Introduction

Fosfomycin tromethamine is a phosphonic acid antibacterial agent that has been approved in the USA for the treatment of uncomplicated urinary tract infections due to Escherichia coli and Enterococcus faecalis. This agent, given as a single 3 g oral dose, has been reported to be comparable with other antimicrobials for the treatment of uncomplicated urinary tract infections in women.\(^1\)\(^-\)\(^4\) The present study was designed to assess the in-vitro activity of fosfomycin by three different test methods. Fosfomycin tromethamine and four other antimicrobial agents were tested against consecutive outpatient urinary tract isolates of E. coli and E. faecalis collected from ten geographically separate North American medical centres.

Materials and methods

Microorganisms

During the winter of 1998, approximately 110 consecutive outpatient urinary tract isolates of E. coli were collected by each of ten medical centres (listed in Acknowledgements), and were shipped frozen to the Clinical Microbiology Institute for testing. In addition, all urinary isolates of enterococci encountered during this period were similarly collected and shipped. Only organisms that were predominant and with colony counts \(\geq 10^4\) cfu/mL were included; mixed flora or isolates of questionable significance were excluded as were multiple isolates from the same patient.

Antimicrobial agents

Fosfomycin tromethamine powder and fosfomycin Etest strips were provided by Forest Laboratories, New York, NY, USA. Ampicillin, ciprofloxacin, nitrofurantoin and trimethoprim/sulphamethoxazole were obtained from their respective manufacturers or from commercial sources. Commercially prepared antimicrobial discs included: fosfomycin, 200 \(\mu\)g; 50 \(\mu\)g of glucose 6-phosphate; ampicillin, 10 \(\mu\)g; ciprofloxacin, 5 \(\mu\)g; nitrofurantoin, 300 \(\mu\)g; and trimethoprim/sulphamethoxazole, 1.25/23.75 \(\mu\)g.

Susceptibility test

Fosfomycin MICs were determined by the agar dilution method as outlined by the National Committee for Clinical Laboratory Standards (NCCLS),\(^5\) using Mueller-Hinton agar supplemented with 25 mg/L of glucose 6-phosphate. Concentrations ranged from 0.06 to 128 mg of fosfomycin per litre (excluding the tromethamine portion of the salt). The inoculum contained approximately 1 \(\times\) \(10^4\) cfu/spot and the results were read after 18–20 h incubation at 35°C in air. The other antimicrobials were tested by the broth microdilution method outlined by the NCCLS\(^3\) with concentrations of 0.03–64 mg/L (ampicillin), 0.015–8.0 mg/L (ciprofloxacin), 0.12–256 mg/L (nitrofurantoin), and 0.03/0.27–64/576 mg/L (trimethoprim/sulphamethoxazole). Disc diffusion tests were performed at the same time by the method outlined by the NCCLS.\(^6\) Fosfomycin Etest strips were also applied to the disc diffusion plates and read according to the instructions.
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of the manufacturer. Etest MIC results that fell between even log₂ dilution intervals were read as the next highest even log₂ concentration.

Quality control

Quality control organisms were tested on each day of testing, and included: E. coli ATCC 25922, Pseudomonas aeruginosa ATCC 27853, Staphylococcus aureus ATCC 29213 and ATCC 25923, and E. faecalis ATCC 29212. Of 368 tests with antibiotic/organism combinations that have NCCLS control limits, 98.6% of results fell within these limits. All quality control results with fosfomycin were within previously recommended ranges for this drug.⁷

Results and discussion

A total of 1097 urinary isolates of E. coli was tested and all (100%) were susceptible to fosfomycin at ≤64 mg/L (Table). The proportion susceptible to the four comparison drugs ranged from 67.7% (ampicillin) to 99.3% (ciprofloxacin). The MIC₉₀ of fosfomycin was 1.0 mg/L and >98% of the isolates were susceptible to ≤2.0 mg/L of fosfomycin. Only minor differences in MIC distributions of all five antimicrobials were observed among the ten participating medical centres.

During that sampling period, 180 urinary isolates of enterococci were collected: 157 were E. faecalis, 20 were E. faecium and three were other enterococcal species. The MICs of all five drugs were significantly higher for E. faecium than for E. faecalis. Though the fosfomycin MICs for enterococci were considerably higher than those for E. coli, 97.5% of E. faecalis and 95.6% of all enterococcci were susceptible to fosfomycin at ≤64 mg/L. The percent susceptible to the other antimicrobials ranged from 59.4% (ciprofloxacin) to 91.7% (nitrofurantoin) (Table). Eight (4.4%) of the enterococcal isolates were resistant to vancomycin and five of those eight strains were susceptible to fosfomycin.

The comparison of fosfomycin MICs determined by agar dilution and by Etest is also shown in Table. The Etest MICs for E. coli averaged slightly more than half of one log₂ concentration higher than those determined by agar dilution, but 94% of the paired results were within one two-fold dilution of each other. For all enterococci, 99.5% of the paired MIC results by the two methods were within one two-fold dilution of each other with a slight skewing toward lower MICs by the Etest. The Etest appears to be an adequate substitute for agar dilution in determining MICs of fosfomycin tromethamine.

Scattergrams of the fosfomycin agar dilution MICs and the disc diffusion zone diameters are provided in the Figure. No major or very major discrepancies occurred with either organism; the minor discrepancy rates were 0.1% for E. coli and 2.5% for E. faecalis. The current susceptible breakpoint for fosfomycin is ≤64 mg/L, and this breakpoint has been shown to correlate well with clinical efficacy.⁸ The good correlation between MICs and disc diffusion zone diameters plus the low discrepancy rates support the previously proposed zone diameter breakpoints.⁹

In the USA fosfomycin tromethamine has not been widely used and, at the moment, virtually all E. coli isolates from outpatient urinary tract infections are susceptible to fosfomycin. This high susceptibility of E. coli

<table>
<thead>
<tr>
<th>Organism</th>
<th>n</th>
<th>Antimicrobial agent</th>
<th>MIC (mg/L)</th>
<th>50%</th>
<th>90%</th>
<th>geometric mean</th>
<th>% Susceptible⁶</th>
</tr>
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<tbody>
<tr>
<td>E. coli</td>
<td>1097</td>
<td>Fosfomycin</td>
<td>0.125–64</td>
<td>0.5</td>
<td>1.0</td>
<td>0.66</td>
<td>100</td>
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<td>Fosfomycin Etest</td>
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<td>1.0</td>
<td>2.0</td>
<td>0.99</td>
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<td></td>
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<td>16</td>
<td>3.75</td>
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<tr>
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<td></td>
<td>Nitrofurantoin</td>
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<td>32</td>
<td>15.38</td>
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<td>0.6</td>
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<td>0.63</td>
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<td>0.027</td>
<td>99.3</td>
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<td>Fosfomycin</td>
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<td>32</td>
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<td>38.14</td>
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<td>16</td>
<td>1.71</td>
<td>67.5</td>
</tr>
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</table>

⁶Susceptible to breakpoint concentrations defined by the NCCLS.⁵ or to ≤64 mg/L of fosfomycin.

⁷Trimethoprim/sulphamethoxazole in a 1:19 ratio.
E. coli and E. faecalis fosfomycin susceptibility

Figure. Scattergrams for fosfomycin MICs and disc diffusion zone diameters for 1097 E. coli isolates (a) and 157 E. faecalis isolates (b). Horizontal lines represent MIC breakpoints and vertical lines represent zone diameter breakpoints.

to fosfomycin in the USA is unchanged from a previous survey. Since E. coli is by far the most prevalent outpatient urinary tract pathogen, fosfomycin appears to be a reasonable alternative for the empirical treatment of uncomplicated outpatient urinary tract infections.

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References


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