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Short communication

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Analysis of Electronic Health Records Reveals Medication-Related Interference on Point-of-Care Urine Drug Screening Assays

Nadia Ayala-Lopez[1], Jennifer M. Colby[1] and Jacob J. Hughey[2,*]

[1]Department of Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center, 1161 21st Ave South, Nashville, TN, 37232 USA, and [2]Department of Biomedical Informatics, Vanderbilt University Medical Center, 2525 West End Ave, Nashville, TN, 37203 USA

*Author to whom correspondence should be addressed. Email: jakejhughey@gmail.com

Abstract

Point-of-care (POC) urine drug screening (UDS) assays provide immediate information for patient management. However, POC UDS assays can produce false-positive results, which may not be recognized until confirmatory testing is completed several days later. To minimize the potential for patient harm, it is critical to identify sources of interference. Here, we applied an approach based on statistical analysis of electronic health record (EHR) data to identify medications that may cause false positives on POC UDS assays. From our institution's EHR data, we extracted 120,670 POC UDS and confirmation results, covering 12 classes of target drugs, along with each individual's prior medication exposures. Our approach is based on the idea that exposure to an interfering medication will increase the odds of a false-positive UDS result. For a given assay–medication pair, we quantified the association between medication exposures and UDS results as an odds ratio from logistic regression. We evaluated interference experimentally by spiking compounds into drug-free urine and testing the spiked samples on the POC device. Our dataset included 446 false-positive UDS results (presumptive positive screen followed by negative confirmation). We quantified the odds ratio of false positives for 528 assay–medication pairs. Of the six assay–medication pairs we evaluated experimentally, two showed interference capable of producing a presumptive positive: labetalol on the 3,4-methylenedioxymethamphetamine (MDMA) assay (at 200 μg/mL) and ranitidine on the methamphetamine assay (at 50 μg/mL). Ranitidine also produced a presumptive positive for opiates at 1,600 μg/mL and for propoxyphene at 800 μg/mL. These findings highlight the generalizability and the limits of our approach to use EHR data to identify medications that interfere with clinical immunoassays.

Introduction

Urine drug screens are commonly based on immunoassays, which are sensitive and cost-effective. As with nearly any laboratory test, however, immunoassays are susceptible to interference by medications, vitamins and other substances. Because many UDS assays are designed to recognize multiple related substances, they may be particularly susceptible to interference from structurally similar compounds (1). Due to these assays' relatively low specificity, positive UDS results are considered presumptive. Distinguishing between true-positive and false-positive UDS results requires confirmatory testing based on mass spectrometry.

Point-of-care (POC) UDS immunoassays are designed to be used at or near the site of patient care, which enables immediate incorporation of the results into patient management. Like the immunoassays performed in a clinical laboratory, POC UDS assays are susceptible to interference from medications. However,

by definition, POC UDS results are routinely acted on before confirmation results are available, and providers are often cautioned about possible interferences and false positives. To educate providers and minimize the potential for patient harm, many laboratories compile lists of interfering substances based on the information from the manufacturer, scientific literature and experience. Unfortunately, these lists tend to be limited in scope, suggesting that many sources of interference remain unknown and many spurious results go unnoticed.

We recently developed and validated an approach, based on statistical analysis of electronic health record (EHR) data, to identify medications that interfere with laboratory-based UDS assays (2, 3). Here, we adapted the approach to search for medications that interfere with POC UDS assays. Our analysis used >120,000 POC UDS results generated over a 5-year period. We then experimentally validated the predicted interferences through spiking studies.

Methods

The Vanderbilt Institutional Review Board reviewed and approved this study as nonhuman subject research (IRB# 081418 and 190165).

Extraction of POC UDS results and medication exposures from EHR data

EHR data came from the Synthetic Derivative, a collection of deidentified clinical data from Vanderbilt University Medical Center (VUMC) (4). We collected UDS results from our institution's POC device (Integrated E-Z Split Key Cup II, Alere, San Diego, CA) and the corresponding reflexed confirmation results. The confirmation assays are laboratory-developed tests based on gas chromatography mass spectrometry (amphetamine, barbiturates, cannabinoids, cocaine metabolite, 3,4-methylenedioxymethamphetamine (MDMA), methadone, methamphetamine, opiates, oxycodone and propoxyphene) or liquid chromatography tandem mass spectrometry (benzodiazepines and buprenorphine). They are performed in accordance with the College of American Pathologists' criteria and are in routine clinical use.

For each person in the dataset, we identified medication exposures documented between 1 and 30 days prior to each UDS result. We excluded UDS results that occurred <30 days after the person's first ever visit at VUMC, since we would lack a prior 30 days of documented drug exposures. Medication exposures are available as structured data in the Synthetic Derivative and come primarily from medication lists. We mapped each medication to its active ingredient(s), which include prodrugs, using RxNorm (5). For simplicity, we refer to these active ingredients as medications in the rest of the manuscript.

As described previously, having a documented exposure within 30 days is only a proxy for being exposed at the time of providing the urine sample (2). For example, even if a person is taking a medication every day, the medication list is only updated when the person visits a health-care provider. Thus, the proxy is valid even if the medication's half-life is <30 days. As this is a retrospective analysis from EHR data, it is impossible to verify the presence of every medication in every patient sample.

Statistical analysis of medication exposures and UDS results

We quantified associations between medication exposures and UDS results using Firth's logistic regression (6, 7). Given the coefficients and standard errors from the regression fits (where each coefficient corresponded to a log odds ratio), we then used an Empirical Bayes approach called adaptive shrinkage (8) to estimate the posterior mean of the log odds ratio and the corresponding 95% credible interval for each assay–medication pair. In each regression model, the independent variable corresponded to the presence or absence of prior documented exposure to the medication. The dependent variable corresponded to the UDS result: negative or false positive for the odds ratio of false positives, OR_{FP}, and negative or true positive for the odds ratio of true positives, OR_{TP}.

Although our analysis did not explicitly account for which results were from which individuals, we only fit a model for an assay–medication pair if exposure to the medication preceded a false positive (for OR_{FP}) or true positive (for OR_{TP}) on the assay in at least two individuals. To distinguish the effects of concurrent exposure to multiple medications, we fit a logistic regression model with a term for each medication of interest. We defined known interferents as substances able to cause a presumptive positive according to the assay's package insert.

Experimental validation of interference

For each selected compound, we spiked a reference standard into drug-free urine at various concentrations and tested the spiked urine samples in the POC device. We purchased reference standards from Sigma-Aldrich (Milwaukee, WI), Tocris Biosciences (Bristol, UK) and Santa Cruz Biotechnology (Dallas, TX). We prepared stock solutions of each standard in 80% dimethyl sulfoxide (DMSO) in water (labetalol, meloxicam and ranitidine), 100% DMSO (5′-carboxy meloxicam), 80% methanol in water (prazosin) and 100% methanol (furosemide). We spiked the urine samples using a fixed volume of 20% spiking solution, made of a combination of diluent and stock solution, including one sample per compound with only diluent to serve as a negative control. In most cases, we tested up to the maximum technically feasible concentration for a compound, given the limits of solubility, the concentration of the reference material and the fixed 20% spiking volume. We performed positive controls using Liquicheck Urine Toxicology Control Level C4 (Bio-Rad, Hercules, CA) and high calibrators from Immunalysis (Pomona, CA). The POC assays provide qualitative results that are interpreted visually.

Results

Using our institution's deidentified EHR data (4), we assembled a dataset of UDS and reflexed confirmation results related to our institution's POC device, which includes immunoassays for 12 classes of target drugs (Table I). The dataset included 120,670 UDS results from 1,163 individuals (mean: 10.2 results per individual per assay), along with each individual's prior documented medication exposures. If a presumptive positive UDS result was accompanied by a positive or negative confirmation, we denoted it as a true positive or false positive, respectively. The highest true-positive rate occurred with the buprenorphine assay, consistent with the POC device's use in our institution's medication-assisted treatment program.

We used the dataset to calculate two types of associations: (i) between medication exposures and false-positive UDS results, yielding an odds ratio OR_{FP} and (ii) between medication exposures and true-positive UDS results, yielding an odds ratio OR_{TP}. As in our previous study (2), we hypothesized that OR_{FP} would identify potential interferents on a given assay and that OR_{TP} would identify assay targets, thereby serving as a positive control. Altogether, we calculated OR_{FP} for 528 assay–medication pairs and OR_{TP} for 1,796 assay–medication pairs (Supplementary Tables 1 and 2). Because of the relatively low counts of false-positive UDS results, we could only

Table I. Characteristics of POC UDS Immunoassays in This Study

Target drug(s)	Cutoff (ng/mL)	Number of UDS results		
		Negative screen	Presumptive positive screen, positive confirmation	Presumptive positive screen, negative confirmation
Amphetamine	1,000	10,101	245	7
Barbiturates	300	10,530	6	5
Benzodiazepines	300	9,912	565	44
Buprenorphine	10	508	6,328	6
Cannabinoids	50	9,472	944	60
Cocaine metabolite	150	10,332	162	47
MDMA	500	9,987	23	59
Methadone	300	10,243	210	57
Methamphetamine	1,000	9,984	92	95
Opiates	300	9,598	491	49
Oxycodone	100	9,524	553	16
Propoxyphene	300	10,413	1	1

Table II. Strongest Associations with False-Positive UDS Results, Which Were Selected for Experimental Evaluation

Assay	Medication	Number of UDS results			Odds ratio (OR_{FP})	95% credible interval		Concentrations causing a presumptive positive (μg/mL)
		Negative	True positive	False positive		Lower	Upper	
Cannabinoids	Meloxicam	5	0	2	28.1	7.1	78.0	-[a]
Cannabinoids	Furosemide	101	1	7	11.4	5.4	22.0	-
MDMA	Labetalol	143	2	30	61.9	39.9	80.5	200
Methadone	Labetalol	171	5	9	10.4	5.3	20.5	-
Methadone	Prazosin	198	1	9	9.0	4.6	18.5	-
Methamphetamine	Ranitidine	97	0	7	7.8	3.6	17.0	50

[a]Neither meloxicam nor 5′-carboxy meloxicam caused a presumptive positive.
Numbers of UDS results correspond to those preceded by exposure to the given medication. "-" indicates the compound did not cause a presumptive positive up to the highest concentration tested (1,600 μg/mL for each compound except 800 μg/mL for the metabolite 5′-carboxy meloxicam).

calculate OR_{FP} for one known interferent. However, most assay targets had among the highest OR_{TP} on their respective assay (Supplementary Figure 1), indicating that our approach detects the effects of drug exposure on POC UDS results.

Based on this analysis and on clinical plausibility we selected the most promising potentially interfering medications for experimental validation (Table II), although we expected that because of the low numbers of false-positive UDS results, fewer selected medications would actually produce a presumptive positive. We selected meloxicam and furosemide for validation on the cannabinoids assay based on multivariate regression (Supplementary Table 3).

Of the six assay–medication pairs we evaluated, two showed interference capable of producing a presumptive positive, validating our analysis (Table II and Supplementary Figure 2): labetalol on the MDMA assay (at 200 μg/mL) and ranitidine on the methamphetamine assay (at 50 μg/mL). As incidental findings, ranitidine also produced a presumptive positive for opiates at 1,600 μg/mL and for propoxyphene at 800 μg/mL. The other assay–medication pairs did not produce a presumptive positive at any tested concentration.

Discussion

Knowledge of substances that can cause spurious results is critical for POC testing. Here, we applied a statistical approach to detect sources of interference on POC UDS assays. Our approach relies on data that are already collected for clinical care.

The current study shares multiple limitations with our previous work that are inherent to analysis of EHR data. Our approach only quantifies associations for assay–medication pairs; it does not predict which medication(s) caused a particular UDS result. A documented prior exposure to a medication does not guarantee that the individual was taking the medication at the time of providing the sample or that the medication was present in the sample. In addition, because medications are given for particular indications, documented exposures to a medication could be correlated with other factors—some recorded in the EHR, some not—affecting UDS results.

We also acknowledge limitations in our validation via spiking experiments. First, drug concentration in urine is highly variable (due to factors such as renal function, hydration status and concomitant drugs) and often poorly characterized, which makes it challenging to ascertain the physiological plausibility of the concentrations causing presumptive positive screens. However, the combination of association in EHR data and validation in spiking experiments strongly suggests that urine concentrations of a given drug and/or metabolite do become high enough to cause false-positive screens in clinical care. Second, although we tested the drug metabolites that were commercially available, it remains possible that some false positives in the EHR data were caused by metabolites we could not test.

The current study also differs from our previous work on laboratory analyzer-based assays in several ways (2). First, the current dataset included ~6-fold fewer UDS results overall and ~16-fold fewer false positives. The latter is at least partly because, compared with the laboratory-based assays, the POC assays have higher cutoff

concentrations for presumptive positives. Second, the current dataset included ~35-fold fewer unique patients, since the POC device at our institution is used primarily in outpatient medication-assisted treatment clinics. All these factors likely contributed to why we identified fewer interfering medications in the current study than in the previous study.

An important future step, especially relevant to POC testing, is to integrate the knowledge of validated sources of interference into the EHR so that providers are automatically notified when a result may be spurious. Such a system could provide an explanation when a patient's samples repeatedly screen positive and confirm negative and provide an impetus to forgo confirmatory testing in some scenarios. Overall, the repeated success of our approach supports its generalizability and the broader potential for analysis of EHR data to advance laboratory medicine.

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Data availability

Code and summary results for this study are available at https://doi.org/10.6084/m9.figshare.12067401.

Supplementary Data

Supplementary data is available at *Journal of Analytical Toxicology* online.

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