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Importance of Nor-naloxone Detection in Compliance Drug Monitoring of Suboxone Medication Assisted Treatment for Opioid Use Disorder

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Abstract

Background: Suboxone (buprenorphine-naloxone combination drug) is prescribed for opioid use disorders (OUD) treatment. Naloxone (in suboxone) acts an antagonist to dissuade drug overdose. Medication compliance is key to OUD treatment. While there are several methodologies to assess compliance for buprenorphine, little has been studied regarding naloxone compliance monitoring issues. Our study sheds more light into the role of naloxone and nor-naloxone in suboxone compliance monitoring and emphasizes the value of combined analysis of urine buprenorphine, norbuprenorphine, naloxone, and nor-naloxone, in medication compliance of OUD patients in suboxone medication-assisted treatment (MAT).

Method: UPLC-MS-MS was utilized to concurrently assess urinary buprenorphine, nor-buprenorphine, naloxone and nor-naloxone levels (limit of quantitation 0.1 ng/mL). Urine concentrations of these analytes were assessed in 3123 patients being treated for OUD employing suboxone MAT.

Results: Compliant patient intake of suboxone resulted in production of characteristic parent drug and metabolite patterns. In suboxone-prescribed patients, presence of buprenorphine and nor-buprenorphine (in an appropriate concentration ratio), and absence of naloxone and/or nor-naloxone, was indicative of non-compliance. Presence of buprenorphine and naloxone, in the absence of nor-buprenorphine and nor-naloxone, was also consistent with non-compliance.

Conclusions: Study demonstrated that naloxone sublingual absorption leads to nor-naloxone detection (above clinical cut-off levels). Presence of nor-naloxone in test results depicts a confirmation of naloxone absorption/metabolism and renal excretion, hence can be used as an additional marker in suboxone compliance monitoring programs where drug adherence is an issue. We postulate that combined analysis of urinary buprenorphine, nor-buprenorphine, naloxone, and nor-naloxone, has clinical utility towards medication compliance assessments.

Keywords: Suboxone; Buprenorphine; Naloxone; Nor-naloxone; Opioid use disorder; Medication assisted treatment; Urine drug screen; Compliance drug monitoring

Introduction

Opioid Use Disorder (OUD) is currently a major global concern, with significant negative public health implications, and a large financial burden. The annual estimated cost of general medication noncompliance in the United States is $100-290 Billion [1]. Various strategies and monitoring programs are employed by the healthcare providers to ensure patient medication compliance during medication assisted treatment (MAT) of OUD. Routine urine compliance drug monitoring (CDM) uses UPLC-MS-MS, which is a highly sensitive and specific analytic method, considered to be the gold standard for screening and quantitation of drug analytes, and assessment of drug compliance [2,3]. Scheduled and random drug testing methods have helped with decreasing the risk of medication non-compliance [4-8].

Studies have shown that suboxone MAT programs can be more effective, with respect to drug adherence, than other types of OUD treatments, such as methadone, tramadol or naltrexone, in part due to lower incidences of adverse drug reactions and side effects [9-12].

Buprenorphine is a semisynthetic opioid, and is a derivative of thebaine, a naturally occurring opium alkaloid of *Papaver somniferum* [13]. Buprenorphine (as a single or combination drug) for OUD treatment, was introduced in the US market in 2002 [14,15]. In Suboxone (with fixed buprenorphine to naloxone ratio of 4:1), buprenorphine acts as a partial opioid mu-receptor agonist, producing less euphoric and opioid effects but still having strong binding affinity for the receptor, which helps with the prevention of withdrawal symptoms in affected patients. Naloxone is a complete antagonist of the opioid mu-receptor, binding strongly to this receptor, and displacing complete agonists from the receptor [16,17]. Suboxone is more prevalent in usage, as compared to buprenorphine-only drug treatment, due in large measure to naloxone's antagonist opioid effect, which renders Suboxone less desirable for intravenous or intranasal drug abusers [13,18]. Suboxone injections can lead to opioid withdrawal precipitation, due to significant naloxone absorption, thus deterring the drug's abuse via the parenteral route. Sublingual Suboxone has been considered a relatively safe drug for use in pregnant females with OUD, in part due to significant first-pass liver metabolism, and lower bioavailability of naloxone [19]. However, the extremely limited data on sublingual naloxone exposure in pregnancy are not sufficient to definitively evaluate a drug-associated risk.

The above-mentioned conclusions were made based on prior publications, indicating that low naloxone bioavailability in sublingual

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or oral forms, and thus not likely negatively impacting buprenorphine's effect and metabolism [20,21]. Studies suggest that pregnant women taking Suboxone, transition to buprenorphine monotherapy, in part due to the possibility of naloxone induced opioid withdrawal syndrome, not only affecting mother, but also the fetus [22,23]. According to Laslo et al. [24], there are not enough data available to recommend safe use of Suboxone during pregnancy. Although Jumah et al. [25] reported no harmful side effects due to combo drug ingestion, they stated that a larger set of data need to be assessed to recommend use of Suboxone during pregnancy. Wiegand et al. [26] showed that naloxone and its metabolites are transferred to the fetus, supporting the above-noted pregnancy precautions.

Strickland and Burson [27], in their clinical study for suboxone compliance monitoring, reported that sublingual absorption of naloxone is significantly higher, as compared to data from previous investigators. In the similar context of compliance drug monitoring of suboxone, recent studies have also investigated the advantage of using buprenorphine to norbuprenorphine ratios [28,29]. Hiekman et al. [30] and Warrington et al. [31] not only note the use of urinary concentrations of buprenorphine, nor-buprenorphine, and naloxone, as indicators of Suboxone medication compliance, but also relay the importance of detecting naloxone levels in the patient samples that are prescribed suboxone combination drug.

Since it is becoming increasingly important to assess metabolites of the parent drugs for compliance drug monitoring, the goal of this study was to establish the presence or absence of nor-naloxone (naloxone metabolite) as an additional verification of suboxone compliance, and to investigate the utility of concurrent measurement of urine concentrations of buprenorphine, nor-buprenorphine, naloxone, and nor-naloxone, in assessing medication compliance in OUD patients being treated with Suboxone MAT.

Method

The AIT Labs Laboratory Information System (LIS) was queried for patients with OUD, undergoing Suboxone-based MAT. We analyzed 3123 samples from patients on Suboxone treatment. All urine samples were obtained from appropriately licensed Clinicians, and all testing was medically indicated for confirmatory urine UPLC-MS-MS drug testing. All samples were analyzed for "sample validity", and all samples were deemed satisfactory for further confirmatory analysis.

Materials

Certified standards solutions were obtained from manufacturers (Cerilliant Round Rock, TX; Cayman Chemical Ann Arbor, MI). β-glucuronidase enzyme was purchased from ChemSci Technologies Inc Belvidere, IL.

Instruments and conditions

Confirmatory urine drug analysis was performed using ultra performance liquid chromatography electrospray ionization tandem mass spectrometry (UPLC-ESI-MS-MS). A Waters Acquity UPLC chromatography unit was coupled with a XEVO TQD triple quadrupole mass spectrometer (Waters Corp, Milford, MA, USA), the latter operated in ESI-positive ionization mode. Chromatographic separations were performed using (A) 0.1% formic acid and 10 mM ammonium formate in ultrapure (18.2 MegOhm) water (Thermo Scientific, Barnstead E-pure Ultrapure Water Purification System, Waltham, MA) and (B) 0.1% formic acid in LCMS grade acetonitrile (Fisher Scientific, Waltham, MA) under linear gradient conditions (A:B 100:0 to 10:90, over 7 min, with a flow rate 0.5 mL/min). Limits of quantitation for all analytes were 0.1 ng/mL, with a maximum reporting limit of 5000 ng/mL. Quantitative and qualitative ion transitions were analyzed, validated, and reported on the basis of retention time (0.03 minutes tolerance with respect to QC and internal standards), calculated concentration (area under peak curve), peak morphology and symmetry, and quantitative-to-qualitative ion area ratios and peak alignment criteria (Figure 1). Total analyte concentrations were measured after pretreating the sample aliquots with beta-glucuronidase to cleave the drug-glucuronide conjugates (produced via liver metabolism) and sample cleanup via a Solid Phase Extraction (SPE) process. Specific gravity, urine creatinine concentration, and pH were analyzed to assess sample validity via a chemical analyzer (Carolina Liquid Chemistry CLC 6410 chemical analyzer, Carolina, Greensboro, North Carolina).

Sample preparation

In a 2 mL microcentrifuge tube, 500 µL of sample urine and 500 µL β-glucuronidase were added, this mixture was incubated at 50°C for 60 minutes. Thereafter, 1 ml of sample was loaded onto a C18 SPE filter plate (Phenomenex, Torrance, CA), preconditioned with 500 ul each of methanol and UP Water, consecutively). Samples were washed (methanol:water, 5:95), then eluted with 500 µl (acetonitrile:water, 75:25). Samples were evaporated (TurboVap© LV, Biotage, Charlotte, NC), reconstituted with 500 ul UPLC Mobile A Buffer (see above), and were transferred to 96-deep-well (2mL/well) plates for UPLC-MS-MS analysis.

Data analysis

All statistical analysis was performed using Microsoft excel. While collating patient test results, no patient identifying data was accessed (including patient's medical history, age, gender, dosage, etc.).

Results

In a three-month period, we identified 3123 patients that were prescribed suboxone (buprenorphine-naloxone combination drug).

The limit of quantitation (LOQ) in our study for buprenorphine, norbuprenorphine, naloxone and nor-naloxone was 0.1 ng/mL (established on the basis of specificity and sensitivity data of validation study). The clinical cutoff set for all these above-mentioned compounds was 10 ng/mL.

We detected buprenorphine and nor buprenorphine concentrations ranging from 0 to 19,120 ng/ml, with an average of 746.98 ng/mL and 727.30 ng/mL, respectively. Similarly, we detected naloxone that ranged from 0 to 14450 ng/mL with an average naloxone level 734.66 ng/mL. Lastly, we detected nor-naloxone ranging from 0 to 341.1 ng/mL with an average of 40.46 ng/mL.

Our data depict a very close ratio for buprenorphine and norbuprenorphine levels and a similar ratio seen for buprenorphine with naloxone levels (Table 1).

Percent compliance rate was deduced as 85.5%, with 451 patients depicting no detection for naloxone and/or nor-naloxone thus suggesting incompliance.

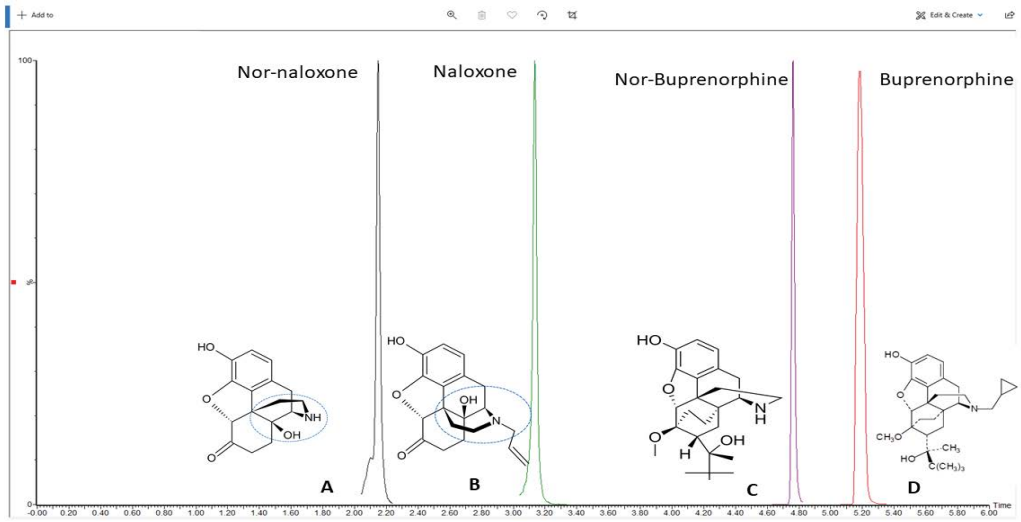

Figure 1: Representative ion chromatograms and corresponding structures of the analytes detected via UPLC-ESI-MS/MS for this study. Nor-naloxone (A), Naloxone (B), Nor-Buprenorphine (C), Buprenorphine (D).

Total sample count, N = 3123		Average Buprenorphine levels (ng/mL)	Average Norbuprenorphine levels (ng/mL)	Average Naloxone levels (ng/mL)	Average Nor-naloxone levels (ng/mL)
Total patients incompliant (or possibly on mono-drug)	451 (14.44%)	746.98	941.56	Not detected	
Total patients compliant	2672 (85.55%)	727.3	844.75	734.66	40.46

Table 1: Urinary concentrations detected in patients prescribed combination (buprenorphine-naloxone) drugs.

Discussion

Due to the common notion, based on previous studies, that naloxone absorption is very low with sublingual form of ingestions, suboxone compliance has been based entirely on buprenorphine and nor buprenorphine ratios and therefore, naloxone levels and nor-naloxone levels in patient urine drug tests have not been much considered as an assessment tool for drug adherence and compliance verification.

While there are previously published studies that have demonstrated not only detectable levels of naloxone in urine, but also suggest usage of naloxone concentrations to be considered for drug adherence assessments [27-31]. To the best of our knowledge, this is the first study that not only utilizes naloxone concentrations to verify compliance, but also employs nor-naloxone (naloxone metabolite) levels as an additional marker in a compliance monitoring program for suboxone MAT, where drug compliance and adherence are common issues.

In 0.9% of patient samples (data not shown), the presence of buprenorphine and naloxone with the absence of metabolites (norbuprenorphine and nor-naloxone) suggested spiking of urine to simulate drug compliance. However, even in patient samples where high parent drug concentrations were seen, the presence (even below the clinical cut-off of 10 ng/mL and above 0.1 ng/mL LOQ) of metabolites suggests drug compliance. This assessment is in concordance with previous reports [32].

This study, however, also depicts a wide range of naloxone and nor-naloxone levels (from 0 to 14,440 ng/mL for naloxone and 0 to 314 ng/mL for nor-naloxone. Noteworthy, is the average nor-naloxone concentration at 40 ng/mL, which is four times above the set clinical cutoff. The wide variations in the concentration ranges can be attributed to variation in patient metabolism (including food and water intake rate, excretion rate, renal functions, and genetics).

The main goal of this study was to show that sublingual absorption of naloxone can be high enough (much above the clinical cutoff) to metabolize to nor-naloxone, which based on our protocol, shows average concentration higher than the clinical cut-off as well. Hence, the presence or the absence of nor-naloxone in patient test results can aid in additional confirmation of drug adherence and compliance.

Conclusion

Our study also emphasizes the clinical utility of combined analysis of urine buprenorphine, nor-buprenorphine, naloxone, and nor-naloxone, in assisting suboxone MAT clinics with their compliance drug monitoring programs.

Despite the insight into the importance of testing the metabolites for compliance drug monitoring, our study suffers from some limitations. The data generated from urine drug testing is only meant for compliance drug monitoring, and therefore a correlation of dosage with respect to naloxone and nor-naloxone urinary concentrations cannot be made. We did not have access to patient's clinical history, nor do we know the clinical outcome. As a future endeavor, the clinical history (including rate of compliance, duration of treatment) of the patient will be tracked to generate a more comprehensive dataset to further corroborate the clinical utility of the conducted study.

Clinical application

Most labs test for buprenorphine and metabolite nor buprenorphine to ensure the buprenorphine absorption in the patient groups (who are on mono or combination drug therapy) but there are no studies and research available or published thus far, that provide a similar

additional verification for naloxone absorption. To the best of our knowledge, this is the first study that provides an insight on naloxone and nor-naloxone detection (upon combination drug ingestion), thus helping in the compliance drug monitoring of combination drug treatment and adherence for pain management, rehabilitation, and addiction patients.

Conflict of Interest

Authors declare no conflict of interest.

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