Fosfomycin susceptibility on uropathogens in a tertiary care hospital, Mandya institute of medical sciences, Mandya

Sharlee R[1,*], Sumangala B[2]

[1]PG Student, [2]Professor and HOD, Dept. of Microbiology, Mandya Institute of Medical Sciences, Mandya, Karnataka, India

***Corresponding Author: Sharlee R**
Email: sharlu.ravi@gmail.com

Abstract

Introduction: Urinary tract infection (UTI) is an important cause of illness in humans with emergence of multidrug resistance. Fosfomycin remains to be effective against MDR uropathogens. We evaluated susceptibility of Fosfomycin against uropathoges.

Materials and Methods: A prospective study was conducted for a period of 6 months in a tertiary care hospital MIMS, Mandya. Significant bacterial growth were identified in urine samples and processed accordingly. Fosfomycin susceptibility was performed by Kirby-Bauer disc diffusion method along with other drugs advised as per CLSI guidelines.

Results: A total of 893 urine samples were received, 150 samples showed significant growth of one or two organisms, yielding a sum of 162 isolates. Out of 162 isolates with significant growth of organisms, majority were Gram negative bacilli (GNB) accounting for 63.6% (103 isolates) followed by Gram positive cocci (GPC) 36.4% (59 isolates).

Out of 103 GNB, ESBL producer were 25.2%, Carbapenamase producer were 1.9%, Amp C were 6.8%, ESBL+ Carbapenamase were 4.9%, Amp C + Carbapenemase were 2.9% and 58.3% were non ESBL, Carbapenamase and AmpC producer.

Out of 162 isolates, 156(96.3 %) were sensitive to Fosfomycin and 6 (3.7%) were resistant to Fosfomycin.

Conclusions: Fosfomycin is effective against MDR, ESBL, AmpC and Carbapenamse producing uropthaogens. It is an effective, convenient and safe drug for treating the patients of all age group and pregnant mothers with uncomplicated UTIs.

Keywords: UTI, MDR, AmpC, ESBL, GPC, GNB.

Introduction

Urinary tract infection (UTI) is an important cause of illness in humans.[1] UTIs are mainly caused by gram negative rods like *E.coli, klebsiella*, gram positive cocci like *Staphylococcus, Enterococcus* species and many others. Younger and sexually active individuals are particularly affected compared to elderly and post-menopausal women.

Uncomplicated lower urinary tract infections (UTIs) are the most common in women.[2] Uropathogens have gained the drug resistance by the use and misuse of empirical antibiotic therapy. Use of Second line drugs like co-trimoxazole, fluoroquinolones habitually in some countries has contributed to drug resistance further.[2] Multi drug resistant uropathogens is the reason for limited treatment option. Fosfomycin is used for the treatment of multi drug-resistant (MDR) organisms causing urinary tract infection (UTI).[3] Fosfomycin is a phosphonic acid derivative, which disrupt cell wall synthesis by inhibiting peptidoglycan assembly.[4] Fosfomycin has broad spectrum of activity against gram positive and gram negative pathogens like *E. coli, Citrobacter diversus, C. freundii, Klebsiella oxytoca, Klebsiella pneumoniae, Enterobacter cloacae, Serratia marcescens, Proteus mirabilis, P.vulgaris, Providencia rettgeri, Pseudomonas aeruginosa, E. Faecalis* and *E. Faecium* [including vancomycin resistant *Enterococcus* (VRE)] species, and *Staphylococcus aureus* including Methicillin resistant *Staphylococcus aureus* (MRSA) associated with UTI.[4]

Fosfomycin has high bactericidal activity, one dose is enough to kill the pathogen and treat AUC (acute uncomplicated cystitis), it may be a good choice for outpatient treatment of acute uncomplicated UTI.[3] Antibiotic resistance is increasing due to antibiotic pressure especially for Fluroquinolones, so evaluating the antibiogram of uropathogens to this antibiotic is important.

This study is taken for the following advantages of Fosfomycin which may be used as a first line empirical treatment. Single dose regimen, oral administration, has high bactericidal concentrations in urine.[3] Dose alteration is not required in hepatic and renal dysfunction, no drug interaction seen, safe among all age group populations including pregnancy because of its less adverse effect, suitable for OPD (outpatient department) based treatment, effective on MDR & ESBL (Extended spectrum beta-lactamses) producing organisms.

Materials and Methods

The present study was conducted after ethical committee approval. It is a prospective study conducted for the period of six months from July 2018 to December 2018 in the Department of Microbiology culture laboratory in Mandya institute of Medical sciences, Mandya. Urine samples of all the age group were included in our study population.

Day 1: The urine samples received in Microbiology laboratory for culture and sensitivity were observed for Microscopic findings and sample were inoculated using 0.1mm Nichrome urine loop onto McConkey agar and blood agar in semi quantitative method and incubated at 37ºC for 18 to 24 hours.[7]

Day 2: Observed for significant growth and samples were processed according to growth and history of patient. Antibiotic susceptibility testing were performed by Kirby-Bauer disc diffusion method according to CLSI guidelines.[9]

Fosfomycin antibiotic disc with strength of 200µg were added to all urinary isolates along with the drugs advised according to standard CLSI guidelines.[7]

Day 3: Zone of inhibition were noted for all the antibiotics along with Fosfomycin. Screening of ESBL were done using disc diffusion method with Ceftriaxone and Cefotaxime and confirmation was done using Cefotaxime and combination of Cefotaxime with Clavulanate (30/10 µg) by disc diffusion method. Amp C screening was done using Cefoxitin disc and Carbapenemase producer using Meropenem disc.[7]

Results

A total of 893 urine samples were received, 150 samples showed significant growth of one or two organisms, yielding a sum of 162 isolates. Out of 162 isolates with significant growth of organisms, majority were Gram negative bacilli (GNB) accounting for 63.6% (103 isolates) followed by Gram positive cocci (GPC) 36.4% (59 isolates).

Out of 103 Gram negative bacilli majority were *E.coli* with 29.1% followed by *Klebsiella* 25.3%, *Pseudomonas aeruginosa* 3%, *Acinetobacter* 3%, *Enterobacter* 1.9% and *Citrobacter* 1.2% species. Out of 59 GPC majority were *Staph aureus* with 22.2% followed by CONS with 11.7% and *Enterococcus* species 2.6%.

Out of 103 GNB, ESBL producer were 25.2%, Carbapenamase producer were 1.9%, Amp C were 6.8%, ESBL+ Carbapenamase were 4.9%, Amp C + Carbapenemase were 2.9% and 58.3% were non ESBL, Carbapenamase and AmpC producer. (Table 1 and 2)

Out of 162 isolates, 156(96.3%) were sensitive to Fosfomycin and 6 (3.7%) were resistant to Fosfomycin. In our study we noticed majority of CONS were resistant to Fosfomycin compared to other organisms. 100% of ESBL producer, Carbapenemase and Amp C producers were sensitive to Fosfomycin.

Table 1: List of gram negative organisms showing ESBL, Carba and Amp C production

Gram negative organisms (n=103)	ESBL producers	Carbapenems producers	Amp C producers	ESBL & Carba Co producers	Amp C & Carba Co producers	NON ESBL, amp C & Carbapenemase producers
E.coli(n=47)	8 (17%)	-	4(8.5%)	2 (4.25%)	2 (4.25%)	31 (66%)
Klebsiella species (n=41)	12 (29.3%)	2(4.9%)	3 (7.3%)	2 (4.9%)	1(2.4%)	21(51.2%)
Acinetobacter species (n=5)	2 (40%)	-	-	1(20%)	-	2(40%)
Pseudomonas aeruginosa (n=5)	3 (60%)	-	-	-	-	2(40%)
Citrobacter(n=2)	-	-	-	-	-	2 (100%)
Enterobacter(n=3)	1(33.3%)	-	-	-	-	2(66.7%)

Table 2: List of gram positive organisms isolated

Gram positive organisms	Total (n=59)
Staphyloccuc.auerus	36 (61%) MRSA- 14(38.9%) MSSA- 22(61.1%)
CONS (*Staph. Saprophyticus and epidermidis*)	19 (32.2%)
Enterococcus species	4 (6.8%)

Table 3: Fosfomycin susceptibility of gram negative and positive organisms

Isolates (n=162)	Sensitive (%)	Resistant (%)
E.coli(n=47)	47(100%)	0(0%)
Klebsiella species(n=41)	40(97.6%)	1(2.4%)
Enterobacter species(n=3)	3(100%)	0(0%)
P.aeruginosa(n=5)	4(80%)	1(20%)
Acinetobacter species(n=5)	5(100%)	0(0%)
Citrobacter species(n=2)	2(100%)	0(0%)
Staph.aureus(n=36)	36(100%)	0(0%)
Staph. saprophyticus and epidermidis (n=19)	15(79%)	4 (21%)
Enterococcus species (n=4)	4(100%)	0(0%)

Discussion

In the present study out of 162 isolates, 156(96.3%) were sensitive to Fosfomycin and 6 (3.7%) were resistant. In comparison to our study, similar results were found in the study conducted by Pullukcu H et al showing 94.3% (49/52) sensitive.[8]

A study conducted by Sabharwal and Sharma et al showed 94.4% of the isolates susceptible to Fosfomycin.[9]

Oral therapy with Fosfomycin bacterial eradication was seen 96.3% in the study conducted by Khawaja et al.[10]

A study conducted by Bozkurt O et al on comparison efficacy of single dose Fosfomycin with Ciprofloxacin in the treatment of urinary tract infection in symptomatic women, shows that 50% of patients received Fosfomycin treatment had 96% better cure rate in comparison with remaining 50% treated with ciprofloxacin.[11]

A study conducted by Auer S et al on oral treatment options for ambulatory patients with urinary tract infections caused by extended-spectrum-beta-lactamase-producing *Escherichia coli*. Patients were treated with Fosfomycin, Nitrofurantoin and Pivemecillinam.

Fosfomycin exhibited excellent in vitro susceptibility to ESBL-producing *E. Coli* in comparison with other two drugs.[6]

A study conducted by Rajenderan et al on Determination of MIC distribution of arbekacin, cefminox, Fosfomycin, biapenem and other antibiotics against gram negative clinical isolates in south India shows that Fosfomycin were sensitive to AmpC and aminoglycoside resistant isolates.[12]

A study conducted by George Zhanel et al on role of Fosfomycin in acute uncomplicated cystitis (AUC) shows that *E.coli* is the most common cause of uncomplicated UTI and Fosfomycin is first line of treatment for uncomplictaed UTI and AUC (acute uncomplicated cystitis).[3]

A study conducted by Crocchiolo P et al on Single-dose Fosfomycin trometamol versus multiple-dose Cotrimoxazole in the treatment of lower urinary tract infections in general practice shows that out of 36 patients with uncomplicated UTI, 19 patients were treated with Fosfomycin and 17 patients were treated with TMP/SMX. Patients treated with Fosfomycin showed 89% cure rate in comparison with patients treated with TMP/SMX showed 76%.[5]

Conclusion

Fosfomycin is effective against MDR, ESBL, AmpC and Carbapenamse producing uropthaogens. Fosfomycin can be used as first line empirical treatment in UTIs as single dose regimen orally; it has an edge over other routinely used antibiotic against uropathogens. It achieves high bactericidal concentration in urine. It is an effective, convenient and safe drug for treating the pregnant mother with uncomplicated UTIs.

Conflict of Interest: None.

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