Quantitative Urine Levels of Cocaine and Other Substances of Abuse

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INTRODUCTION

Quantitative urine levels of cocaine and other substances of abuse hold the promise of providing new and important information that goes beyond the scope of qualitative results. This chapter describes clinical and treatment research applications of quantitative urine levels of substance abuse analytes. A historical review is presented, caveats are discussed, and a single-step dilution Abbott ADX/TDX method is provided. Examples are presented that support the utility of quantitative urines in pharmacotherapy trials of cocaine and other substances of abuse, in health services research, in studies of polysubstance abuse, and in studies associating biological markers with phases of physiological dependence and risk to relapse.

By tradition, substance abuse urine results are expressed in qualitative terms of positive or negative. However, urine levels of substance of abuse may also be expressed with quantitative/scalar values. For example, a patient's urine level of the cocaine metabolite benzoylecgonine (BE) can range from 0 to 300,000 ng/mL or higher. The numerator of a quantitative urine analyte level contains either a measure of weight of the respective analyte (e.g., ng) or its molarity (e.g., mol). The denominator contains either a measure of urine volume (e.g., mL) or the amount of excreted creatinine (Cn). Cn is employed as an indicator of renal clearance since it is a byproduct of cellular metabolism excreted steadily by the kidney and not reabsorbed through the renal tubule. Analyte adjustment with Cn compensates for dilute or concentrated urine resulting from the patient's fluid intake. Cn adjustment is helpful in a number of circumstances, including when a patient has ingested large volumes of liquid, perhaps in order to defeat the urine test. A Cn-adjusted level is produced by dividing the concentration (mg/mL) of excreted Cn into the analyte concentration. As an example, Cn values of 0.5 and 2.0 mg/mL would adjust a BE level of 100,000 ng/mL to 200,000 ng/mg and 50,000 ng/mg, respectively.

BACKGROUND

Quantitative urine levels of lead and other toxins, adjusted for urine dilution, have been employed in the fields of environmental and industrial medicine for 50 years (Levine and Fahy 1945, reviewed by Elkins and Pagnotto 1974). In the early 1970s, smoking cessation investigators embraced the quantitative method and Cn adjustment for expressing urine levels of the nicotine metabolite cotinine (reviewed by Sepkovic and Haley 1985). Yet, despite the long-standing recognition of urinalysis as a critical tool in the treatment of substance abuse (Harford and Kleber 1978), only a limited number of substance abuse investigators have employed quantitative urines.

Manno (1986) described how replacing qualitative results with Cn adjusted quantitative urine levels of the carboxy metabolite of delta-9-tetrahydrocannabinol prevented both false-positive and false-negative interpretations of cannabinoid use (see figure 1). Additional publications have supported this position for cannabinoids (Bell et al. 1989; Lafolie et al. 1991), as well as cocaine (Weiss and Gawin 1988, Wilkins et al. 1994*a*), opioids and benzodiazepines (Lafolie et al. 1991), and buprenorphine, a mixed agonist/antagonist opioid (Watson 1992). Weiss and Gawin (1988) noted that quantitative urine BE levels allowed for differentiation of positive BE levels arising from washout, from positive BE levels resulting from new cocaine use. The demonstration of protracted BE washout in cocaine-using patients (Burke et al. 1990; Cone and Weddington 1989) amplifies the need to distinguish washout from new cocaine use in clinical practice and research.

SINGLE-STEP DILUTION PROTOCOL

Table 1 outlines a single step dilution protocol for the determination of quantitative urine BE levels, based on the Abbott ADX/TDX Net P value (Wilkins et al. 1994*b*). The Net P value is inversely proportional to the analyte concentration (see figure 2), representing the intensity of polarization/fluorescence produced by the sample. Since the Abbott ADX/TDX printout provides the Net P value in all of its assays, the dilution protocol can be applied to a number of substance abuse analytes (see table 2). For example, the initial Abbott ADX/TDX run of a sample presumably containing BE will produce a numeric value from 0 to 5,000, or the printout will state “greater than 5,000”; i.e., out of the Abbott

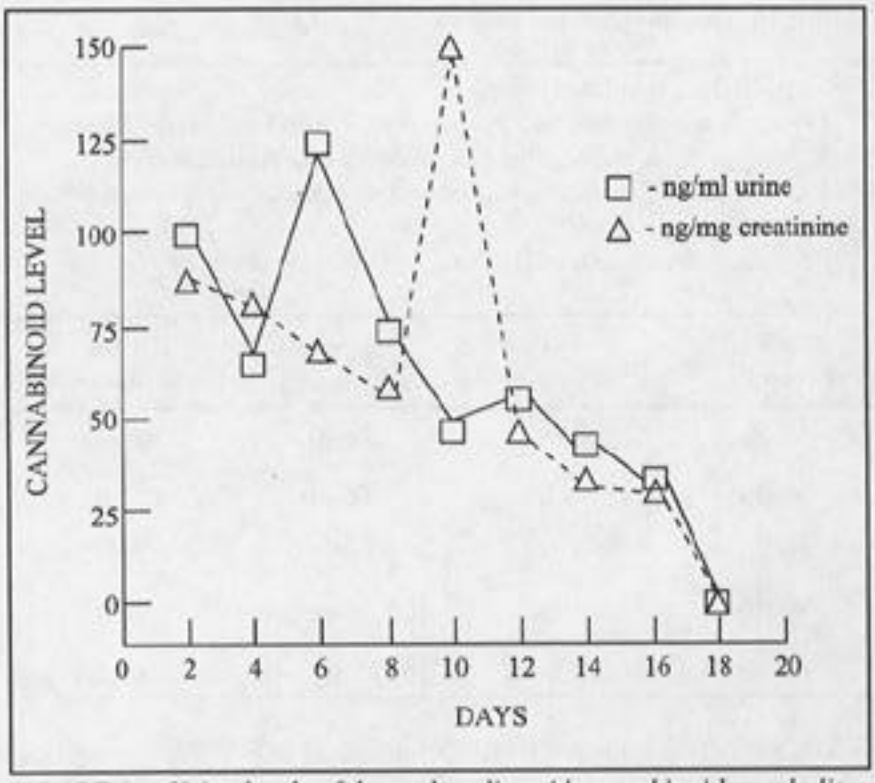

FIGURE 1. *Urine levels of the carboxylic acid cannabinoid metabolite in one patient. When the cannabinoid metabolite is expressed as ng/mg of excreted creatinine, a false-positive interpretation is avoided on day 7 and a false-negative interpretation is avoided on day 11.*

SOURCE: Manno (1986).

assay range. In this latter case, a dilution step and subsequent rerun of the assay is required. The single-step dilution protocol provides BE values to 150,000 ng/mL (a maximum dilution of thirtyfold times 5,000), a range that includes most sample values and identifies new cocaine use in most circumstances. If following the dilution step the Abbott printout again reads "greater than 5,000," this indicates that the BE value is > 150,000. The author's laboratory generally employs 150,000 as its maximal reporting value since a second dilution step significantly increases the range of dilution-based error and routine clinical needs do not require values beyond 150,000 ng/mL. When it is desirable to

TABLE 1. *One-step dilution protocol.*

1. First, analyze undiluted sample.
2. Do not dilute if within assay range (i.e., < 5,000 ng/mL for BE).
3. If exceeds assay range, dilute as follows using Abbott buffer.
4. Mix sample before taking aliquot and mix diluted sample well before assay.
5. Can adjust final result by dividing by excreted creatinine.

1st run Net P	Dilution*	Sample Volume	Diluent Volume
75-80	1:3	100 L	200 L
70-75	1:5	100 L	400 L
60-70	1:10	100 L	900 L
50-60	1:20	100 L of 1:10	100 L
40-50	1:30	100 L of 1:10	200 L

KEY: * = Repeat sequence if postdilution result is > 5,000.

NOTE: The one-step process dilutes samples up to a maximum of 150,000 ng/mL (generally over 90% of samples encountered in a pharmacotherapy trial).

produce values over 150,000, a second dilution step is performed according to the same steps employed for the first dilution. Once a diluted value is produced, adjustment with Cn can be performed.

Using samples obtained from a pharmacotherapy trial of cocaine abuse/dependence (Margolin et al. 1995), the reliability of the single-step dilution protocol was evaluated by comparing final BE concentrations with the levels predicted by the Abbott ADX/TDX Net P values. Almost all of the 1,619 samples (97.5 percent) were diluted correctly by the procedure. The validity of the single-step dilution protocol was evaluated by split-sample comparisons of Abbott's fluorescence polarization immunoassay (FPI) method with high-pressure liquid chromatography (HPLC) and diode array detection according to a modification of Svenson (1986). Across 26 random samples, a Pearson

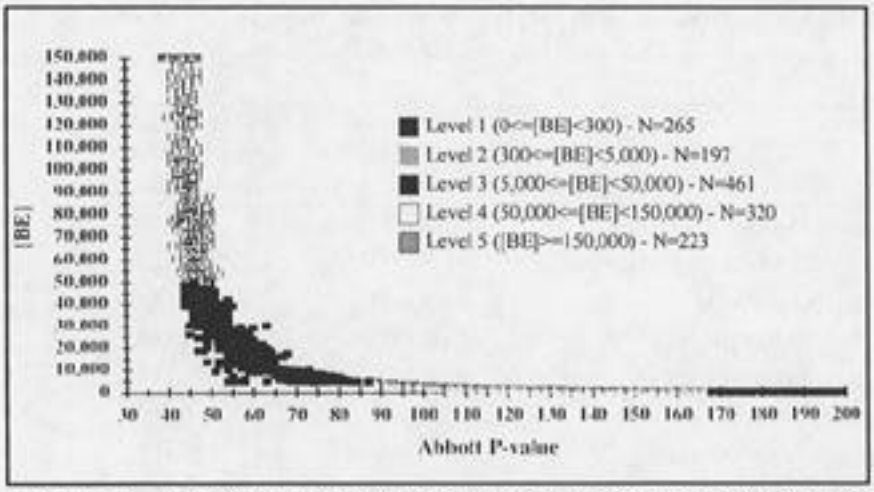

FIGURE 2. *Relationship between initial Abbott net P values and diluted semiquantitative urine BE levels in 1,466 samples from 48 patients. 93% of levels were > 100,000 when Net P was <42; 96% of levels were > 40,000 when Net P was < 46; 96% of levels were > 20,000 when Net P was < 55.*

correlation of 0.992 was demonstrated between the FPI and HPLC methods. Once urine BE levels exceeded 150,000 ng/mL, the FPI values were consistently higher than the HPLC values, producing an across-sample variance of 11.79 percent.

HEALTH SERVICES RESEARCH

Quantitative urine levels for substance of abuse have been used to define the prevalence of substance use in the week prior to admission in patients admitted to psychiatric inpatient programs at the Veterans Administration Medical Center (VAMC) West Los Angeles (Shaner et al. 1993; Wilkins et al. 1991). Quantitative urine levels have also been used to define the cascade process that begins with a mentally ill patient's use of a substance of abuse and ends with hospitalization (Shaner et al. 1995). In this latter study, serial quantitative urine BE levels from 155 schizophrenic patients were analyzed to track new cocaine use. New use was defined within 3-day intervals. The results demonstrated a clear relationship between receipt of disability pension money, subsequent cocaine use, the development of cocaine-associated psychiatric symptomatology, and subsequent admission to the hospital.

TABLE 2. *Application of single step dilution protocol to Abbott Assays of abusable substances other than cocaine.*

	Predilution upper limit of assay	New upper assay limit following thirtyfold dilution
Amphetamine class[1]	8,000	240,000
Amph./methamphetamine II[2]	8,000	240,000
Barbiturates II U	2,000	60,000
Benzodiazepines	2,400	72,000
Benzodiazepines serum	2,400	72,000
Cannabinoid	135	4,050
Cocaine metabolite	5,000	150,000
Ethanol (urine)	300	9,000
Methadone	4,000	120,000
Opiates	1,000	30,000
Phencyclidine II	500	15,000
Propoxyphene	1,500	45,000

KEY: [1] = Includes both dextro and levo isomers of amphetamines.
[2] = Assays only dextro isomer of amphetamine and methamphetamine.

The investigators are continuing to use quantitative levels to evaluate the impact on cocaine use from treatment interventions based on contingency management.

POLYSUBSTANCE ABUSE

Serial collection of quantitative urine levels can be used to track sequences of polysubstance abuse. As an example, opioid and cotinine levels have been compared across time using Box-Jenkins Time Series analysis (Wilkins et al., in review, see figure 3). These results suggest that cigarette smoking and opioid use are behaviorally linked.

QUANTITATIVE URINE LEVELS AND BIOLOGICAL MARKERS OF SUBSTANCE ABUSE

Biological markers may prove clinically useful in characterizing a patient's level of physiological dependence as well as risk to relapse

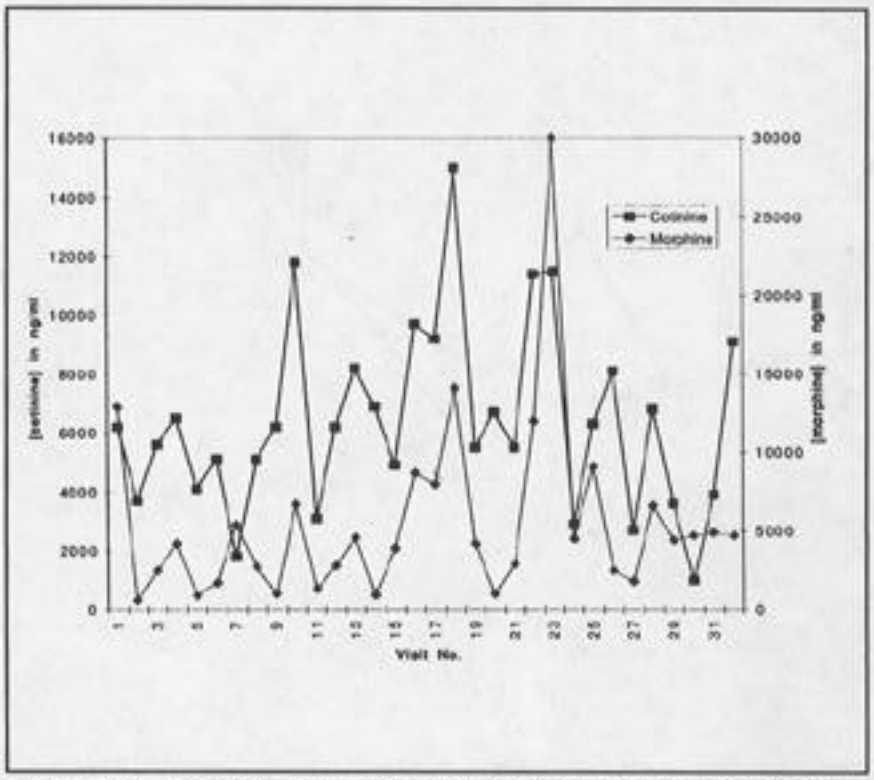

FIGURE 3. *Parallel patterns of semiquantitative urine levels of cotinine and morphine for one buprenorphine-maintained patient across 11 weeks (i.e., 32, three per week visits). Across all visits, the Box-Jenkins autocorrelation value was 0.57.*

once abstinent. Preliminary data suggest that quantitative urine levels may be useful as covariates in identifying endogenous substance abuse-associated biological markers. At a 1-year followup of patients treated for cocaine abuse, circulating levels of cortisol and prolactin (HPrl) were found to vary according to the range of the quantitative urine BE level (Wilkins et al. 1992; figure 4). Cortisol levels reached their highest elevations when urine BE reflected a later stage of abstinence (i.e., < 200 ng/mL > 0) and returned to baseline when BE was no longer present in the urine. Circulating HPrl levels were at their lowest when BE levels reflected recent cocaine use (i.e., > 50,000 ng/mL), increased when BE levels reflected early abstinence (i.e., > 10,000 ng/mL), and, unlike cortisol, remained elevated above baseline even when BE levels were no longer present. The cortisol results suggest that patients

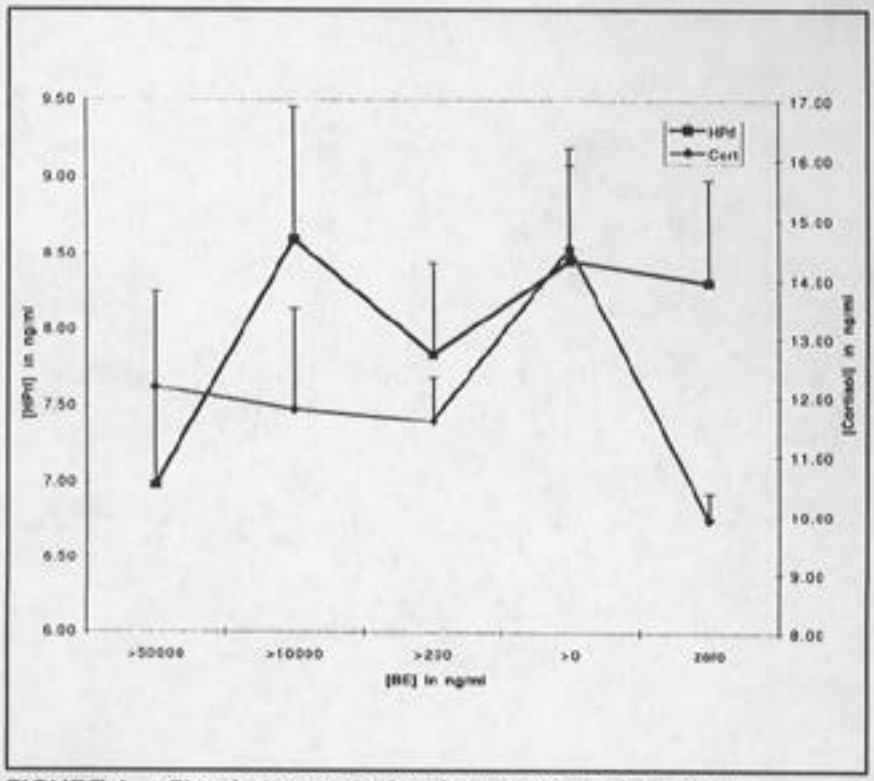

FIGURE 4. *Circulating cortisol and prolactin in 191 patients categorized according to semiquantitative urine levels of BE. Blood and urine were collected between 9-10:30 a.m. as part of a 1-year followup for patients previously treated for cocaine abuse/dependence. The number of samples for each BE category is as follows: >50,000 (14), >10,000 (24), >200 (35), >0 (19), and zero (99).*

experience a significant stress response approximately 3 to 4 days after initiating abstinence from cocaine. Relatively lower HPrl levels at the earliest stages of abstinence are consistent with inhibition of HPrl release secondary to cocaine-induced increases in hypothalamic dopamine. Subsequent elevations of HPrl, as abstinence from cocaine progresses, are consistent with previous studies demonstrating elevated HPrl during most phases of cocaine abstinence (Dackis and Gold 1985; Mendelson et al. 1988). In sum, these preliminary results suggest that HPrl and cortisol may serve as biological markers of the varying stages of abstinence from cocaine.

PHARMACOTHERAPY TRIALS OF COCAINE ABUSE

Quantitative urine levels of abused substance may become an important adjunctive measure in pharmacotherapy trials for cocaine and other substances of abuse. Based on their ability to detect changes in amount and frequency of cocaine use (Li et al. 1995), quantitative urine levels may be used to screen potential subjects, assist in determinations of sample size power analysis, and provide pre- and postmedication outcome comparisons.

Inclusion criteria in substance abuse pharmacotherapy studies are employed, in part, to assure that study patients are selected from the same population. Quantitative urine levels may distinguish a study population based on baseline substance use. For example, although the two patients represented in figure 5 would meet conventional study inclusion criteria for cocaine use based on qualitative urines positive for BE (i.e., > 300 ng/mL), quantitative urine levels reveal a fiftyfold variance between the patients in baseline BE levels. According to their baseline cocaine use, these potential subjects may not represent the same population. Thus, inclusion of both patients into a pharmacotherapy trial as equals may introduce confounds contributing to a Type II error.

Premedication quantitative baseline levels may also be helpful in power analysis determinations. For example, quantitative urine BE values are substantially different for the two populations demonstrated in figure 6. Although both groups are made up of cocaine-using, methadone-maintained patients, significantly different research designs may be required to test for medication effect in each population. Total abstinence might be the goal for the population with 56.7 percent positive urines, whereas a consistent diminution in urine BE levels might be the endpoint for the population with 90.8 percent urines positive for BE.

In addition, quantitative urine levels have been proposed to serve as a primary outcome variable in pharmacotherapy trials for cocaine abuse (Batki et al. 1993). The author notes that qualitative urine measures would have failed to recognize a potential therapeutic effect of fluoxetine for the treatment of cocaine abuse. The study results, confounded by elevated premedication BE levels in the placebo group, raises a number of timely questions including whether it is useful to identify medications that do not necessarily produce complete abstinence but reliably reduce cocaine use and frequency.

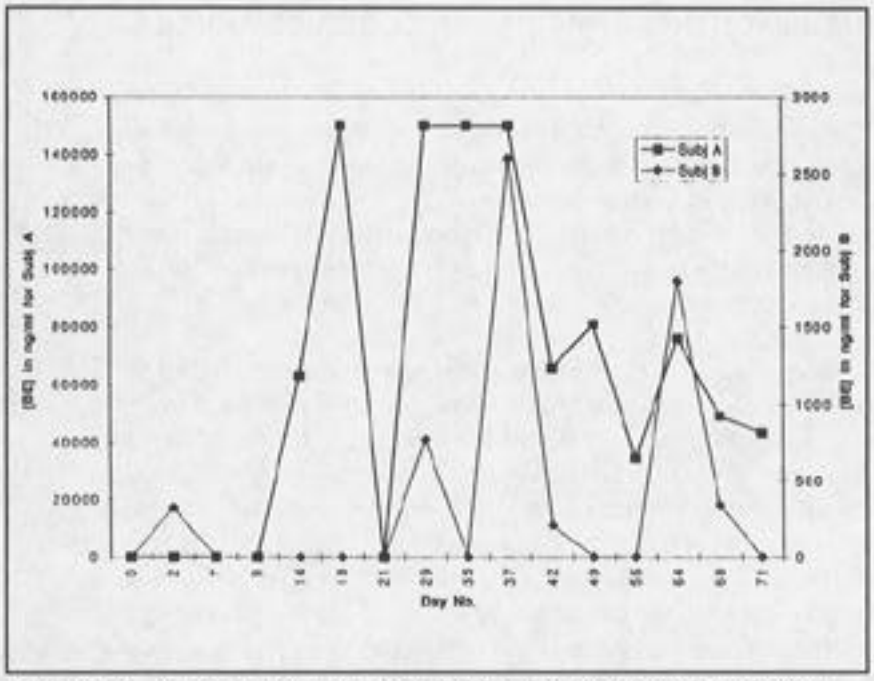

FIGURE 5. *Semiquantitative urine BE levels in two cocaine-abusing subjects. Urine levels from subject A are approximately fiftyfold higher than those in subject B.*

CAVEATS

Despite the strengths offered by quantitative urine levels, research investigators and clinicians need to proceed with caution when interpreting the clinical significance of the levels. Tracking of quantitative urine levels does not definitively demonstrate the dose, time of drug usage, clinical condition and/or behavioral impairment at the time of sample collection (Jatlow 1992), despite careful and thorough evaluation by Ambre and colleagues (1991). Quantitative and qualitative urine results are influenced by variance in the appearance of substance abuse analytes in urine (see reviews by Catlin et al. 1992, Chiang and Hawks 1986, and Osterloh 1993) resulting from interindividual differences in frequency and amount of substance used, the presence of contaminants in the substance, route of administration, sex, race, age, weight, diet, metabolic enzyme activity (e.g., cholinesterase activity for cocaine), rate of excretion, formation of condensation products (e.g., cocaethylene in users of cocaine and alcohol), drug interactions, and

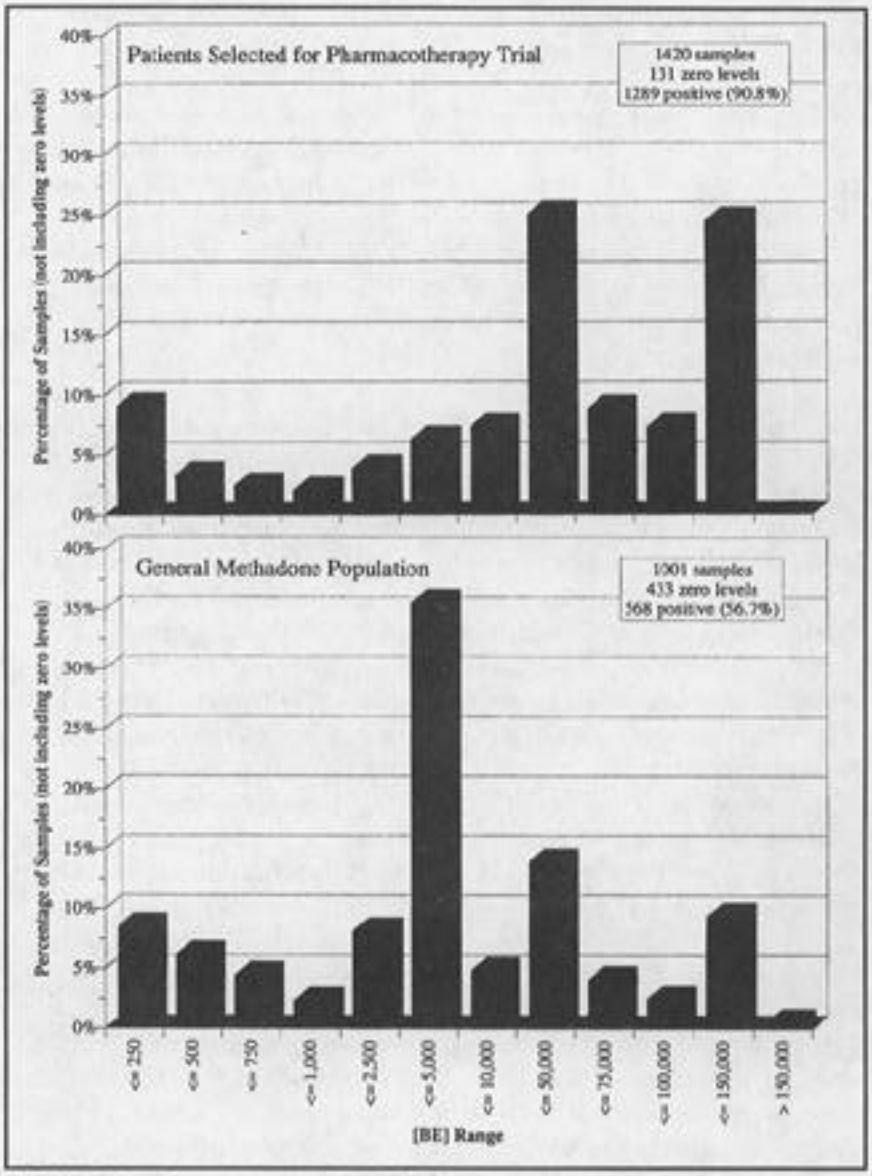

FIGURE 6. *Quantitative urine BE levels in two methadone maintenance populations: patients selected for a pharmacotherapy trial and general methadone patients. The incidence rate of urines positive for BE is 57% in the general methadone population positives compared to 91% in the pharmacotherapy population. BE levels in the general population are under 5,000 ng/mL 65% of the time, while 50% of the pharmacotherapy population has BE levels > 10,000 ng/mL and 25% between 100,000-150,000 ng/mL.*

physiological parameters including blood flow, urine flow, and body fluid pH.

Variability in the appearance of a substance abuse analyte is evident in serial urine samples collected from subjects who received intravenous cocaine (see figure 7) as part of a cardiovascular protocol (Nademanee et al. 1990). BE excretion varied despite the use of identical doses administered at the same time of day. It is noteworthy that this problem may be reduced by employing recently introduced algorithms that control for interindividual differences in BE excretion (Preston and Cone, this volume).

Caveats also apply to Cn adjustment of analyte levels. Extremely low or high Cn levels (e.g. < 0.1 or > 4.0) may produce spurious results. Each investigative group needs to define a range that avoids excessive adjustment with Cn, pending further research. In addition, all substance abuse analytes may not be appropriate for Cn adjustment. Alessio and colleagues (1985) have noted that not all environmental toxins parallel Cn in renal excretion. Similarly, additional data analysis from a pharmacotherapy-cocaine interaction safety study of 52 serial urines collected over 3 days of cocaine administration in four subjects (Haberny et al. 1995) suggests that not all urine substance abuse analyte levels parallel urine Cn levels. Pearson correlation coefficients of Cn and analyte urine levels demonstrate close correlations between Cn and amphetamine (0.95) and methamphetamine (0.91), a reduced correlation between Cn and BE (0.65), and even less of a correlation between Cn and ecgonine methyl-ester (0.48) and Cn and cocaine (0.35).

Thompson and colleagues (1990) have proposed a methodology to improve Cn adjustment in smoking cessation studies with potential applications to other substance abuse research. In a study of 279 male smokers, they demonstrated an increased correlation from 0.83 to 0.91 between urinary cotinine and plasma cotinine when the urine Cn value was modified according to a regression line of log-transformed, population-specific urine Cn levels. Alternatively, Simpson and associates (1993) have proposed a cost-saving procedure of limiting laboratory measures of Cn only when the urine color suggests dilution. They report that 96.5 percent of 516 samples were correctly identified by a visual inspection procedure, although the method has been criticized as being too subjective (Lafolie 1991). Li and colleagues (1996) performed a preliminary evaluation of various

methods to adjust BE with urine Cn levels. This exercise has yet to identify a superior method, even when

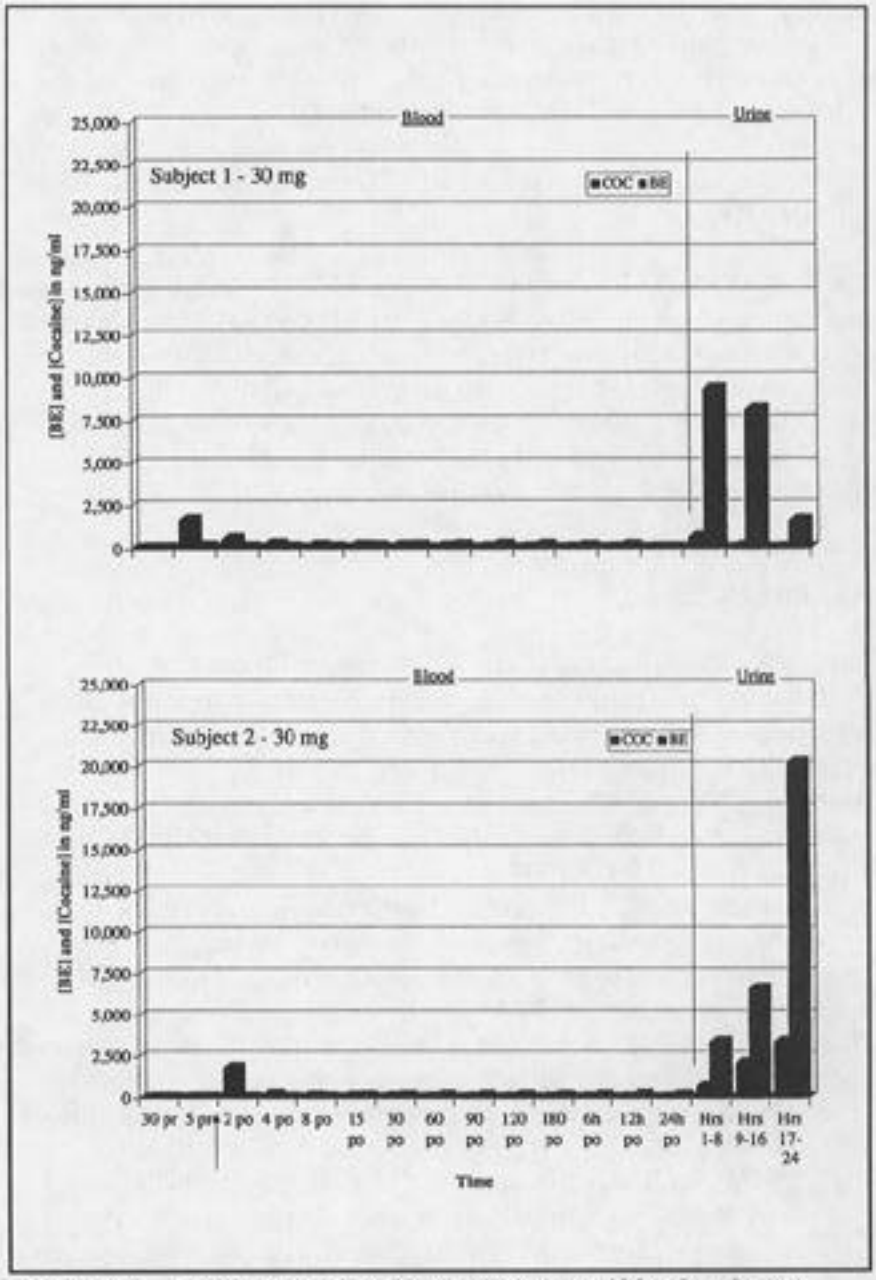

FIGURE 7. *Comparison of 24-hour monitoring of blood and urine following an IV bolus of 30 mg cocaine in two subjects. Interindividual differences in the timing of BE excretion kinetics across the three 8-hour urine collection periods are evident with quantitative urine BE levels decreasing in subject 1 and increasing in subject 2.*

employing the Thompson method. The effort is hampered by the lack of an obvious "gold standard" for comparison with quantitative urine levels (i.e., the kinetics of renal clearance differ from the kinetic processes producing blood, brain, and cerebrospinal fluid).

SUMMARY

Used appropriately, quantitative levels can address research hypotheses and clinical issues that are otherwise untested by traditional qualitative urine results. Quantitative urine levels can provide new information in health services research, pharmacotherapy trials, studies of the interaction of cigarette smoking and substance abuse, additional studies of polysubstance abuse, and the linking of biological markers with phases of addiction and risk to relapse.

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