Rifampin Interference with Opiate Immunoassays

To the Editor:
Clinical toxicology in emergency situations necessitates the availability of rapid analytical tests for different substances in a variety of settings. The primary question asked by clinicians is what compounds may have been ingested. In cases of suspected drug abuse or overdose, rapid screening by immunoassays has made this possible. However, many limitations are inherent in these methods, which necessitate confirmation by an alternative method such as gas chromatography–mass spectrometry (1). Here we present a case of drug interference with certain screening methods for opiates in urine.

A 7-year-old male (Table 1, patient 1) presented to the emergency unit at the American University of Beirut Medical Center with a progressive decrease in his level of consciousness over the previous 3 weeks. He was transferred from another hospital because of a suspicion of tuberculous meningitis. As part of the workup for this case, a urine drugs of abuse screen was ordered, which was positive for opiates by the Syva RapidTest (Dade Behring) on two occasions after being negative at the time of admission (Table 1). However, the patient was never on any opiates or opiate-like medication. After a review of the patient’s chart, the interfering substance in this positive opiate screen was suspected to be rifampin (rifampicin) (2). Confirmation of opiates in a urine sample collected on day 4 after admission by gas chromatography–mass spectrometry was negative. The actual opiates targeted by this analysis were pholcodine, codethyline, codeine, morphine, and monoacetylmorphine.

To further characterize this interference, two patients taking rifampin at our institution were followed up. Patient 2 was on rifampin for brucellosis and patient 3 for pulmonary tuberculosis (Table 1). Urine samples from both patients were collected before initiation of therapy and 1 h after a 600-mg rifampin dose. Patients consented to urine drugs of abuse screens before samples were collected. The original screen was performed using the Syva RapidTest for drugs of abuse. In parallel, we also tested the Triage (Biosite Diagnostics) and Genix RapidTech (Genix Technology) immunoassays (Table 1). Pre-rifampin samples were negative for opiates by the three methods, but 1-h post-rifampin samples were positive for opiates by the Syva and Genix reagents and negative by the Triage. These positive samples were negative when analyzed by gas chromatography–mass spectrometry. To investigate the concentration at which rifampin interferes with the Syva and Genix opiate methods, we added different rifampin concentrations to a previously tested blank urine sample. At 300 mg/L, rifampin started to interfere with the Syva reagents. For the Genix reagents, the interference occurred at a much lower concentration (0.05 mg/L).

Table 1. Opiate results for different screening methods and for gas chromatography–mass spectrometry.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sample</th>
<th>Syva</th>
<th>Genix</th>
<th>Triage</th>
<th>GC/MS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>At admission</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>Day 2</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>Day 4</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>2</td>
<td>Pre-rifampin</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>Post-rifampin</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>3</td>
<td>Pre-rifampin</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>Post-rifampin</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

*GC/MS, gas chromatography—mass spectrometry.

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The antibiotic rifampin is usually part of the treatment of tuberculosis, especially in patients with concomitant human immunodeficiency virus infection. Generally, drug abuse in some of these patients necessitates screening for opiates (4). In addition, in cases of mental confusion associated with tuberculous meningitis or rifampin toxicity, it is not uncommon for a drug of abuse screen to be ordered. Depending on the specificity of the method, rifampin interference could be the cause of false-positive opiate screening results. Therefore, the presence of rifampin treatment mandates confirmatory testing for opiates because it can interfere with the predictive value of certain rapid screening assays (5).

We recommend that each laboratory evaluates rifampin interference with the opiates immunoassay in use. In addition, each laboratory should maintain an updated listing of reported interference problems with immunoassays, as part of a quality assurance program, and disseminate this information to the medical community (6). However, this rapid screen serves the need for emergency drug testing, but it must always be complemented by confirmation.

We would like to acknowledge the support of Elie Salameh and Pasteur Cerba Laboratories (95066 Cergy Pontoise, Cedex 9, France) for performing the gas chromatography–mass spectrometry analysis of opiates in this study as a gift.

References

Note
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Effect of Piperacillin-Tazobactam on Clinical Capillary Zone Electrophoresis of Serum Proteins

To the Editor:

Over the last 5 years, capillary zone electrophoresis (CZE) has emerged as an automated technique for the separation of serum proteins in clinical laboratories (1–5). In conventional methods, quantification of the protein fractions is based on dye binding, whereas CZE uses ultraviolet detection at 214 nm for direct protein quantification via the peptide bonds. Any substance or drug that is present in serum and that absorbs at 214 nm potentially can interfere with CZE analysis. It has been reported that radio-contrast media, which absorb at 214 nm, interfere with CZE and can simulate a monoclonal component (6–8). In the present report, we describe that the antibiotic piperacillin-tazobactam (Tazocin®, Wyeth Lederle) produces a small peak at the anodal site of the β-globulin fraction.

In Fig. 1, panels A and C show the β and γ fractions of CZE electrophorograms (Beckman Paragon CZE 2000, software version 2.21) of two samples obtained from patients who received piperacillin-tazobactam (4 g of piperacillin/500 mg of tazobactam three times per day). In the sample shown in panel C, there was a small monoclonal protein in the γ region. The antibiotic was given intravenously over a 30-min period. The samples were obtained 10 min (Fig. 1A) and 30 min (Fig. 1C) after administration of the antibiotic. In each case, a small but distinct peak was observed at the anodal site of the transferrin peak in the β-globulin fraction. Such a peak is absent in a normal CZE electropherogram and was not seen in the CZE electropherogram of a specimen from the same patient as in Fig. 1A collected 2 days after piperacillin-tazobactam administration (Fig. 1B). After this time period, the antibiotic had been cleared from the blood stream. The elimination half-life of piperacillin-tazobactam is 0.7–1.2 h in patients with normal kidney function. Protein binding for piperacillin is 16% at serum concentrations of 200–300 mg/L; for tazobactam, protein binding is 20–23%. Addition of piperacillin-tazobactam to a normal serum led to the appearance of an abnormal peak on the CZE electropherogram of an abnormal peak in the same location as the extra peak observed in the electropherogram from patients receiving the antibiotic (Fig. 1D). Parenteral administration of vancomycin (Vancocin®, 1 g twice per day; Eli Lilly) or ceftazidim (Gla-zidim®, 1 g three times per day; Glaxo Wellcome) did not lead to the appearance of an abnormal peak on CZE (data not shown).

Collectively, intravenously administered piperacillin-tazobactam produces a small peak in the β region in CZE. Such peaks might simulate a small monoclonal protein.