *t*, É M, is the amount collected during t_2 and t_1. É M equals to M (t_2) - M (t_1) and is given by subtracting equation 6 from equation 5.

$$\Delta M=(k*f*dose)*(km*e^{-(k*t)}*(e^{k}-e^{(-k)})-k*e^{-(km*t)}*(e^{km}-e^{(-km)}) / k*(km-k) \quad (7)$$

Urinary flow rate is assumed to be 1 mL/min or 0.06 L/hr. The urine volume for the 2-hour interval is (0.06*2). The BE concentration at time *t* obtained by dividing equation 7 by the urine volume (0.06*2) yields

$$(BE)t=(k*f*dose)*(km*e^{-(k*t)}*(e^{k}-e^{(-k)})-k*e^{-(km*t)}*(e^{km}-e^{(-km)}) / k*(km-k)*(0.06*2) \quad (8)$$

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