Journal of Communicable Diseases
Volume 50, Issue 2 - 2018, Pg. No. 34-37
Peer Reviewed & Open Access Journal

Research Article

Susceptibility of Multi-Drug-Resistant Organisms (MDROs), Isolated from Cases of Urinary Tract Infection to Fosfomycin (The New Antibiotic) vis-a-vis other Antimicrobial Agents

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DOI: https://doi.org/10.24321/0019.5138.201812

Abstract

Introduction: Urinary tract infection (UTI) is one of the commonest infections encountered in the hospital. Most of the hospital UTIs are caused by MDROs. There is scarcity of available drugs to treat MDR infections. In this scenario, reevaluation of the old antimicrobial agents is being done. Fosfomycin is one such old molecule. The studies suggest that Fosfomycin may provide a useful option for the treatment of patients with the MDR/XDR difficult-to-treat infections.

Materials and Methods: Urine samples (including catheter samples) were collected in sterile containers; cultured on CHROME agar, using calibrated loop; colony count was done in positive cultures; identification and antimicrobial susceptibility of the organism was done by VITEK2 compact system. Susceptibility pattern of antimicrobial agents used for treatment of UTI including Fosfomycin was analyzed.

Results: Of the 502 urinary MDRO isolates, 74.9% were ESBLs and 29.49% were CROs. MDRO susceptibility was 88% to Fosfomycin, 70.52% to Ertapenem, 53.98% to Nitrofurantoin, 37.05% to Trimethoprim-Sulfamethoxazole, 22.31% to Norfloxacin, 20.91% to Ciprofloxacin, and 10.96% to Ampicillin respectively.

Discussion: Gupta et al.[10] reported 52.6% E. coli urinary isolates to be ESBLs and all were susceptible to Fosfomycin. In the present study, 76.8% Escherichia coli isolates were ESBLs and 98.5% only were susceptible to Fosfomycin.

Keywords: MDROs, UTI, Fosfomycin

Introduction

Urinary tract infections (UTIs) are common and account for a significant burden of hospital admission and associated healthcare expenditure.[1] The scarcity of available drugs for the treatment of infections caused by multidrug-resistant (MDR) and extensively drug-resistant (XDR) pathogens is recognized as a public health problem.[2] In particular, ESBL-producing urinary tract pathogens pose a considerable difficulty in the clinical treatment of UTIs because of the limited options for treatment.[3]

ESBL producers are no longer sensitive to majority of beta-lactam antimicrobials, and also the associated co-resistance to other antimicrobials limits the therapeutic options even further. The alternative treatment options for

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How to cite this article: Shilpa, Baveja UK, Govil D et al. Susceptibility of Multi-Drug-Resistant Organisms (MDROs), Isolated from Cases of Urinary Tract Infection to Fosfomycin (The New Antibiotic) vis-a-vis other Antimicrobial Agents. *J Commun Dis* 2018; 50(2): 34-37.

ESBL-producing organisms are carbapenems, tigecycline, beta-lactam-beta-lactamase inhibitor combinations (BL/BLI) and aminoglycosides. But all these drugs are to be administered parenterally, which may not be always feasible particularly in outpatient setting. Increased emergence of resistance among uropathogens and the decline in newly developed antibiotics makes it necessary to reintroduce old antimicrobial efforts in infection control and in addition to facilitating and promoting new drug development.[4] Since carbapenems are considered drug of choice for serious infections caused by these microorganisms, use of these drugs is increasing, which is contributing to the selection and spread of carbapenem-resistant Gram-negative bacilli (CRO).[2] Fosfomycin trometamol may be an interesting alternative to the currently used treatments of UTI.[5] Fosfomycin is an old broad-spectrum bactericidal antibiotic agent that inhibits the synthesis of the bacterial cell wall. Its pharmacokinetic profile encourages its use for UTIs; the mean peak urinary concentration of a single oral dose of 3 g Fosfomycin occurs within 4 h, while concentrations sufficient to inhibit the majority of the urinary pathogens are maintained for 1 to 2 days in urine[6].

Meta-analysis data indicates that Fosfomycin has in vitro activity against majority of E. coli isolates, as well as many other Enterobacteriaceae.[7] Fosfomycin therapy also appears to be safe, even in pregnant women. The use of Fosfomycin could prevent hospital admission for treatment of MDR UTIs and also decrease length of hospital stay by allowing substitution of oral for intravenous therapy.[8]

Materials and Methods

This prospective study was conducted in a tertiary care hospital. Patients of all age groups with complaints of dysuria, urgency, frequency, pain lower abdomen, fever, etc., were subjected to detailed history and clinical examination. Freshly collected mid-stream clean catch urine samples were collected from the non-catheterized, alert, conscious, adult patients with indications for urine culture as assessed by the clinicians from various inpatient and outpatient departments. If the patients were catheterized, then urine samples were collected from the catheter with proper asepsis with needle and syringe as described in erstwhile standard technique guidelines.

The urine samples were processed immediately (within 30 min) after collection. Direct microscopy of the uncentrifuged urine sample was done, and pus cells and bacteria were noted. Centrifuged deposits were examined under microscope for casts and crystals. The urine samples were plated using calibrated loop for semi-quantitative method on CHROME agar and incubated at 37°C overnight and, if required, till 48 hours. The colony counts were taken in case of positive culture. The isolates obtained from the samples with significant bacteriuria in the background of relevant supportive clinical features of UTI and/or the presence of significant number of (>5–10/hpf) pus cells on direct microscopy, as described in the standard guidelines, were only included in the study.

The identification and antimicrobial susceptibility of the organism was done by VITEK 2 compact system (BioMérieux Inc., France) as per standard protocols.

Susceptibility of micro-organisms for Fosfomycin and other antibiotics was noted and compared. Statistical analysis was done by using two-proportion z test.

Result

Amongst 502 Gram-negative bacilli (GNB) urinary isolates studied, 332 (66.13%) were Escherichia coli, 134 (26.69%) were Klebsella pneumoniae, 20 (3.98%) were Proteus species, 9 (1.79%) Morganella species and rest 7 (1.39%) were Providencia species. Fosfomycin susceptibility of these isolates was compared with susceptibility to Ertapenem, Nitrofurantion, Trimethoprim-Sulfamethoxazole, Ampicillin, Ceftriaxone, Ciprofloxacin and Norfloxacin, respectively. Overall, 442 (88%) isolates were sensitive to Fosfomycin. Proteus species showed maximum sensitivity of (20/20) 100% to Fosfomycin followed by E. coli 327/332 (98.5%), K. pneumonia 92/134 (68.7%), Provendcia species 3/7 (42.9%), respectively. None of the Morgenella species showed sensitivity to Fosfomycin.

Antibiotic susceptibility patterns of MDR uropathogens to different antibiotics are shown in Table 1. Amongst the isolates, 74.9% were ESBL producers, of which 85.83% were sensitive to Fosfomycin. Similarly, 29.49% were CROs; of these, 70.63% were susceptible to Fosfomycin. Of the 46.02% Nitrofurantoin-resistant isolates, 66.46% were found to be sensitive to Fosfomycin. Fosfomycin was found to have significantly higher susceptibility than other antibiotics for all the 502 urinary isolates, including Ertapenem ($P<0.0001$), Nitrofurantoin ($P<0.0001$), Trimethoprim-Sulfamethoxazole ($P<0.0001$), Ceftriaxone ($P<0.0001$), Ampicillin ($P<0.0001$), Ciprofloxacin ($P<0.0001$) and Norfloxacin ($P<0.0001$). The statistical significance of susceptibility of MDROs to Fosfomycin vis-à-vis other antibiotics for Gram-negative urinary isolates is depicted in Table 2.

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.201812

Table 1.Antibiotic Susceptibility Pattern of Various Uropathogens

	Fosfomycin (1)	Ceftriaxone (2)	Ertapenem (3)	Nitrofurantoin (4)	Trimethoprim-Sulfamethoxazole (5)	Ampicillin (6)	Ciprofloxacin (7)	Norfloxacin (8)
Escherichia coli	327/332 (98.5%)	79/332 (23.8%)	273/332 (82.6%)	257/332 (77.3%)	126/332 (37.95%)	49/332 (14.76%)	58/332 (17.47%)	60/332 (18.07%)
Klebsiella spp	92/134 (68.7%)	34/134 (25.4%)	57/134 (42.35)	13/134 (9.7%)	52/134 (38.80%)	0/134 (0.0%)	38/134 (28.36%)	38/134 (28.36%)
Proteus spp.	20/20 (100%)	8/20 (40.0%)	14/20 (70.0%)	1/20 (5.0%)	7/20 (35.0%)	6/20 (30.0%)	7/20 (35.0%)	10/20 (50.0%)
Morganellaspp	0/9 (0.0%)	4/9 (44.4%)	9/9 (100%)	0/9 (0.0%)	2/9 (22.22%)	0/9 (0.0%)	2/9 (22.22%)	3/9 (33.33%)
Providencia spp	3/7 (42.9%)	1/7 (14.3%)	1/7 (14.3%)	0/7 (0.0%)	1/7 (14.28%)	0/7 (0.0%)	0/7 (0.0%)	1/7 (14.28%)
Total	442/502 (88.0%)	126/502 (25.09%)	354/502 (70.52%)	271/502 (53.98)	186/502 (37.05%)	55/502 (10.96%)	105/502 (20.91%)	112/502 (22.31%)

Table 2.Significance/Comparison of Susceptibility of Various Uropathogens to Fosfomycin and Other Antibiotics

	1 vs 2	1 vs 3	1 vs 4	1 vs 5	1 vs 6	1 vs 7	1 vs 8
Escherichia coli	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*
Klebsiella spp	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*
Proteus spp.	<0.0001*	0.008	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*
Morganella spp	<0.0001*	0.008	<0.0001*	0.1358	-	0.1358	0.593
Providencia spp	0.236	0.236	0.051	0.2294	0.502	0.502	0.2294
Total	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*

*p-value < 0.05, statistically significant.

Discussion

Fosfomycin is an old molecule being re-evaluated for susceptibility of bacterial pathogens and its use in various infections.[9] Fosfomycin has good in vitro activity against common pathogens causing UTI, particularly towards the Enterobacteriaceae members. Fosfomycin is active against both Gram-negative and Gram-positive pathogens, including Entererococcus spp., Staphylococcus aureus, E. coli, Salmonella spp., Shigella spp., Klebsiella, Enterobacter spp., Serratia spp., Citrobacter spp., and P. mirabilis.[9] As the global prevalence of drug resistance increases, Fosfomycin is likely to be increasingly called upon for the oral treatment of UTI as well as for other infections of the urogenital tract including prostatitis.[1]

Current guidelines published by the Infectious Diseases Society of America (IDSA) and the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) recommend Fosfomycin, Nitrofurantoin, and Trimethoprim-sulfamethoxazole (TMP-SMX) as first-line agents to treat acute uncomplicated UTIs in adult females, reserving Fluoroquinolones, Amoxicillin-clavulanate, and other β-lactams as second-line agents.[10] E. coli was found to be the common uropathogen in this study. We aimed to analyze the in vitro activity of Fosfomycin against urinary isolates and to compare it with in vitro activity of other antimicrobials. In a study done by Gupta et al. from Chandigarh, amongst 150 uropathogenic strains of E. coli, 52.6% of isolates were ESBL producers, and all strains were susceptible to fosfomycin.[11] In another study by Mittal et al., it was found that 100% of uropathogenic E. coli were sensitive to Fosfomycin.[12] The present study showed 76.2% ESBL producers were E. coli, out of which 98.5% only were susceptible to Fosfomycin which is similar to the findings of the above-mentioned studies. Over all, 74.9% ESBL producers were detected, and of these 88.0% were susceptible to Fosfomycin. In vitro activity of Fosfomycin in this study was found to be superior to other oral antimicrobials tested against all the Enterobacteriaceae isolates (p <0.05). Maraki et al. in 2009 reported that Fosfomycin was active in vitro against a considerable percentage of urinary isolates – the isolates which exhibited high antimicrobial resistance against the conventionally used antimicrobial agents for the treatment of UTIs.[13]

Apart from Fosfomycin, Nitrofurantoin is another option for oral antimicrobial treatment of ESBL-associated, uncomplicated, urinary tract infections. Nitrofurantoin has been used for the treatment of acute uncomplicated cystitis, and has high rates of antimicrobial activity against E. coli urinary isolates in vitro.[7] In the present study, only 53.98% isolates were found to be sensitive to Nitrofurantoin. All

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.201812

the Morganella morganii isolates were found to be resistant to Fosfomycin[14] in this study and same has been reported earlier also.

Conclusion

In this study, Fosfomycin showed excellent in vitro activity against Gram-negative uropathogens including MDR organisms like ESBL and MBL producers except for Morganell morgani sp. Fosfomycin showed encouraging in vitro activity in urinary isolates from all age groups, irrespective of the comorbid conditions. Fosfomycin seems to be a promising oral alternative for treatment of uncomplicated MDR UTIs in the era of anti-microbial resistance (AMR). Although, the clinical evidence is still limited, Fosfomycin might be a valuable treatment option for community-acquired resistant urinary tract infections caused by these pathogens. However, since the resistance to Fosfomycin also develops on inappropriate use, this drug should be used judiciously in cases where other antibiotic options are not available.

Legend

- **F:** Fosfomycin
- **C:** Eftriaxone
- **E:** Rtapenem
- **N:** Itrofurantoin
- **T:** Rimethoprim-Sulfamethoxazole
- **A:** Mpicillin
- **C:** Iprofloxacin
- **N:** Orfloxacin

Conflict of Interest: None

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Date of Submission: 2018-01-11

Date of Acceptance: 2018-01-12