Clinical Biochemistry 68 (2019) 50–54

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Commonly used fluoroquinolones cross-react with urine drug screens for opiates, buprenorphine, and amphetamines

Jennifer M. Colby[a,*], Pratish C. Patel[b], Darwin Y. Fu[c], Nicola J. Rutherford[a]

[a] Department of Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center, 1301 Medical Center Drive, Nashville, TN 37232, United States
[b] Department of Pharmaceutical Services, Vanderbilt University Medical Center, 1301 Medical Center Drive, Nashville, TN 37232, United States
[c] Department of Biomedical Informatics, Vanderbilt University Medical Center, 1301 Medical Center Drive, Nashville, TN 37232, United States

ARTICLE INFO

Keywords:
Fluoroquinolone
False positive urine drug screen
Levofloxacin
Cross-reactivity

ABSTRACT

Objectives: Fluoroquinolone antibiotics are commonly used in the treatment of infections and have previously been confirmed to cross-react with previous generations of opiates immunoassays. In this work we evaluated the cross-reactivity of the three fluoroquinolones in use at our institution with a panel of 10 urine drug screens.
Design and methods: Drug preparations of levofloxacin, ciprofloxacin, and moxifloxacin that were designed for intravenous delivery were added to drug-free urine at varying concentrations. Spiked urine samples were screened for illicit and therapeutic drugs on an Abbott Architect c16000 automated chemistry analyzer. Percent cross-reactivity was calculated.
Results: Levofloxacin displayed clinically relevant cross-reactivity with the Abbott MULTIGENT opiates and Thermo CEDIA® buprenorphine immunoassays but did not cross-react with the Abbott MULTIGENT oxycodone or methadone immunoassays. Moxifloxacin displayed clinically relevant cross-reactivity only with the Abbott MULTIGENT amphetamine/methamphetamine assay. Ciprofloxacin did not cross-react with any of the 10 immunoassays.
Conclusions: This study demonstrates that levofloxacin cross-reacts with modern immunoassays for two related opioids (buprenorphine and morphine) and moxifloxacin cross-reacts with the amphetamine/methamphetamine assay. Urine concentrations of these fluoroquinolones that are consistent with therapeutic use produced results above commonly used-cutoffs for positivity. This underscores the necessity of confirmatory testing of presumptively positive urine drug screens.

1. Introduction

Urine drug testing is commonly used in a variety of clinical contexts, including detection of poisonings and assessment of illicit drug use. Immunoassays are the most frequently used screening tools for urine drug testing, and they have the distinct advantages of being relatively inexpensive and offer a short turnaround time [1]. A variety of formats exist, from manual test strips or cups performed at the point of care to fully automated assays performed on chemistry analyzers [2]. In a class-based immunoassay, antibodies are generally targeted toward one drug but are designed to also bind to structurally related compounds [3]. For example, this cross-reactivity is what allows hydromorphone, an opioid related to morphine, to be detected in an assay targeted toward morphine. However, if the structure recognized by the antibody is non-specific, "off-target" cross-reactivity can lead to false positive results.

False positives are a common challenge in a variety of immunoassays [1,4]. During assay development manufacturers assess the specificity of their test and report any cross-reacting compounds in the package insert. Given the thousands of potentially cross-reacting compounds, a comprehensive assessment is not realistic. Even if a manufacturer has tested a compound, the concentration tested may not be representative of the concentrations and/or compound distribution observed in patient samples, and false positives can still occur [3]. Many cross-reactive compounds are discovered by laboratorians fielding calls from physicians or following up on false positive results.

A question about false-positive opiates and buprenorphine screens prompted our investigation into the cross-reactivity of fluoroquinolone antibiotics with the urine drug screening assays in use at our institution. Oral and intravenous preparations of fluoroquinolones are commonly used for a variety of bacterial infections and though they are not structurally related to drugs of abuse, several fluoroquinolones have

* Corresponding author.
E-mail address: jennifer.colby@vumc.org (J.M. Colby).

https://doi.org/10.1016/j.clinbiochem.2019.04.009
Received 24 January 2019; Received in revised form 12 April 2019; Accepted 13 April 2019
Available online 13 April 2019

Table 1
Urine drug screen assay parameters.

Assay	Format	Manufacturer/brand	Cutoff (ng/mL)
Amphetamine/methamphetamine (amphetamines)	homogeneous enzyme immunoassay	Abbott MULTIGENT	500
Barbiturates	homogeneous enzyme immunoassay	Abbott MULTIGENT	200
Benzodiazepines	homogeneous enzyme immunoassay	Abbott MULTIGENT	200
Buprenorphine	CEDIA® immunoassay	Thermo Scientific	5
Cannabinoid metabolite	homogeneous enzyme immunoassay	Abbott MULTIGENT	50
Cocaine metabolite	homogeneous enzyme immunoassay	Abbott MULTIGENT	300
Methadone	homogeneous enzyme immunoassay	Abbott MULTIGENT	300
Opiates	homogeneous enzyme immunoassay	Abbott MULTIGENT	300
Oxycodone	homogeneous enzyme immunoassay (DRI®)	Thermo Scientific	300
Tricyclic antidepressants	homogeneous enzyme immunoassay	Abbott MULTIGENT	300

been reported to cause false positive results in urine drug screens. Cross-reactivity has been reported with the Abbott TdxFlx amphetamines assay [5] and the AxSym, CEDIA, EMIT II, Abuscreen OnLine, and SYNCHRON opiates assays [6–8]. Many of these assays have been reformulated or otherwise updated in the 20 years since the initial reports of cross-reactivity, and it is not clear if modern assays are similarly affected. The goal of this study was to determine whether current-generation urine drug screens cross-react with any of the three fluoroquinolones in use at our institution (levofloxacin, ciprofloxacin, moxifloxacin). We accomplished this by testing spiked urine samples on each of the 10 assays in our urine drug screen panel. We then used spectrophotometry and molecular similarity analysis to investigate possible mechanisms of cross-reactivity.

2. Materials and methods

2.1. Preparation of spiked samples

Sterile intravenous drug preparations were acquired for ciprofloxacin (2 mg/mL in 5% dextrose; Hospira Inc., Lake Forest IL, USA), moxifloxacin (1.6 mg/mL in 0.8% sodium chloride; Mylan Institutional LLC, Rockford, IL, USA), and levofloxacin (5 mg/mL in 5% dextrose; SAGENT Pharmaceuticals, Schaumburg, IL, USA). Sterile 0.9% sodium chloride solution (saline; EKI, Joliet, IL, USA) was used to prepare fluoroquinolone standards. Standards and saline were mixed with drug free urine from a de-identified donor in varying proportions to keep the total percent of spiking material at 20% of the total volume. A total of 21 urine samples were prepared; 7 samples per fluoroquinolone. Each sample contained a different concentration of fluoroquinolone. Levofloxacin was tested at 0, 30, 60, 120, 240, 480 and 960 μg/mL. Ciprofloxacin was tested at 0, 20, 40, 80, 160, 320 and 400 μg/mL. Moxifloxacin was tested at 0, 25, 50, 100, 150, 240, and 320 μg/mL.

2.2. Spectrophotometric evaluation

Full-strength intravenous drug preparations, sterile saline, and drug free urine were subjected to UV-VIS spectrophotometric examination using a NanoDrop 2000c spectrophotometer (Thermo Scientific, Waltham, MA, USA). A 1 mm pathlength was used. The absorbance spectrum from 190 to 840 nm was collected for each of the 5 solutions.

2.3. Urine drug screen testing

Each of the 21 spiked urine samples was tested with each of the 10 assays included in our urine drug screening panel. Testing was performed in a single batch on an Abbott Architect c16000 autoanalyzer (Abbott Diagnostics, Abbott Park, IL, USA). The initial performance of each of the urine drug screens was verified according to the College of American Pathologists' criteria, detailed in the All Common and Chemistry/Toxicology checklists. Positive and negative quality controls were tested on each assay within 8 h of the batch analysis and met laboratory-defined acceptance criteria. All assays had coefficients of variation of < 5% in routine quality control monitoring. Urine drug screening included the following Abbott MULTIGENT assays: amphetamine/methamphetamine (amphetamines), barbiturates, benzodiazepines, cannabinoid metabolite, cocaine metabolite, methadone, opiates, and tricyclic antidepressants (all from Abbott Diagnostics, Abbott Park, IL, USA). These 8 homogeneous enzyme immunoassays are based on competition between free drug in the sample and enzyme labelled drug for binding to a drug-specific antibody. In the absence of free drug, the antibody binds to the enzyme-labelled drug and inhibits the activity of the enzyme, which is determined by measuring absorbance spectrophotometrically at 340 nm. Therefore, the amount of free drug in the sample is directly proportional to absorbance at 340 nm. The urine drug screen also included a DRI® oxycodone assay (homogenous enzyme immunoassay, detection at 340 nm) and a CEDIA® buprenorphine assay (detection at 660 nm) (both from Thermo Scientific, Waltham, MA, USA). The cloned enzyme donor immunoassay (CEDIA) relies on two complementary inactive enzyme fragments, with one fragment labelled with drug, that come together and form active enzyme. In the absence of free drug in the sample, an antibody within the reagent binds to the enzyme-labelled drug, preventing formation of the active enzyme. When free drug is present in the sample the blocking antibody binds to free drug, allowing enzyme fragments to combine and form active enzyme. Enzyme activity is directly related to drug concentration, and the product of the enzyme-catalyzed reaction is measured spectrophotometrically at 660 nm. Specific details of each assay and the cutoff for positivity in use in our laboratory can be found in Table 1.

2.4. Molecular similarity analysis

Structures for levofloxacin, moxifloxacin, and ciprofloxacin were compared pairwise against opiates assay target compound, morphine; buprenorphine assay target, buprenorphine; and the related compounds heroin, codeine, hydrocodone, and oxycodone using the ChemmineR package [9]. Maximum common substructure Tanimoto similarities were calculated by identifying the largest chemical fragment shared by the two comparator molecules [9]. A compound compared to itself would have a perfect Tanimoto similarity of 1.0.

2.5. Data analysis

Absorbance values and calculated concentrations were reported for each of the 21 samples. Analysis of cross-reactivity was performed using Microsoft Excel (Seattle, WA, USA). Percent cross-reactivity was defined as the measured concentration divided by the known concentration multiplied by 100%. The mean percent cross-reactivity for all tested concentrations was reported. Graphs were prepared using Origin version 6.1 (Origin Lab, Northampton, MA, USA).

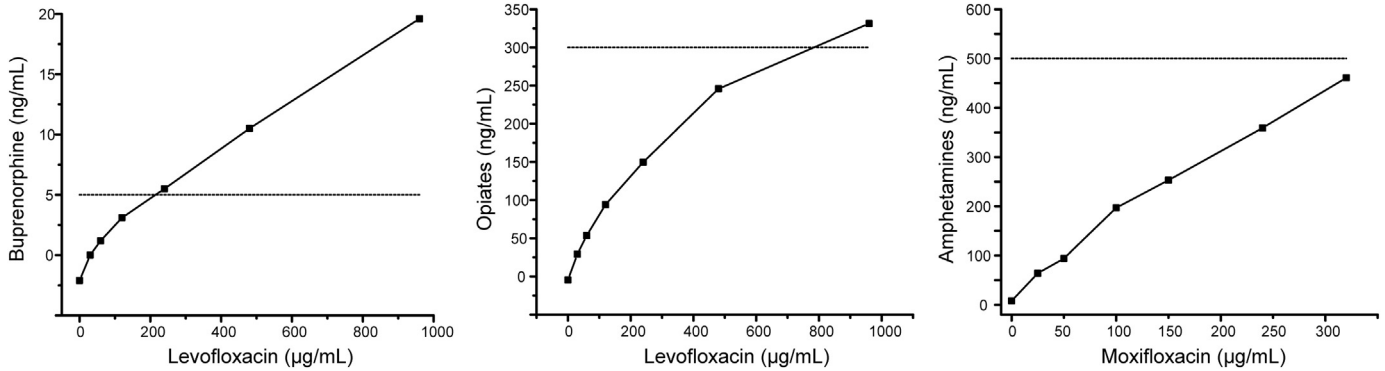

Fig. 1. Analysis of urine samples spiked with fluoroquinolones on urine drug screen assays. The horizontal dotted line represents the cutoff to produce a positive result for the assay in question. Only assay/fluoroquinolone pairs producing positive results are shown.

3. Results

3.1. Assessment of cross-reactivity

Seven spiked urine samples were prepared for each fluoroquinolone, with one of the samples containing only saline. Matrix effects were minimized by fixing the total volume of diluent at 20%. Concentrations ranged from 0 to 960 µg/mL for levofloxacin, 0–400 µg/mL for ciprofloxacin, and 0–320 µg/mL for moxifloxacin. Analytical details for the 10 urine drug screens we tested and the positivity cutoff for each assay can be found in Table 1.

The fluoroquinolone concentration and the measured drug concentration for each fluoroquinolone/assay pair in which a signal was detected are plotted in Fig. 1. Both the buprenorphine and opiates assays produced values greater than the cutoff for levofloxacin containing samples. The mean percent cross-reactivity was 0.069% with the opiates assay and 0.002% with the buprenorphine assay (Table 2). At the highest concentration tested, moxifloxacin produced a measured amphetamines concentration (461 ng/mL) slightly below the cutoff (500 ng/mL). Due to the 20% limit set on the volume of the spiking solution and the concentration of the available moxifloxacin preparation, higher concentrations could not be tested. The mean cross-reactivity of moxifloxacin with the amphetamines assay was the highest we observed at 0.184% (Table 2). For the remaining fluoroquinolone/assay pairs, the highest concentration sample produced results similar to the blank sample. Notably, ciprofloxacin did not cross-react with any of the 10 assays we tested.

3.2. Investigation of the mechanism of cross-reactivity

We measured the absorbance spectrum of each of the full-strength intravenous drug preparations to determine whether the cross-reactivity we observed was a result of absorbance at the detection wavelength of a given immunoassay. The absorbance spectrum for each drug preparation, the saline diluent, and the drug free urine are displayed in Fig. 2. Each drug preparation absorbed strongly below 300 nm and considerably in the range of 340 nm, with levofloxacin displaying the strongest absorbance at this wavelength. None of the preparations absorbed at 660 nm. Drug free urine absorbed weakly at 340 nm and not at all at 660 nm. Saline showed no appreciable absorbance at either wavelength of interest.

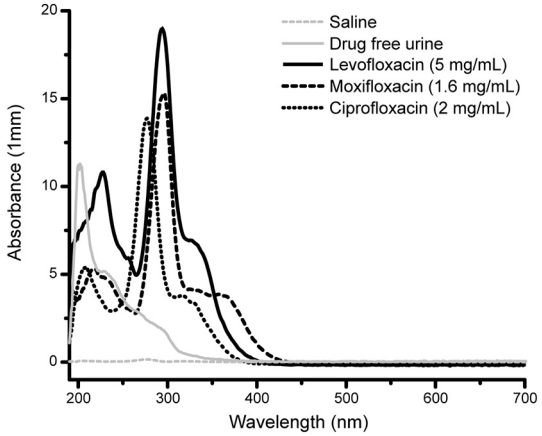

Fig. 2. UV-VIS absorbance spectra of full-strength intravenous solutions of fluoroquinolones measured by absorbance spectrophotometry with a 1 mm pathlength.

Table 3
Tanimoto Similarities for Fluoroquinolones and Selected Opioids.

	Levofloxacin	Moxifloxacin	Ciprofloxacin
Buprenorphine	0.20	0.15	0.12
Morphine	0.27	0.19	0.15
Heroin	0.23	0.17	0.13
Codeine	0.26	0.19	0.15
Hydrocodone	0.26	0.19	0.15
Oxycodone	0.26	0.18	0.15

A simple molecular similarity comparison of each of the three fluoroquinolones with the assay targets, buprenorphine and morphine, did not find large regions of structural similarity (Table 3). Overall levofloxacin showed the most similarity with morphine and buprenorphine (similarity of 0.27 and 0.20, respectively) compared to moxifloxacin (0.19 and 0.15, respectively) or ciprofloxacin (0.15 and 0.12, respectively). Of note, the observed Tanimoto similarities for fluoroquinolones and any of the tested target compounds were substantially

Table 2
Calculated cross-reactivity for fluoroquinolone/assay pairs.

Assay	Assay Target (cutoff concentration, ng/mL)	Analyte	Mean cross-reactivity	Approximate Concentration of Analyte to Produce Positive Screen (µg/mL)
Abbott MULTIGENT Opiates	Morphine (300)	Levofloxacin	0.069%	434
Thermo CEDIA Buprenorphine	Buprenorphine (5)	Levofloxacin	0.002%	250
Abbott MULTIGENT Amphetamines	d-Amphetamine (500)	Moxifloxacin	0.184%	350

lower (0.12–0.27) than between opioid pairs such as buprenorphine-morphine (0.57), codeine-heroin (0.81), or oxycodone-hydrocodone (0.96).

4. Discussion

The cross-reactivity of fluoroquinolones with opiates immunoassays targeted toward morphine is well established, with the first report dating from 1997 [6]. Several reports have characterized the cross-reactivity of fluoroquinolones with opiates assays from a variety of manufacturers [7,10]. One report characterized cross-reactivity with an amphetamines assay [5]. Over the past 20 years, many of the immunoassay reagents that were tested in these original works have been updated or reformulated. One additional report of cross-reactivity has been published in the past 10 years, for an assay that was not tested previously [8]. In this study we demonstrate that fluoroquinolone antibiotics continue to cross-react with modern immunoassays for opiates (levofloxacin), and provide the first evidence of cross-reactivity with buprenorphine (levofloxacin) and amphetamines (moxifloxacin) assays.

We prepared a series of spiked urine samples using intravenous preparations of the three fluoroquinolones in use at our institution. We collected semi-quantitative results for each of the 21 samples on a panel of 10 urine drug screen immunoassays (Table 1). The assays were performed on an Abbott Architect c16000 autoanalyzer. The results were interpreted with common cutoffs for positivity, consistent with our practice for patient care (Table 1). The highest concentration of ciprofloxacin, 400 μg/mL, produced responses similar to the blank sample for all 10 assays. Levofloxacin cross-reacted with the buprenorphine and opiates assays at concentrations less than the maximum tested and produced positive results when the signal was interpreted relative to the cutoff (Fig. 1). The highest concentration of levofloxacin tested, 960 μg/mL, produced responses similar to the blank sample for the remaining 8 assays.

Moxifloxacin cross-reacted with the amphetamines assay at all concentrations tested, but because the cutoff of this assay is 500 ng/mL, even the highest concentration of moxifloxacin tested did not cause a positive result (Fig. 1). We were unable to test higher moxifloxacin concentrations due to the limitations of our starting concentration and the maximum spike volume set at 20%. However, single oral doses of moxifloxacin produce urine moxifloxacin concentrations of < 100 μg/mL in healthy volunteers, and the peak urine concentration with standard dosing is similar [7,11]. Even though the percent cross-reactivity of moxifloxacin with the amphetamines assay was the highest we observed (Table 2), we expect this cross-reactivity to impact very few patients because of the unexpectedly high urinary moxifloxacin concentration that would be required to produce a positive result.

As demonstrated by the case that prompted this investigation, the cross-reactivity between levofloxacin and the opiates and buprenorphine assays is clinically relevant. Though the percent cross-reactivity is low, particularly for the buprenorphine assay, the threshold for a positive result is also low (Table 1, Table 2). The CEDIA® buprenorphine assay is known to have a high false positive rate, which can be improved by increasing the cutoff for positivity to > 10 ng/mL [12,13]. A patient on a standard dose of levofloxacin could have a peak urine concentration of 1000 μg/mL, which is higher than the highest concentration we tested [7]. Even with a buprenorphine cutoff of 20 ng/mL this patient would still be expected to screen positive (Fig. 1). Though the cross-reactivity of levofloxacin is higher with the opiates assay than the buprenorphine assay (Table 2), the cutoff for a positive opiates result is high enough (300 ng/mL) that only the highest levofloxacin concentration (960 μg/mL) produced a positive result. Still, this is within the expected urine concentration range for standard dosing, and false positive opiates results are expected. A patient receiving a standard dose of ciprofloxacin could be expected to have a maximum urine concentration of 400 μg/mL, which was our highest tested concentration [7]. Given that we did not detect any cross-reactivity at this concentration, we do not believe that ciprofloxacin presents a clinically relevant source of cross-reactivity in the assays we tested.

Most immunoassay cross-reactivity can be explained by structural similarities between the target compound, e.g. morphine, and the cross-reactant, e.g. levofloxacin, or by spectral interference, e.g. bilirubin. To determine whether spectral interference was causing the false positive results, we measured the absorbance spectra of the full-strength IV preparations of each drug. While there is notable absorbance in the measured range, the maxima are not at the measurement wavelengths of the assays (340 nm and 660 nm, Fig. 2). In addition, the 8 Abbott MULTIGENT assays measure the same wavelength (340 nm). A spectral interference would be expected to interfere with all 8 assays equally, which is not what we observed. In our study levofloxacin cross-reacted with two assays that use different wavelengths for detection, and a previous study demonstrated cross-reactivity with a fluorescence polarization opiates immunoassay, which does not use absorbance spectrophotometry for detection [7]. Taken together, these data indicate that spectral interference is unlikely to be the source of the cross-reactivity.

The remaining explanation for cross-reactivity is a reaction between a reagent component, e.g. an antibody, and the fluoroquinolone. One potential scenario is a structural similarity between the fluoroquinolone and the reagent antibody target driving binding to the antibody, much like the opioid hydromorphone binds the reagent antibody that targets the closely related opioid morphine. However, the structures of opioids and fluoroquinolones are not overtly similar to a casual observer, so we undertook a computational comparison to quantify the largest chemical fragment shared by each pair of molecules of interest. The relative size of the shared structural element is reflected by the Tanimoto similarity. A perfect match would have a Tanimoto similarity of 1.0, and closely related compounds like hydrocodone and oxycodone have a Tanimoto similarity approaching this (0.96). Of the three fluoroquinolones, levofloxacin had the maximum Tanimoto similarity to morphine and buprenorphine, but the measure was < 0.3 for all fluoroquinolone/target pairs (Table 3). Previous work suggests compound pairs with Tanimoto similarity above a 0.70–0.80 cutoff tend to bind similarly [14]. In our analysis, compounds of the same pharmacological class, such as codeine and heroin, surpassed this cutoff. The similarity score for levofloxacin and morphine (0.27) was well below the similarity score for buprenorphine and morphine (0.57) but was higher than the score for moxifloxacin and morphine (0.15) or ciprofloxacin and morphine (0.12). Similarity scores below 0.3 are not indicative of high homology between compound pairs, which is consistent with what an observer would note when looking at the chemical structures. In spite of the lack of obvious structural similarity, the relatively higher Tanimoto similarity for levofloxacin with tested opioids and the previous reports of cross-reactivity with predicate opiates assays supports the idea that structural similarity may play a role in the cross-reactivity. While our data suggest there may be an interaction between levofloxacin and an opiate- or buprenorphine-specific reagent component, we are unable to determine the precise mechanism of that interaction. In addition to binding at the antibody epitope target site, a variety of other mechanisms are possible, including allosteric interaction of the fluoroquinolone with the antibody that prevents binding to the drug labelled with enzyme or enzyme donor, or that the fluoroquinolone is indirectly increasing enzyme activity.

Our work suggests that compounds with different biological effects and seemingly little structural similarity may still be similar enough that cross-reactivity occurs when the off-target compound is present at high concentration. Because cross-reactivity can't always be predicted, assay manufacturers generally recommend that presumptively positive drug screens be confirmed by mass spectrometry. This confirmatory testing is time consuming and expensive, and in some hospital locations, such as emergency departments, results may not be available until days after a patient is discharged. In an attempt to reduce extraneous testing, our institution no longer reflexes confirmatory testing for

drug screens performed on patients in the emergency department, though they are performed by provider request. Our work highlights an important source of false positive results that if not recognized, could lead to inappropriate interpretations of a patient's drug use. Although the cross-reactivity between fluoroquinolones and opiates immunoassays has been known since the late 1990s, and levofloxacin was shown to cross-react with the predicate Abbott opiates assay, fluoroquinolones were not listed as cross-reactants in the package insert for the MULTIGENT opiates assay [15]. Laboratories like ours that do not reflex confirmatory testing for every presumptive positive screen need to be especially aware of the limitations of the package insert. Additionally, laboratorians in community hospitals may not have access to medical journals, so we encourage assay manufacturers to test and list cross-reactants that have been documented in the medical literature in the package insert.

Acknowledgements

The authors would like to acknowledge Kara Newton for her assistance with the analysis of the spiked urine samples.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] A. Saitman, H.-D. Park, R.L. Fitzgerald, False-positive interferences of common urine drug screen immunoassays: a review, J. Anal. Toxicol. 38 (2014) 387–396, https://doi.org/10.1093/jat/bku075.
[2] J.R. Wiencek, J.M. Colby, J.H. Nichols, Rapid assessment of drugs of abuse, Adv. Clin. Chem. 80 (2017) 193–225, https://doi.org/10.1016/bs.acc.2016.11.003.
[3] N.E. Heger, T.C. Kwong, Challenges in interpreting unexpected urine drug test results, J. Appl. Lab. Med. AACC Publ. 2 (2018) 640–643, https://doi.org/10.1373/jalm.2017.024893.
[4] K.L. Johnson-Davis, A.J. Sadler, J.R. Genzen, A retrospective analysis of urine drugs of abuse immunoassay true positive rates at a national reference laboratory, J. Anal. Toxicol. 40 (2016) 97–107, https://doi.org/10.1093/jat/bkv133.
[5] M.A. Nomier, H.K. Al-Huseini, False-positive TDxFLx urine amphetamine/Metamphetamine II assay from Ofloxacin, Saudi Pharma. J. 12 (2004) 42–46.
[6] R. Meatherall, J. Dai, False-positive EMIT II opiates from ofloxacin, Ther. Drug Monit. 19 (1997) 98–99.
[7] L.R. Baden, G. Horowitz, H. Jacoby, G.M. Eliopoulos, Quinolones and false-positive urine screening for opiates by immunoassay technology, JAMA. 286 (2001) 3115–3119.
[8] Q. Shafiq, A. Mutgi, Urine opiate screening: false-positive result with levofloxacin, Can. Med. Assoc. J. 182 (2010) 1644–1645, https://doi.org/10.1503/cmaj.091508.
[9] Y. Cao, A. Charisi, L.-C. Cheng, T. Jiang, T. Girke, ChemmineR: a compound mining framework for R, Bioinformatics. 24 (2008) 1733–1734, https://doi.org/10.1093/bioinformatics/btn307.
[10] M. Backmund, K. Meyer, M. Zielonka, D. Eichenlaub, Ofloxacin causes false-positive immunoassay results for urine opiates, Addict. Biol. 5 (2000) 319–320, https://doi.org/10.1111/j.1369-1600.2000.tb00197.x.
[11] G.E. Stein, S. Schooley, Urinary concentrations and bactericidal activities of newer fluoroquinolones in healthy volunteers, Int. J. Antimicrob. Agents 24 (2004) 168–172, https://doi.org/10.1016/j.ijantimicag.2004.01.013.
[12] J. Berg, J.D. Schjøtt, K.O. Fossan, B. Riedel, Cross-reactivity of the CEDIA buprenorphine assay in drugs-of-abuse screening: influence of dose and metabolites of opioids, Subst. Abus. Rehabil. (2015) 131, https://doi.org/10.2147/SAR.S88935.
[13] S.E.F. Melanson, M.L. Snyder, P. Jarolim, J.G. Flood, A new highly specific buprenorphine immunoassay for monitoring buprenorphine compliance and abuse, J. Anal. Toxicol. 36 (2012) 201–206, https://doi.org/10.1093/jat/bks003.
[14] D.Y. Fu, J. Meiler, Predictive power of different types of experimental restraints in small molecule docking: a review, J. Chem. Inf. Model. 58 (2018) 225–233, https://doi.org/10.1021/acs.jcim.7b00418.
[15] Abbott Diagnostics, Opiates Package Insert REF 3L34–20, (2014).