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Fosfomycin in the treatment of extended spectrum beta-lactamase-producing *Escherichia coli*-related lower urinary tract infections

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Abstract

Fosfomycin tromethamine (FT) is effective in vitro in extended spectrum beta-lactamase (ESBL)-producing *Escherichia coli* strains. The aim of this study was to evaluate the effect of FT in the treatment of ESBL-producing *E. coli*-related lower urinary tract infection. All patients were aged >18; had dysuria or problems with frequency or urgency in passing urine; had >20 leukocytes/mm^3 in urine sediment and an ESBL-producing *E. coli* urine culture (>10^5 cfu/mm^3); no leukocytosis or fever; and were treated with FT between September 2004 and July 2006 in our outpatient clinic and hospital. ESBL detection was performed by double disk synergy tests. All patients had received FT (3 g × 1 every other night, three times) and had a control urine culture taken 7 to 9 days after this therapy. Clinical success was defined as resolution of symptoms on the control visit; microbiological success was defined as a sterile control urine culture. In all, 52 patients (aged 55.0 ± 18.3, range 19–85; 25 males, 27 females) were included in the study. Overall clinical and microbiological success was 94.3% (49/52) and 78.5% (41/52), respectively. Although it is not a randomized controlled study, these data show that FT may be a suitable, effective and cheap alternative in the treatment of ESBL-producing *E. coli*-related lower urinary tract infection.

Keywords: ESBL; Lower urinary tract infection; Cystitis; Uncomplicated urinary tract infection; Complicated urinary tract infection

1. Introduction

Urinary tract infections (UTIs) are the most common nosocomial infections [1]. *Escherichia coli* is the most common bacterial agent in both nosocomial and hospital-acquired UTIs [2,3]. Extended spectrum beta-lactamase (ESBL)-producing *E. coli* and *Klebsiella pneumoniae* are growing problems in many parts of the world [4–6]. The antibiotics of choice, carbapenems, usually require hospitalization and are associated with higher drug costs [5]. Fosfomycin tromethamine (FT), which is derived from phosphonic acid and affects cell wall synthesis by enolpyruvate transferase inhibition, has entered the Turkish market very recently. FT is effective in vitro against ESBL-producing and non-ESBL-producing *E. coli* strains [2,7]. The aim of this study was to evaluate the effect of FT in the treatment of ESBL-producing *E. coli*-related lower UTI.

2. Methods

We retrospectively evaluated the hospital records of 52 patients aged >18 with dysuria or problems with frequency or urgency in passing urine; >20 leukocytes/mm^3 in urine microscopy and culture-proven ESBL-producing *E. coli* in the urine (>10^5 cfu/mm^3); no leukocytosis or fever; and who were treated empirically with FT (Bilim, Istanbul, Turkey) between September 2004 and July 2006 in our outpatient clinic and hospital.

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Clean-catch urine samples obtained from patients were inoculated onto 5% blood agar and eosin–methylene blue agar with 0.01 mL calibrated loops. Identification of *E. coli* was performed by conventional methods. Susceptibility to FT, ciprofloxacin, trimethoprim/sulfamethoxazole (TMP/SMX), imipenem/cilastatin and meropenem were determined and interpreted according to NCCLS criteria by means of disk diffusion susceptibility tests on Mueller Hinton agar (Oxoid) [8]. ESBL detection was performed by double disk synergy test (Oxoid).

In the case of an indwelling urinary catheter, diabetes mellitus, neurogenic bladder, obstruction due to nephrolithiasis, tumour or fibrosis, urinary retention due to benign prostatic hypertrophy, bladder cancer or other urological anatomical abnormalities, the UTI was considered to be complicated.

All patients had received FT (Monurol sachet, Bilim, Turkey, peroral, 3 g × 1 every other night, three times) and had a control urine culture taken 7 to 9 days after this therapy. Clinical success was defined as resolution of symptoms on the control visit; microbiological success was defined as a sterile control urine culture.

Relapse was defined as isolation of ESBL-producing *E. coli* in the control urine cultures performed 28 days after the end of therapy. Reinfection was defined as isolation of any pathogen in the control urine cultures performed 28 days post therapy.

3. Results

In all, 52 patients (aged 55.0 ± 18.3, range 19–85; 25 males, 27 females) were included in the study. All pathogens were resistant to ciprofloxacin and TMP/SMX and were susceptible to FT, imipenem/cilastatin and meropenem. The most common underlying problem was the presence of an indwelling urinary catheter (Table 1).

Overall clinical and microbiological success was 94.3% (49/52) and 78.5% (41/52), respectively. Clinical and microbiological failure was similar in patients without or with an underlying risk factor ($P > 0.05$, 0/16 versus 3/33; and $P > 0.05$, 4/16 versus 7/36, Fisher's exact test). Control urine culture performed 28 days after the end of therapy was available in 28 of 52 patients with microbiological success. Relapse and reinfection rates were 0% (0/28) and 10.7% (3/28), respectively.

Table 1
Complicating factors of patients with lower UTI

Complicating factor	*n*
None	16
Indwelling urinary catheterization	7
Hemi- or quadriparesis	2
Malignity involving urinary tract	4
Other malignities	4
Diabetes mellitus	5
Renal transplantation	5
Nephrolithiasis	3
Recent urological intervention	6

4. Discussion

E. coli is the most common aetiological agent in either community-acquired or hospital-acquired UTI [1–3]. ESBL-producing bacteria increase the risk of morbidity and mortality in hospital-acquired infections and are associated with high antibiotic costs [5].

Community-acquired ESBL is an emerging problem [9]. Arslan et al. reported an ESBL rate of 7.9% in 514 community-acquired UTI-associated *E. coli* strains [9]. The antibiotic of choice in ESBL-producing *E. coli*- or *K. pneumoniae*-related infections is generally carbapenems [5]. None of the isolates from the patients in this study was susceptible to TMP/SMX or ciprofloxacin and the patients were therefore candidates for aminoglycoside or carbapenem treatment. In Turkey the drug acquisition cost of a 14-day carbapenem treatment is 42 to 56 times more than 3 g × 1 of FT every other night, three times (depending on the selected carbapenem, imipenem/cilastatin or meropenem).

Ciprofloxacin is the second most commonly prescribed agent in UTI [10]. Taking ciprofloxacin is a risk factor for acquiring infection with ESBL-producing bacteria and also a risk factor for ciprofloxacin resistance [9]. High resistance rates for beta-lactams, TMP/SMX and ciprofloxacin restrict empirical antibiotic use in ESBL-producing bacteria-related UTI. Although FT is indicated in non-complicated UTI with *E. coli*, our data show that the drug can be effective in complicated cases without fever or leukocytosis.

Antibiotic resistance to commonly used agents such as TMP/SMX and ampicillin often exceeds 30–50%. FT, despite many years of usage, continues to be characterized by an extremely low incidence of resistance (about 1%) in *E. coli* strains worldwide [1,13]. FT resistance is also rare in UTI-related *E. coli* strains in Turkey. Previous studies have reported a fosfomycin-resistance rate of 0%, 0.3% and 0% in 72, 288 and 100 strains [2,9,11]. Fosfomycin resistance is very rare in ESBL-producing *E. coli* strains related to UTI too. Pullukcu et al. reported a resistance rate of 3.1% to FT in 344 ESBL-producing *E. coli* strains [7].

Resistance to FT is shown in *fosA*-positive *E. coli* strains [12]. The metalloglutathione transferase FOSA catalyses the conjugation of glutathione to carbon-1 of the antibiotic fosfomycin, rendering it ineffective as an antibacterial drug. There is no animal feed that contains the drug; resistance is most frequently acquired by chromosomal mutations that do not spread to other organisms easily [13]. The reason that FT resistance is rare is possibly due to very high and sustained concentrations of urine, which rapidly kill uropathogens and reduce the opportunity for mutant selection [13].

Fosfomycin is indicated in the treatment of uncomplicated cystitis, along with the advantage of only needing one dose [14]. A single dose of FT had activity comparable with a

5-day course of TMP in a trial where the causative organism and its sensitivity were unknown. In another trial FT showed better long-term eradication compared with a 5-day course of cephalexin, and other studies suggested a single dose of FT was comparable with a 7-day course of nitrofurantoin or norfloxacin [15–18]. In our study, FT was initiated empirically in all patients in our outpatient clinic or during consultations of hospitalized patients. Nearly all ESBL + *E. coli* UTI are referred to the infectious diseases outpatient clinic due to a restriction of carbapenems without the prior authorization of infectious diseases specialists. FT treatment was continued for two more doses after the bacteriological results, since some of the infections were hospital-acquired, all but 16 had one of several underlying risk factors and there were no data about the efficacy of the drug in ESBL+ *E. coli*-related UTI. A microbiological success rate of 80.5% in our patients with complicated UTI is comparable with the microbiological success rate of imipenem/cilastatin (81% in 82 patients) and meropenem (90% in 95 patients) in the study performed by Cox et al. on patients with complicated UTI [19]. The fact that the microbiological cure rate in our study is about 15% lower than other studies performed with one dose of FT supports the need for three or more doses of FT in this patient group [16,17].

Testing of cultures was performed 7 to 9 days after the last dose of the drug in concordance with Infectious Diseases Society of America guidelines [20].

Relapses are common after UTIs. Since this was not a prospective study only 28 (68.2%) of 41 patients with microbiological success who were on routine follow-up in our outpatient clinic had a control urine culture taken 28 days after the end of therapy. Relapse and reinfection rates were 0% and 10.7%, respectively. These rates are in concordance with the relapse rates in published trials with one dose of 3 g FT [17,18].

In our study none of the patients stated any side effects. In the published trials there were few serious side effects with FT and it was considered a safe and effective first line treatment in lower uncomplicated UTI [14].

To our knowledge this is the first study in which FT was used in the treatment of lower UTI due to ESBL+ *E. coli*, and in patients with complicated UTI, with a prolonged dose regimen of FT. Although it is not a randomized controlled study our data show that fosfomycin may be a suitable, effective and cheap alternative in the treatment of ESBL-producing *E. coli*-related lower UTI. A prospective randomized controlled study can help to find out if these retrospective findings are generalizable.

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Conflict of interest: none.

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