International Journal of Science and Research (IJSR)
ISSN: 2319-7064
ResearchGate Impact Factor (2018): 0.28 | SJIF (2018): 7.426

Fosfomycin Susceptibility among Uropathogenic E.Coli and K. Pneumoniae

Sruti Dalai[1], Meera Modak[2], Kunal Lahiri[3]

[1]Junior Resident, Department of Microbiology, BVDUMC, Pune, India
[2]Professor, Department of Microbiology, BVDUMC, Pune, India
[3]H.O.D, Department of Microbiology, BVDUMC, Pune, India

Abstract: ***Introduction: UTIs are among the commonest types of bacterial infections. There is an increase in resistance among gram negative bacilli to nitrofurantoin, fluoroquinolones, cotrimoxazole, cephalosporins. Production of extended-spectrum beta-lactamases (ESBLs) by uropathogens is making the treatment challenging. So we conducted this study to see the sensitivity of fosfomycin against the ESBL, carbapenem resistant and multidrug resistant E.coli and K.pneumoniae. Methods: We conducted a retrospective study of six months to determine the fosfomycin susceptibility among E.coli and K.pneumoniae. Results: 280/289 (96.8%) isolates of E.coli and 96/105 (91.4%) isolates of K.pneumoniae were sensitive to fosfomycin. Conclusion: Fosfomycin has shown high in vitro activity against the common uropathogens. With increasing resistance to various antibiotics among these uropathogens, fosfomycin can be a potential alternative drug.***

Keywords: fosfomycin, E.coli, K.pneumoniae

1. Introduction

Urinary tract infection (UTI) is a commonly encountered clinical entity both in outpatient and inpatient setting. Urinary tract infections (UTIs) are among the commonest types of bacterial infections [1]. Gram negative organisms are increasingly becoming resistant to nitrofurantoin, fluoroquinolones, cotrimoxazole, cephalosporins [2].

The emergence of uropathogens, exhibiting high rates of resistance due to the production of extended-spectrum beta-lactamases (ESBLs) is making the treatment further challenging. Increased use of carbapenems in complicated infections is causing spread of carbapenem resistance (CR) in gram negative bacilli. Multidrug resistant (MDR) organism is bacteria which is resistant to three or more antimicrobial classes [3].

Fosfomycin is a broad spectrum bactericidal antibiotic agent. [4] The drug has a convenient oral route of administration. As it is excreted in urine, it acts effectively against uropathogens. It maintains high urinary concentrations for over 24 hours. [5] Hence it can be prescribed as a single oral dose.

This study was done with the objective to determine *in vitro* fosfomyc in susceptibility among commonly isolated uropathogens, Escherechia coli (E.coli) and Klebsiella pneumoniae (K.pneumoniae); and determining the efficacy of fosfomycin against ESBL, Carbapenem resistant and MDR E.coli and K. pneumoniae.

2. Methods

A retrospective study was conducted for a period of 6 months from July 2018 to December 2018 in the Department of Microbiology of Bharati Hospital, Pune, India. Urine samples were collected from symptomatic patients. Patients were recruited from both in- and outpatient setting. Samples were collected and transferred according to recommended guidelines to prevent contaminations. Urine samples were processed within 30 minutes of receiving samples. Direct microscopy of the uncentrifuged sample was done. Samples were plated on blood and MacConkey agar and incubated at 37^0C. The growth of the organism and colony count were noted. The organisms were identified by conventional biochemical tests and VITEK2 Compact System (BioMerieux. Inc., France). The antimicrobial susceptibility was performed by VITEK2 Compact System (BioMerieux. Inc., France). Detection of ESBL and Carbapenemase production were determined by VITEK2 Compact system. MDR *Enterobacteriaceae (*MDRE) are organisms that are resistant to any three different classes of antibiotics as defined by the guidelines. In our study, it includes resistance to any three of the following groups – cephalosporins, fluoroquinolones, aminoglycosides, folate pathway inhibitors (trimethoprim-sulfamethoxazole), and nitrofurantoin.

3. Results

A total of 2346 urine samples were included in the study. Out of these, a total of 394 isolates of E.coli and K.pneumoniae, 289 and 105 respectively. Out of 394 isolates, 143 were from OPD patients, 210 were IPD patients and 41 patients were from Intensive Care Units (ICU). Among the 289 isolates of E.coli, 189 (65.3%) were ESBL producers, 11 (3.8%) were Carbapenem resistant and 43 (14.8%) were multidrug resistant. Overall sensitivity to fosfomycin among E.coli is 280/289 i.e 96.8%. Fosfomycin susceptibility among ESBL producing E.coli is 96.8%; among carbapenem resistant is 90.9% and among multidrug resistant E.coli is 95.3%. Sensitivity of fosfomycin among ESBL producing and non ESBL producing E.coli is almost equal.

Among the 105 isolates of K.pneumoniae, 39 (37.1%) were ESBL producers, 16 (15.3%) were carbapenem resistant and 23 (21.9%) were multidrug resistant. Fosfomycin susceptibility among ESBL producing K.pneumoniae is 87.1%; among carbapenem resistant K.pneumoniae is 87.5% and among multidrug resistant K.pneumoniae is 91.3%.

Overall sensitivity among K.pneumoniae is 96/105 i.e. 91.4%.

Table 1: Location wise distribution of organisms

Location	*E.coli*	*K.pneumoniae*	*Total*
OPD	112	31	143
IPD	146	64	210
ICU	31	10	41
Total	289	105	394

Table 2: Fosfomycin sensitivity among ESBL producing Enterobacteriaceae

Organisms	ESBL producers	Non ESBL producers
E.coli	183/189 (96.8%)	97/100 (97.0%)
K.pneumoniae	34/39 (87.1%)	62/66 (93.9%)
Total	217/228 (95.1%)	159/166 (95.7%)

Table 3: Fosfomycin sensitivity among Carbapenem resistant Enterobacteriaceae (CRE)

Organisms	*CRE*	*Non CRE*
E.coli	10/11 (90.9%)	270/278 (97.1%)
K.pneumoniae	14/16 (87.5%)	82/89 (92.1%)
Total	24/27 (88.8%)	352/367 (95.9%)

Table 4: Fosfomycin sensitivity among multidrug resistant Enterobacteriaceae (MDRE)

Organisms	MDRE	Non MDRE
E.coli	41/43 (95.3%)	239/246 (97.1%)
K.pneumoniae	21/23 (91.3%)	75/82 (91.4%)
Total	62/66 (93.9%)	314/328 (95.7%)

4. Discussion

Fosfomycin, originally called as Phosphonomycin, is an old broad-spectrum broad spectrum antibiotic first found in fermentation broth of Streptomyces fradiae (ATCC 21096) in Spain in 1969. [6] It acts by inhibiting enzyme pyruvyl transferase, responsible for synthesizing the precursors of peptidoglycan, the key component of bacterial cell wall. [7]Fosfomycin is a less commonly used antibiotic that has good in vitro activity and favourable resistance pattern against common uropathogens. It is active against both gram-positive and gram-negative organisms. [8] Dastidar et al. in 1997 had shown powerful activity against E.coli and Klebsiella spp. [9] Gupta et al from PGIMER, Chandigarh reported, 52.6% of E.coli isolates were ESBL producing strains and all were susceptible to fosfomycin. [10] Mittal et al. reported all uropathogenic E.coli strains to be sensitive to fosfomycin. [11] A study conducted by N.K.Tulara showed a fosfomycin sensitivity of 87.7% among ESBL producing K.pneumoniae which is similar to our study with a sensitivity of 87.1%. [12] In our study 94.1% isolates were susceptible to fosfomycin, which is similar to the results obtained by Sabharwal and Sharma where susceptibility was 94.4%. [13] Khawaja et al. reported bacterial eradication in 96.3% patients after oral therapy with fosfomycin. [14] In our study 96.8% E.coli and 91.4% K.pneumoniae were susceptible to fosfomycin. Susceptibility among MDR E.coli, which is the most common isolated organism in UTI is 95.3%. Unlike colistin and polymyxin, fosfomycin is not nephrotoxic. [15] Hence it is logical to use fosfomycin in such patients harbouring MDR organisms.

5. Limitations

This study evaluates in vitro activity of fosfomycin but doesn't analyse the clinical efficacy. Since the study was retrospective, we have used only VITEK reports for analyzing the susceptibility of fosfomycin.

6. Conclusion

Fosfomycin is an underprescribed drug in our country for the treatment of UTI, inspite of the fact that it shows high in vitro activity against common uropathogens, including MDR organisms, ESBL producers and carbapenem-resistant Enterobacteriaceae. As compared to other drugs, it has the advantage of being a oral agent with single daily dosing. It can be used in both in-and outpatient settings. Hence its use should be encouraged by clinicians. However, further studies are needed to evaluate clinical utility of fosfomycin.

References

[1] Foxman, B., K. L. Klemstine, and P. D. Brown. 2003. Acute pyelonephritis in US hospitals in 1997: hospitalization and in-hospital mortality. Ann. Epidemiol. 13:144–150

[2] Mandell GL, Bennett JE, Dolin R. Mandell, Douglas and Benett's Principles and Practice of Infectious Diseases. 6th ed. Philadelphia: Elsevier Churchill Livingstone; 2005. pp. 2789–95.

[3] Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: An international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012;18:268–81

[4] Skarzynski T, Mistry A et.al 1996. Structure of UDP-N-acetylglucosamine enolpyruvyl transferase, an enzyme essential for the synthesis of bacterial peptidoglycan, complexed with substrate UDP-N-acetylglucosamine and the drug fosfomycin. Structure4:1465–1474. doi:10.1016/S0969-2126 (96)00153-0.

[5] Nabin K, Shrestha JW. Fosfomycin: A review. Infect Dis Clin Pract. 2001;10:255–60.

[6] Hendlin D, Stapley EO, Jackson M, et al. Phosphonomycin. A new antibiotic produced by strains of streptomyces. Science. 1969;166:122–123.

[7] Gardiner BJ, Stewardson AJ, Abbott IJ, Peleg AY. Nitrofurantoin and fosfomycin for resistant urinary tract infections: old drugs for emerging problems. *Aust Prescr*. 2019;42 (1):14-19.

[8] Falagas ME, Vouloumanou EK, Samonis G, Vardakas KZ. Fosfomycin. Clin Microbiol Rev. 2016;29:321–47.

[9] Dastidar SG, Mazumdar A, Mookerjee M, Chakrabarty AN. Antimicrobial potentiality of a new beta-lactam antibiotic fosfomycin. Indian J Exp Biol. 1997;35:300–1.

[10] Gupta V, Rani H, Singla N, Kaistha N, Determination of extended-spectrum ß-lactamases and AmpC production in uropathogenic isolates of *Escherichia coli* and susceptibility to fosfomycin. J Lab Physicians. 2013; 5:90–3.

[11] Mittal S, Sharma M, Chaudhary U. Fosfomycin use in multi drug resistant uropathogenic Escherichia coli. Infect Disord Drug Targets. 2015;15:196–201.
[12] Tulara NK. Nitrofurantoin and Fosfomycin for Extended Spectrum Beta-lactamases Producing *Escherichia coli* and *Klebsiella pneumoniae*. *J Glob Infect Dis*. 2018;10 (1):19–21.
[13] Sabharwal ER, Sharma R. Fosfomycin: An alternative therapy for the treatment of UTI amidstescalating antimicrobial resistance. J Clin Diagn Res. 2015;9:DC06–9.
[14] Khawaja AR, et al. Fosfomycin tromethamine. Antibiotic of choice in the female patient: A multicenter study. Cent European J Urol. 2015; 68:371–5.
[15] Morin JP, Olier B, Viotte G, Fillastre JP. [Can fosfomycin reduce thenephrotoxicity of aminoglycosides?]. Pathol Biol (Paris). 1984 May;32 (5):338-42.