ORIGINAL ARTICLE

Use of an algorithm applied to urine drug screening to assess adherence to an OxyContin® regimen

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ABSTRACT

Objective: *This study examined the ability of an algorithm applied to urine drug levels of oxycodone in healthy adult volunteers to differentiate among low, medium, and high doses of OxyContin®.*

Participants and interventions: *Thirty-six healthy volunteers were randomized to receive 80, 160, or 240 mg of daily OxyContin® to steady state while under a naltrexone blockade. During days 3 and 4 of the study, urine samples of all participants were collected, and oxycodone levels detected in the urine were obtained using a liquid chromatography-mass spectrometry (LC-MS-MS) assay.*

Outcome measures: *The concordance was calculated for raw and adjusted LC-MS-MS urine oxycodone values within each study participant between their third and fourth day values. Also, an analysis of medians was calculated for each of the dosage groupings using Bonett-Price confidence intervals for both raw and adjusted LC-MS-MS values.*

Results: *The concordance correlation coefficient for the raw LC-MS-MS values between days 3 and 4 was 0.689 (95% confidence intervals = 0.515, 0.864), whereas the concordance correlation coefficient for the LC-MS-MS values using the algorithm (ie, normalized values) was 0.882 (95% confidence intervals = 0.808, 0.956). Because of greater variability in the raw values, some overlap was observed in the confidence intervals of the various OxyContin® doses, whereas no overlap was observed in the normalized confidence intervals regardless of the application of a Bonferroni adjustment.*

Conclusions: *In contrast to raw LC-MS-MS values, an algorithm that normalizes oxycodone urine drug levels for pH, specific gravity, and lean body mass discriminates well among all three of the daily doses of OxyContin® tested (80, 160, and 240 mg), even with correcting for multiple analyses.*

Key words: urine drug testing, medication adherence, OxyContin®, oxycodone, algorithm

INTRODUCTION

Although hydrocodone stands as the most prescribed opioid in the United States, the opioid that is responsible for the most emergency department (ED) visits in the United States is oxycodone. According to the Drug Abuse Warning Network, approximately 77,000 ED visits in 2007 were due to the nonmedical use of oxycodone, ie, 16 percent more than ED visits due to hydrocodone.[1] The *2007 National Survey on Drug Use and Health* estimates that 4.3 million Americans will abuse OxyContin® sometime during the course of their lifetime.[2] Given the propensity for abuse of oxycodone containing medications and the high incidence of ED visits associated with abuse, monitoring patients for compliance while being prescribed a pain regimen is an important component of their care.

Previous studies have demonstrated the use of urine drug test (UDT) results, when coupled with a compensatory algorithm, in approximating plasma methadone concentrations.[3,4] This study examines the aforementioned oxycodone algorithm and its ability to differentiate among low, medium, and high doses of OxyContin® using the highly sensitive liquid chromatography-mass spectrometry (LC-MS-MS) assay.

METHODS

Study design

This study was a single-group, multiple-dose study of clinically relevant doses of OxyContin® in healthy adult volunteers. Subjects (Table 1) were nonsmoking, 18-50 years of age, with body mass index between 18 and 32 kg/m^2. Women were required to have a negative urine pregnancy test before the study initiation as well as to use a medically accepted method of contraception throughout the duration of the study. All participants were screened for phenotypic variation of the CYP2D6 enzymes using a commercially available screening test (PGXL Laboratories, Louisville, KY), and ultrarapid, rapid, and poor metabolizers were excluded from the study. Other exclusions included individuals with histories of substance abuse, significant disease, recent illness, or abnormal findings on physical examination, electrocardiogram, laboratory studies, or drug screens. Additionally, those with recent histories of prescription, over the counter, and herbal drug use were excluded. The subjects with allergies or hypersensitivities to naltrexone, oxycodone, other opioids, or similar compounds were ineligible to participate. These subjects were forbidden to use alcohol, ingest grapefruit, grapefruit juice, caffeine, or xanthene-containing products 48 hours before dosing and during the dosing periods. The participants in recent drug studies or the aforementioned hydrocodone study were not included.

Thirty-six healthy volunteers (15 females and 21 males) each received naltrexone blockade throughout the study (50 mg daily naltrexone dosing was initiated 12 hours before OxyContin® administration and continued through day 4) according to the study protocol. The subjects ranged in age from 18 to 50 years (mean = 23.58) and averaged 68 inches in height and 159 pounds in weight. Thirty-two participants were Caucasian.

Table 1. Characteristics of study participants

Variable	Data	Mean	SD
Number of subjects	36		
Female subjects	15		
White	32		
Age, y	18-50	23.58	3.14
Height, in		68.04	3.59
Weight, lbs		159.21	29.27
Body mass index (BMI), kg/m^2	18-30	24.12	3.46

The subjects were randomized to one of the three dosages of OxyContin®, 80, 160, or 240 mg/d dosed every 12 hours through day 4. On day 2, two presteady-state urine samples were collected every 12 hours. The half-life of OxyContin® is 4.5 hours, and most patients will reach steady state after 4-5 half lives of a drug, leaving most patients taking OxyContin® at steady state before day 3. Previous pharmacokinetic studies have confirmed that upon repeated dosing of OxyContin®, patients achieve steady-state levels within 24-36 hours.[5] Beginning on day 3 at midnight, urine samples of all subjects were collected through 23:59 on day 4, while subjects were at steady state. During this study, a total of 373 urine samples were collected while the subjects were in steady state for each dose of OxyContin®. In addition, pK blood and oral fluid samples were collected three times on days 3 and 4. Laboratory, medication, physical examination, and adverse event findings were collected in the event of early termination or at the follow-up visit.

Analytical approach

This study assessed how well the algorithm that adjusted raw urine drug levels for urine pH, urine specific gravity, and lean body mass discriminated among the three clinically relevant doses of OxyContin® (80, 160, and 240 mg/d) when compared with raw values of the oxycodone LC-MS-MS substrate. All LC-MS-MS values reported in this study are the aggregated total of the noroxycodone, oxymorphone, and oxycodone levels detected in the urine.

First, the concordance was tested[6,7] between each pair of raw and adjusted LC-MS-MS values for each study participant between their third and fourth day values. The rationale for this was twofold: (1) to confirm that participants achieved steady state at the given drug dose at days 3 or 4, and (2) to assess which of the two methods (raw or adjusted LC-MS-MS) achieved better concordance. In the case of the former, whether a patient achieves steady state is of clinical importance because during the accumulation phase, interpatient variability in elimination and accumulation can have exaggerated effects on

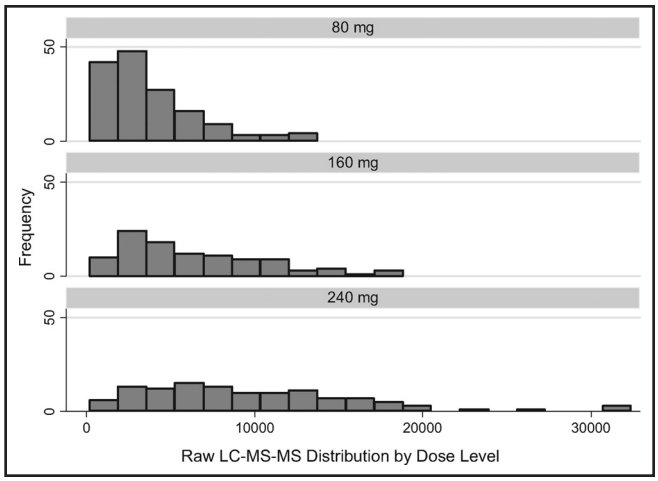

Figure 1. Distribution of raw LC-MS-MS values (in ng/mL) by dose.

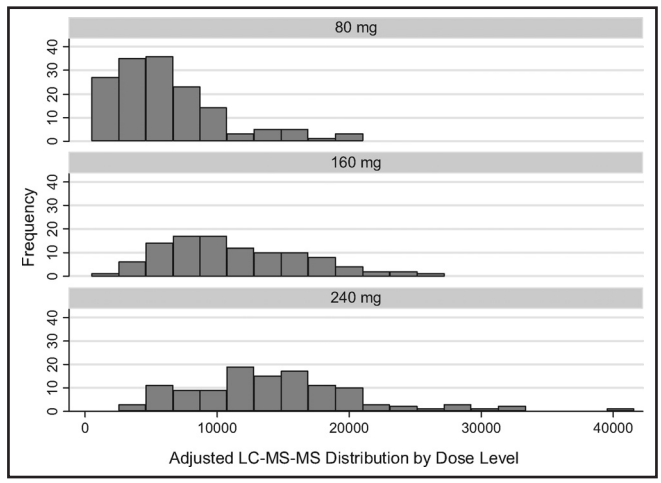

Figure 2. Distribution of adjusted LC-MS-MS values (in ng/mL) by dose.

observed serum and urine levels. In the case of the latter, it can be hypothesized that the method which achieves better concordance is also likely to show better discrimination between doses, as a direct result of lowered variability within each dose.

Second, an analysis of medians was conducted for each of the dosage groupings using Bonett-Price confidence intervals[8-10] for both raw and adjusted LC-MS-MS values. In this study, an analysis of medians is a more appropriate choice than an analysis of means, given that (a) the distribution of values in this relatively small sample appears skewed at each dose level (Figures 1 and 2), (b) no information as to the true population distribution of LC-MS-MS values is available, and (c) the analysis of medians is robust to almost any type of non-normality that would likely be encountered in practice. The Bonett-Price confidence interval method was chosen in particular because of its superior performance in simulation experiments of small samples.[8] To establish even more conservative estimates, a Bonferroni adjustment was applied to the confidence intervals.

All statistical analyses were conducted using Stata (version 10.1) software (Stata Corp., College Station, Texas). Concordance was estimated using "concord," a user-written program for Stata by Steichen and Cox.[11,12] Pairplots (Figures 3 and 4) were created using "pairplot," a user-written program for Stata by Cox.[13] The Bonett-Price confidence intervals were estimated using "BPMEDIAN," a user-written program for Stata by Newson.[14]

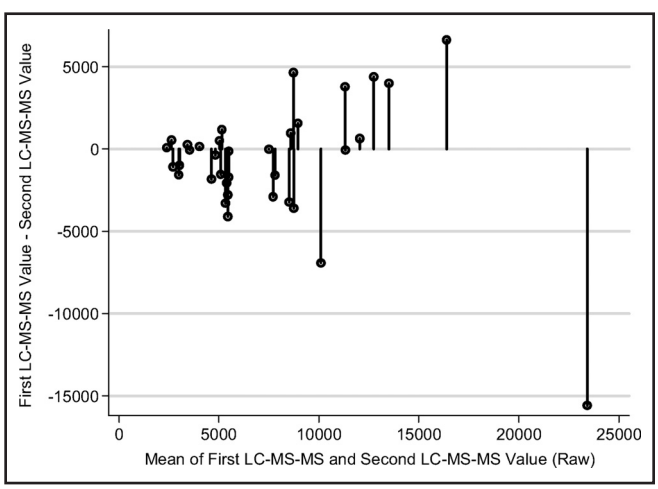

Figure 3. A plot of difference versus mean for first and second raw LC-MS-MS levels (in ng/mL).

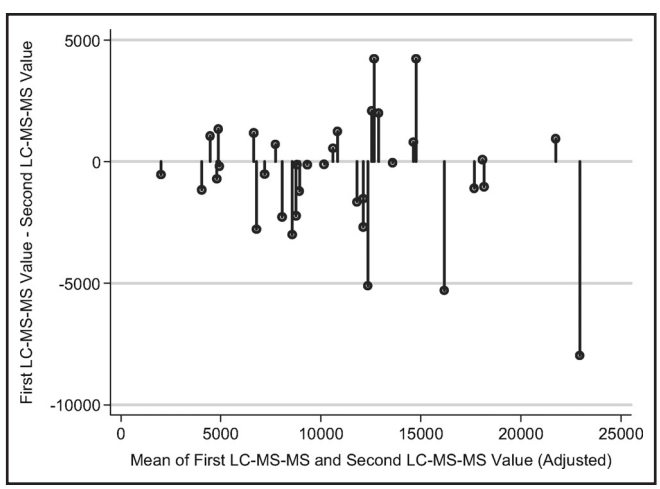

Figure 4. A plot of difference versus mean for first and second adjusted LC-MS-MS levels (in ng/mL).

Table 2. Number of LC-MS-MS tests administered on days 3 and 4 by daily dosage.

Dose per day, mg	N	Number of LC-MS-MS tests		Total
		Day 3	Day 4	
80	12	84	68	152
160	12	55	49	104
240	12	63	54	117
Total	36	202	171	373

RESULTS

The characteristics of the 36 participants are presented in Table 1. The participants were mostly white (89 percent), young (mean = 23.6 years), and generally at the upper range of normal weight (mean BMI = 24.12). There were slightly more males than females (58 percent male vs 42 percent female).

Table 2 shows the number of LC-MS-MS lab tests administered on days 3 and 4 by respective dose. In general, more tests were administered on day 3 than day 4, with 152, 104, and 117 total lab tests administered (for 80, 160, and 240 mg/d, respectively).

The concordance correlation coefficient[7] for the raw LC-MS-MS values between days 3 and 4 was 0.689 (95% confidence intervals = 0.515, 0.864), whereas the concordance correlation coefficient for the LC-MS-MS values using the algorithm (ie, normalized values) was higher at 0.882 (95% confidence intervals = 0.808, 0.956). The reason for the higher level of concordance in the normalized versus the raw LC-MS-MS values can be observed in Figures 3 and 4. Figure 3 shows that the difference between days 3 and 4 values of many pairs approaches or exceeds 5,000 points with one extreme spike exceeding 15,000 points (the negative scale value indicates that the day 4 value was higher than the day 3 value). Conversely, Figure 4 illustrates a more uniform distribution of concordance between days 3 and 4 measurements of normalized LC-MS-MS levels, with fewer spikes exceeding 5,000 points and that one outlier is now reduced to approximately 8,000 points (as opposed to 15,000 points on the raw index scale).

Figures 1 and 2 illustrate the distributions of raw and normalized LC-MS-MS values, respectively, by the daily doses under study. Upon visual inspection, it is clear that none of the doses under either method represent normal distributions. Moreover, there is no consistency in the general form among the distributions. The estimators of shape parameters are not reported, such as skewness and kurtosis coefficients, because they generally exhibit large sampling variability in small samples and are biased (toward normality) in non-normal distributions.[8] These concerns led to the choice of a median analysis using Bonett-Price confidence intervals.

Table 3. Median estimates and Bonett-Price 95% confidence intervals for raw and adjusted LC-MS-MS values by dose (with and without Bonferroni adjustment).

Dose per day, mg	Median	LCI	UCI	Bonferroni adjusted	
				LCI	UCI
Raw LC-MS-MS, ng/mL					
80	3,172	2,730	3,613	2,632	3,711
160	5,245	4,311	6,178	4,105	6,384
240	8,249	6,647	9,851	6,292	10,206
Adjusted LC-MS-MS, ng/mL					
80	5,471	4,796	6,147	4,646	6,296
160	10,385	9,004	11,765	8,699	12,071
240	13,894	12,426	15,361	12,101	15,686

LCI, lower confidence interval;
UCI, upper confidence interval.

Table 3 presents the median estimates and Bonett-Price 95% confidence intervals for raw and normalized LC-MS-MS values by dose, both with and without Bonferroni adjustment. As shown, the confidence intervals for the raw LC-MS-MS levels do not overlap among any of the three doses (80, 160, and 240 mg/d), but in applying the more conservative Bonferroni adjustment, discrimination between the 160 and 240 mg/d doses disappears. Conversely, the confidence intervals for the normalized LC-MS-MS levels do not overlap among any dose level, Bonferroni adjusted or not. The reason that confidence intervals around 160 and 240 mg/d overlap using the raw values and not the normalized values is due to the greater variability in the raw values. For example, the range for 95% confidence intervals of the raw 240 mg/d dose is 3913.03, whereas the range for the normalized 240 mg/d dose is 3584.35 (this is in light of the fact that the median of the adjusted LC-MS-MS for the 240 mg/d dose was 5644.64 points higher than the raw LC-MS-MS median at the 240 mg dose).

In summary, the normalized LC-MS-MS method using the algorithm shows excellent discrimination among 80, 160, and 240 mg/d doses of OxyContin® even when conservative adjustments are applied to account for multiple comparisons.

DISCUSSION

This study using OxyContin® utilizes a proprietary algorithm previously studied in an addiction setting in a more structured environment using healthy volunteers. The results of this study suggest that, in contrast to raw LC-MS-MS values, an algorithm that normalizes oxycodone urine drug levels for pH, specific gravity, and lean body mass, using LC-MS-MS urine drug assays, discriminates well among all three of the daily doses of OxyContin® tested (80, 160, and 240 mg). These findings persisted even when conservative confidence intervals were applied to address the use of multiple group comparisons. These results may have important clinical implications in the monitoring of pain management in patients through the use of normalized UDT results to inform clinical assessment of patient adherence with a prescribed opioid regimen.

While this algorithm cannot currently be used to determine or predict the dose of a drug a given patient is taking, application of the algorithm can provide additional information that, when combined with observations of aberrant behavior, structured risk assessments (eg, ORT, COMM), pill counts, and medical chart reviews, should help clinicians assess the possibility of drug misuse or nonadherence. For example, a patient on a stable 40 mg q12h regimen of OxyContin® to control their chronic pain, who has a history of aberrant behaviors and has a normalized opioid UDT level for oxycodone that is lower than the lower bound of a 95% confidence limit (ie, range) that is constructed from a large sample of compliant patients, has a higher likelihood of being nonadherent (eg, binging and then running out of medications, or diverting their drugs) than similar patients with a normalized oxycodone level within the expected range.

The limitations of the study must be considered when interpreting the results. This study enrolled healthy volunteers who had not taken any medication 30 days prior to start. However, some patients encountered in the clinical setting use one or more medications that inhibit the CYP2D6 enzymes, which could affect the metabolism of oxycodone and thus levels detected in the urine.[15] Participants were excluded from this investigation if they were determined to be a poor, rapid, or ultrarapid CYP2D6 metabolizer. Approximately 7 percent of White Americans and 2-4 percent of Black Americans have CYP2D6 drug metabolism phenotypes that classify these individuals as poor metabolizers. It has been estimated that another 2-7 percent of Caucasians are rapid or ultrarapid metabolizers of CYP2D6.[16,17] Thus, although this study included the majority of CYP2D6 phenotypes that were present at the clinics of the United States, a small but significant number of phenotypes were excluded. However, genetic tests are commercially available to identify individuals with atypical phenotypes, whose resulting urine levels of drug metabolites may be chronically low or high based on their particular polymorphism.

In addition, because all subjects in this study were consistently taking OxyContin®, further work in a larger trial is required to define the sensitivity and specificity of the algorithm with respect to patient adherence. Finally, this study examined the oxycodone algorithm specific only to OxyContin® (controlled release oxycodone) and did not look at participants dosed with immediate-release oxycodone.

The results of this study demonstrate the superior ability of this algorithm to produce adjusted urine drug levels that correlate more closely with dose than do unadjusted urine drug levels. When used with other clinical data, this methodology should provide insights about medication adherence that go beyond whether a patient is merely taking any of their prescribed opioid(s). Further research to define the operating characteristics of the algorithm in a larger study will be helpful and will enhance the use of this innovative approach to monitor patient adherence.

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ACKNOWLEDGMENTS

Dr. Couto discloses no current or foreseeable conflicts of interest other than his employment. Dr. Webster is the Director of Lifetree Clinical Research and Lifetree Pain Clinical. Dr. Webster is a member of the Ameritox Scientific Advisory Board. The Lifetree Clinical Research received funding from Ameritox, Ltd., to conduct this study. Ms Romney discloses no current or foreseeable conflicts of interest other than her employment. Dr. Leider is the Chief Medical Officer and an employee of Ameritox, Ltd. Funding for this study has been provided to Lifetree Clinical Research and Lifetree Pain Clinical by Ameritox, Ltd. Funding for this study has been provided to the Jefferson School of Population Health by Ameritox, Ltd. Dr. Leider discloses no current or foreseeable conflicts of interest other than his employment. Dr. Linden received funding from Ameritox, Ltd., for performing data analysis services.

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