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Evaluation of Fosfomycin Susceptibility among Multidrugresistant Gram Negative Urinary Isolates in a Tertiary Care Hospital

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Abstract

Introduction: Urinary tract infections are one of the commonest types of bacterial infections.Multidrug resistance in Gram negative bacteria is an ever increasing problem worldwide. Of particular concern, the spread of Extended Spectrum b Lactamases and Carbapenamases is increasing worldwide.Fosfomycin, an old broad spectrum antibiotic is found to be bactericidal against multidrug resistant uropathogens.

Aim of the study: This study aimed to evaluate the in vitro susceptibility of Fosfomycin against multi drug resistant gram negative urinary isolates

Materials and Methods: This is a prospective study conducted between April-Sep 2017,in which 100 non -repetitive multidrug resistant gram negative urinary isolates were collected and their anti microbial susceptibility patterns to Fosfomycin were determined as per CLSI and EUCAST guidelines

Results: E.coli (97%)and Klebsiella pneumonia (88%),Klebsiella oxytoca(80%) were found to be sensitive to Fosfomycin. Among non Enterobacteriaceae ,Pseudomonas spp were found to be 100% sensitive and Acinetobacter spp (17%) was found to be least sensitive.

Conclusion: Fosfomycin is active in vitro against considerable percentage of multidrug resistant urinary isolates. Consequently Fosfomycin appears to be the best treatment option for the urinary tract infections.

Keywords: Fosfomycin, ESBLs, Carbapenemases, UTI, Gram negative infections

Introduction

Urinary tract infections are one of the most common infectious diseases. UTI is primarily caused by Gram –negative bacteria. The organism causing uncomplicated UTI and pyelonephritis is most commonly by Escherichia coli, Klebsiellapneumoniae [(5)].

The antibiotic treatment for UTI is associated with potential medical and economical complications. There is increased irrational and empirical use of antibiotics like Cotrimoxazole, Fluroquinolones, nitrofurantoin and second and third generation cephalosporinsfor UTI [(4)]. Multidrug resistance is increasing among Enterobacteriaceae particularly Escherichia coli, Klebsiellaspp and Proteus vulgaris.

Multidrug resistance means resistant to two or three class of antimicrobials.[(1)]Emergence of resistance due to Extended Spectrum b-Lactamases is worrisome.Multi drug resistance among gram negative bacteria is aserious global crisis and it is has been catalyzed by the rapid increase in carbapenem resistance in gram negative bacterialinfections [(6)].

Fosfomycin, anphosphonic acid derivative, was isolated from strains of Streptomyces (Streptomyces fradiae, Streptomyces wedomorensis, Streptomyces viridochromogenes)[(4)].Fosfomycin an old broad spectrum antibiotic is found to be bactericidal against this multi drug resistant uropathogens.

Fosfomycin inhibits the synthesis of bacterial cell wall earlier than b-lactams and glycopeptides by inhibiting peptidoglycan synthesis via inactivation of cytosolic N-acetyl glucosamine enolpyruvyl transferase (MurA)which catalyses the conversion of UDP-N-acetyl glucosamine to UDP-N-acetyl muramicacid which ultimately leads to death of the bacteria.It enters the cytoplasm of bacteria through glycerol 3 phosphate transporter or glucose 6 phosphate transporter present in the cell wall[(1,5)].Cyclic adenosine monophosphate controls the expression of this both transporters and glucose 6 phosphate acts as a inducer. Hence glucose 6 phosphate is needed for the Fosfomycin to express its bactericidal activity.

Fosfomycin is best absorbed if given before food intake and is excreted in urine. It achieves high concentration in urine of 2000ug/ml and maintains high levels for 24 hours. So, single time oral therapy is recommended in uncomplicated UTI.

Today Fosfomycin is produced synthetically. Fosfomycin has the smallest molecular mass (138Da).Formulated with salts like calcium, trometamol and disodium is available. Intravenous formulation is available as a water soluble salt of disodium [4,6]. The intravenous formulation is now licensed in few countries for serious systemic infections like complicated urinary tract infections, acute lower respiratory tract infections, osteomyelitis, bacterial meningitis and bacteraemia.

This study is conducted to determine the in vitro susceptibility of fosfomycin against multidrug resistant gram negative urinary isolates at a tertiary care hospital at Chennai

Aim

To evaluate the in vitro susceptibility of Fosfomycin against Extended Spectrum B-Lactamases and Carbapenamases producing Gram negative urinary isolates in patients admitted for urinary tract infections at Rajiv Gandhi Government General Hospital in Chennai

Objective

- To isolate and identify the Extended Spectrum B-Lactamases and Carbapenamases producing gram negative bacilli in patients with urinary tract infections.
- To evaluate the in vitro susceptibility of Fosfomycin among the resistant uropathogens.

Study Design

Study population:Patients admitted with suspected urinary tract infections in Rajiv Gandhi Govt General Hospital at Chennai.

Sample Size : 100
Study Period : April 2017 to September 2017
Type ofStudy : Prospective Study

Sample Collection

Urinary isolates of Gram Negative bacteria resistant to carbapenem group and ESBLs producers.

Inclusion Criteria

All gram negative urinary isolates resistant to carbapenem andESBL producing isolates.

Exclusion Criteria

Age less than 18 years.

Repeated samples from the same patient.

Materials &Methods

- Isolation and identification of gram negative bacteria among urinary isolates by standard microbiological procedures.
- Detection of antibiotic susceptibility pattern of the isolates by Kirby Bauer disc diffusion method as per CLSI guidelines
- Carbapenamase detection by synergy test with imipenem&EDTA combination disc methodfor metallob lactamases.
- Fosfomycin susceptibility test wasdone by disk diffusion test on Mueller Hinton agar with Fosfomycin 200ug disc containing 50ug of glucose 6 phosphate
- Fosfomycin E -test strips supplemented with Glucose 6 phosphate was used for determination of Minimum Inhibitory Concentrations.
- The antimicrobial susceptibility pattern of Fosfomycin is determined as per CLSI and EUCAST guidelines

Results

Table 1: Distribution of multidrug resistant gram negative uropathogens inOP, IP ,ICU (n=100)

Gram Negative Bacteria	OP	Medicine ward	Urology ward	ICU	Surgery ward	Total
E.coli	3	8	9	2	14	36
Klebsiellapneumoniae	-	12	6	3	5	26
Pseudomonas spp	2	3	2	1	4	12
Acinetobacterspp	-	1	3	1	1	6
Klebsiellaoxytoca	1	9	5	3	2	20

Table 2:Fosfomycin Susceptibility among ESBL producing Gram Negative Isolates (n=19)

Gram negative bacteria	ESBL producer	Fosfomycinsusceptiblity
E.coli	9	8(89%)
Klebsiellaoxytoca	3	2(67%)
Klebsiellapneumoniae	2	1(50%)
Pseudomonas spp	2	2(100%)
Acinetobacterspp	3	0(0%)

Table 3: FosfomycinSusceptiblity among Carbapenem Resistant Gram Negative Urinary Isolates (n=81)

Gram negative Bacteria	Carbapenem Resistant	FosfomycinSusceptiblity
E.coli	27	27(100%)
Klebsiellaoxytoca	17	14(82%)
Klebsiellapneumoniae	24	22(92%)
Pseudomonas spp	10	10(100%)
Acinetobacterspp	3	1((33%)

Table 4:Fosfomycin Minimum Inhibitory Concentration for Multi Drug Resistant Gram Negative Urinary Isolates(n=100)

	FosfomycinMic(ug/ml)									
Gram Negative Isolates	<0.5	1	2	4	8	16	32	64	128	256
E.coli(36)		35	1							
Klebsiellaoxytoca(20)			16		4					
Klebsiellapneumonia(26)			23			3				
Pseudomonas spp(12)	12									
Acinetobacterspp(6)						1	5			

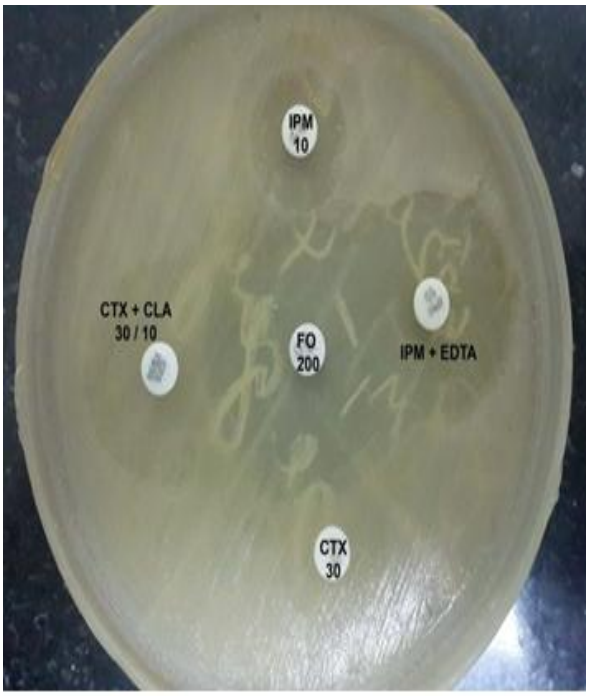

Figure 1: Fosfomycin 200ug disc sensitivity in ESBLs producer &Carbapenem resistant strain

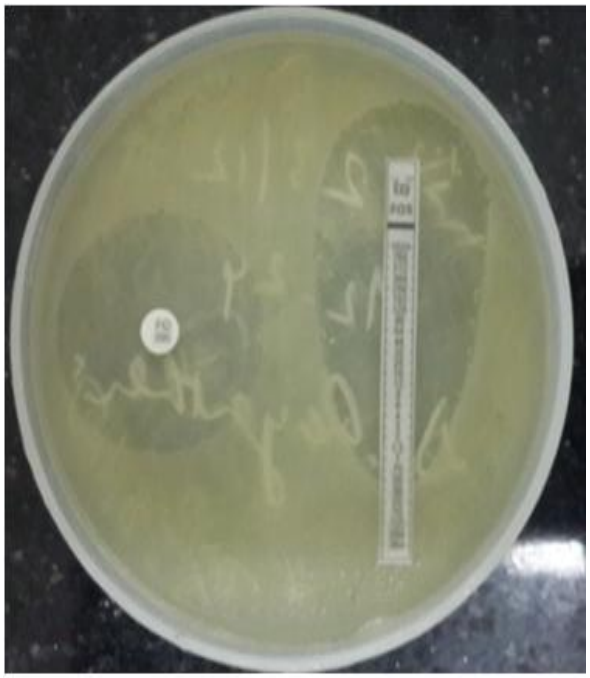

Figure 2: Fosfomycin Sensitivity by disc diffusion method & MIC Determination by E-Strip

Results

100 multi drug resistant gram negative uropathogens isolated from patients with urinary tract infections werestudied. Among them 63 from male patients and 37 from female patients.

Out of the 100 multidrug resistant isolates, 6 OPD, 33 medicine ward, 25 urology ward, 10 ICU and 26 surgery. There were 36 E.coli, 26Klebsiella pneumonia, 12 pseudomonas spp, 6Acinetobacter spp and 20Klebsiellaoxytocae.

Among the 36 isolates of E.coli 9 were found to be ESBL producers and 27 were resistant to carbapenems.They showed extensive resistance to cephalosporins, Cotrimoxazole & Fluroquinolones. 35 (97%) were sensitive to Fosfomycin and MIC of 1ug/ml.

Of the 26 isolates of Klebsiella pneumoniae, 2 were ESBL producers&24 were resistant to carbapenem. 23(88%) were sensitive to Fosfomycin and MIC OF 2ug/ml. Among the 20 isolates of Klebsiella oxytoca, 3 were ESBL producers and 17 were resistant to carbapenem. 16 (80%) were sensitive to Fosfomycin and MIC of 2ug/ml.

Among the 12 isolates of Pseudomonas spp, 2 were ESBL producers and 10 were resistant to carbapenem. All the isolates (100%) sensitive to Fosfomycin and have a MIC of less than 0.5 ug/ml. Among the 6 isolates of Acinetobacter spp, 3 were ESBL producers and 3 were resistant to carbapenem. Only17% of isolates were found to be sensitive to Fosfomycin and have a MIC of 16ug/ml.

Discussion

Fosfomycin is an old broad spectrum antibiotic and had a good in vitro sensitivity against uropathogens like E.coli, Klebsiella pneumoniae, Klebsiella oxytoca andPseudomonas spp. In the present study, E.coli and Klebsiella spp showed high susceptibility to Fosfomycin. The study by P.V Saiprasad et al also reported the same results [(4)].Mean while, there is high degree of Fosfomycin resistance was observed in Acinetobacter spp in the present study. The study bySofia maraki et al(2009) and p.v Saiprasad et al (2016) alsoreported a reduced susceptibility of Fosfomycin to Acinetobacter spp[(4,5)].Also the present study the pseudomonas spp showed higher sensitivityto Fosfomycin. In contrast,the study conducted by Sofia maraki et alwhere they showed higher degree of Fosfomycin resistance to non fermenting gram negative bacilli like pseudomonas spp[(5)].

Conclusion

Fosfomycin, an old broad spectrum antibiotic showed high in vitro activity against commonest uro pathogens.

The increasing prevalence of multi drug resistance limits the treatment options for the infections caused by these organisms. As the new drugs are unavailable, there is a valid rationale for testing this old broad spectrum antibiotic Fosfomycin which retained the activity against multidrug resistant gram negative bacilli.

Fosfomycin appears to be the best treatment option for the multidrug resistant uropathogens and it has higher susceptibility to E.coli and Klebsiellaspp

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