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Interpreting quantitative urine buprenorphine and norbuprenorphine levels in office-based clinical practice

Joseph H. Donroe[a,*], Stephen R. Holt[b], Patrick G. O'Connor[c], Nitin Sukumar[d], Jeanette M. Tetrault[e]

[a] Yale University School of Medicine, Department of Internal Medicine,1450 Chapel Street, Office M330, New Haven, CT 06511, USA
[b] Yale University School of Medicine, Department of Internal Medicine, 1450 Chapel Street, Office P312, New Haven, CT 06511, USA
[c] Yale University School of Medicine, Department of General Internal Medicine, 367 Cedar Street, Suite 402, New Haven, CT 06510, USA
[d] Yale University School of Public Health, Yale Center for Analytical Sciences, 300 George Street, Suite 511, New Haven, CT 06510, USA
[e] Yale University School of Medicine, Department of Internal Medicine, 367 Cedar Street, Suite 305, New Haven, CT 06510, USA

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ABSTRACT

Background: Quantitative urine buprenorphine testing is used to monitor patients receiving buprenorphine for the treatment of opioid use disorder (OUD), however the interpretation of urine buprenorphine testing is complex. Currently, interpretation of quantitative buprenorphine testing is guided by data from drug assay development studies and forensic labs rather than clinical treatment cohorts.

Methods: In this retrospective study, we describe the patterns of urine buprenorphine and norbuprenorphine levels in patients prescribed sublingual buprenorphine for OUD in an office-based addiction treatment clinic. Urine buprenorphine and norbuprenorphine levels were analyzed in patients who reported having adulterated their urine, patients clinically suspected of adulterating their urine, and patients without concern for urine adulteration. Finally, we tested the accuracy of urine buprenorphine, norbuprenorphine, and norbuprenorphine: buprenorphine ratio (Norbup:Bup) to identify adulterated urine samples.

Results: Patients without suspicion for urine adulteration rarely provided specimens with buprenorphine > = 1000 ng/ml (4.4%), while the proportion provided by those who endorsed or were suspected of urine adulteration was higher (42.9%, 40.6%, respectively). Compared to patients without reported urine adulteration, specimens from patients who reported or were suspected of urine adulteration had significantly higher buprenorphine ($p = 0.0001$) and lower norbuprenorphine (< 0.0001) levels, and significantly lower Norbup:Bup ratios ($p = 0.04$). Buprenorphine > = 700 ng/ml offered the best accuracy for discriminating between adulterated and non-adulterated specimens.

Conclusion: This study describes the patterns of urine buprenorphine and norbuprenorphine levels from patients with OUD receiving buprenorphine treatment in an office-based addiction treatment clinic. Parameters for identifying urine adulterated by submerging buprenorphine medication in the urine specimen are discussed.

1. Introduction

Buprenorphine is an opioid agonist medication used for the treatment of opioid use disorder (OUD). One advantage buprenorphine has over methadone is that it can be prescribed in office-based treatment programs, allowing physicians who complete an 8-h and nurse practitioners and physician assistants who complete a 24-h training course to deliver care to patients with OUD in a wider array of clinical settings (i.e., primary care offices, HIV clinical settings, emergency departments, etcetera) (D'Onofrio et al., 2015; Fiellin et al., 2006; Tetrault et al., 2012). Urine toxicology screening is a recommended component of addiction treatment monitoring, and can aid in detection of continued illicit substance use and medication diversion (Lofwall and Walsh, 2014). The interpretation of urine toxicology testing can be complex, however. Failure to correctly interpret the results may lead to missed opportunities to engage with patients who continue to use illicit substances, failure to identify medication misuse and medication diversion, and to unjustified actions towards patients based on inaccurate conclusions. Accurate interpretation of urine toxicology testing requires knowledge of drug metabolism and factors that influence it, including

* Corresponding author.
E-mail addresses: joseph.donroe@yale.edu (J.H. Donroe), stephen.holt@yale.edu (S.R. Holt), patrick.oconnor@yale.edu (P.G. O'Connor), nitin.sukumar@yale.edu (N. Sukumar), jeanette.tetrault@yale.edu (J.M. Tetrault).

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co-prescribed medications and genetic variability, as well as the limitations of the assays themselves.

Buprenorphine is a semisynthetic opioid derived from thebaine, with partial agonist activity at the opioid mu receptor, and antagonist activity at the opioid kappa receptor. In the treatment of OUD, it can be administered in a sublingual, buccal, or the recently approved subcutaneous implant formulation. It is metabolized by a combination of N-dealkylation, primarily via liver cytochrome p450 (CYP) 3A4 enzyme, and glucuronidation (Cone et al., 1984; Ohtani, 2007). Its metabolites are buprenorphine-3-glucuronide (B-3-G), norbuprenorphine, and norbuprenorphine-3-glucuronide (NB-3-G) (Ohtani, 2007). The majority of metabolite excretion is via the feces, while the minority is excreted by the kidney, primarily as metabolites rather than parent compound (Cone et al., 1984; Ohtani, 2007). Buprenorphine metabolism, and ultimately metabolites detectable in the urine, can be influenced by inhibitors or inducers of CYP3A4, including a host of medications, food products, and certain conditions, such as pregnancy (Harris et al., 2003; Kacinko et al., 2009). Genetic polymorphisms of CYP3A4 can also influence metabolism and metabolite detection (Lamba et al., 2012).

Buprenorphine urine testing can be performed using immunoassay (IA), gas chromatography-mass spectrometry (GC–MS), and liquid chromatography-tandem mass spectrometry (LC–MS/MS) assays. GC–MS and LC–MS/MS can quantify the concentration of buprenorphine and its metabolites in the urine and generally have better sensitivity and specificity than IA at the expense of time and cost. Currently, interpretation of urine buprenorphine and norbuprenorphine levels in clinical practice is guided by information obtained from urine drug assay development studies, the majority of which tested for total buprenorphine (free buprenorphine + B-3-G) and total norbuprenorphine (free norbuprenorphine + NB-3-G) levels (Bottcher and Beck, 2005; George et al., 2004; Heikman et al., 2014; Hull et al., 2008; Kacinko et al., 2009; Kronstrand et al., 2008; Kronstrand et al., 2003; McCance-Katz et al., 2006; McMillin et al., 2012; Tzatzarakis et al., 2015; Vincent et al., 1999).

From these studies, several clinically relevant observations have been made. First, most studies have noted that buprenorphine dose and urine total buprenorphine and norbuprenorphine levels do not correlate well and thus urine drug levels alone should not be used as evidence of medication adherence (Bottcher and Beck, 2005; Heikman et al., 2014; Kacinko et al., 2009; Kronstrand et al., 2008; Tzatzarakis et al., 2015). Notably, one study found wide variability in levels of urine buprenorphine and norbuprenorphine between patients receiving the same dose of medication (Kronstrand et al., 2008). The one study reporting a significant positive correlation between buprenorphine dose and urine buprenorphine level only included 11 subjects receiving a tapering course of buprenorphine for acute opioid detoxification, and thus is unlikely to be generalizable to patients receiving maintenance therapy for OUD (George et al., 2004).

Second, the timing of urine testing in relation to last administered dose of buprenorphine may influence urine drug levels. Kronstadt et al. tested 170 specimens from 18 subjects after a single 0.4 mg sublingual buprenorphine dose, and found that the Norbup:Bup ratio became greater than 1.0 approximately 7 h after dose administration, with a ratio < 0.5 indicating very recent use (Kronstrand et al., 2008). Likewise, McCance-Katz et al. demonstrated that in patients maintained on a stable dose of buprenorphine, the rate of plasma rise and fall is steeper for buprenorphine than norbuprenorphine, suggesting that the ratio between the two will depend on the time of administration (McCance-Katz et al., 2006).

Third, for nearly all studies, in the majority of urine specimens tested, total norbuprenorphine level was greater than total buprenorphine (Bottcher and Beck, 2005; George et al., 2004; Heikman et al., 2014; Hull et al., 2008; Kacinko et al., 2009; Kronstrand et al., 2003; McMillin et al., 2012; Tzatzarakis et al., 2015). In a toxicology lab-based study reviewing urine specimens from patients receiving buprenorphine treatment, Hull et al. identified 8 of 174 specimens with a Norbup:Bup ratio less than 0.02, and suggested this as a cutoff indicating urine adulteration by submerging the medication directly in the urine specimen (Hull et al., 2008).

The aim of this paper is to report on quantitative urine buprenorphine and norbuprenorphine levels in patients actively engaged in addiction treatment who are prescribed sublingual buprenorphine for OUD. We aim to highlight differences in urine buprenorphine and norbuprenorphine levels between patients who have reported adulterating their urine and those who have not, and to report on the accuracy of different parameters for discriminating between specimens adulterated by submerging buprenorphine medication directly in the urine and non-adulterated urine specimens.

2. Materials and methods

2.1. Study design and population

This is a retrospective study in which the charts of patients attending an internal medicine residency −based addiction treatment clinic between January 2015 and January 2016 were reviewed (Holt et al., 2017). Chart review was performed by the principal investigator (JD). Demographic data, as well as information regarding clinic attendance, buprenorphine dose, urine buprenorphine and norbuprenorphine levels, patient endorsement of urine adulteration, and physician concerns for potential urine adulteration were recorded. Three groups of patients were identified for description and analysis. Patients in Group 1 (Reference Group) did not self-report and had no physician documented concerns for urine adulteration. Patients in Group 2 (Confirmed Group) admitted after being questioned by providers to having adulterated the urine specimen in question by submerging their medication directly into the urine immediately after the urine was provided in clinic. Patients from this group did not specify if previous specimens had also been adulterated. Two patients endorsed urine adulteration after January 2016 and those samples were also included in the analysis. Patients in Group 3 (Suspected Group) had physician documented concern for urine tampering, however this suspicion was not corroborated by the patient. When documented, the rationale for physician suspicion included unusually high or low urine buprenorphine levels and concerning patient behaviors.

Patterns of urine buprenorphine, norbuprenorphine, and Norbup:Bup were evaluated in the three groups. To identify differences in urine buprenorphine and norbuprenorphine levels between groups, urine specimens from patients in the Reference Group and patients in the Confirmed Group were compared. The Reference Group was also compared to the Confirmed/Suspected Groups combined. Finally, using specimens from the Confirmed Group, we tested the accuracy of urine total buprenorphine and total norbuprenorphine levels and the ratio of Norbup:Bup to identify adulterated urine samples.

2.2. Definitions

For the purposes of the study, the following definitions apply:

2.2.1. Urine adulteration

This specifically refers to the act of submerging sublingual buprenorphine medication (tablets or film) into the urine specimen during the process of urine collection and submission for analysis by the patient.

2.2.2. Urine buprenorphine

Refers to total urine buprenorphine (free buprenorphine + B-3-G).

2.2.3. Urine norbuprenorphine

Refers to total urine norbuprenorphine (free norbuprenorphine + NB-3-G).