False positive results for leucocytes in urine dipstick test with common antibiotics

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We found positive results for leucocyte esterase in the dipstick test in two patients with acute leukaemia who had had documented aplasia for several days. They were treated with imipenem for fever of unknown origin and had no symptoms of urinary tract infection; the sediment and culture were negative. The dipstick test for leucocyte esterase was also positive in vitro with imipenem, and this prompted us to investigate further.

Methods and results

We dissolved the antibiotics to be tested as recommended by the manufacturers at the concentrations used for infusion or more dilute (table 1). The drugs were used in their commercially available form or provided as single substances by the manufacturers. Spontaneous degradation (aging) was allowed for by testing after standing for 5, 12, and 24 hours at room temperature. We used the Combur^{9}Test (Boehringer Mannheim, Germany), and the Ames Multistix 10 SG (Bayer-Diagnostics, Leverkusen, Germany). The strips were read by eye and confirmed by colorimeters provided by the manufacturers (Uritron, Boehringer and Clinitek 100, Ames/Bayer). Since both dipsticks showed a positive reaction (although the Multistix had a lower sensitivity) and since the two tests are similar, we used the Combur^{9}Test for all experiments and repeated only the positive and critical results with the Multistix.

The separate analysis of imipenem and cilastatin showed that only imipenem produced a positive reaction. Clavulanate and meropenem gave positive results, but sulbactam and tazobactam gave negative results (table 1). The concentrations covered the range found in urine.

Comment

The manufacturers of the drugs and of the test strips have had no reports of false positive reactions induced by antibiotics. The diagnostic accuracy and reliability of the dipstick test have been reviewed.[1 2] False positive results have been shown with formaldehyde and false negative or reduced reactions with doxycycline, gentamicin, cephalexin, and cephalothin; excessive glucose concentrations (20g/l)); or high concentrations of oxalic acid (information from dipstick packaging). Imipenem may interfere with the colorimetric determination of porphobilinogen and 5-aminolevulinic acid,[3] and substances that colour the urine—for example nitrofurantoin—may mask the reaction.

Positive results do not seem to be produced by the degradation products of the antibiotics as treatment with β lactamase did not affect the results. However, spontaneous degradation greatly increased the positive result for clavulanic acid (table 1). Zinc and copper ions and Tris buffer have a strong catalytic effect on the hydrolysis and aminolysis of imipenem,[4] but neither the test strips nor our buffers contained these substances. Both the indoxyl-ester and the diazonium salt of imipenem were required to give a positive reaction; when tested separately they gave negative results.

The similar ring structure of the sulfapenems sulfabactam and tazobactam, which gave negative results, and the oxapenem clavulanic acid, which gave a positive result, suggests that the β lactam ring alone may not be responsible for the reaction and that the reactivity of the side chain may be important.

We conclude that positive dipstick tests for leucocyte esterase are induced by commonly used antibiotics. This knowledge may be useful in patients who are treated with these drugs and may help to avoid unnecessary investigations. It implies that urine culture is the only reliable method of diagnosis.

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1 Hurlbut TA 3d, Littenberg B. The diagnostic accuracy of rapid dipstick tests to predict urinary tract infection. *Am J Clin Pathol* 1991;96:582-8.
2 Bonnardeaux, Somerville P, Kaye M. A study on the reliability of dipstick urinalysis. *Clin Nephrol* 1994;41:167-72.
3 Verstraeten L, Ledoux MC, Moos B, Callebaut B Cornu G, Hassoun A. Interference of tienam in colorimetric determination of 5 aminolevulinic acid and porphobilinogen in serum and urine. *Clin Chem* 1992;38:2557-8.
4 Mendez R, Alemany T, Martin-Villacorta J. Catalysis of hydrolysis and aminolysis of non-classical beta-lactam antibacterial agents by metal ions and metal chelates. *Chem Pharm Bull* 1992;40:3228-33.

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Table 1—*Results of urine dipstick tests with antibacterial drugs*

	Freshly dissolved (×10^6 leucocytes/l)	After 5 h (×10^6 leucocytes/l)	After 24 h (×10^6 leucocytes/l)	Lowest positive concentration (mg/l)
Imipenem with cilastatin (350 mg/l)	10-25	25-75	25-75	35
Imipenem (50 mg/l)	10-25	25-75	25-75	5
Cilastatin (175 mg/l)	Negative	Negative	Negative	
Co-amoxiclav (1200 mg/l)	10-25	>500	>500	12 (at 24 h)
Clavulanic acid (200 mg/l)	10-25	25-75	>500	2 (at 24 h)
Amoxycillin (1000 mg/l)	Negative	Negative	Negative	
Meropenem (1120 mg/l)	10-25	10-25	10-25	110

Negative results were also obtained with freshly dissolved and aged penicillin G (300 mg/l), amoxycillin (500 mg/l), flucloxacillin (500 mg/l), cefuroxime (37.5 mg/l), cephazoline (1g/l), ceftazidime (1g/l), gentamicin (400 mg/l), amikacin (10 mg/l), erythromycin (300 mg/l) , doxycycline (200 mg/l), ciprofloxacin (20 mg/l), vancomycin (500 mg/l), metronidazole (50 mg/l), clindamycin (1.5 g/l); 6-aminopenicillanic acid, 7-aminocephalosporanic acid, and 3-aminomonobactam acid (10 mmol/l each) also gave negative results with or without enzymatic treatment with penicillinase (1.4-36 U/ml) for 60 min at room temperature.