



Letter to the Editor

Outcomes of Fosfomycin Use in Ceftriaxone-Resistant Enterobacteriaceae Urinary Tract Infection in the Elderly



Sir,

Fosfomycin is a cell-wall active antibiotic with bactericidal activity against many Gram-positive and -negative bacteria. One dose of 3 g oral fosfomycin is indicated for uncomplicated cystitis in females [1]. Increasingly, fosfomycin is used to treat cystitis caused by drug-resistant organisms but data on patients with renal impairment are lacking. We conducted a retrospective study to determine the safety and efficacy of fosfomycin in treatment of cystitis caused by extended spectrum beta-lactamase (ESBL) Enterobacteriaceae in a 1400-bed teaching hospital.

Following hospital protocol, patients with cystitis due to ceftriaxone-resistant Enterobacteriaceae with no oral alternatives were given one dose of 3 g fosfomycin trometamol (FT). Patients with complicated cystitis could be given 3 g FT every other day for three doses (with no prior active antibiotic), or the required number of doses to make up for the effective treatment duration if FT was switched from an active empirical or definitive therapy. Active empirical antibiotic was defined as the use of empirical antibiotic for at least 48 h that was later found to be active against the isolated uropathogen. Active definitive antibiotic was defined as a culture-directed, non-fosfomycin antibiotic for at least 24 h before switching to FT. Antibiotic susceptibility was determined and interpreted according to Clinical and Laboratory Standards Institute (CLSI) criteria.

Cystitis was defined as positive urine culture (>10000 colony-forming units [CFU]/mL) associated with symptoms (dysuria, urgency, frequency, incontinence, retention, acute mental state change) and raised inflammatory markers or fever. Patients with pyelonephritis or polymicrobial urine cultures were excluded. Complicated cystitis was defined as catheter-associated urinary infections and infections in patients with urogenital abnormalities or renal calculus [2]. Clinical cure was defined as resolution of signs and symptoms at completion of therapy. Microbiological cure was defined as no bacterial growth on repeated culture (if any) at completion of therapy. Recurrence was defined as occurrence of another urinary infection within 3 months of the index episode. In cases of recurrence we documented the susceptibility of subsequent uropathogen to FT to determine rates of resistance development. Adverse reactions to FT during a treatment course were recorded on medical charts.

A total of 115 patients received oral FT from 01 March 2013 to 30 June 2014. Baseline characteristics for these patients are listed in Table 1. Overall, 82 (71.3%) patients achieved clinical cure with no reported adverse drug events. Microbiological cure was documented in 21 (60%) patients. Thirty-three (28.7%) patients had recurrent urinary infections within 3 months and, of these, 11

Table 1

Baseline patient characteristics (N = 115).

Demographic data	n (%) ^a
Age, median (IQR)	79 (70.0, 86.0)
Female sex	72 (62.6)
Drug allergy	
Beta-lactam	24 (20.9)
Quinolone	1 (0.9)
Co-trimoxazole	5 (4.3)
Creatinine clearance	
Median (IQR)	40.4 (27.6, 56.5)
<30 mL/min	34 (29.6)
30–50 mL/min	41 (35.7)
>50 mL/min	40 (34.8)
Co-morbidities	
Charlson's co-morbidity score, median (IQR)	6.0 (4.0, 8.0)
Cardiovascular disease	43 (37.4)
Cerebrovascular disease	46 (40.0)
Diabetes mellitus	49 (42.6)
Diagnosis	
Cystitis	77 (67)
Complicated cystitis	38 (33)
Catheterisation	32 (27.8)
Urogenital abnormalities	4 (3.5)
Renal calculus	2 (1.7)
Microbiology	
<i>Escherichia coli</i>	71 (61.7)
<i>Klebsiella pneumoniae</i>	44 (38.3)
No. of fosfomycin trometamol doses	
3 g once	88 (76.5)
3 g × 3 doses	22 (19.1)
Others	5 (4.3)
Use of other antibiotics	
Active empirical	30 (26.1)
Active definitive (non-fosfomycin)	37 (32.2)

^a Results are n (%) unless indicated as Median (IQR). IQR – interquartile range.

(30.0%) had bacteria resistant to FT. Patients received a median of 3 days (IQR: 2,5) of prior active antibiotics before switching to FT. Of the 67 (58.2%) patients who received prior active antibiotics, 48 (71.6%) achieved clinical cure. Of the 88 (76.5%) patients who received one dose of FT, 63 (71.6%) achieved clinical cure and 25 (28.4%) developed recurrent urinary infections, with 6 of them having bacteria resistant to FT. On the other hand, of 27 (23.5%) patients who received more than 1 dose of FT, 19 (70.3%) achieved clinical cure and 8 (29.6%) developed recurrent urinary infections with 5 having bacteria resistant to FT.

The rate of development of resistance in our study (30%) is higher than rates reported in the literature (2.3–6.7%) [3]. The high biological cost that comes with development of resistance was thought to be the reason for low resistance rate [4]. However, these studies were conducted at a time when fosfomycin consumption was low compared with other antibiotics like beta-lactams or flu-

oroquinolones. Oteo et al. evaluated 17 602 *E. coli* urinary infections from 2003 to 2008 and found that a 50% increase in fosfomycin use resulted in an increase of fosfomycin-resistant ESBL *E. coli* strains from 2.2% to 21.7% [5].

In conclusion, fosfomycin is effective for treating ESBL Enterobacteriaceae urinary infections in elderly patients with mild renal impairment. However, this should be further validated in studies with larger cohorts and clinical pharmacokinetic studies. Development of resistance is a pressing issue and to preserve the utility of fosfomycin, it may be prudent to limit fosfomycin to culture-directed use only.

Declarations

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Competing Interests

None.

Ethical Approval

This study is approved by National Health Group Domain Specific Review Boards (Ref: 2015/00513-SRF0001).

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