Urine is superior to oral fluid for detecting buprenorphine compliance in patients undergoing treatment for opioid addiction

Jaime R. Ransohoff[a,b], Athena K. Petrides[a,c], Greg J. Piscitello[a], James G. Flood[c,d], Stacy E.F. Melanson[a,c,*]

[a] Department of Pathology, Brigham and Women's Hospital, 75 Francis St., Boston, MA, 02115, USA
[b] Department of Medicine, Brigham and Women's Hospital, 75 Francis St., Boston, MA, 02115, USA
[c] Harvard Medical School, 25 Shattuck St., Boston, MA, 02115, USA
[d] Department of Pathology, Massachusetts General Hospital, 55 Fruit St., Boston, MA, 02114, USA

ARTICLE INFO

ABSTRACT

Background: Buprenorphine (BUP) is commonly used in opioid agonist medication-assisted treatment (OA-MAT). Oral fluid (OF) is an attractive option for compliance monitoring during OA-MAT as collections are observed and evidence suggests that OF is less likely to be adulterated than urine (UR). However, the clinical and analytical performance of each matrix for monitoring BUP compliance has not been well studied.
Methods: We collected 260 paired OF and UR specimens. Concentrations of buprenorphine (BUP) and norbuprenorphine (NBUP) were measured by liquid chromatography-tandem mass spectrometry (LC–MS/MS) in each matrix. The glucuronide metabolites and naloxone concentrations were also measured in UR by LC–MS/MS. Medications were reviewed and UR creatinine concentrations were determined.
Results: 147/260 specimens (57%) were positive for BUP and/or metabolites in one or both matrices. BUP and/or metabolites were more likely to be detected in UR (p < 0.001). 1 OF specimen and 12 UR specimens were considered adulterated/substituted. The majority of patients prescribed BUP were positive for BUP in UR (97%) as opposed to OF (78%). The detection of undisclosed use approximately doubled in UR.
Conclusions: UR is the preferred matrix for detecting both buprenorphine compliance and undisclosed use. Clinicians should consider the ease of collection, risk of adulteration and detection of illicit drug use when deciding on an appropriate matrix. If OF testing is clinically necessary, UR should be measured in conjunction with OF at least periodically to avoid false negative BUP results.

1. Introduction

Between 2002 and 2017, the number of drug overdose deaths in the United States tripled (Overdose Death Rates, 2019; Seth et al., 2018). Furthermore, overdose deaths involving heroin and general opioids have continuously increased from 2007 to 2017 (Overdose Death Rates, 2019; Seth et al., 2018), and many of these deaths are predicated by prescription painkiller misuse (Opioid Addiction 2016 Facts and Figures, 2016Opioid Addiction, 2016Opioid Addiction 2016 Facts and Figures, 2016). Repeated opioid use fundamentally changes brain neurochemistry through over-activation of mu-opioid and dopamine receptors, resulting in opioid addiction (Kraly, 2014). Opioid addiction, a biopsychosocial chronic relapsing disease, is considered a national epidemic in the United States (DuPont, 2010; Hernandez and Nelson, 2010).

Individualized multidimensional approaches that include detoxification, pharmacotherapy, and group or individual counseling are widely regarded as ideal for the treatment of addiction as they comprehensively address the social, psychological, and neurological symptoms of these disorders (Carroll and Weiss, 2017; Dugosh et al., 2016; Kraly, 2014; Simoneau et al., 2018; Weiss et al., 2011). Medications can be utilized to prevent withdrawal symptoms during detoxification and relapse at any other phase (Rosenthal and Goradia, 2017). Pharmacotherapy for opioid addiction often comprises opioid agonist medication-assisted treatment (OA-MAT) using buprenorphine-naloxone combinations or methadone (Jones et al., 2015). Buprenorphine is readily available and the most popular medication utilized in OA-MAT (Bonhomme et al., 2012; Hansen et al., 2016). Its low efficacy and high affinity for the mu-opioid receptor result in a lower risk of relapse and overdose (Rosenthal and Goradia, 2017). Furthermore, the

Suboxone (Buprenorphine-Naloxone) formulation, administered sublingually, has superior bioavailability and significantly reduces abuse potential (Mendelson et al., 1997; Rosenthal and Goradia, 2017).

Random drug testing by liquid chromatography-tandem mass spectrometry (LC–MS/MS) is an important adjunct to OA-MAT as it can effectively assess medication compliance and enforces patient accountability (Christo et al., 2011; Jannetto et al., 2018; Manchikanti et al., 2008, 2006; Verstraete, 2004). Urine (UR) has been the gold standard matrix for drug testing in a variety of settings including OA-MAT and chronic pain (Christo et al., 2011; Jannetto et al., 2018; Manchikanti et al., 2006; Verstraete, 2004). However, UR is difficult to obtain in patients with shy bladder or anuria (Allen, 2011) and can be diluted, substituted or adulterated (e.g. ingestion of large amounts of fluids, shaving a pill directly into the urine) (McMillin et al., 2012). Recently, oral fluid (OF) has gained popularity as collections are monitored and adulteration is less likely (Allen, 2011; Arvidsson et al., 2018; Vindenes et al., 2011). However, oral contamination and its effects on OF results should be considered (Crouch, 2005).

Several studies have compared the performance of paired OF and UR specimens in patients on OA-MAT (Vindenes et al., 2011; Miller et al., 2017; West et al., 2018; Petrides et al., 2018), but in only one study were the majority of patients prescribed buprenorphine (West et al., 2018). This study suggested that both OF and UR are useful for monitoring OA-MAT with buprenorphine; however, the detection rate was higher in UR and buprenorphine glucuronides were not measured (West et al., 2018). The other studies also acknowledge the benefits and challenges of both matrices for other medications and illicit drugs (Miller et al., 2017; Petrides et al., 2018; Vindenes et al., 2011).

In this study, we compare the analytical and clinical utility of UR and OF in paired specimens in order to make recommendations for the optimal matrix to assess BUP compliance in addiction management.

2. Methods

2.1. Specimen acquisition

A total of 260 paired OF and UR specimens were collected from 140 unique patients at the Massachusetts General Hospital (MGH) addiction-psychiatry clinics during routine visits and processed at the MGH Clinical Chemistry Laboratory (Boston, MA). For OF collection, the Orasure Intercept Sample Collection Device (Orasure Technologies, Bethlehem, PA) was utilized per the manufacturer's collection instructions with added steps to reduce the likelihood of OF contamination (Flood et al., 2016; Olestad et al., 2007; Intercept [package insert], 2017). OF and UR pairs were received by the laboratory within 2–10 h of collection. OF was refrigerated overnight and tested the next day. UR was frozen within 8 h of receipt and tested in batches at a later date. The Partners Human Research Committee approved this study.

2.2. Oral fluid testing

As published previously, OF was analyzed at MGH using a laboratory-developed LC–MS/MS method (Flood et al., 2016; Petrides et al., 2018). The drugs and metabolites detected in OF were buprenorphine (BUP) and norbuprenorphine (NBUP) at a limit of detection (LOD) of 1.4 ng/mL and 1.9 ng/mL, respectively.

OF specimens were mixed with internal standard solution containing deuterated analogues of BUP (d4) and NBUP (d3). The analytes and internal standards were isolated on a Cyclone-P turbulent-flow extraction column (Thermo-Fisher, Franklin, MA) and then transferred to an Ascentis Phenyl analytical column (Supelco, Bellefonte, PA) after injection onto a TLX2 chromatograph (Thermo Scientific, Waltham, MA). The analytes were then separated using a gradient elution program and detected using a Thermo Quantum Ultra triple quadrupole MS (Thermo Scientific, Waltham, MA) equipped with a heated electrospray ionization (HESI-II) operated in the positive ion mode.

2.3. Urine testing

UR was analyzed at the Brigham and Women's Hospital (BWH) Clinical Chemistry Laboratory (Boston, MA) using a laboratory-developed LC–MS/MS method as published previously (Dahlin et al., 2019 *in press*; Petrides et al., 2018). Internal standard solutions contained deuterated analogues of BUP (d4) and NBUP (d3). Chromatographic separation was achieved on an ACQUITY UPLC I-Class (Waters, Milford, MA) using a CORTECS C18 analytical column (Waters, Milford, MA) and mass spectrometric analysis was performed on a tandem triple quadrupole Xevo TQS (Waters, Milford, MA) preceded by HESI. The lower limit of quantitation (LLOQ) for BUP, NBUP, BUP-GLUC and NBUP-GLUC in UR was 5 ng/mL, while the LLOQ for naloxone in UR was 100 ng/mL.

2.4. Creatinine calculations and specimen adulteration

UR creatinine was measured using the rate-blanked Jaffe reaction with Roche Diagnostics reagents on a Roche Cobas e501 (Roche Diagnostics, Indianapolis IN). Quantitative UR drug measurements for BUP, NBUP, BUP-GLUC and NBUP-GLUC were corrected for creatinine levels using the following formula: [Drug in ng/mL]/[UR Creatinine in mg/dL] × 100.

Urines were considered adulterated (i.e., the patient shaved some of the BUP into their UR) if the free NBUP:BUP ratio was ≤ 0.02 (Hull et al., 2008; McMillin et al., 2012) or if naloxone was detected. Urines were considered dilute or substituted if UR creatinine was between 5–19 ng/mL or < 5 ng/mL; respectively (Federal Guidelines for Opioid Treatment Programs, 2015). OF was considered adulterated if the BUP concentration was > 15,000 ng/mL (Cone et al., 2007).

2.5. Data analysis, medication review and illicit drug use

In UR, buprenorphine was considered positive if any of the following were detected: BUP, NBUP, BUP-GLUC, and/or NBUP-GLUC. In OF, buprenorphine was considered positive if either BUP and/or NBUP was detected. The electronic health records of all patients were reviewed to determine if the patient had an active buprenorphine prescription at the time of specimen collection.

Paired specimens with UR creatinine < 20 mg/dL were chosen to assess illicit drug use in dilute and substituted specimens. Medical records of this subset of patients were reviewed to determine all active medications at the time of specimen collection. The presence of cocaine/cocaine metabolite, methamphetamine or 6-acetylmorphine (6-AM) as well as the presence amphetamine or morphine without a prescription was considered illicit drug use.

2.6. Statistical analysis

The non-parametric McNemar's symmetry test was used to assess agreement between paired OF and UR specimens. The Chi-square test was used to determine if BUP was detected more frequently in UR or OF in specimens from patients prescribed low (≤ 8 mg/day) versus high (> 8 mg/day) doses of buprenorphine. A p-value < 0.05 was considered statistically significant.

3. Results

Of the 260 paired specimens, 147 (57%) were positive for BUP and/or metabolites in OF and/or UR. The detection rate for BUP was higher in UR with 55% of samples positive compared to only 41% in OF. BUP and/or metabolites were significantly more likely to be detected in UR than in OF (p < 0.001) (Fig. 1).

The majority of UR specimens (133/143 or 93%) were positive for BUP and/or NBUP; both glucuronides were also detected in most of these cases (120/133 or 90%). There were only 10 UR specimens (7%)
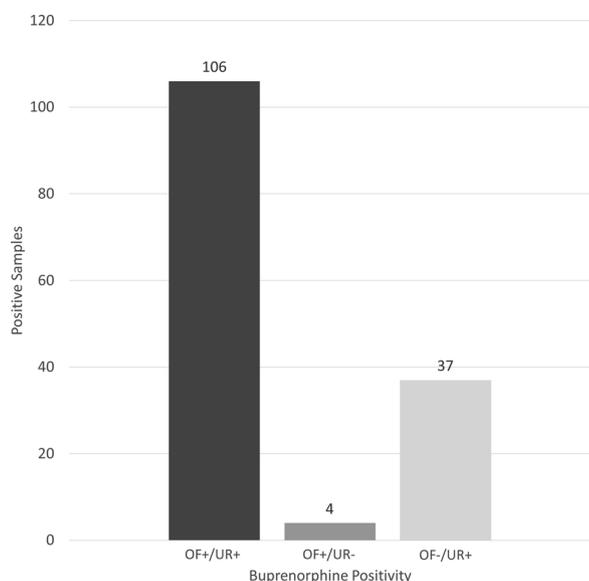
Fig. 1. The number of paired specimens positive for buprenorphine in both matrices (dark gray), oral fluid only (medium gray) and urine only (light gray) is depicted. A McNemars symmetry test shows that buprenorphine is more likely to be detected in urine (p < 0.001).

in which only the glucuronides were detected. In OF, BUP was detected in the majority of specimens (105/110 or 95%). Only 5 OF specimens (5%) had NBUP alone. For the 37 paired specimens for which BUP and/ or metabolites was detected in UR only the pattern of results was similar to all positive UR specimens. Of the 4 paired specimens which were positive only in OF, one paired UR was substituted (creatinine of 2 mg/dL), another was dilute (creatinine of 16 mg/dL) and a third had a creatinine of 25 mg/dL. The last specimen had a creatinine of 331 mg/ dL, undetectable BUP and NBUP of 12.2 ng/mL.

Eleven UR specimens were categorized as adulterated; indicating the patients shaved some of their BUP into the UR (Table 1). Nine had NBUP:BUP ratio ≤ 0.02 and a positive naloxone, while two (specimens #8 and 11) had ratio ≤ 0.02 and naloxone < 100 ng/mL. In the nine cases, UR naloxone concentrations ranged from 236 to 7544 ng/mL and 67% (6/9) had no detectable BUP metabolites. 44% (4/9) had no BUP detected in OF and the other five had BUP OF concentrations that

ranged 2 to 762 ng/mL and low or undetectable NBUP. The pattern of results for specimen #11 was similar to the nine with positive naloxone. However, specimen #8 had higher concentrations of metabolites than most other adulterated specimens. The one substituted urine (specimen #12) with a creatinine < 5 mg/dL had undetectable BUP and metabolites in UR and the presence of only BUP in OF (668 ng/mL) (Table 1). There was one case of adulterated OF (specimen #13) which had an OF BUP concentration of 24,297 ng/mL and NBUP of 14 ng/mL (Table 1). The corresponding UR had creatinine of 160 mg/dL and BUP-GLUC of 27 ng/mL.

Thirteen UR specimens were categorized as dilute (creatinine 5–19 mg/dL) or substituted (creatinine < 5 mg/dL). BUP and/or metabolites were detected in 7 of the 13 (54%) (five in both UR and OF and two in OF only). Interestingly, illicit drugs were detected in one or more matrix in 6 of the 13 (46%) paired specimens with dilute or substituted UR (data not shown). Illicit use (cocaine) was detected in only OF in the one paired specimen with substituted UR (creatinine < 5 mg/dL). In the one paired specimen positive for illicit drugs in UR only the cocaine metabolite was detected. In the other 4 specimens illicit drugs were detected in both UR and OF (amphetamine (n = 1), morphine/6-acetylmorphine (n = 1), cocaine/cocaine metabolite (n = 2)).

All patients in the study with a buprenorphine prescription were prescribed the sublingual Suboxone formulation. Of the 130 specimens taken from patients prescribed Suboxone, 100 (77%) were positive for BUP and/or its metabolites in both matrices, 26 (20%) were positive in UR only, 1 (1%) was positive in OF only and 3 (2%) were negative in both matrices (Table 2). Detection of BUP in UR versus OF was not dependent on the dose when grouping patients into those prescribed > 8 mg/day or ≤ 8 mg/day (p = 0.22). Of the 13 specimens categorized as adulterated/substituted; 8 were from patients were prescribed > 8 mg/day and 5 from patients prescribed ≤ 8 mg/day. Undisclosed buprenorphine use was detected in 20 specimens and an associated 14 patients (Table 2). Detection of undisclosed use almost doubled from 7% to 13% when UR was the matrix.

4. Discussion

The rate of opioid addiction is increasing and BUP is commonly used in OA-MAT. The detection rate of BUP is significantly higher in UR in patients undergoing OA-MAT and false negative results may be obtained when OF is utilized alone. Both of which suggest that UR is the

Table 1
Characteristics of 13 adulterated/substituted specimens in urine and oral fluid.

Specimen	Urine Results							Oral Fluid Results	
	CRT (mg/dL)	BUP (ng/mL/mg CRT)	NBUP (ng/mL/mg CRT)	BUP-GLUC (ng/mL/mg CRT)	NBUP-GLUC (ng/mL/mg CRT)	NAL (ng/mL)	NBUP: BUPRatio	BUP (ng/mL)	NBUP (ng/mL)
Urine Adulterated									
1	31	167768	19	ND	ND	7544	0.0001	762	ND
2	70	106920	11	ND	ND	7078	0.0001	2	ND
3	180	18487	ND	ND	ND	7193	N/A	26	ND
4	56	15204	ND	ND	ND	795	N/A	ND	ND
5	192	8134	ND	ND	ND	592	N/A	ND	ND
6	230	5133	10	46	47	1167	0.002	39	4
7	175	3327	ND	ND	ND	1464	N/A	ND	ND
8	17	3159	53	276	276	ND	0.02	3	3
9	107	2506	ND	ND	ND	236	N/A	257	3
10	173	1715	ND	ND	ND	259	N/A	ND	ND
11	86	163	ND	ND	ND	ND	N/A	2	ND
Urine Substituted									
12	2	ND	ND	ND	ND	ND	N/A	668	ND
Oral Fluid Adulterated									
13	160	ND	ND	27	ND	ND	N/A	24297	14

CRT = creatinine, BUP = buprenorphine, NBUP = norbuprenorphine, BUP-GLUC = buprenorphine-glucuronide, NBUP-GLUC = norbuprenorphine-glucuronide, NAL = naloxone, ND = not detected, N/A = not applicable.

Table 2
Utility of urine and oral fluid to assess buprenorphine compliance and undisclosed use.

Prescription Status	Number	Both Positive (106)	Oral Fluid Only (4)	Urine Only (37)	Negative (113)
Suboxone	130	100 (77%)	1 (1%)	26 (20%)	3 (2%)
> 8 mg/day	88	70 (80%)	1 (1%)	14 (16%)	3 (3%)
≤ 8 mg/day	42	30 (71%)	0 (0%)	12 (29%)	0 (0%)
No Suboxone Prescription	130	6(5%)	3 (2%)	11 (8%)	110 (85%)

superior matrix to assess BUP compliance. However, specimen substitution and adulteration are more common with UR collections; 12 specimens versus 1 specimen in our study. Addiction clinics utilizing OF for its collection benefits and lower likelihood of adulteration should consider implementing UR testing at least periodically to improve assessment of BUP compliance.

The higher sensitivity of UR for detection of BUP is understandable given the significant amounts of desalkylated and glucuronidated metabolites present in UR and the presumably longer detection window of BUP in UR. The timing of drugs in OF is similar to plasma and therefore less indicative of remote use (Bosker and Huestis, 2009). Concentrations of OF NBUP are also typically much lower than OF BUP, and the BUP and NBUP glucuronide metabolites are not present in OF. However, UR creatinine concentrations can vary widely between specimens which may affect the interpretation of results and necessitate the use of creatinine-corrected values. There were 4 specimens in which BUP was detected in OF only. In 3 of the 4 specimens, the UR creatinine was < 26 mg/dL (i.e. 2, 16 and 25 mg/dL) and the concentrations of BUP and NBUP in OF were low or undetectable, explaining the absence of BUP in UR. However, the explanation for the fourth specimen with a UR creatinine of 331 mg/dL and similarly low concentrations of BUP and NBUP in OF is unclear.

Quantitative UR concentrations should not be utilized to predict the dosage or timing of drug ingestion (Jannetto et al., 2018). However, we did find some qualitative patterns of BUP and metabolites in both UR and OF. BUP glucuronides were infrequently detected alone in UR and laboratories should consider the utility of reporting the glucuronide metabolites. Similarly, NBUP was infrequently detected alone in OF and therefore our laboratory performing OF testing has stopped reporting NBUP.

The rate of specimen adulteration/substitution in UR was 5% (12/260). Of the 143 UR positive for BUP and/or any BUP metabolite 11 (8%) met our adulteration criteria. However, after removing the adulterated and substituted specimens from the analysis, the sensitivity of UR remained higher (p < 0.001). We utilized recent literature, when available, to define specimen adulteration (Donroe et al., 2017; Hull et al., 2008; Suzuki et al., 2017). Of note, the NBUP:BUP ratio of less than or equal to 0.02 was determined in a study measuring total not free BUP and NBUP levels (Hull et al., 2008). When standard guidelines were not available, we utilized expert clinical and laboratory recommendations. There was only one adulterated OF specimen; however, our study is limited by the lack of definitive guidelines for specimen adulteration in both matrices. The presence of naloxone > 100 mg/dL appears to be a sensitive indicator of adulteration with 9 out of 11 specimens meeting that criteria; however, the presence of naloxone can only be utilized in patients prescribed Suboxone (i.e., formulations that include naloxone).

Although the majority of adulterated UR specimens had no detectable metabolites, four had detectable NBUP and two had detectable glucuronides. This could indicate remote use along with shaving the tablet into their UR. It may also be explained by cytochrome P450 activity in UR. The corresponding OF results in adulterated UR specimens are challenging to explain. The higher levels of BUP in OF did not meet the criteria for OF adulteration but may still represent aberrant behavior in the patient. In our experience the patients may be placing a tablet in their mouth, rinsing prior to collection and retaining some

rinse in an attempt to test positive in OF. Otherwise, it appears that the majority of patients who adulterated their UR did not simultaneously adulterate OF. Despite the higher frequency of adulteration in UR, adulteration is at least detectable when reviewing the results allowing the providers to initiate a discussion with the patient.

All the patients with a BUP prescription were prescribed the sublingual Suboxone formulation. UR was the preferred matrix to assess both BUP compliance as well as undisclosed use. Interestingly, 3 of the 4 specimens in which BUP was detected in OF only were from patients without a Suboxone prescription. All patients that adulterated or substituted their UR or OF were prescribed BUP. Surprisingly, there was no statistical difference in BUP detection in either matrix when comparing patients on high (> 8 mg/day) and low (≤ 8 mg/day) doses, even though the false negative rate in OF increased from 16% to 29%; respectively. The detection of BUP in OF in patients on lower doses (i.e. ≤ 8 mg/day) may be related to the timing between drug ingestion and sample collection. Lower doses may be sufficient to trigger a positive result in OF if the patient more recently ingested their medication.

In addition to assessing compliance to prescribed drugs, drug testing is equally important to detect illicit drug use in OA-MAT patients. OF has the distinct advantage of observed and less invasive collections, as well as the ability to be utilized in anuric patients. Furthermore, despite the higher sensitivity of UR for BUP detection, dilute or substituted UR may obscure illicit drug use and necessitate the utility of OF. It has been previously published that false negative results may be obtained in substituted or dilute UR (Cone et al., 1998). Our study did not show a high number of false negative UR results for illicit drugs; however, the number of dilute specimens was low. Laboratories utilizing UR to asses compliance should consider lowering cutoffs for illicit drug detection to avoid false negative results in dilute specimens.

To our knowledge this is the first study to compare paired OF and UR specimens collected within 2 h of each other in a patient population in which 50% of patients are prescribed BUP. In contrast to other studies (West et al., 2018), UR adulteration was 5% in our study and UR creatinine data was reported. Importantly, prescription data including formulation and dosage was available to allow us to determine the optimal matrix for detection of undisclosed use and to correlate medication dosage with detection rates in both UR and OF.

The decision to utilize UR, OF or a combination is multifactorial. The sensitivity of UR and OF depends on the drug(s) of interest. If recent heroin use and presence of 6-acetylmorphine is a priority, OF may be the appropriate choice (Petrides et al., 2018). Whereas UR, as shown in this study, may be more appropriate for BUP detection. The collection method and how it affects the providers relationship with the patient it also important; the observed collection of OF may be preferred. In the end, an addiction clinic or other settings may choose of combination of both matrices to meet their clinical needs.

Role of source funding

has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

Contributors

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author.

Declaration of Competing Interest

No conflict declared.

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