

Urinary Buprenorphine Concentrations in Patients Treated with Suboxone® as Determined by Liquid Chromatography–Mass Spectrometry and CEDIA Immunoassay

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Abstract

We report on the utility of urine total buprenorphine, total norbuprenorphine, and creatinine concentrations in patients treated with Suboxone® (a formulation containing buprenorphine and naloxone), used increasingly for the maintenance or detoxification of patients dependent on opiates such as heroin or oxycodone. Patients received 8–24 mg/day buprenorphine. Two-hundred sixteen urine samples from 70 patients were analyzed for both total buprenorphine and total norbuprenorphine by liquid chromatography–mass spectrometry (LC–MS–MS). Buprenorphine concentrations in all 176 samples judged to be unadulterated averaged 164 ng/mL, with a standard deviation (SD) of 198 ng/mL. Nine samples (4.2%) had metabolite-parent drug ratios < 0.02, and 33 (15.3%) had no detectable buprenorphine. The metabolite/parent drug ratio in 166 samples had a range of 0.07–23.0 (mean = 4.52; SD = 3.97). Fifteen of 96 available urine samples (16.7%) had creatinine less than 20 mg/dL. We also found sample adulteration in 7 (7.3%) available samples. Using a 5 ng/mL urine buprenorphine cutoff, the sensitivity and specificity of the Microgenics homogeneous enzyme immunoassay versus LC–MS–MS were 100% and 87.5%, respectively. The 5 ng/mL cutoff Microgenics CEDIA buprenorphine assay results agreed analytically with LC–MS–MS in 97.9% of samples.

Introduction

Buprenorphine is a synthetic partial opioid agonist derived from thebaine. It is used as an injectable analgesic (Buprenex®, Reckitt Benckiser Pharmaceuticals, Richmond, VA) in treatment of moderate-to-severe pain, and in low doses it is many times more potent than morphine. Buprenorphine has been

used since 1996 in France as a substitute for methadone in heroin maintenance and withdrawal programs, and is itself an abused drug (1).

In 2002, the United States Food and Drug Administration approved two sublingual buprenorphine formulations for use in opioid addiction treatment: Subutex® (containing buprenorphine as the only active ingredient) and Suboxone (a combination of buprenorphine and the opioid antagonist naloxone that was developed for the U.S. market in an attempt to curb abuse potential) (Reckitt Benckiser Pharmaceuticals). This approval, along with the Drug Addiction Treatment Act of 2000 (2) effectively allowed treatment of opioid addiction to expand beyond the setting of methadone clinics, and into physician private office practice. At our institution, Suboxone prescriptions greatly outnumber Subutex prescriptions.

Buprenorphine has good bioavailability when taken sublingually, and naloxone does not (4). If Suboxone tablets are taken as directed, buprenorphine's effects will predominate. If a tablet is dissolved and the contents injected by the patient, naloxone's effects will predominate because of its higher parenteral bioavailability. This is likely to cause an opioid withdrawal syndrome, which should deter further abuse by injection of dissolved Suboxone tablets (3). Still, buprenorphine's significant abuse and diversion potential require that patients' compliance with their Suboxone regimen be closely monitored. Patients may also avoid buprenorphine intermittently when they anticipate using illicit opiates, the subjective value of which may be diminished in the presence of buprenorphine.

Methods for monitoring buprenorphine concentrations in biological fluids include gas and liquid chromatography using mass spectrometric (5,6) detection, and radioimmunoassay (7). Recently, reports on non-isotopic immunoassays employing the enzyme-linked-immunosorbant (8,9) and homogeneous enzyme (10) techniques have appeared. Microgenics (Freemont, CA) commercialized the homogeneous enzyme-immunoassay (10) utilizing the Cloned Enzyme Donor Im-

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muno-Assay (CEDIA) principle. In this study, our goals included characterizing the urine buprenorphine and norbuprenorphine concentrations using liquid chromatography–tandem mass spectrometry (LC–MS–MS) in our clinical practice in patients receiving Suboxone therapy, and evaluating the performance of the Microgenics CEDIA Buprenorphine immunoassay as an alternative to LC–MS–MS. We also describe our findings regarding urine adulteration and/or dilution in this patient population.

Materials and Methods

Naloxone HCl was purchased from Sigma Chemicals (St. Louis, MO).

Sample inclusion criteria

Over the eight-month period from 1/1/06 to 8/31/06, the Toxicology laboratory received 216 urine samples from 70 patients that had a quantitative buprenorphine concentration requested. Data from all these samples are included in this report and are labeled as the group “ $n = 216$ ”. A subset of these samples, labeled as “ $n = 96$ ”, consists of samples from the “ $n = 216$ ” group that also had sufficient specimen volume remaining for additional testing after LC–MS–MS analysis. All samples were frozen at -20°C in amber vials until analyzed.

CEDIA urine buprenorphine immunoassay

We used buprenorphine reagents as recommended by Microgenics (catalogue # 100190, Microgenics, Freemont, CA) on two Hitachi 911 analyzers (Roche Diagnostics, Indianapolis, IN). These reagents can be used in two modes: qualitative and semi-quantitative. The qualitative mode was used in this study. We used assay calibrator and control materials containing 0, 5, and 20 ng/mL buprenorphine (Microgenics # 100241, 100242, and 100243). We used the 5 ng/mL material as the cutoff calibrator to distinguish positive from negative samples. The 0 and 20 ng/mL materials were run as controls with every group of patient samples.

LC–MS–MS urine buprenorphine and norbuprenorphine analysis

Urine total (free plus conjugated) buprenorphine and norbuprenorphine were measured at a reference laboratory (National Medical Services, Willow Grove, PA, Analysis Code 0801U) using LC–MS–MS. The detection limit for both buprenorphine and norbuprenorphine was 5 ng/mL.

LC–MS–MS

The method has a linear range of 5–2000 ng/mL for both buprenorphine and norbuprenorphine. In summary, 0.50 mL aliquots of urine are hydrolyzed using β -glucuronidase (Patella Vulgata) for 3 h at 50°C . To a 0.1-mL aliquot of each hydrolyzed sample, internal standards (buprenorphine- d_4 and norbuprenorphine- d_4) were added, and the mixture made acidic with acetic acid. Following solid-phase extraction using a Strata-X-C polymer column, the final eluent (2% ammonium hydroxide, 20% isopropanol, 78% ethyl acetate) was

evaporated and reconstituted with a solution of mobile phase components. Samples were analyzed using a Waters Micro-Quattro Micro LC–tandem MS instrument with electrospray ionization, and a Waters Acquity Ultra Performance LC with an Acquity UPLC BEH C18 (1.0 mm \times 50 mm, 1.7-micron average-particle diameter) analytical column (Milford, MA). Two ion transitions were monitored for each analyte and the internal standards to assure that there were no interferences. Each analytical run was independently calibrated at concentrations of 0.5, 1.0, 5.0, 20, 50, and 200 ng buprenorphine and norbuprenorphine/mL. Urine samples are diluted 10-fold during hydrolysis, so the effective range of calibration is 5.0 to 2000 ng/mL. This LC–MS–MS method had between-run percent coefficients of variation (CV) of 18.5 and 3.73 at 1.0 and 40 ng/mL, respectively, for buprenorphine; and between run %CV of 15.9 and 4.87 at 1.0 and 40 ng/mL, respectively, for norbuprenorphine. Buprenorphine and norbuprenorphine eluted at approximately 3.4 and 3.7 min, respectively, and their internal standards co-elute with each analyte.

LC with diode-array detection (DAD) analysis of urine for naloxone

To further characterize urine samples suspected of adulteration, we analyzed them for naloxone using LC–DAD (11). The limit of detection for naloxone is 100 ng/mL with this method. In our experience, urine naloxone concentrations are undetectable in the urine of patients taking Suboxone as prescribed (sublingually). Naloxone elutes at about 2.21 min. The identity of peaks was confirmed by retention time and by matching the UV spectra of suspected naloxone peaks to the known spectrum of naloxone in the mobile phase contained in the DAD computer library. Appropriate calibrators and control materials containing authentic naloxone were processed with each run of patient samples.

Urinary creatinine

Creatinine in the 96 available samples was measured using a rate Jaffe method on a Hitachi 911 analyzer with reagents from Roche Diagnostics (Indianapolis, IN).

This investigation was performed as part of a quality assurance program, so institutional review board review was not needed.

Results

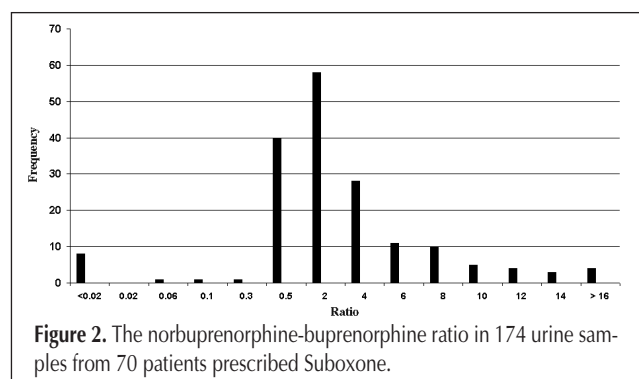
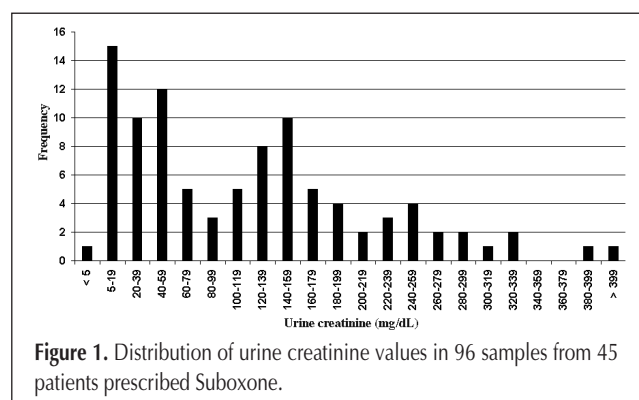
Two-hundred-sixteen samples from 70 patients comprise the sample group in this report. There was sufficient sample remaining in 96 cases (61 male, 35 female) from 45 patients (28 male, 17 female) to perform additional testing. The distribution of urine creatinine concentrations in these 96 samples is shown in Figure 1. By way of comparison, the lower reference limits for random urine creatinine were determined by Gowan and Frazer (13) to be 41 and 19 mg/dL in adult males and females, respectively. In this study, 20.8% (20 of 96) of samples had values less than these reference limits. Sixteen (16.7%) of these samples had values in the range the U.S. Department of Health and Human Services Substance Abuse and

Mental Health Services Administration guidelines classify as qualifying to be "dilute" (< 20 mg/dL).

LC-MS-MS was used to quantitate total buprenorphine and total norbuprenorphine in all 216 samples included in this study. Of these samples, 33 had undetectable concentrations of buprenorphine. The remaining 183 samples had detectable concentrations of both buprenorphine and norbuprenorphine. In 8 of these 183 samples, norbuprenorphine was detected but could not be quantitated (in seven cases, a sample matrix interference precluded quantitation, and in the eighth the sample had norbuprenorphine > 2000 ng/mL and insufficient volume remaining to perform a dilution). Norbuprenorphine was quantitated but buprenorphine was not (the result was > 10,000 ng/mL) in another sample. The distribution of the ratio of norbuprenorphine to buprenorphine in the remaining 174 samples is shown in Figure 2. Eight samples had ratios less than 0.02 (mean = 0.009; SD = 0.006). The remaining 166 samples had a ratio range of 0.07–23.0 (mean = 4.52; SD = 3.97) ng/mL. In 156 of these 166 (94.0%) urines, the metabolite concentration was greater than the parent drug.

In the 96-sample group, 80 had detectable concentrations of both buprenorphine and norbuprenorphine. In four samples, norbuprenorphine could not be quantified because of a suspected interference, and these samples were excluded from further metabolite/parent drug ratio calculations. Six other samples were excluded for likely adulteration because their metabolite/parent drug ratio was less than 0.02. The mean, standard deviation, and coefficient of variation of the buprenorphine concentrations in the remaining 70 samples were 161 ng/mL, 223 ng/mL, and 139% with a buprenorphine concentration range of 6–1200 ng/mL.

Thirty-three of 216 samples (15.3%) had buprenorphine



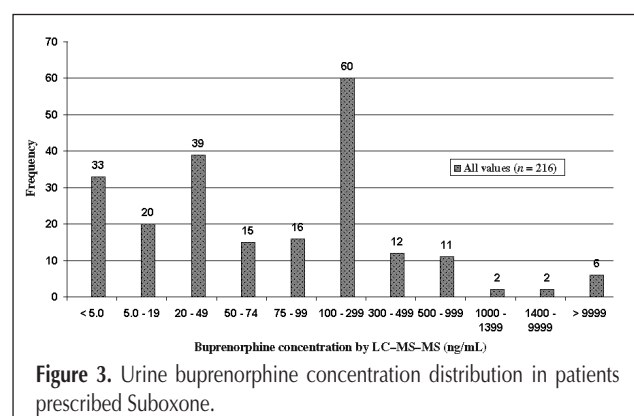
concentrations < 5.0 ng/mL, the detection limit of the LC-MS-MS assay. In 27 of these samples, the norbuprenorphine concentration was also less than the assay's 5.0 ng/mL detection limit. The remaining six samples had norbuprenorphine concentrations of 9, 9, 24, 31, 31, and 54 ng/mL.

The distribution of urine buprenorphine concentrations by LC-MS-MS for the 216 sample group is shown in Figure 3. Six of 7 samples with buprenorphine greater than 1399 ng/mL also had norbuprenorphine-buprenorphine ratios less than 0.020. Such low relative metabolite concentrations raise the possibility that undigested tablets were dissolved in these urine specimens. The seventh sample is from patient D in Table I and is also a likely adulterated sample.

Figure 4 shows the difference in CEDIA enzyme rates (in mAU/min) between the 20 ng/mL buprenorphine control/calibrator and the 0 ng/mL blank control/calibrator. This data was obtained over approximately 18 consecutive weeks, using 2 Hitachi 911 instruments and 2 lots of CEDIA reagent (the second lot was put into use on day 54 in Figure 4). The mean difference between the 20 and 0 ng/mL buprenorphine calibrator materials, combining all data from both instruments and reagent lots, was 98.3 mAU/min, with the SD being 6.2 ($n = 57$, CV = 6.3%). Also plotted in Figure 4 is the mean difference between the 5 (cutoff calibrator) and 0 ng/mL buprenorphine materials. The mean difference was 24.1 mAU/min, with the SD being 3.1 ($n = 57$, CV = 12.7%).

Table I lists the performance characteristics of the CEDIA qualitative immunoassay compared to quantitative LC-MS-MS. This comparison was done using two different buprenorphine cutoff calibrators: 5 and 20 ng/mL. There was 97.9% and 99.0% analytical agreement between CEDIA and LC-MS-MS using the 5 and 20 ng/mL cutoffs, respectively. Table I also shows the difference in clinical performance using these two different cutoffs/calibrators. The clinical sensitivity and negative predictive value deteriorate significantly upon changing from the 5 to 20 ng/mL cutoff calibrator. While this change eliminates two false-positives (that is, two fewer erroneous conclusions that patients were taking the drug), the Table I data indicate that 10 samples then become falsely negative evidence for patient non-compliance with their Suboxone regimen, as their concentrations were between 5 and 20 ng/mL. None of these 10 samples would be judged as evidence of non-compliance using a 5 ng/mL assay cutoff.

Figure 5 shows the correlation between the CEDIA enzyme



rate and urine buprenorphine by LC–MS–MS over the 5–180 ng/mL range. The correlation coefficient, slope, and intercept in the 5 to 80 ng/mL range were 0.923, 4.22, and 15.7, respectively, for $n = 39$ samples. The manufacturer claims linearity to 75 ng/mL using the “semi-quantitative” mode of the assay. Above 100 ng/mL, the slope of the enzyme rate versus buprenorphine concentration curve flattens considerably, with no rate increase at all over the range 180–49,000 ng/mL.

Discussion

The practice of overhydrating so as to pass an impending drug test is well described (14,15). Patients do this in an attempt to flush drugs and metabolites out of their system quicker, and to dilute urine analytes below the cutoff concentrations (limits of detection) of immunoassays. Patients may also hydrate in anticipation of the need to urinate at a clinical visit even absent the use of illicit drugs. The high number of low random urine creatinine values in this patient population is unusual. In a much larger study supported by the Correctional Service of Canada, a “diluted” (i.e., < 20 mg/dL) urine sample frequency of only 6.8% of 109,761 samples was reported (15). In Kronstrand and co-workers’ report (5) involving 16 patients on Subutex, none had creatinine < 20 mg/dL. The uncontrolled nature of the present study perhaps contributed

to the high number of dilute samples, as we put no limit on the number of samples a patient contributed to this study. Thus only 3 patients accounted for 8 of the 20 values below the urine creatinine reference limits. Also, during the 8-month period when samples were collected, no feedback was given to patients regarding urine dilution. It is possible that the lack of dilution “deterrence” contributed to the high dilution frequency observed here. Although we do not claim that dilute urine is synonymous with adulteration, we do recommend that urine creatinine concentrations be measured automatically with all urine buprenorphine testing to aid in ensuring the validity of the sample. Creatinine concentrations may be useful in tracking the inter- and inpatient urine buprenorphine concentration variability, which may also prove helpful in monitoring patient compliance.

There was strong evidence that 9 of 216 (4.2%) samples, from 6 of 70 (8.6%) patients, were adulterated or substituted. Seven of these samples were available to us for additional testing. Table II summarizes our findings on these samples and compares them to two samples we judged as authentic/unadulterated. Six adulterated samples had norbuprenorphine/buprenorphine ratios less than 0.02, and norbuprenorphine could not be quantitated in the seventh sample (this

Table I. Performance of the CEDIA Buprenorphine Immunoassay Using 5 and 20 ng/mL Cutoff Calibrators in Patients Prescribed Suboxone ($n = 96$ samples, from 45 patients)

	Analytical Performance Versus LC–MS–MS		CEDIA Clinical Interpretation Versus LC–MS–MS*	
Cut-off used	5 ng/mL	20 ng/mL	5 ng/mL	20 ng/mL
Sensitivity	100.0%	100.0%	100.0%	87.5%
Specificity	87.5%	96.3%	87.5%	100.0%
Positive predictive value	97.6%	98.6%	97.6%	100.0%
Negative predictive value	100.0%	100.0%	100.0%	61.5%
True positives	80	69	80	70
True negatives	14	26	14	16
False positives	2	1	2 [†]	0*
False negatives	0	0	0 [†]	10*
Analytical agreement	97.9%	99.0%	NA [‡]	NA
Clinical agreement	NA	NA	97.9%	89.6%

* This represents how CEDIA results are interpreted by a clinician (positive or negative, at 5 or 20 ng/mL), compared to actual buprenorphine LC–MS–MS results.
† A clinical false positive is defined as a positive CEDIA result using the stated cutoff indicating patient compliance (i.e., taking buprenorphine), when in reality the patient was not compliant (as determined by an LC–MS–MS buprenorphine result < 5 ng/mL). A clinical false negative result is defined as a negative CEDIA result using the stated cutoff indicating patient non-compliance, when in reality the patient was compliant (as determined by an LC–MS–MS buprenorphine result > or = 5 ng/mL).
‡ NA = not applicable.

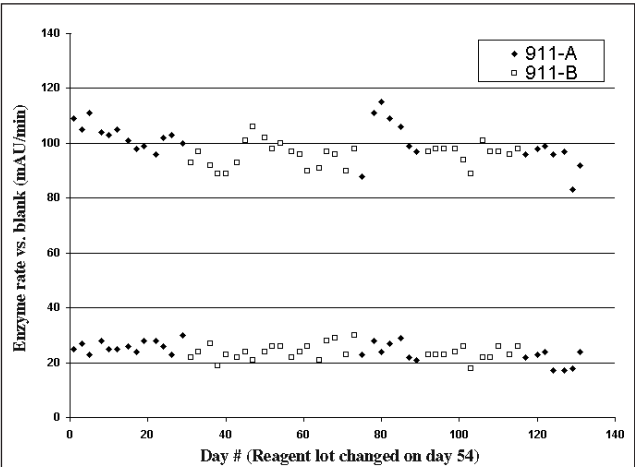


Figure 4. Enzyme rate difference between the 20 ng/mL buprenorphine control (top series in 100 mAU/min range) and 5 ng/mL cutoff calibrator (bottom series) and the blank (0 ng/mL buprenorphine) calibrator/control over nearly 140 days.

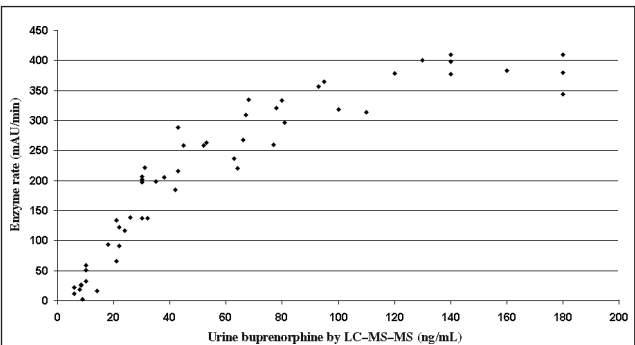


Figure 5. Plot of CEDIA enzyme rate versus buprenorphine concentration for 39 samples in the $n = 96$ sample group over the range 5–180 ng/mL.

sample had creatinine < 5.0 mg/dL). Four adulterated samples had buprenorphine concentrations in the 10,000–50,000 range. These ratios and absolute concentrations are very abnormal compared to other studies. In Kronstrand and co-workers' Subutex report (5), no ratios less than 0.99 or concentrations above 1080 ng/mL were found. The lowest ratio reported by Böttcher and Beck (10) in 72 patients (300 samples) prescribed Subutex was 0.31, and the highest concentration was only 2936 ng/mL. The extremely high naloxone concentrations found here in five of the seven adulterated samples indicate that a common method of adulteration is to attempt to dissolve a Suboxone tablet directly into a urine sample, and submit the resulting solution as a legitimate urine specimen. Such an adulteration method explains many of the findings seen here (i.e., extremely high buprenorphine and naloxone concentrations in a sample with an extremely low metabolite/parent drug ratio). Although samples from patients G and H in Table II also have reasonably high buprenorphine concentrations, their typical metabolite/parent drug ratios and lack of naloxone suggest they are authentic, unadulterated samples.

The CEDIA buprenorphine assay can be calibrated so as to produce "positive" results when urine buprenorphine concentrations exceed 5, 20, or 50 ng/mL. Which cutoff calibrator is used has important ramifications regarding the clinical use of the assay, as 30.2% of all samples in this study had buprenorphine concentrations between 5.0 and 50 ng/mL. Except where noted, we used a 5 ng/mL cutoff calibrator for this study. Analytically, we continue to use the 5 ng/mL cutoff in patients prescribed Suboxone, as it provides a stable signal distinct from a blank or negative urine. Clinically, the few false positives at 5 ng/mL in patients prescribed Suboxone are much preferred by this institution's clinicians compared to the many false negatives that would result using a 20 ng/mL cutoff calibrator. Reasons for avoiding false negatives include a physician's distinct distaste for incorrectly accusing a patient of diverting medicines and/or non-compliance. The performance of the CEDIA assay in urine samples from patients not prescribed Suboxone is under investigation in this laboratory.

The CEDIA assay has many advantages over LC–MS–MS, including lower reagent, labor, and instrumentation costs and the potential for much quicker availability of results. A disadvantage of switching from a chromatography-based technique like LC–MS–MS to an immunoassay is frequent loss of the ability to separately detect and/or quantitate both parent drug and metabolite(s). This disadvantage eliminates the detection of adulterated specimens such as the eight with abnormal metabolite/parent drug ratios found here. The importance of this disadvantage cannot be evaluated without a better understanding of the nature and prevalence of the adulteration method(s) encountered here. In the $n = 96$ patient group studied here, simple creatinine measurements identified approximately 3 times as many "suspect" (possibly adulterated and/or diluted) urine samples as did complex,

expensive, quantitative buprenorphine, norbuprenorphine, and naloxone measurements. In total, 17 of 45 patients (38%) submitted at least one suspicious urine sample in this study. Thirteen had urinary creatinine < 20 mg/dL, and four had a norbuprenorphine/buprenorphine ratio < 0.02. Two of these 17 patients had both a ratio < 0.02 and creatinine < 20 mg/dL in at least one sample.

Buprenorphine metabolism primarily involves dealkylation and glucuronidation (16,17). Dealkylation yields norbuprenorphine. Both the parent drug and metabolite are also glucuronidated. The four predominant species in urine are usually buprenorphine, buprenorphine-glucuronide, norbuprenorphine, and norbuprenorphine-glucuronide. The glucuronides predominate in urine (16). Vincent et al. (6) discussed the advantages of detecting/quantitating both buprenorphine and norbuprenorphine individually in urine samples, versus only buprenorphine. The CEDIA buprenorphine assay cross-reactivity profile in the kit's package insert indicates that both buprenorphine and buprenorphine-glucuronide are detected with nearly equal sensitivity. We think this equivalence is advantageous, as buprenorphine is excreted primarily as the glucuronide conjugate, so no glucuronide-hydrolysis step should be needed to sensitively detect total (free plus glucuronidated) buprenorphine using the CEDIA assay. The insert also indicates the assay is very insensitive to norbuprenorphine and norbuprenorphine-glucuronide (1000 ng/mL of either will still yield a negative result, corresponding to < 0.015% cross-reactivity). In this study, 33 samples had undetectable buprenorphine concentrations (< 5.0 ng/mL), yet 6 (18.2%) of these had norbuprenorphine concentrations detectable by LC–MS–MS. Only two of the six samples were available for additional testing. The CEDIA assay of these two samples yielded negative results in both cases, as predicted by the combination of the package insert claims and LC–MS–MS results. These two samples raise the question of what analytical findings should the clinician consider to be urinary evidence of patient non-compliance with their daily Suboxone regimen: lack of parent drug or lack of both parent drug and metabolite?

Table II. Characteristics of Seven Urine Samples Judged to be Adulterated (Patients A–F) Compared to Samples Judged to be Authentic Samples (Patients G–H)

Patient	Creatinine (mg/dL)	Buprenorphine (ng/mL)	Norbuprenorphine (ng/mL)	Ratio*	Naloxone (ng/mL)
A	101.8	220	< 5.0	†	< 100
B	54.6	610	6.7	0.011	113
C	13.5	1400	19	0.014	624
D	< 5.0	10,000	Present‡	†	4103
E	51.6	13,000	230	0.018	4260
E	56.0	29,000	270	0.009	11,636
F	37.4	49,000	250	0.005	15,155
G	292.4	990	1200	1.212	< 100
H	308.8	1200	1000	0.833	< 100

* Ratio = urine norbuprenorphine/buprenorphine.

† Cannot be calculated.

‡ Norbuprenorphine was detected but could not be quantitated.

One of these two samples is listed in Table II (patient D) and was adulterated. The other samples's urine creatinine was 37.6 mg/dL, but that patient's other four samples in this study all had urine creatinine concentrations < 15 mg/dL. Thus in the two cases with only norbuprenorphine and available sample, both had strong evidence of adulteration and/or dilution. In the larger sample group, 6 of 216 samples had no parent drug and only metabolites present. Should such metabolite-only samples classify the patient as "compliant" with their daily buprenorphine treatment regimen? If we assume that such metabolite-only samples reflect a patient's having taken buprenorphine as prescribed, two of these six would then be erroneously considered to be "compliant". We therefore felt that without the presence of parent drug, we should not rely on metabolite presence to indicate compliance. We felt metabolite detection was not valuable as a tool to evaluate compliance when the parent drug was not detectable (< 5.0 ng/mL). The CEDIA assay's selectivity for buprenorphine over norbuprenorphine should be a significant advantage in monitoring Suboxone therapy, as the metabolite has a longer terminal elimination half-life than the parent drug (18). A positive result using the CEDIA assay should therefore provide stronger evidence for recent or daily drug use (i.e., compliance) than an immunoassay that detects a combination of both parent drug and metabolite. Further work characterizing individual differences in buprenorphine metabolism may be useful in this regard.

Conclusions

Our findings indicate the need for close, compliance-oriented monitoring of patients treated with Suboxone, a drug with significant street-market diversion potential. We recommend that all urine samples submitted for buprenorphine testing automatically have a creatinine test. We also emphasize the significance of the norbuprenorphine-buprenorphine ratio of < 0.02 in detecting adulterated urine specimens, as in samples judged to be authentic, the ratio was higher. The vast majority of samples contained metabolite in excess of the parent drug. The absence of metabolite, or its presence in low relative concentrations may prove to be a useful clinical indicator of specimen adulteration.

We found the CEDIA buprenorphine assay to be analytically accurate when compared to LC-MS-MS. Other advantages of CEDIA versus LC-MS-MS include expense per test and test turnaround time. The major clinical drawback to replacing LC-MS-MS with CEDIA that we experienced was that we lost much capability to detect specimen adulteration using Suboxone pills. We are currently investigating the prevalence of this particular type of adulteration, and cost-effective ways to detect it. We also see the need to better understand patient behavior regarding oral fluid, urine, and blood buprenorphine testing. We also suggest testing the hypothesis that consistent reporting of toxicology results to patients will alter patient behavior and reduce the rates of repeated adulteration. Such feedback may enhance clinical outcomes related to the complex medical problem of opiate addiction.

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