

EDITORIAL

Fosfomycin trometamol and the single-dose treatment of cystitis

The launch of fosfomycin trometamol on the UK market for the single high-dose treatment of acute lower urinary tract infection introduces to these islands an old compound that was not previously available here. It also provides the latest example of the commercial exploitation of much truncated dosage regimens for simple cystitis, previous examples being the 2 × 3-g sachet presentation of amoxicillin and the 3-day treatment packs of fluoroquinolones. A review of the agent and this therapeutic approach is, therefore, timely.

Fosfomycin is a naturally occurring antibiotic that was described originally under the name phosphonomycin in 1969.¹ It has an unusually simple epoxypropylphosphonic acid structure² and acts at a very early stage in bacterial cell wall synthesis by inhibiting the pyruvyl transferase enzyme that catalyses the condensation of phosphoenolpyruvate with N-acetylglucosamine to form N-acetylmuramic acid.³ Fosfomycin has a fairly broad spectrum of antibacterial activity, but the precise level of activity is difficult to assess; various constituents of culture media, including glucose, phosphates and sodium chloride, as well as pH and other test conditions, affect the activity, so that different results are obtained with different media. Lowest MIC values are observed generally with simple nutrient broth (or agar); MIC values are usually much higher in Mueller-Hinton medium.^{4–6} The susceptibility of some bacteria, notably *Escherichia coli*, is markedly enhanced in the presence of glucose-6-phosphate, which is routinely added to media for tests of susceptibility to fosfomycin. The potentiation occurs because, in *E. coli* and some other gram-negative bacilli, glucose-6-phosphate induces a hexose-phosphate transport pathway that can be used by fosfomycin to greatly improve access to the intracellular target.³ Mutations affecting this uptake system, which can be easily selected *in vitro*, abolish potentiation by glucose-6-phosphate and confer relative resistance to fosfomycin. There is presumably little opportunity for this type of resistance to develop *in vivo*, since the selection pressure is minimal, but mutations in the constitutive α -glycerophosphate pathway that the drug also uses may give rise to clinical resistance. These types of resistance involve chromosomal genes, but plasmid-mediated resistance associated with enzymic inactivation of fosfomycin has also been described^{7,8} and plasmids carrying the resistance trait are circulating in Spain and other countries where the drug has been used extensively.⁹

Until recently, fosfomycin was available only as the sodium salt (for injection) and the calcium salt (for oral use). The advantage of the new trometamol formulation is that it is very soluble in water and provides greatly improved bioavailability compared with the calcium salt.¹⁰ However, on a weight-for-weight basis the trometamol salt has half the activity of the other derivatives since trometamol—also known as tromethamine, or tris- (hydroxymethyl) -amino-methane—which is antibacterially inactive, almost doubles the mol. wt.

After absorption, fosfomycin is excreted by the renal route, with the trometamol salt achieving peak concentrations in bladder urine of *c.* 2000 mg/L after the recommended single oral dose of 3 g; the elimination half-life is about 4 h¹¹ and concentrations sufficient to inhibit most urinary pathogens are maintained for about 48 h.¹²

It has been clear since the work of Charlton and his colleagues¹³ that abbreviated 3-day regimens are as effective as traditional 10-day treatment in uncomplicated cystitis. Single high-dose therapy was popularised by Bailey in New Zealand in the 1970s^{14–16} although its antecedents were much earlier.¹⁷ The perceived benefits of this practice are that it not only provides reliable treatment at minimum cost and maximum convenience, but that it also helps to identify the patients who may require more intensive urological investigation, because they do not respond to minimal therapy. Single-dose therapy is also likely to be safer than conventional regimens and reduces the opportunity for the emergence of bacterial resistance.

To ask of an antimicrobial agent that it should clear infection in a single passage through the urinary tract is a stringent test of its efficacy. Consistent success can be expected only of agents with half-lives that are sufficiently long to sustain effective concentrations in bladder urine. Fosfomycin trometamol is acceptable in this respect, but so too are trimethoprim and the fluoroquinolones. Rapidly excreted agents, such as nitrofurantoin and the β -lactam antibiotics are much less suitable, and use of massive doses is, contrary to popular belief, unlikely to much prolong the period for which inhibitory concentrations of the drug appear in bladder urine.¹⁸

Uncomplicated urinary tract infection is commonly overtreated and single high-dose therapy undoubtedly works in many cases. However, this therapeutic approach should not be seen as a universal panacea, even in infection that is confined to the lower urinary

tract.¹⁹ The benefits of economy and convenience provided by single high-dose therapy also apply to treatment with a single conventional dose of any one of various oral agents each night for three nights. This approach also has the advantage of offering the patient

the reassurance of therapy that continues for the usual duration of the symptoms.

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