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Susceptibility of uropathogenic multidrug-resistant *Escherichia coli* to Fosfomycin

Deepak Kumar, Arghya Das, Manish Kumar Purbey, Nidhi Gupta, Gopal Nath

Abstract:

CONTEXT: *Escherichia coli* is one of the most important causes of urinary tract infections (UTIs). Increased antibiotic resistance may limit the therapeutic options for the treatment of *E. coli* infections. Fosfomycin an orally dispensed antibiotic has shown promising *in vitro* activity against multidrug-resistant (MDR) urinary *E. coli* pathogen; however, current resistance data from India are scarce.

AIM: The aim of this study is to evaluate the *in vitro* Fosfomycin activity against uropathogenic MDR *E. coli.*

MATERIALS AND METHODS: A total of 150 previously confirmed MDR *E. coli* urinary isolates were included in this study. Susceptibility testing and result interpretation of isolates to Fosfomycin was performed by the disc diffusion method as per the Clinical and Laboratory Standards Institute M100-S25 recommendations.

RESULTS: Fosfomycin appears to exhibit excellent *in vitro* activity against the MDR *E. coli* urinary isolates. The susceptibility for Nitrofurantoin was fair, whereas for Ampicillin, Ofloxacin, Norfloxacin, Cefazoline and Trimethoprim/Sulphamethoxazole was found poor.

CONCLUSION: In view of the high *in vitro* susceptibility to Fosfomycin in this population and the lack of cross-resistance between Fosfomycin and other agents, Fosfomycin may be considered a useful reserve drug in the treatment of uncomplicated UTIs caused by MDR *E. coli*.

Keywords:

Escherichia coli, Fosfomycin, multidrug-resistance

Introduction

There has been an increase in the proportion of urinary tract infection (UTI) due to multidrug-resistant (MDR) *Escherichia coli*.[1] An infection by these MDR bacteria remains a challenge for the clinician. Due to the slow rate of introduction of new antibiotics effective against these MDR pathogens, old antibiotic agents, such as Fosfomycin is re-emerging as a promising agent for the treatment of urinary MDR pathogen.[2,3]

Fosfomycin is an orally dispensed antibiotic with excellent *in vitro* activity against *E. coli*.[4] It inhibits bacterial cell wall synthesis by acting as a phosphoenolpyruvate analogue, irreversibly inhibiting enolpyruvyl transferase, an enzyme that catalyses the first step in the biosynthesis of peptidoglycan.[5] Use of alpha-glycerophosphate and glucose-6-phosphate active transport bacterial system is necessary to achieve membrane lysis of the targeted pathogen while minimising the possibility of cross-resistance with other antibiotics.[6]

Fosfomycin tromethamine is approved by the US Food and Drug Administration as a single 3g dose, given orally as a powder sachet for treatment in women with uncomplicated UTIs caused by *E coli*.[7] The

Department of Microbiology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

Address for correspondence:
Dr. Deepak Kumar, Department of Microbiology, Institute of Medical Sciences, Banaras Hindu University, Varanasi - 221 005, Uttar Pradesh, India.
E-mail: deepak.mln30@gmail.com

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emergence of resistance is a reasonable concern when evaluating Fosfomycin for clinical use. Certainly, only limited current resistance data from India are available. It is thus important to monitor the trends of resistance to Fosfomycin in the *E. coli* causing UTI. The aim of this study was to evaluate the *in vitro* Fosfomycin activity against uropathogenic MDR *E. coli.*

Materials and Methods

This study was carried out in the Department of Microbiology, Institute of Medical Science, Banaras Hindu University, Varanasi, India. The total duration of study was one year extending from April 2014 to March 2015. The urine samples were received in the Department of Microbiology for Culture and Sensitivity from Sir Sundarlal Hospitals, Banaras Hindu University, Varanasi, India.

After isolation and identification, the *E. coli* strains were kept at -20°C in peptone/glycerol (30% w/v), and before Fosfomycin susceptibility testing, the strains were purified twice on blood agar plates. Multidrug resistance was defined as resistance to at least one agent in three or more antimicrobial classes.[7]

Susceptibility testing of the isolates to Fosfomycin was performed by the disc diffusion method as per the Clinical and Laboratory Standards Institute (CLSI) M100-S25.[8] Mueller-Hinton agar (HiMedia Laboratories) was used as testing media. Fosfomycin discs (200 µg) containing 50 µg of glucose-6-phosphate were used (HiMedia Laboratories). The inoculated plates were incubated in ambient air at 37°C for 16 to 18 h. *E. coli* ATCC 25922 was used as control strains and zone of inhibition was interpreted using CLSI M100-S25(2015) breakpoints.

Results

A total of 150 clinical urinary isolates were included in this study. Table 1 shows the epidemiological characteristics and distribution of various *E. coli* isolates. Of these 150 isolates, 61 (41%) were isolated from male patients, whereas 89 (59%) were from female patients. Department-wise distribution of the isolates was as follows [Table 1]. The highest rate of isolation was from Urology Department, 79 (52.7%) followed by Obstetrics and Gynaecology Department 19 (12.7%). Of these 150 isolates, 118 (78.7%) were isolated from patients above 18 years of age while remaining 32 (21.3%) were isolated from paediatric patients.

None of the *E. coli* isolates were resistant to Fosfomycin [Figure 1] and 139 (93%) of the isolates were found to be sensitive to Nitrofurantoin. The percentage susceptibility was 7%, 11%, 12%, 20% and 23%, respectively, for Ampicillin, Ofloxacin, Norfloxacin, Cefazoline and Trimethoprim/Sulphamethoxazole as shown in Figure 1.

Discussion

The data presented in this study regarding the antibacterial activity of Fosfomycin tromethamine against uropathogenic *E. coli*, support the findings of studies performed worldwide. Increasing level of resistance among *E. coli* strains to Ampicillin, Trimethoprim/Sulphamethoxazole or Fluoroquinolones has been reported previously in various clinical settings.[9-11] Our study supports the above finding, as a high level of antimicrobial resistance in *E. coli* isolates was found. The reported rates of *E. coli* resistance to Fosfomycin by many authors were lower.[12,13] The results of this study are consistent with the results of other studies. All the *E. coli* isolates tested were susceptible to Fosfomycin.

The high *in vitro* susceptibility of the isolates tested to Fosfomycin and low-resistance prevalence may be

Table 1: Epidemiological characteristics and distribution of *Escherichia coli* isolate

Patients characteristic	Number of isolates, *n* (%)
Gender	
Male	61 (40.7)
Female	89 (59.3)
Age	
<1 month	5 (3.3)
1 month to 1 year	10 (6.6)
1-19 years	17 (11.3)
>19 years	118 (78.7)
Location	
Medicine	18 (12.0)
Surgery	14 (9.3)
Urology	79 (52.7)
Obstetrics and gynaecology	19 (12.7)
Paediatrics	10 (6.7)
Other	10 (6.7)

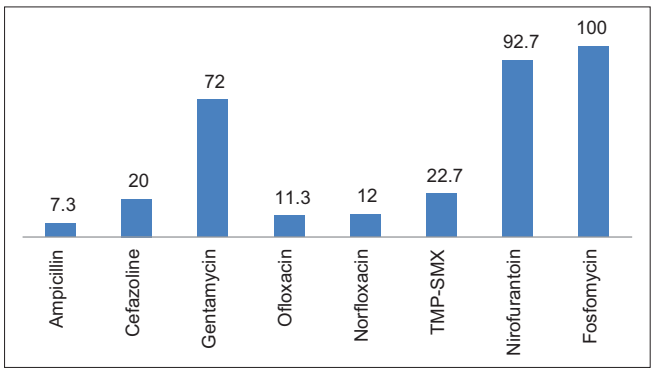

Figure 1: Susceptibility of *Escherichia coli* isolates to various antibiotics

related to its restricted use for the treatment of UTIs in our hospital. According to a few studies, increased Fosfomycin usage has been shown to correlate with increasing resistance among extended spectrum beta-lactamase producing *E. coli* isolates.[4] On the contrary, many countries have shown no measurable increase in resistance and absence of cross-resistance with other compounds by the clinical use of Fosfomycin tromethamine.[14-16] The development of cross-resistance to Fosfomycin by the use of other classes of antibacterial agents such as beta-lactams and aminoglycosides has not been regarded as significant, probably due to the unique target of action of Fosfomycin. Moreover, the main type of resistance to Fosfomycin appears to be chromosomal rather than plasmid-mediated.[17]

Fosfomycin is generally well tolerated; a 3 g oral single dose is recommended for adults and adolescent females (>12 years of age). Its safety and efficacy in children below 12 years of age have not been established. Rare side effects reported are rashes, acute hypersensitivity reactions, vomiting, anorexia, diarrhoea, liver enzyme elevation, headache, dizziness and fatigue. Contraindications to the administration are hypersensitivity to its active substance, patients with severe renal insufficiency (creatinine clearance <10 ml/min), and patients undergoing haemodialysis. Food may delay its absorption with a consequent slight decrease in peak plasma levels and urinary concentrations. It is, therefore, preferable to take the drug on an empty stomach or about two–three hours after meals.[18]

According to Schito, Fosfomycin tromethamine remains a reliable therapeutic option for the treatment of uncomplicated UTI due to its main advantages, including single dose usage and very high and sustained urinary concentrations that rapidly kill bacteria, reducing the opportunity for mutant selection. In addition, Fosfomycin tromethamine has excellent tolerability and safety.[19] It should be remembered that the inadvertent use of Fosfomycin must be checked which may lead to the development of resistance. This could be a challenging task for a country like India, where a major problem is with regard to over the counter sale, injudicious use and poor control over antibiotics which must be restricted for exceptional situations. Therefore, it becomes necessary to know the prevalence of plasmid-mediated resistance in clinical *E. coli* through surveillance programs. However, several other microbiological considerations, such as minimal rates of recurrences with the use of Fosfomycin, prevention of biofilm formation and the ability to partially disrupt slime in mature biofilm structures, supports the primary role of Fosfomycin tromethamine as a reserve antibiotic in microbiologically confirmed cases of UTI due to Fosfomycin susceptible MDR isolates.[17]

Conclusion

The available evidence shows that Fosfomycin has a high level of antimicrobial activity against *E. coli* isolates with advanced resistance to antimicrobial drugs. Low level of resistance compared to other oral agents and lack of cross-resistance with other compounds makes it an effective and safe drug in the treatment of UTIs due to MDR pathogens.

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Conflicts of interest
There are no conflicts of interest.

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