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FOSFOMYCIN : AN EFFECTIVE TREATMENT MODALITY FOR MULTIDRUG RESISTANT ENTEROBACTERIACEAE URINARY TRACT INFECTION

Microbiology

Sanjay Pratap Singh — Professor, Department of Microbiology,Armed Forces Medical College, Pune

Manish Ranjan* — Resident, Department of Microbiology, Armed Forces Medical College, Pune, *Corresponding Author

Sourav Sen — Professor & Head, Department of Microbiology,Armed Forces Medical College, Pune

ABSTRACT

Introduction: Urinary tract infections (UTIs) are amongst the commonest types of bacterial infections worldover. There has been rapid emergence and spread of resistance amongst *Enterobacteriaceae* with multidrug resistant (MDR) and extensively drug resistant (XDR) uropathogens drastically reducing the number of effective drugs for UTI. Fosfomycin is an old broad-spectrum bactericidal antibiotic agent used in the United States and Europe but sparingly used in India and is not a part of antibiotic recommended for UTI in our National Antibiotic policy.

Aim : To evaluate the antibiotic susceptibility profile of MDR *Enterobacteriaceae* (MDRE) uropathogens and to assess efficacy of Fosfomycin.

Methods: A total of 138 non-duplicate urinary isolates of MDR *Enterobacteriaceae* were included in the study.Identification and susceptibility testing was done according to standard phenotypic microbiological procedures and AST as per recommendations of CLSI.

Results: Total number of urine samples processed were 2476, of which 382 samples grew significant *Enterobacteriaceae*. Of these, 138 isolates were found to be MDR. The common isolates were *E. coli* (60%) followed by *Klebsiella pneumonia*e (24%). The rates of resistance to drugs recommended as first line - Nitrofurantoin, trimethoprim-sulfamethoxazole, Ciprofloxacin, Norfloxacin, were 44%, 67%, 72%,and 77% respectively. Sensitivity to Fosfomycin was highest 94.8%. Of 17 Imipenem resistant *Enterobacteriaceae* (Carbapenem-resistant *Enterobacteriaceae*), 14 were sensitive to fosfomycin.

Conclusion: Fosfomycin sensitivity amongst MDR uropathogens is highest amongst all antimicrobials with convenience of a single-dose regimen for out patients makes it an ideal option for treating MDR UTIs. It is recommended that the Fosfomycin should be kept as a reserve drug for treatment of MDR UTIs. There also appears to be an imperative need to include the same in the National Antibiotic Policy guideline.

KEYWORDS

Fosfomycin, MDR urinary tract infection, Enterobacteriaceae, National Antibiotic Policy

INTRODUCTION

Urinary tract infections are one of the most common presentations in clinical setting accounting for almost 30% of hospital visits. An estimate of the global prevalence of UTI cases ranges from about 150 – 200 million cases annually.[1] An estimated 40-50 % of females & 5-10 % of Males will develop UTI at least once in their lifetime. Majority of these infections are caused by members of family *Enterobacteriaceae* with *Escherichia coli* being the predominant organism.[2]

Much like in other systemic infections, urinary tract infections too has witnessed an upsurge in drug resistant pathogens not amenable to treatment with commonly used antibiotics.[3,4] This not only adds up to increased hospital visits in outpatient cases and increased duration of hospital stay in inpatients, but also puts a huge economic burden on the individual patient and the country. The situation is further compounded by emergence of Multidrug resistant organisms (MDROs) often requiring management with costlier higher antibiotics.[5,6,7]

MDRO is defined by the European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC) in 2011 as organism non-susceptible to ≥ 1 anti-microbial agent in ≥3 antimicrobial categories. The consensus group also defined Extensive drug resistance(XDR) and Pan drug resistance (PDR) as non-susceptible to ≥1 agent in all but ≤2 anti microbial categories and non-susceptible to all antimicrobial agents respectively.[8]

In context of widespread uroinfection by MDR *enterobacteriaceae* (MDRE), it has become imperative to carry out study to check efficacy of some long forgotten antibiotics. Fosfomycin is one such class of drug which inspite of its discovery way back in 1969, has remained an underutilized agent in the long and exhaustive armamentarium of antimicrobials.[9] Fosfomycin tromethamine is primarily approved for the treatment of uncomplicated UTIs as standard first line treatment of UTI in the USA and Europe.[9,10] The drug however has yet not been in the antibiotic recommended for UTI in our National Antibiotic policy Guidelines.[11,12]

The present study aims to evaluate effectiveness of fosfomycin as a treatment modality for urinary tract infections caused by multidrug resistant *Enterobacteriaceae* (MDRE).

MATERIAL & METHODS

Study design : A prospective observational study was carried out in the Department of Microbiology in a tertiary care centre. Principle objective of the study was to study the in vitro sensitivity of Fosfomycin against MDRE uropathogens isolated consecutively from 01 Apr 2017 to 31 August 2017. Instituitional ethical committee approval was obtained to carry out this study. Informed consent was obtained from all participating individuals.

Inclusion criteria : Non-duplicate urinary isolates of MDR *Enterobacteriaceae* were included in the study. MDR definition was taken as defined by European Centre for Disease Prevention and Control (ECDC) and the Centre for Disease Control and Prevention (CDC) consensus group definition which defines MDR as acquired non-susceptibility to at least one agent in three or more antimicrobial categories.[8]

Sample size calculation : Sample size was calculated by using level of confidence as 95%, expected proportion of Fosfomycin sensitive isolates as 95%, with absolute error of margin of 5%. Total required sample size worked out to 73.

Microbiological Methods

Urine culture & AST

Isolation and identification from the urine samples was carried out using semi-quantitative culture technique on cysteine lactose electrolyte – deficient medium CLED agar (Hi-Media, India). Further identification was performed using standard biochemical tests and also using Vitek2 Compact SL (Bio-Meriuex Inc, France). Antibiotic susceptibility testing was performed by Kirby Bauer disk diffusion method on Mueller-Hinton agar (Hi-Media, India) and results obtained were interpreted as per CLSI 2016 guideline(15,21). The antibiotics tested were Ampicillin (10µg), Amoxycillin/ Clavulanate (30µg), Ampicillin-Sulbactam (10/10µg), Piperacillin-tazobactam (100/10µg), Cefazolin (30µg), Ceftriaxone (30µg), Cefotaxime (30µg), Imipenem (10µg), Ertapenem (10µg), Aztreonam (30µg), Gentamicin (50µg), Amikacin (10µg), Norfloxacin (5µg), Ciprofloxacin (5µg), Levofloxacin (1µg), Cotrimoxazole (23.75/1.25µg), Nitrofurantoin (200µg), & Fosfomycin (200µg).

The data obtained was compiled in Excel sheet and statistically analysed.

RESULTS :

A total of 2476 urine samples were received during the study period of which 382 showed significant growth of *Enterobacteriaceae*. Of these, 138 (36%) *Enterobacteriaceae* were found to be MDR using the definitions of multi-drug resistant as stated earlier.[8] Distribution of MDR isolates according to resistance to number of antimicrobial category is depicted in Table1. *Escherichia coli* was the commonest bacteria to be isolated (n=83 ; 60 %) followed by *Klebsiella pneumoniae* (n=33 ;24%). Other predominant isolates were *Citrobacter sp* (n = 12 ; 9%), *Proteus sp*(n= 4; 3 %). (Fig 1)

In patients demographic profile, there was preponderance of samples from females than that of males(85 females vs 63 males). 62% of such MDRE isolated came from admitted patients and 38% from out patients departments.

The rates of resistance to drugs recommended as first line Nitrofurantoin, trimethoprim-sulfamethoxazole, Ciprofloxacin, Norfloxacin was found to be 43.7%, 67%, 72%,and 77.1% respectively. Even Cephalosporins such as cefazolin and ceftriaxone showed a low sensitivity of 43% & 41.7% respectively. Piperacillin-Tazobactum sensitivity was only 46.9%. Higher sensitivity rates were detected to second line drugs such as Amikacin, Ertapenem and Imipenem of scale of 78.9%, 77.8% and 84.0% respectively. The AST pattern of MDRE isolates is depicted in Fig 2.

Overall sensitivity of MDREs to Fosfomycin was highest 94.8% (95%CI being from 91.0% - 98.8%) . Sensitivity of *E coli* isolates was 93.2% and that of *Klebsiella pneumoniae* isolates was 100%.

Significantly, of the total of 17 isolate that were detected to be imipenem resistant (carbapenem-resistant *Enterobacteriaceae*), 14(82%) were sensitive to Fosfomycin. Likewise out of a total of 27 Amikacin resistant isolates, 24 (89%) isolates were found to be sensitive to Fosfomycin.

DISCUSSION :

Multi drug resistance has been reported in UTIs with increasing frequency in last decade. Till the year 2010, there was no clear consensus on criteria adopted to label an organism as MDR. The European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC) in the year 2011 developed a consensus guidelines to define Multi drug resistance (MDR) organism. The common drugs used to treat such multi drug resistant strains have been Carbapenems. With emergence of Carbapenem resistant *Enterobacteriaceae* (CREs), it is imperative to revisit few anti- microbials from the past. One such anti-microbial which is hardly used in India is Fosfomycin.[13]

Fosfomycin, is a low molecular weight (138Da)[14] phosphonic acid derivative isolated from *Streptomyces* spp in 1969 in Spain.[14,15] It is the sole member of the epoxide group and acts by inhibiting the first step in peptidoglycan synthesis pathway.(14) This class of antibiotic exhibits a broad spectrum bactericidal activity and in vitro studies have demonstrated remarkable activity against MDROs viz methicillin resistant Staphylococcus aureus (MRSA), vancomycin resistant enterococci (VRE) and ESBL producing *enterobacteriaceae* to name a few.[15,16]

Fosfomycin tromethamine is primarily approved for the treatment of uncomplicated UTIs in the USA & Europe. It has been adopted by the Infectious Diseases Society of America (IDSA) and the European Society for Clinical Microbiology and Infectious Diseases in 2011 as recommended first line agents for the treatment of acute uncomplicated UTIs & pyelonephritis in adult females .[9,17] Various studies have also demonstrated promising results about its use either alone or in combination for treatment of severe infections requiring critical care management.[17-21]

Evidence suggests high activity of fosfomycin against ESBL producing *E.coli* and also against Carbapenemase producing organisms.[8,9,16] High efficacy of Fosfomycin for CREs and Aminoglycoside resistant organisms which correspond to similar studies carried elsewhere.[22,23] Sahni et al (2013) found 81 % susceptibility of ESBL producing *E.coli* to Fosfomycin.[20] Vardakas et al in their systematic review evaluated the susceptibility of contemporary isolates to Fosfomycin observed 95.1%,83.8% susceptibility amongst ESBL *E.coli* and *Klebsiella pneumoniae* respectively.[17] Fosfomycin was found to be susceptible to 73.5% of CRE *K.pneumoniae*.[16] Lawhale MA et al (2017) in the study conducted in Maharastra,India found 100% of gram negative isolates to be sensitive to Fosfomycin which substantiates the need to gather more local and global data on the susceptibility pattern and also on patient outcomes in so far Fosmomycin naïve individuals.[24-26]

The findings of this study demonstrates remarkable in vitro efficacy of Fosfomycin against multidrug resistant isolates of family *Enterobacteriaceae*. 94.6% of all MDR isolates showed sensitivity to Fosfomycin. What is more interesting is that 100% of *Klebsiella pneumoniaeae* which were resistant to Imipenem were sensitive to Fosfomycin.

This necessitates its use to be restricted in countries with high disease burden of MDREs like in our country and its inclusion in the Government's National Action Plan on Antimicrobial Resistance Policy guidelines.

CONCLUSION:

Fosfomycin as an ideally suited antimicrobial to be kept as reserve drug for cases of Multidrug Resistant *Enterobacteriaceae* (MDRE). This also needs to be incorporated in our National Antiobiotic usage guidelines.

Conflict of Interest: None to declare

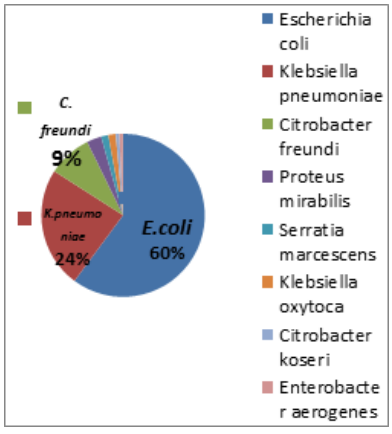

Fig 1 : Pie chart showing distribution of urinary *Enterobacteriaceae* pathogens

Reistance to antimicrobial cateogories	No. of Resistant Isolates	%of Resistant Isolates
>3 - ≤5	51	36.9%
≥6 - ≤10	54	39.1%
≥11	33	23.9%

Table 1: Distribution of MDR isolates according to number of antimicrobial cateogories (n = 138)

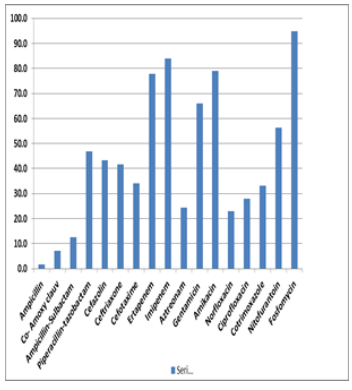

Fig 2 : Bar graph showing AST pattern (%sensitivity) of urinary MDR Enterobacteriaceae isolates (n = 138)

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