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Original Article

Fosfomycin Versus Nitrofurantoin Efficacy Against Multi-Drug Resistant Gram Negative Urinary Pathogens.

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Abstract

Background: To compare antimicrobial susceptibility pattern of fosfomycin and nitrofurantoin against multi-drug resistant gram negative uropathogens.

Methods: In this descriptive study identification of 200 isolates of gram negative bacteria was done by using standard microbiological techniques and the antimicrobial susceptibility was carried out by employing Kirby-Bauer disc diffusion technique. The susceptibility pattern of isolates was then recorded in frequency and percentages.

Results: Out of total 200 urinary samples, 97 were multi-drug resistant (MDR) and 103 were non multi-drug resistant gram negative bacteria. Both MDR and non MDR Escherichia coli(E. coli) followed by Klebsiella pneumoniae(K. pneumoniae) were more commonly isolated uropathogens. MDR E. coli was more susceptible to fosfomycin (98%) as compared to nitrofurantoin (81%). Similarly, for MDR K. pneumoniae, same results of better susceptibility of fosfomycin as compared to nitrofurantoin were observed. Maximum resistance was observed in 4 to 5 drugs in MDR E.coli and K. pneumonia and the most predominant resistant pattern was observed in ampicillin and cephalosporins .

Conclusion: Fosfomycin holds much better in vitro efficacy as compared to nitrofurantoin against MDR E. coli, K. pneumoniae and P. stuartii.

Key Words:Enterobacteriaceae, Fosfomycin, Multi-drug resistant, Nitrofurantoin.

Introduction

Urinary tract infections (UTIs) are among the most commonly observed infections in clinical practice.[1]One of the most important challenges is to deal with recurrent UTI in women.[2,3] But, approximately one third or more of hospital-acquired infections are preventable.[4] The gram negative organisms which usually cause UTI include Escherichia coli (E. coli), Proteus species, Klebsiella species, Citrobacter species and Pseudomonas aeruginosa.[5] The development of antimicrobial resistance among various Gram-negative pathogens has been progressive. Another problem is of multi-drug resistance in Enterobacteriaceae causing urinary tract infections.[6] Multi-drug resistance in gram negative isolates is defined as resistance to at least one agent in three or more than three antimicrobial categories.[7] Trimethoprim-sulfamethoxazole and ampicillin use in the past have remained choices for treating uncomplicated urinary tract infections which are now losing their efficacy.[8]The extended spectrum cephalosporins and quinolones which are used as first-line therapy have also shown emergence of resistance. The resistant genes have predominated among hospital-acquired organisms. In particular, CTX-M-15 is the most widespread and this β-lactamase has frequently been associated with uropathogenic E. coli clone.[6] As the agents commonly used to treat these pathogens have become outmoded. Of the few new drugs available, many have already become resistant.[9]Due to current situation, the use of fosfomycin and nitrofurantoin are returning, owing to its broad spectrum activity against both gram positive and Gram negative bacteria.[10,11]Fosfomycin is a unique antibiotic that is chemically different from any other known antibacterial agent.The drug is well tolerated and has a low incidence of harmful side-effects.[12] It has shown better in vitro activity against Extended-spectrum β-lactamase (ESBL) producing E. coli and Klebsiella pneumoniae(K. pneumoniae) with in particular good activity against ESBL producing urinary Enterobacteriaceae.[13]However, development of bacterial resistance under therapy is a frequent occurrence and makes fosfomycin unsuitable for prolonged therapy as regards severe infections.[14] Nitrofurantoin is bactericidal and its mechanism of action is unique from usual antimicrobials. It stops biochemical processes involving DNA and RNA synthesis by producing reactive intermediates as a result of reduction with bacterial flavoproteins and

finally cell wall synthesis also halts.It has particularly better activity against MDR urinary pathogens. Rare resistant mutants and its uncommon cross resistance with other antimicrobials makes worth its use in Gram negative urinary tract infections.[15,16] The global problem of accelerating antimicrobial resistance has revived interest in use of fosfomycin and nitrofurantoin more recently.

Patients and Methods

This descriptive study was conducted in department of Microbiology, Fauji Foundation Hospital, Rawalpindi/Foundation University Medical College, Islamabad campus from January 2015 to October 2015. Total 200 urinary isolates were considered for study. All gram negative bacteria from urinary isolates received from Medicine, Surgery, Gynaecology/Obstetrics and Paediatric wards (indoor and outdoor) of Fauji Foundation Hospital, Rawalpindi were included in the study. All duplicate samples, patients already receiving antimicrobials for UTI or other ailment were excluded from the study. All gram negative urinary isolates were collected from the patients admitted in different units of Fauji Foundation Hospital, Rawalpindi. Urine specimens were inoculated on Cysteine Lactose Electrolyte Deficient (CLED) agar and incubated aerobically at 35 ± 2^0C for 16 to 18 hours. Gram negative rods were identified by colony morphology, Gram staining, biochemical reactions and confirmed by API 20E. Antimicrobial susceptibility testing was performed by Kirby Bauer's disc diffusion method, according to guidelines published by the Clinical Laboratory Standards Institute (CLSI). All gram negative urinary isolates were tested by ampicillin (25 µg), ceftriaxone (30 µg), aztreonam (30 µg), gentamicin (10 µg), amikacin (30 µg), ciprofloxacin (5 µg), imipenem (10 µg), nitrofurantoin (300 µg), fosfomycin (200 µg) and trimethoprim-sulfamethoxazole (1.25/ 23.75 µg) discs. Standard strain of Escherichia coli using American Type Culture Collection(ATCC 25922) was included in each batch of tests. Incubation was done at 35+ $\underline{2}^0$C for 16- 18 hours. All zone sizes were interpreted according to CLSI.[17] Isolates showing resistance to at least one agent in three or more than three antimicrobial categories was considered as multidrug resistant (MDR).[7]

Results

Out of total 200 urinary isolates, 97 were MDR and 103 were non-MDR Gram negative bacteria. Highest number of bacteria isolated was E. coli followed by *K.* pneumoniae and least isolated pathogen was Providencia stuartii (P. stuartii). Only E. coli(n= 89), K. pneumoniae(n= 4)and P. stuartii(n= 4) were isolated as MDR (Table 1).Overall nitrofurantoin showed maximum resistance in MDR*P.* stuartii(67%), K. pneumoniae(60%) and E. coli(19%) as compared to fosfomycin (Table 2).Percentage of resistance to three drugs was almost the same for MDR E. coli and MDR K. pneumoniae. Resistance to four to five drugs was maximum in MDR E. coli. Whereas, for six drugs the resistance was maximum inMDR K. pneumoniae as compared to MDR E. coli (Table3).

Table 1: Distribution of MDR and non MDR Gram negative urinary isolates (n=200)

Uropathogens	All isolates (n=200)	Non- MDR isolates (n=103)	MDR isolates (n=97)
E. coli	163	74 (37%)	89 44.5%)
K. pneumoniae	19	15 (7.5%)	4 (2%)
P. stuartii	6	2 (1%)	4 (2%)
P. rettgeri	3	3(1.5%)	-
Proteus mirabilis	5	5 (2.5%)	-
C. freundii	4	4 (2%)	-
Total	200	100%	-

Table 2: Susceptibility pattern of MDR producing Gram negative rods against fosofomycin and nitrofurantoin (n=97)

MDR producing Urinary isolates	n	Fosfomycin		Nitrofurantoin	
		Susceptible	Resistant	Susceptible	Resistant
E. coli	89	87 (98%)	2 (2%)	72(81%)	17 (19%)
Klebsiella pneumonia	5	3(60%)	2 (40%)	2 (25%)	3 (60%)
Providencias Stuartii	3	2 (67%)	1 (33%)	1 (33%)	2(67%)

Table 3. Multi drug resistance of urinary E. coli and K. pneumoniae to various antimicrobials

Number of antimicrobials	MDR E. coli (n=89)	Predominant resistant pattern (MDR E. coli)	MDR K. pneumonia (n=9)	Predominant resistant pattern (MDR K. pneumoniae)
3 drugs	20%	AMP-CRO-CIP	20%	AMP-CRO-GEN
4-5 drugs	62%	AMP-CRO-SXT-CIP-GEN	60%	AMP-CRO-ATM-AMK
6 drugs	18%	AMK-SXT-CIP-GEN-CRO-ATM-	20%	AMP-IPM-CRO-SXT-CIP-ATM

AMP- Ampicillin;CRO- Ceftriaxone;GEN- Gentamicin;SXT-Trimethoprim-sulfamethoxazole;CIP-Ciprofloxacin;AMK-Amikacin;IPM- Imipenem;ATM- Aztreonam

Discussion

Urinary tract infection takes the second lead after respiratory tract infection in community acquired infections.[18]One of serious health problem is threatening rise in resistance to antimicrobials.[19]In our study, out of 97 MDR gram negative urinary isolates, multi-drug resistance in E. coli was predominant (44.5%) as compared to K. pneumoniae (2%). A study from Iran reported 50% MDR E. coli and 46.6% MDR K. pneumoniae which is more than our results.[20].Another study conducted in USA shows almost similar results with high multi-drug resistance in E.coli (76%) as compared to K.pneumoniae(5%).[21] Similar group of bacteria reveals multi-drug resistance reported in Nepal, E. coli (74%) and K. pneumoniae (44%) and Ethiopia,E.coli (94.6%) and K. pneumoniae (80%).[22,23]The higher MDR rates in these previous studies may be due to genetic, geographical and social variations in different regions. However, unlike our study Khawcharoenporn et al isolated 6% of MDR Proteus mirabilis and Citrobacter species and only 2% of Providencia species.[21]

Better susceptibility results of fosfomycin in present study as compared to nitrofurantoin against MDR urinary E. coli, Klebsiella and P. stuartii have backed up the use of fosfomycin. About 98% of MDR E. coli isolates were susceptible to fosfomycin and 81% to nitrofurantoin in our study. These results coincided with a study conducted in Taiwan against MDR E.coli, where 95.5% and 75.1% isolates were susceptible to fosfomycin and nitrofurantoin respectively.[24] Bano et al concluded maximum susceptibility to fosfomycin (100%) and nitrofurantoin (100%) against K. pneumoniae in a study conducted in Pakistan. Whereas, for E. coli, 89.28% and 96.43% of isolates were susceptible to fosfomycin and nitrofurantoin respectively.[25]On the contrary, a study conducted in Dera Ismael Khan showed fosfomycin susceptibility against E.coli (97.2%) was much better than K. pneumoniae (3.6%) which was in agreement to the findings of this present study.[26] Similar results of better susceptibility of fosfomycin against MDR E. coli and K. pneumoniae were again almost consistent with a study conducted by Liu et al.[24] The resistant rates of fosfomycin and nitrofurantoin against E. coli were 0.3% and 4% respectively in a study conducted in Turkey.[27]

In present study, 20% of MDR E.coli isolates showed resistance to 3 drugs. Similar studies from Pakistan and Iran also showed 20% of isolates were resistant to less than 5 drugs and 3 drugs respectively. [28,29]In our study, maximum resistance was observed in 4-5 drugs (62%) against MDR E. coli with ampicillin-cefriaxone-trimethoprim-sulfamethoxazole-ciprofloxacin-gentamicin being the predominant resistant pattern. A study from Iran revealed the trend of maximum antimicrobial resistance was more in favor of 3 drugs against MDR E. coli namely ampicillin, tetracycline and trimethoprim-sulfamethoxazole.[29]This high resistance pattern in our set up may be due to over the counter use of antimicrobials. A study from Sudan reported MDR E. coli resistance to more than 8 drugs with most frequent resistance pattern of ampicillin, amoxicillin, tetracycline, trimethoprim-sulfamethoxazole and sulfonamide.[30]As regards, MDR K. pneumoniae, more resistance was observed in 6 drugs in which ampicillin and ceftriaxone were observed as the most predominant resistant pattern. The resistance in other classes was almost equal in number. There is not enough data available to support the phenotypic resistance pattern of antimicrobials against MDR K. pneumoniae. However, a study conducted in Morocco, showed maximum resistance in MDR K. pneumoniae to amoxicillin-clavulinic acid followed by trimethoprim-sulfamethoxazole.[31]

Several studies on fosfomycin from different parts of the world have shown that resistance to this drug is still very low.[26]It has broad spectrum activity against E. coli, Citrobacter spp, Klebsiellaspp, Proteus spp., Pseudomonas aeruginosa, Serratia spp and Salmonella spp.It has effective tissue penetration and single oral dose with less side effects as compared to nitrofurantoin.[32]Asthese findings are in vitro, more clinical trials are needed to support both drugs efficacy in vivo. Still more research is needed on the use of fosfomycin for complicated urinary tract infections and non-urinary tract infections which has not been extensively evaluated in our setup.

Conclusion

Fosfomycin reserves its in vitro activity against MDR E. coli, K. Pneumonia and P. Stuartii when compared to nitrofurantoin. Fosfomycinhas shown in particular potent results against MDR E.coli. Keeping in view, its better susceptibility results and convenient use, it can be used as an empirical therapy in treating uncomplicated UTIs in our setup.

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