

# Quinolones and False-Positive Urine Screening for Opiates by Immunoassay Technology

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IN RESPONSE TO PUBLIC CONCERNS regarding use of illicit drugs, random drug testing has become a common practice for employees in the workplace, for individuals incarcerated or under suspicion by the criminal justice system, and in other circumstances.<sup>1</sup> This practice has been sanctioned by legislation and affirmed by court decisions, including the US Supreme Court.<sup>2-6</sup> In general, samples are usually subjected to screening by relatively inexpensive, rapid, and reliable immunoassays, with samples testing positive requiring confirmation by an alternative method. When such strict protocols are followed, false-positive screening test results do not cause problems.

It is now widely appreciated that immunoassays are extremely reliable and have relatively few false-positive results. As a result, at least for some applications, it has been advocated that confirmation is not necessary.<sup>7,8</sup> Thus, as testing expands beyond the strictly controlled legal arenas, there is a possibility that positive results will be acted on in the absence of confirmatory testing. Such is the case in most hospital laboratories, and thus it becomes important for clinicians to know that false-positive test results do occur and to request confirmatory testing by alternative

**Context** Millions of assays are performed each year to monitor for substance abuse in various settings. When common medications cross-react with frequently used testing assays, false-positive results can lead to invalid conclusions.

**Objective** To evaluate cross-reactivity of quinolone antimicrobials in common opiate screening assays and to assess the in vivo implications of this phenomenon.

**Design, Setting, and Participants** The reactivity of 13 quinolones (levofloxacin, ofloxacin, pefloxacin, enoxacin, moxifloxacin, gatifloxacin, trovafloxacin, sparfloxacin, lomefloxacin, ciprofloxacin, clinafloxacin, norfloxacin, and nalidixic acid) was tested in 5 commercial opiate screening assays from September 1998 to March 1999. In 6 healthy volunteers, we confirmed the cross-reactivity of levofloxacin or ofloxacin with these opiate screening assays.

**Main Outcome Measure** Opiate assay activity (threshold for positive result, 300 ng/mL of morphine).

**Results** Nine of the quinolones caused assay results above the threshold for a positive result in at least 1 of the assays. Four of the assay systems caused false-positive results for at least 1 quinolone. Eleven of the 13 compounds caused some opiate activity by at least 1 assay system. At least 1 compound caused opiate assay activity in all 5 assay systems. Levofloxacin, ofloxacin, and pefloxacin were most likely to lead to a false-positive opiate result. Positive results were obtained in urine from all 6 volunteers.

**Conclusion** Greater attention to the cross-reactivity of quinolones with immunoassays for opiates is needed to minimize the potential for invalid test interpretation.

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methods (as would be required in legal settings) when there is a question about the validity of screening results. For this reason, information concerning therapeutic use of possible cross-reacting prescription medications should assist authorities in testing and ultimately help the individual who is being tested.

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Meatherall and Dai<sup>9</sup> reported in 1997 that ofloxacin could result in a false-positive test result for opiates by the EMIT [enzyme multiplied immunoassay technique] II assay (Syva, San Jose, Calif). However, this fact does not appear to be widely known among clinicians. We encountered a patient in whom a false-positive urine screening

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test for opiates during therapy with levofloxacin nearly resulted in his ejection from a drug-treatment center. As a result, we examined systematically the propensity of various quinolones to cause false-positive reactions for opiates using 5 major commercially available screening assays.

## METHODS

Thirteen quinolones (levofloxacin, ofloxacin, pefloxacin, enoxacin, moxifloxacin, gatifloxacin, trovafloxacin mesylate, sparfloxacin, lomefloxacin, ciprofloxacin hydrochloride, clinafloxacin, norfloxacin, and nalidixic acid) were either provided by the manufacturer or purchased from a biologic company. All antibiotics were made soluble as per standard techniques<sup>10</sup> to a concentration of 5000 µg/mL to ensure we exceeded possible in vivo urinary levels and dilutions to concentrations of approximately 1700 µg/mL and 600 µg/mL were made.

These samples were then analyzed by 5 different commercial immunoassays: (1) EMIT II reagents, which were run on Hitachi 717 analyzer (Roche Diagnostics, Indianapolis, Ind), (2) AxSYM fluorescence polarization immunoassay (Abbott Laboratories, Abbott Park, Ill), (3) CEDIA

[cloned enzyme donor immunoassay] reagents (Microgenics, Concord, Calif), which were run on Hitachi 912 analyzer (Roche Diagnostics), (4) Roche Abuscreen OnLine reagents (Roche Diagnostics), which were run on the Dimension XL analyzer (Dade Behring, Newark, Del), and (5) Beckman opiate reagents, which were run on the Synchron CX analyzer (Beckman Instruments, Brea, Calif).

For those samples that tested positive in a given assay at the lowest concentration (600 µg/mL), further dilutions were performed to determine the approximate lowest concentration that would test positive. Controls with morphine concentrations of 0, 225, 300, and 375 ng/mL were run simultaneously on each assay. All assays were run in accordance with the manufacturers' recommendations. Specifically, the threshold for a positive result was set at 300 ng/mL of morphine, and samples with error messages not amenable to troubleshooting protocols were not run on dilution (as recommended by manufacturers). A more detailed investigation of the dose-response curves for ofloxacin and levofloxacin was performed with the EMIT II 717 system, spanning the range of concentrations from 5000 µg/mL to 0.005 µg/mL.

With approval from the Committee on Human Studies and informed consent from the participants, in 1999, 6 healthy volunteers were given a single oral dose of antibiotic (3 received 500 mg of levofloxacin and 3 received 400 mg of ofloxacin) and urine samples were collected at approximately 6-hour intervals for the following 48 hours. These samples were analyzed for opiates by the EMIT II 717 system. Select samples were run on the other 4 assay systems.

## RESULTS

### Assay Cross-Reactivity

The results of the screening assays for the 13 quinolones tested in vitro are shown in TABLE 1. A concentration of 300 ng/mL of morphine was set as the positive threshold, as previously suggested by the Department of Health and Human Services and widely used by clinical laboratories.<sup>11-14</sup> By convention, a value of 250 ng/mL would be considered a negative value for opiates, although substantial opiate activity above baseline (0 ng/mL) is present. The following quinolones cross-reacted to cause a positive test result for opiates at concentrations assayed: levofloxacin and ofloxacin (using Abbott AxSYM, CEDIA, EMIT II, and Roche OnLine assays), pefloxacin (using CEDIA, EMIT

**Table 1.** Expected Urinary Concentration of Quinolones and the Concentration Required for Immunoassay Activity\*

Quinolone	In Vivo Peak Urinary Concentration With Standard Dosing, µg/mL†	Quinolone Concentration Causing Assay Positivity for Opiates, µg/mL				
		Abbott AxSYM	CEDIA	EMIT II	Roche	Synchron
Levofloxacin	1000	1700-5000	60-200	140	200-600	S
Ofloxacin	400	1700-5000	60-200	140	200-600	S
Pefloxacin	40	S	60-200	600-1700	200-600	N
Enoxacin	8	S	1700-5000	600-1700	S	N
Gatifloxacin	300-400	S	S	600-1700	S	N
Lomefloxacin	300	N	S	S	1700-5000	N
Moxifloxacin	69	N	S	S	1700-5000	N
Sparfloxacin	12	N	S	S	S	N
Ciprofloxacin	400	N	S	S	1700-5000	N
Clinafloxacin	147	N	S	S	N	N
Norfloxacin	400	N	S	S	1700-5000	N
Trovafloxacin	12	N	N	N	N	N
Nalidixic acid	1000	N	N	N	N	N

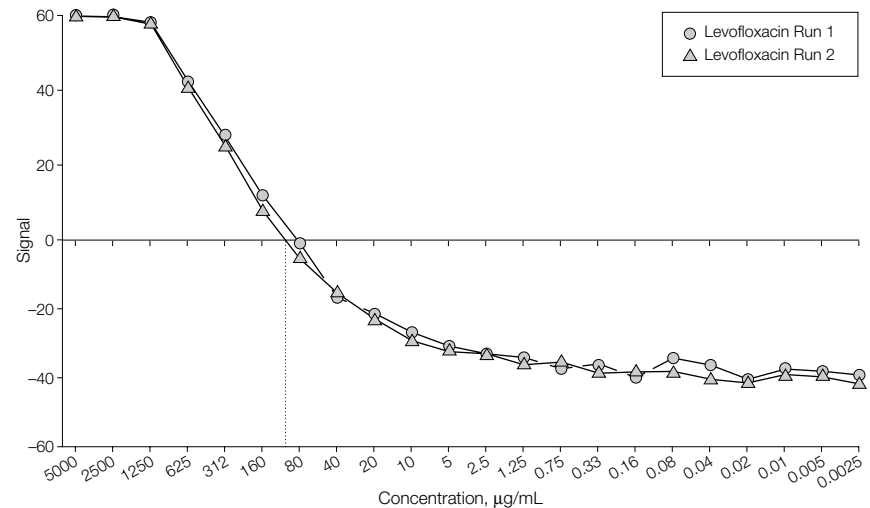
\*Expected urinary concentrations of quinolones and concentrations triggering a positive result for the different assays are demonstrated. Levofloxacin and ofloxacin would be expected to trigger a positive opiate assay by the EMIT II, CEDIA, and Roche OnLine assays. Several of the quinolones cause demonstrable assay activity, but below the threshold concentration for assay positivity. S indicates signal detected at maximum concentration tested, but below the threshold value, may contribute in an additive fashion with other cross-reacting compounds; N, no signal detected at maximum concentration tested. See the "Methods" section for details about the assays.

†Data obtained from several sources.<sup>15-25</sup>

II, and Roche OnLine assays), enoxacin (using CEDIA and EMIT II assays), gatifloxacin (using EMIT II assay), and lomefloxacin, moxifloxacin, ciprofloxacin, and norfloxacin (using Roche OnLine assay). Sparfloxacin, clinafloxacin, trovafloxacin, and nalidixic acid did not cross-react to cause a positive test result with any of the assays. To properly interpret the clinical relevance of these observations, the urinary concentrations of these quinolones<sup>15-25</sup> must be considered. Based on these *in vitro* data and given the anticipated urinary concentrations, pharmacodynamics, and dosing interval, the quinolones most likely to cause a false-positive urinary test result for opiates are levofloxacin and ofloxacin (using CEDIA, EMIT II, and Roche OnLine assays) and pefloxacin (using CEDIA).

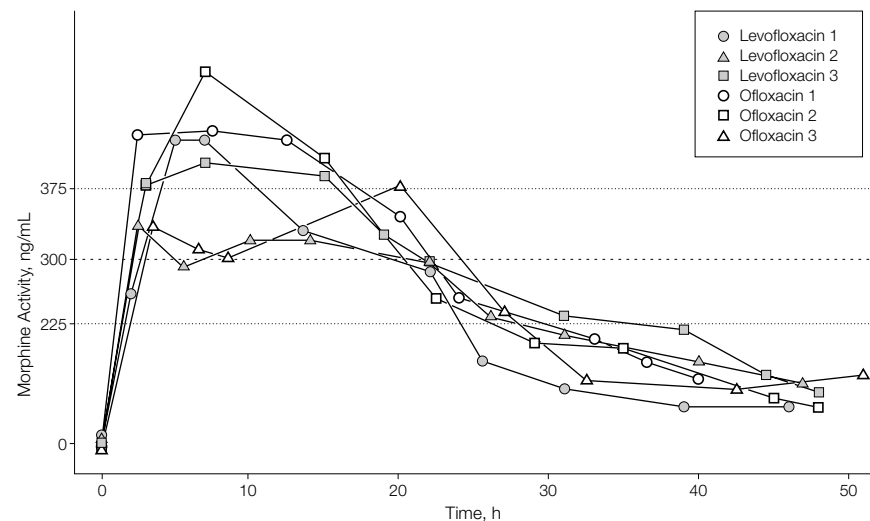
These screening assays for opiates are qualitative (threshold) tests and should not be used quantitatively. However, it is important to consider low-concentration opiate cross-reactivity (below the threshold) as this may, in certain settings, facilitate reaching assay threshold—thus, a false-positive test result. Detailed analysis of 2-fold serial dilutions of levofloxacin (FIGURE 1) and ofloxacin (using EMIT II assay) demonstrates dose-responsive assay activity between concentrations of 5 µg/mL to 1250 µg/mL, with the assay threshold being achieved at approximately 110 µg/mL. The following quinolones have some opiate activity but below the assay threshold; thus, they have the potential to act in an additive manner to trigger a positive opiate assay: levofloxacin and ofloxacin (Synchron assay); pefloxacin (Abbott AxSYM assay); enoxacin (Roche OnLine and Abbott AxSYM assays); gatifloxacin (Abbott AxSYM, CEDIA, and Roche OnLine assays); sparfloxacin (CEDIA, EMIT II, and Roche OnLine assays); and lomefloxacin, moxifloxacin, clinafloxacin, ciprofloxacin, and norfloxacin (CEDIA and EMIT II assays) (Table 1). At the concentration levels tested, trovafloxacin and nalidixic acid demonstrated no detectable opiate cross-reactivity by any of the assays.

**Figure 1.** EMIT II Immunoassay Activity Due to Levofloxacin



Opiate assay activity as a function of levofloxacin concentration by the EMIT II system is demonstrated. The threshold value for assay positivity (300 ng/mL, represented by zero on the y-axis) is approximately 110 µg/mL of levofloxacin. Assay activity corresponding to a morphine concentration of 225 and 375 ng/mL are -15 and 15 units on the y-axis, respectively.

**Figure 2.** Urine Opiate Activity Due to a Single Dose of Levofloxacin or Ofloxacin in Volunteers



Urine opiate assay results by the EMIT II system for 3 healthy volunteers who received a single dose of levofloxacin (500 mg) or ofloxacin (400 mg). For both antibiotics, the assay became positive as soon as 2 hours after dosing and remained positive for approximately 20 to 25 hours. Significant assay activity was maintained for 30 to 40 hours postdosing, though below the threshold value for opiate positivity.

### Volunteer Studies

A single dose of 500 mg of levofloxacin caused a false-positive test result using the EMIT II assay within 2 hours for as long as 22 hours in all 3 healthy volunteers (FIGURE 2). Ofloxacin

(single dose of 400 mg) revealed a similar pattern. Detectable opiate activity in the urine was seen for more than 30 hours with both antimicrobials.

Selected urine samples from these subjects were run on the other 4 as-

**Table 2.** Duration of Urine Opiate Activity in Volunteers After a Single Dose of Levofloxacin or Ofloxacin\*

Time, h	Urine Concentration Causing Assay Positivity for Opiates, µg/mL				
	Abbott AxSYM	CEDIA	EMIT II	Roche	Synchron
0	N	N	N	N	N
7	S	≥375	≥375	≥375	≥225
20	S	≥375	≥300	≥225	S
24	S	≥300	≥225	S	S

\*Duration of opiate activity by 5 different immunoassay technologies after a single dose of levofloxacin (500 mg) or ofloxacin (400 mg). The given opiate assay would be considered positive for values of 300 ng/mL or greater. S indicates signal detected at maximum concentration tested but less than 225 ng/mL control, may contribute in an additive fashion with other cross-reacting compounds; N, no signal detected at maximum concentration tested.

says and were found to cause assay positivity above the 375 ng/mL level by the CEDIA assay and positivity persisted above the 300 ng/mL concentration for over 24 hours (TABLE 2). The Roche OnLine assay found positivity above 375 ng/mL, with persistent (slight) assay activity at 24 hours. The Synchron assay had activity above the 225 ng/mL level at 7 hours after dosing, with persistent activity detected at 24 hours. The Abbott AxSYM assay demonstrated some opiate reactivity; however, this was below the 225 ng/mL concentration and persisted for over 24 hours.

## COMMENT

Few compounds have been identified that cross-react with the common opiate screening assays<sup>26</sup> and include rifampin (described for the kinetic interaction of microparticles in solution method), ofloxacin (described for the EMIT method),<sup>9</sup> and poppy seeds (described not for cross-reactivity, but detection of minute amounts of opiates).<sup>27-34</sup> We have shown that several quinolones have the potential to yield false-positive test results by a number of commonly used opiate screening assay systems currently used in the United States. It is important to note that several of the quinolones are metabolized in vivo and the metabolites (eg, norfloxacin as a metabolite of pefloxacin) may be excreted into the urine.<sup>15,35</sup> We did not assess the potential contributions of other metabolites in this study. Because of the enormous ramifications for an unrecognized false-positive test result, the results of our study strongly support the use of confirmatory testing when a per-

son receives a positive opiate test result in the setting of recent quinolone use.

What all of these assays have in common is that an antibody directed against opiate epitopes is exposed to labeled drug in the reagent system and free drug in the sample. With higher concentrations of drug in the sample, less of the labeled drug in the reagent system binds to the antibody. Depending on the specific assay, the signal detected (turbidity, enzyme activity, fluorescence polarization, etc) is changed by the concentration of free drug in the sample in a predictable, although typically not proportional manner. When the signal exceeds that of an arbitrary standard (typically, for opiates, 300 ng/mL of morphine), the assay is considered positive (ie, contains an opiate with a concentration whose reactivity exceeds that of 300 ng/mL of morphine).

Until recently, the recommended cutoff for opiate assay positivity (by the Department of Health and Human Services) was 300 ng/mL of morphine.<sup>11-14</sup> To minimize the unnecessary gas chromatography/mass spectrometry effort and expense due to poppy-seed food products, the opiate screening threshold was raised from 300 ng/mL to 2000 ng/mL of morphine in December 1998. This cutoff, however, has been reported to have only a 70% sensitivity for detecting opiates.<sup>11</sup> In part, due to this sensitivity concern and for purposes of clinical rather than forensic testing, most clinical laboratories continue to use the 300-ng/mL threshold for assay positivity. Given the clinical implications of quinolone cross-reactivity with opiate testing, we re-

port the 300 ng/mL as our cutoff for assay positivity.

Why certain quinolones react with some opiate screening assays is unclear, as there is no obvious structural similarity between morphine and this class of drugs nor is there an obvious structural relationship between the quinolones that cross-react. These data are of particular importance given the widespread use of these agents, such as for the treatment of community-acquired pneumonia, nosocomial-acquired pneumonia, sexually transmitted diseases, multidrug-resistant tuberculosis, and the prophylaxis for possible anthrax exposure.<sup>15,36-45</sup> As many of these infections occur in patients who might be susceptible to substance abuse, the potential for misinterpretation of testing is self-evident. In addition, the care of patients in clinical situations may be misguided by a positive urine test for opiates, such as inappropriately halting the evaluation of a change in mental status.

It is important to realize that the screening assays are designed to be positive when the urine concentration of morphine is 300 ng/mL or greater. These are qualitative not quantitative tests. Different immunoreactive compounds can have an additive effect on reaching the threshold for a given assay. For example, if a given quinolone would lead to 225 ng/mL and a poppy seed muffin to 100 ng/mL of immunoreactivity, consumption of either product alone would not induce a positive urine opiate test result. However, if both were consumed simultaneously, the test threshold might be achieved. Thus, a compound that induces signal activity by a given immunoassay technology, albeit below assay threshold, could additively contribute to a positive urine screening test result when other cofactors are present.

When a screening test for drugs frequently abused returns positive, it is essential to obtain appropriate confirmatory testing, such as gas chromatography, mass spectrometry, or high-performance liquid chromatography.<sup>32,46,47</sup> Quinolones are not misin-



terpreted as opiates by these methods. Confirmatory testing should not be done by another immunoassay technique for the reasons demonstrated in this analysis. Confirmatory testing does not always resolve the issue of substance abuse as consumption of poppy seeds or medicinally prescribed opiates have been reported as innocent explanations for positive opiate screening test results.<sup>29,31,46</sup> The major limitations to obtaining confirmatory testing are time and money. In circum-

stances in which resources are limited, the significant cost of additional testing will remain a formidable obstacle to accurate test interpretation. These data demonstrate the need for vigilance in identifying unintended consequences of new therapies.

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