FOSFOMYCIN WAS NOT mentioned as a therapeutic option for the treatment of urinary tract infections (UTIs) in the latest editions of two major textbooks of infectious diseases [1,2], despite the fact that it has been available in the United States for 4 years. It has been a commonly prescribed antibiotic in Japan and many parts of Europe for 2 decades. Fosfomycin was listed as a potentially useful antibiotic for the treatment of uncomplicated cystitis in an earlier review [3]. Currently, it has the approval of the U.S. Food and Drug Administration for the treatment of adult women with uncomplicated UTIs that are caused by *Escherichia coli* and *Enterococcus faecalis*. These introductory facts prompted this review of fosfomycin. We believe this discussion will be useful to practicing clinicians, especially those in the fields of internal medicine, gynecology, urology, and infectious diseases.

Fosfomycin trometamol was first described in 1969 [4]. It is a phosphonic acid derivative, which acts primarily by interfering with bacterial peptidoglycan synthesis, thereby disrupting cell wall synthesis [5]. It has a broad spectrum of activity against aerobic bacteria, including those that cause UTIs [6]. There seems to be little cross-resistance between fosfomycin and other antibiotics commonly used to treat UTIs; thus, its efficacy is not affected by development of resistance to other antibiotics. It can be administered orally with a convenient dosing schedule, including single-dose therapy for uncomplicated cystitis.

**Mechanism of Action**

Fosfomycin enters bacteria by utilizing the L-α-glycerophosphate transport system [5]. This is the major route of entry. There is also a secondary transport system, the hexose phosphate uptake system, which can be induced by glucose-6-phosphate [5]. Once inside the bacterium, it acts as an analogue of phosphoenolpyruvate and irreversibly inhibits the enzyme pyruvyl transferase, which catalyzes the first step of peptidoglycan biosynthesis. By blocking the action of this enzyme, fosfomycin inhibits cell wall synthesis.

**Pharmacokinetic Properties**

Fosfomycin has good oral bioavailability. Peak plasma levels of 22 to 32 mg/L occur 2 to 2.5 hours after a single oral dose of fosfomycin [7]. The drug is not bound to plasma proteins. It does not undergo metabolism in the body and is primarily excreted unchanged in the urine by glomerular filtration [8]. Peak urinary concentrations occur within 4 hours of dosing. After a single 3-g oral dose, urine fosfomycin levels >128 mg/L are maintained for at least 36 to 48 hours [9]. These levels are sufficient to inhibit most urinary pathogens. It has good penetration of the kidneys, bladder wall, prostate, and seminal vesicles [10]. Urinary fosfomycin levels are not compromised by mild degrees of renal insufficiency [11]. Cerebrospinal fluid penetration is about 25% [12].

Fosfomycin tromethamine is available in the unusual form of sachets, each containing the equivalent of 3 g of fosfomycin. The powdered preparation has to be dissolved in cold water before being administered orally. The taste is not objectionable. There is an intravenous formulation too, but this is not available in the United States.

**Spectrum of Activity**

Fosfomycin is a broad-spectrum antimicrobial with activity against most of the aerobic gram-positive and gram-negative bacteria. *In vitro* studies show that, at concentrations achieved in the urine, most of the commonly encountered urinary pathogens, including vancomycin-resistant enterococci (VRE) are susceptible to fosfomycin. In most studies, more than 90% of strains of *E. coli, Citrobacter diversus, C. freundii, Klebsiella oxy-
toxa, Klebsiella pneumoniae, Enterobacter cloaceae, Serratia marcescens, Proteus mirabilis, P. vulgaris, Providencia rettgeri, Pseudomonas aeruginosa, E. faecalis, and E. faecium were susceptible to fosfomycin.

In 10 North American medical centers, 100% of 1097 E. coli isolates and 97.5% of 157 E. faecalis isolates from outpatient urine specimens were susceptible to fosfomycin tromethamine [14]. Of 118 VRE isolates tested in Germany, only 3% to 7% of the strains were found to be resistant to fosfomycin [15]. Seventy-four of these isolates were E. faecium, of which only four were resistant to fosfomycin. In a study of 75 isolates of vancomycin-resistant E. faecium in the United States, 98.7% of the isolates were susceptible to fosfomycin (submitted for publication, data from the Cleveland Clinic Foundation).

Tolerability
Fosfomycin is very well tolerated. Mild, self-limiting gastrointestinal disturbances, usually diarrhea, are the most frequently reported adverse effects. Only one case of pseudomembranous colitis was noted in a post-marketing study involving 35,481 patients over a 6-year period in Japan [16]. Other common but minor adverse effects are dizziness, headache, and vaginitis.

Clinical Uses of Fosfomycin
Fosfomycin is essentially a urinary antibiotic. It has been used for other indications, but this is not common. In the United States, it is only available as an oral formulation and thus we will focus on its oral use for most of this discussion.

Treatment of uncomplicated lower UTIs in adult women. There have been several trials comparing fosfomycin with other antibiotics for the treatment of uncomplicated UTIs in adult women in Europe; a few have been double-blind trials. The antibiotics that fosfomycin was compared with included norfloxacin, ofloxacin, amoxicillin, amoxicillin-clavulanate, pefloxacin, pipemidic acid, and ceftriaxone. The antibiotics were variably given as a single dose or for 3 or 5 days. A review of these studies showed that at 1 week of follow up, bacteriologic eradication rates were about 90% with fosfomycin and from 80% to 90% with the other drugs [17]. At 4 to 6 weeks of follow up, eradication rates ranged between 60% and 90% for whatever drugs were used. Fosfomycin was safe and very well tolerated. Single oral dose therapy was at least as effective as other commonly used antibiotics for treating uncomplicated UTIs in adult women. A recent, randomized, double-blind study in the United States similarly found single-dose fosfomycin therapy of uncomplicated cystitis to be as effective as a 7-day course of nitrofurantoin [18].

The Infectious Diseases Society of America issued guidelines for the treatment of uncomplicated acute bacterial cystitis and pyelonephritis in women. These guidelines recognize trimethoprim-sulfamethoxazole (TMP-SMX) as the gold standard for the treatment of cystitis and compares other agents in relation to this drug [19]. They consider TMP and the fluoroquinolones to be equally effective. There have been no studies directly comparing fosfomycin with TMP or the fluoroquinolones in the treatment of UTIs are outlined in Table 1. These studies have used different definitions for their end points. In an attempt to compare them meaningfully, we chose to define “eradication” as eradication of the initial infecting strain at the follow-up visit closest to 7 days after the initiation of therapy, and “recurrence” as a new episode of bacteriuria within 6 weeks of therapy after eradication of the initial infecting strain, just as the Infectious Diseases Society of America guidelines had done. We took all adverse events as they were reported in the individual studies. These studies indicate that fosfomycin is at least as effective as the above-mentioned classes of drugs in the treatment of uncomplicated cystitis. One of the studies found a greater incidence of adverse effects with fosfomycin, but most of these were mild gastrointestinal problems.

Treatment of bacteriuria in pregnancy. Symptomatic and asymptomatic UTIs are very common during pregnancy and are clinically important. In this situation, single-dose therapy would be the ideal treatment because of minimal exposure of the fetus to the drug. Controlled studies have been performed in pregnant women who were treated with a 3-g single dose of fosfomycin trometamol for asymptomatic bacteriuria. In these studies, fosfomycin therapy was compared with a 7-day course of nitrofurantoin, or a 7-day course of pipemidic acid, or a single dose of amoxicillin. The eradication rates were similar for the drugs compared and approached 90% to 95% at 2 to 4 weeks and about 70% to 75% at 6 weeks after completion of therapy [25]. Fosfomycin seems to be relatively safe for use during pregnancy. No significant fetotoxicity has been reported in studies of treatment of asymptomatic bacteriuria in pregnancy with fosfomycin. It has been rated “pregnancy category B” in the United States (Table 2).
Treatment of pediatric UTIs. Few studies have looked at the use of fosfomycin tromethamine as single-dose therapy of UTIs in children. When used as a single dose, it was as effective as single-dose intramuscular netilmicin for the treatment of UTIs, with similar cure rates of about 80% and recurrence rates of about 10% [26]. Children with congenital abnormalities had a less impressive response with either drug. Fosfomycin has also been compared with pipemidic acid in this population but with small numbers of subjects. These studies have been reviewed, but because of lack of homogeneity in the studies, it is difficult to conclude that one treatment is better than the other [27]. Moreover, because UTIs in children are frequently caused by congenital anomalies of the genitourinary tract, children with such defects should not be treated with single-dose therapy. From the available data, fosfomycin seems to be safe and effective as single-dose therapy for the treatment of uncomplicated UTIs in children.

**TABLE 1. Randomized studies comparing single-dose fosfomycin with at least 3 days of trimethoprim or norfloxacin in the treatment of uncomplicated acute cystitis**

<table>
<thead>
<tr>
<th>Study design [Ref. no.]</th>
<th>n</th>
<th>Comparator drug</th>
<th>Follow up (w)</th>
<th>Parameter</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double-blind [20]</td>
<td>111</td>
<td>NFX 400 mg bid for 7 d</td>
<td>6</td>
<td>Eradication</td>
<td>60/61 (98%) vs 61/61 (96%) NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Recurrence</td>
<td>20/54 (37%) vs 17/50 (35%) NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adverse events</td>
<td>10/79 (13%) vs 2/79 (3%) .02b</td>
</tr>
<tr>
<td>Open-label [21]</td>
<td>261</td>
<td>Trimethoprim 200 mg bid for 5 d</td>
<td>4</td>
<td>Eradication</td>
<td>147/177 (83%) vs 70/84 (83%) NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Recurrence</td>
<td>14/96 (15%) vs 2/42 (5%) NS</td>
</tr>
<tr>
<td>Open-label [22]</td>
<td>60</td>
<td>NFX 400 mg bid for 7 d</td>
<td>4–5</td>
<td>Eradication</td>
<td>27/30 (90%) vs 25/30 (83%) NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Recurrence</td>
<td>4/27 (15%) vs 3/25 (12%) NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adverse events</td>
<td>1/30 (3%) vs 2/30 (7%) NS</td>
</tr>
<tr>
<td>Open-label [23]</td>
<td>63</td>
<td>NFX 400 mg bid for 5 d</td>
<td>4</td>
<td>Eradication</td>
<td>31/33 (94%) vs 28/30 (93%) NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Recurrence</td>
<td>6/31 (19%) vs 7/26 (27%) NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adverse events</td>
<td>9/33 (27%) vs 4/30 (13%) NS</td>
</tr>
<tr>
<td>Open-label [24]</td>
<td>32</td>
<td>NFX 400 mg bid for 3 d</td>
<td>4</td>
<td>Eradication</td>
<td>15/16 (94%) vs 15/16 (94%) NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Recurrence</td>
<td>2/15 (13%) vs 6/15 (40%) NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adverse events</td>
<td>1/16 (6%) vs 1/16 (6%) NS</td>
</tr>
</tbody>
</table>

Note. The numbers in the table may be different from those reported in the actual studies, because we have adjusted the numbers according to the definitions for eradication and recurrent bacteriuria that we used for our analysis. Individual studies had used definitions that were not necessarily identical to each other. Abbreviation used: NS, not significant; NFX, norfloxacin; Comp., comparator drug.

* This number includes only the bacteriologically evaluable patients. Total of patients for whom adverse events were reported may be different, because this number includes all patients included in the study.

b Chi-square test.

**TABLE 2. Pregnancy category rating of antibiotics useful in treating urinary tract infections**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Pregnancy rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fosfomycin</td>
<td>B</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>B</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>B</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>B</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>C</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>C</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>C</td>
</tr>
<tr>
<td>TMP</td>
<td>C</td>
</tr>
</tbody>
</table>

Note. Abbreviations used: TMP-SMX, trimethoprim-sulfamethoxazole.

**Prophylaxis before urological procedures.** Oral fosfomycin has been used for prophylaxis in patients undergoing transurethral resection of the prostate as dual-dose therapy and has been shown to decrease the incidence of postoperative fevers and bacteriuria as
compared with prophylaxis using amoxicillin and TMP-SMX. In one study, fosfomycin was administered in two 3-g doses, one 3 hours before surgery and one 24 hours after surgery. The incidence of symptomatic infections was found to be approximately 2% for subjects treated with fosfomycin as compared with more than 8% for those treated with either of the other two drugs [28]. The role of routine prophylaxis in otherwise healthy adults undergoing transurethral resection of the prostate is a controversial issue, but if used, oral fosfomycin seems to be simple, safe, and as effective as any other antibiotic. Asymptomatic bacteriuria before urologic surgery, however, should be treated [29].

**Treatment of pyelonephritis and complicated UTIs.** The antimicrobial and pharmacokinetic profiles of fosfomycin suggest that it might also be useful for the treatment of some cases of complicated UTIs caused by most urinary pathogens. Little has been published about the use of multiple doses for the treatment of upper UTIs and complicated UTIs. It has been used successfully to treat recalcitrant prostatitis caused by a VRE in a patient who wished to avoid intravenous therapy [30]. In this instance, it was administered orally once every 3 days for 3 weeks, based on the fact that therapeutic levels of the drug are known to be present in the urine for at least 36 to 48 hours after a single oral dose. Linezolid is a recently approved oral antimicrobial for the treatment of severe VRE infections, but is prohibitively more expensive than fosfomycin. Given the *in vitro* activity of fosfomycin against VRE, its long serum half-life, prolonged high urinary concentrations in the urine, good penetration of the kidneys and prostate, and potential for convenient oral administration, it is another useful drug for the treatment of VRE UTIs. However, it should not be used in patients with complicated UTIs caused by obstruction that need surgical intervention, because it cannot be expected to provide lasting clearance of bacteriuria in this situation.

**Use of Parenteral Fosfomycin**

Most of the published literature on fosfomycin deals with the use of single doses of the oral preparation. Much less has been written about the use of intravenous fosfomycin. There have been reports of successful treatment of severe pneumonia [31] in Denmark in 1983–1984, staphylococcal and enterococcal meningitis in France [32], and methicillin-resistant *Staphylococcus aureus* infective endocarditis in Japan [33], using fosfomycin in combination with other antibiotics. However, these have been only case reports and it is not known how many times fosfomycin has been used for similar cases and failed. Randomized studies have also shown a combination of intravenous fosfomycin and metronidazole to be effective for the prophylaxis of infection during elective [34] and emergent [35] abdominal surgery.

Because of lack of availability of a parenteral form of fosfomycin in the United States, this review has concentrated on its role in this country as a potentially useful oral antimicrobial agent.

**Resistance**

Bacterial resistance to fosfomycin is usually chromosomally mediated. In rare instances, it may be plasmid mediated. Of 60 isolates tested in Italy, only five carried plasmids encoding fosfomycin resistance [36]. As described above, fosfomycin uptake into the bacterial cell is mediated by the L-α-glycerophosphate and hexose phosphate uptake transport systems. Chromosomally mediated resistance occurs essentially because of mutations that interfere with these two transport mechanisms [5], resulting in reduced intracellular concentrations of the drug in the target bacteria.

Since the first report of plasmid-mediated resistance to fosfomycin in *S. marcescens* in 1980 [37], there have been reports of similar resistance in other bacteria including *S. liquefaciens, K. oxytoca, K. pneumoniae*, and *E. coli*. One of these plasmid-harbored genes has been characterized and is called the *fosA* gene. The protein encoded by the *fosA* gene brings about glutathione conjugation of fosfomycin, rendering it ineffective [38]. The *fosA* gene has not been found in gram-positive bacteria. Some *S. aureus* and *S. epidermidis* bear a different fosfomycin-resistance gene, *fosB* [39]. The mechanism of resistance conferred by the *fosB* gene has not been determined.

Fosfomycin acts at a target site that is not affected by other antimicrobials. As a result, there seems to be little cross-resistance between fosfomycin and the other commonly used urinary antibiotics. Concerns have been expressed about the potential for development of resistant mutants if fosfomycin is used for prolonged periods of time to treat difficult infections. A survey conducted in the early 1990s of 7453 urinary pathogens in three hospitals in Italy showed that the prevalence of resistance to fosfomycin was only approximately 2.8% after several years of widespread use of fosfomycin as single-dose therapy for uncomplicated UTIs [40]. It is not known whether the same would hold true
if the drug was used widely for prolonged courses of therapy.

Cost

The cost of a sachet of fosfomycin is U.S. $28 [41]. The medication cost of treating one episode of uncomplicated UTI with this drug is approximately U.S. $28, which is comparable to the cost of a 3-day course of ciprofloxacin (U.S. $25) or ofloxacin (U.S. $33) [41]. TMP-SMX would be less expensive, costing about $6 for a 3-day course for the treatment of cystitis.

Conclusions

The efficacy of single-dose fosfomycin in the treatment of uncomplicated UTIs in women has been well established in clinical studies and extensive clinical application in several countries in Europe and in Japan. So far, such use has not led to the development of resistance. There are no compliance issues with fosfomycin because it involves a single dose. The cost of treating one episode of cystitis compares favorably with most treatments currently available.

Distinguishing between infection and colonization is important to avoid the indiscriminate use of fosfomycin in asymptomatic bacteriuria in the elderly and in patients with chronic indwelling urinary catheters. In recurrent UTIs that are not caused by a surgically correctable abnormality, prudent use of fosfomycin could decrease development of resistance by decreasing antibiotic selection pressure. In patients with UTIs and allergies to multiple classes of antibiotics, fosfomycin may have a unique niche. In this situation, it is another easily administered oral antibiotic that can be used before resorting to the use of an aminoglycoside or another parenteral antimicrobial agent.

Fosfomycin seems to be an excellent alternative antibiotic for the treatment of uncomplicated cystitis. It is superior to the fluoroquinolones when efficacy, ease of administration, and cost are considered together. It is an excellent choice for the treatment of bacteriuria during pregnancy. Fosfomycin should also be considered an option for the treatment of complicated UTIs in certain situations.

References


