ORIGINAL ARTICLE

IN VITRO EFFICACY OF FOSFOMYCIN AGAINST VARIOUS URINARY ISOLATES

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ABSTRACT

Background: Urinary tract infections are one of the most common infections especially in young adults and pregnant women. Due to increase in fluoroquinolones use, empirical therapy in uncomplicated urinary tract infections with this group is now controversial. In recent years, fosfomycin has emerged as an economical and effective single dose agent in uncomplicated urinary tract infections. The objective of this study was to evaluate the in-vitro sensitivity of fosfomycin against various urinary isolates.

Material & Methods: This descriptive laboratory based study was carried out at the Department of Pathology, Combined Military Hospital, Dera Ismail Khan. A total of 120 clinical isolates cultured from urine specimens were processed from July 2012 through February 2013. All the isolates were checked for their susceptibility testing against fosfomycin and other routine antibiotics used for urinary pathogens.

Results: Out of total 120 urinary isolates, percentages of sensitivities of fosfomycin against *Escherichia coli, Klebsiella pneumoniae, Pseudomonas spp, Proteus spp, Enterobacter spp, Enterococcus spp, and Staphylococcus aureus* were 97.2, 63.6, 80, 87.5, 71.4, 83.3, and 80% respectively.

Conclusion: Our study suggests that fosfomycin has reasonably good in-vitro activity against common urinary isolates. Therefore it can reliably be used in uncomplicated urinary tract infections as empirical therapy. However, further studies are needed on larger specimen size to support our evidence.

KEY WORDS: Fosfomycin, Urine culture, Urinary tract infections.

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INTRODUCTION

After respiratory tract infections, urinary tract infections (UTIs) are most common infections.[1] Treatment of UTIs with antibiotics has certain economical and medical implications.[2] According to an estimate, in United States, about 8 to 10 million people visit to clinicians for suspected UTIs.[3,4] Sulfamethaxazole-trimethoprim (cotriamoxazole) was most commonly used drug along with the beta lactam drugs in the past for treatment of UTIs.[5] However, growing resistance to this combination led the clinicians to switch to fluoroquinolones. But unfortunately, due to misuse and over use, resistance to fluoroquinolones has also been reported thus limiting the oral therapy option for UTIs.[6,7]

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Fosfomycin tromethamine, an old broad spectrum bactericidal antibiotic, acts by inhibiting the peptidoglycan synthesis, thus inhibiting the cell wall formation of bacteria. In uncomplicated UTIs, this agent is recommended and can be used as a 3 grams single dose therapy against *Escherichia coli* and *Enterococcus faecalis*.[8] It has good activity both against Gram positive and Gram negative bacteria isolated from urine cultures. It has little cross resistance with other antimicrobial agents due to its chemical composition and site of action. Therefore, this study was aimed to evaluate the in-vitro efficacy of fosfomycin against various urinary isolates by disc diffusion susceptibility testing method.

MATERIAL AND METHODS

This laboratory based descriptive study was carried out at the Department of Pathology, Combined Military Hospital, Dera Ismail Khan Pakistan from July 2012 through February 2013. All the urine specimens, with pus cells more than 4-5 cells/HPF under microscope were included in the study period. Repeat specimens, specimens with broken or

leaked containers, and specimens yielding mixed growth were excluded from the study. In the protocol we followed, all the urine specimens were inoculated on CLED (Oxoid, UK) medium and incubated at 37ºC for 24-48 hours. Colonies were subjected to Gram stain and conventional tests. Species identification of gram negative organism was done by using API 10S (Biomerieux, France). Antibiotic susceptibility testing was carried out on Muller-Hinton Agar (Oxoid, UK) by using modified Kirby-Bauer disk diffusion method.[9] Antibiotic discs used were: fosfomycin 50 µg (Oxoid, UK), nitrofurantoin 300ìg (Oxoid, UK), ampicillin 10µg (Oxoid, UK), gentamicin 10µg (SPAN Diagnostic, France), ceftazidime 30µg (Oxoid,UK), tazobactem/piperacillin 10/100µg (Oxoid,UK), sulbactam/cefoperazone 105µg (Oxoid, UK), trimethoprim/sulfamethoxazole 1.25/23.75µg (Oxoid, UK), vancomycin 30µg (Oxoid,UK), and imipenem 10µg (Oxoid, UK). *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 25923, and *Pseudomonas aeruginosa* ATCC 25853 were used as control strains.

Gender and age in years were demographic while isolation of microorganisms and their sensitivity to different antibiotics were research variables. Age in years was analyzed for mean, standard deviation and range while rest of the three variables were analyzed for frequency (number) and relative frequency (%).

RESULTS

A total of 120 isolates were included in the final analysis. Out of total 120 clinical isolates, 42 (35%) were from male and 78 (65%) were from female patients. The mean age of patients was 29 ± 10.4 (8-78) years. *E. coli* was the dominant isolate followed by *Klebsiella pneumonia* and *Pseudomonas* as shown in Table 1.

E. coli showed maximum sensitivity to fosfomycin 71(97.2%) (figure 1) followed by *Pro-*

Table 1: Frequency of various urinary isolates cultured (n = 120).

S. No.	Organism	Frequency (Number)	Relative frequency (%)
1.	*E. coli*	73	60.8
2.	*K. pneumoniae*	11	9.1
3.	*Pseudomonas*	10	8.3
4.	*Proteus spp.*	8	6.7
5.	*Enterobacter spp.*	7	5.8
6.	*Enterococcus spp.*	6	5.1
7.	*Staphylococcus*	5	4.1
Total		120	100 %

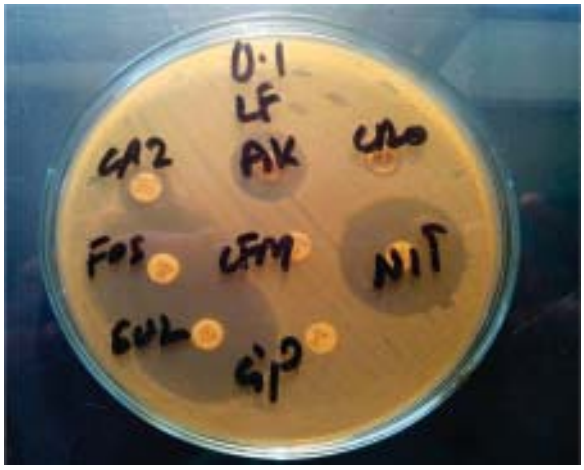

Fig 1: An *E. coli* strain showing sensitivity to fosfomycin (zone diameter > 16mm).

Table 2: In vitro susceptibility of urinary isolates to fosfomycin (n=120).

S. No.	Isolate	Number	Sensitive	Resistant
1.	*E. coli*	73	71 (97.2%)	2 (2.8%)
2.	*K. pneumoniae*	11	7 (63.6%)	4 (36.4%)
3.	*Pseudomonas spp.*	10	8 (80%)	2 (20%)
4.	*Proteus spp.*	8	7 (87.5%)	1 (12.5%)
5.	*Enterobacter spp.*	7	5 (71.4%)	2 (28.5%)
6.	*Enterococcus spp.*	6	5 (83.3%)	1 (16.6%)
7.	*Staph aureus*	5	4 (80%)	1 (20%)
	Total	120	107 (89.2%)	13 (10.8%)

teus spp. 7 (87.5%) and *Enterococcus* spp 5 (83.3%). Overall out of total 120 isolates, 107 (89.2%) were sensitive to fosfomycin. *Klebsiella pneumonia* showed maximum resistance to fosfomycin as shown in Table 2.

In our study, there were 18 (15%) isolates which were Extended Spectrum Beta Lactamase (ESBL) producer. Out of these 18 isolates, 16 (88.9%) were sensitive to fosfomycin.

DISCUSSION

Fosfomycin, an old drug has proved to be very effective in uncomplicated urinary tract infections. In recent years, a number of studies were done to evaluate its in vitro activity in urinary isolates.[10,11] Due to increase use of fluoroquinolones, an attempt to empirically treat uncomplicated UTIs with this class of antibiotic may be a futile attempt. Therefore, it is the need of the hour to use a safe, cost effective and appropriate antibiotic. Recent studies on two antibiotics that is fosfomycin and nitrofurantion proved that both these drugs have emerged as "return of old friend in the wake of growing resistance". Studies in various parts of the world on fosfomycin have proved that resistance to this drug is still very low.[12,13]

In our study, out of total 120 isolates, *E. coli* showed the maximum sensitivity levels that is 97.2%. This has very practical implications on the use of fosfomycin empirically in uncomplicated UTIs as in most of the cases, *E. coli* is the dominant cause. In a study done by Maraki S, et al in 2009, *E. coli* showed 100 % susceptibility to fosfomycin.[12] Similarly in another recent study done by Lu CL et al in 2011, *E. coli* showed 100% sensitivity to fosfomycin.[14]

In our study, the second most common urinary isolate, that is *K. pneumonia* showed lowest sensitivity (63.3%). In one study, the non-multidrug resistant (MDR) strains of *K. pneumonia* showed 82.3% susceptibility while the MDR strains showed 58.3 %.[12] In another study, 92% of the *K. pneumonia* strains were sensitive to fosfomycin.[14] The lower sensitivity rates of *K. pneumonia* to fosfomycin may be due to the fact that the total number of *K. pneumonia* isolates were less as compared to other studies. Our study has also shown a fairly good sensitivity of fosfomycin to other common urinary pathogens such as *Proteus spp, Enterococcus spp, Pseudomonas spp* and *S. aureus*. A very good sensitivity of fosfomycin to these pathogens is also documented in some other studies.[12-14] These studies have also concluded that fosfomycin is also very effective against MDR pathogens such as methicillin resistant *S. aureus* (MRSA), vancomycin resistant enterococci (VRE), and ESBL producing isolates. In our study, there were 18 ESBL isolates out of which only two were resistant to fosfomycin but unfortunately, no urine specimen yielded growth of MRSA, and VRE isolates.

CONCLUSION

Our study concluded that fosfomysin had a high level of antibacterial activity in-vitro against the commonly isolated urinary pathogens. It has also shown good activity against multi-drug resistant urinary pathogens. However, further in-vitro research work on the use of fosfomycin for complicated urinary tract infections is recommended.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.
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None declared.