Fosfomycin: A potential oral option for treatment of urinary tract infections in Sri Lanka in the context of high antibiotic resistance

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Abstract

Introduction Fosfomycin is an effective treatment for urinary tract infections (UTIs). It is not currently used in Sri Lanka to treat UTIs. Hence, this study was conducted to assess the fosfomycin susceptibility for *E. coli* in urinary isolates, with an aim to find the usability of fosfomycin in the context of high antibiotic resistance.

Methods *E. coli* isolates were identified by the colony appearance and by performing biochemical tests for the urinary coliform isolates collected from two different hospitals in Western Province Sri Lanka, during the period of November 2021 to February 2022. Susceptibility to fosfomycin 200 µg disc was performed following the Clinical Laboratory Standard Institute (CLSI) disc diffusion method.

Results A total of 101 *E. coli* isolates from both oncology patients (52.5%) and non-oncology patients (47.5%) were identified and included in the study. The study sample showed majority of females (63.3%). Ampicillin showed the highest resistance rate (72.2%) while fosfomycin was the only antibiotic that showed 100% in vitro susceptibility to all the tested clinical isolates. The overall presence of multidrug-resistant (MDR) and carbapenem-resistant (CR) *E. coli* were 47.5% and 9.9% respectively.

Conclusions Fosfomycin is a potential antibiotic option especially for MDR and CR organisms, with 100% in vitro susceptibility. Further studies involving multiple centers, with larger sample size and clinical efficacy studies would be important to assess the potential use of fosfomycin especially for the treatment of UTI-causing MDR and CR organisms.

Keywords Fosfomycin, urinary tract infections, antibiotic resistant.

Introduction

More than 150 million cases of urinary tract infections (UTIs) are reported annually in the world and the frequency is higher in females.[1] UTIs can affect the lower urinary tract leading to cystitis, or the upper urinary tract, leading to pyelonephritis. It is one of the most common causes of sepsis resulting in high mortality rates. UTIs are commonly caused by *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Enterococcus*

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faecalis and *Staphylococcus aureus*, out of which the main etiological agent for uncomplicated UTIs is *E. coli* followed by *Klebsiella* spp.[2,3] According to published data, there is a significant increase in the prevalence of UTIs caused by extended spectrum beta-lactamase (ESBL)-producing *E. coli.*[4] In Sri Lanka, this rate is about 40% based on the published literature; with the emergence of ESBL producers and carbapenem-resistant organisms, antibiotic resistance is becoming more prevalent among urinary isolates, making these infections further complicated and difficult to treat.[5-7]

Antibiotic resistance varies with time, place and type of strain, population demographics and risk factors. On the macro level, it varies among geographical locations as new resistant species emerge and spread. The emergence and spread of multidrug-resistant (MDR) Gram-negative bacteria (GNB), associated with UTIs in the community and in hospitals are significantly increasing in the world.[8] This threatens the effectiveness of most of the routinely used antibiotics. Furthermore, limitation of available treatment options and development of resistance for most of the first line antibiotics for UTIs, increase healthcare associated costs and negatively impact the target population. Therefore, regional assessment of antibiotics susceptibility patterns is important to ensure that the UTIs remain treatable in the future.

Re-evaluation of 'older', 'forgotten' and 'neglected' antibacterial drugs is one approach to reduce the burden of uncomplicated UTIs. Fosfomycin is such an antibiotic, which has been called back. Rapid absorption after oral treatment, concentration for excretion in urine and its efficacy against many MDR organisms including ESBL producers are some of the characteristics shown by fosfomycin for being selected to treat UTIs over the other classes of antibiotics. Oral fosfomycin is well tolerated, with very few side effects which are considered as serious. According to a study, only 5% have reported side effects, out of which the most common was diarrhea.[9] Furthermore, recent in vitro studies have demonstrated an excellent effectiveness of fosfomycin against MDR GNB including ESBL producers and carbapenem-resistant Enterobacteriaceae (CRE) isolated from patients suffering from UTIs.[10]

Even though fosfomycin is suggested as an effective option for uncomplicated UTIs caused by MDR uropathogenic *E. coli* and *Klebsiella* spp.,[11] published data from Sri Lanka on fosfomycin sensitivity is scarce and the antibiotic is not currently being used in the country. The aim of our study was to identify fosfomycin as a potential oral option for treatment of UTIs in the context of high antibiotic resistance.

Methods

This was an in vitro cross-sectional study conducted to assess the susceptibility to fosfomycin for *E. coli* isolated from urine samples from November 2021 to February 2022 (5 months). The *E. coli* isolates which gave significant pure growth on CLED (cysteine lactose electrolyte deficient) agar plates from urine samples received for the routine diagnosis, and which fell within the inclusion and exclusion criteria, were included in the study. Urinary *E. coli* isolates were collected from the University Hospital Kotelawala Defence University (UHKDU) Sri Lanka, which included non-oncology patients, and from the National Cancer Institute (NCI) Maharagama, Sri Lanka, which included oncology patients. The laboratory work was conducted at microbiology laboratories of particular hospitals. These *E. coli* isolates were further identified by colony appearance and by performing biochemical tests (indole, methyl red, Voges-Proskauer, citrate (IMViC) tests and motility test) according to standard operating procedures.

Antimicrobial susceptibility testing (AST)

Fosfomycin sensitivity testing was performed according to the disc diffusion method using fosfomycin 200 µg disc (Hi Media Laboratories Pvt. Limited, India) as per the CLSI 2021 guidelines.[12] The disc diameters for *E. coli* isolates were interpreted according to the CLSI 2021 standard. MDR isolates were confirmed according to the CDC definition i.e., an isolate resistant to at least one antibiotic in three or more drug classes.[13] Carbapenem resistance was considered as resistance to imipenem and/or meropenem by disc diffusion testing. All the tests were quality controlled with standard *Escherichia coli* ATCC 25922 quality control strain.

Laboratory data

Susceptibility testing results for all the routinely used 1st line and 2nd line antibiotics by disc diffusion method were taken from laboratory records.

Statistical analysis

Statistical data were interpreted using SPSS 25 software (IBM Corp., USA). Descriptive statistics were performed to interpret the distribution of MDR and CR organisms among *E. coli* isolates in the sample. The Mann-Whitney U test was used to compare the mean susceptibility patterns of antibiotics with two variables such as sensitive and resistant while the Kruskal-Wallis test was used to compare the median values of susceptibility patterns of antibiotics with three variables such as sensitive, intermediate and resistant with a 95% confidence interval. Statistical significance was considered using $p<0.050$.

Ethical considerations

The ethical approval for the study was obtained from the Ethics Review Committee of the Faculty of Medicine, KDU (RP/S/2021/17) prior to the initiation of the project. The process of the research is in accordance with the ethical standards of Helsinki declaration. As the data were collected from the laboratory records and the patients were not contacted for this research, the Ethics Committee waived the requirement for informed consent. The collected data from laboratory records included age, gender, history of prior antibiotic usage and AST patterns. The leftover specimens received for the routine diagnosis were used for this study. Bacterial isolates were identified only by the laboratory identification number and patients could not be traced back.

Results

A laboratory-based cross-sectional study was conducted, with the inclusion of 101 *E. coli* isolates. The study sample was comprised of 53 (52.5%) *E. coli* isolates from oncology patients and 48 (47.5%) *E. coli* isolates from non-oncology patients. The age of the study sample showed a normal distribution with a mean age ± standard deviation (SD) of 49±23 years. The majority of the participants were female (66.3%, n=67).

The highest antibiotic resistance rates were observed for ampicillin and nalidixic acid (72.16% and 52.48% respectively). The lowest resistance rate (0.0%) was observed for fosfomycin (0.0%) and netilmicin (2.38%). Fosfomycin was the only antibiotic that showed 100% sensitivity rate for all the tested isolates. As a guide to provide more precise information on empirical and alternative treatment for MDR organisms, the antibiotic susceptibility rates of the different antibiotics used in the selected study sample are represented in Table 1. Accordingly, a statistically significant difference was noted between the susceptibility rates observed for both first line antibiotics (norfloxacin, cefuroxime, and cephalexin) and second line antibiotics (netilmicin, trimethoprim-sulfamethoxazole, ciprofloxacin, cefotaxime, cefepime, piperacillin-tazobactam, imipenem and meropenem). Some antibiotics were not tested for all the isolates, due to the limitation of antibiotic discs at particular laboratories, during the study period. Among the sample, 30.7% (n=31/101) of the patients had a history of taking antibiotics. In the sample, 47.5% (n=48/101) were MDR *E. coli* isolates while 9.9% (n=10/101) were carbapenem resistant *E. coli* isolates.

The zone diameter values of fosfomycin among all the tested 101 *E. coli* isolates ranged from 24 mm to 32 mm and the mean ± SD was 27.92±1.27 mm. The majority (46.50%) of the *E. coli* isolates showed 28 mm as the zone diameter.

Discussion

The antibiotic resistance rate among patients with UTI is becoming more prevalent, making these infections further difficult to treat. UTIs are commonly caused by *E. coli* and therapeutic

Table 1. Antibiotic susceptibility patterns of the uropathogenic *E. coli* isolates among the sample

Antibiotic class	Name of the antibiotic	No. of isolates tested (n)	No. of sensitive isolates (%)	No. of intermediate isolates (%)	No. of resistant isolates (%)	p value
Aminoglycosides	Gentamicin (GEN)	101	84 (83.7%)	3 (2.97%)	14 (13.86%)	0.105[1]
	Netilmicin	42	40 (95.24%)	1 (2.38%)	1 (2.38%)	<0.001[1]*
	Amikacin (AMK)	99	88 (88.89%)	3 (3.03%)	8 (8.08%)	0.413[1]
Sulfonamides	Trimethoprim/ sulfamethoxazole (TMP/SMX)	52	34 (65.38%)	1 (1.92%)	17 (32.69%)	<0.001[1]*
Quinolones	Nalidixic acid (NAL)	101	44 (43.56%)	4 (3.96%)	53 (52.48%)	0.345[1]
	Norfloxacin (NOR)	101	58 (57.42%)	1 (0.99%)	42 (41.58%)	0.043[1]*
	Ciprofloxacin (CIP)	98	48 (48.98%)	4 (4.08%)	46 (46.94%)	0.008[1]*
Nitrofurans	Nitrofurantoin (NIT)	100	82 (82.00%)	2 (2.00%)	16 (16.00%)	0.223[1]
Betalactams	Ampicillin (AMP)	97	27 (27.84%)	0	70 (72.16%)	0.175[2]
	Mecillinam (MEL)	101	83 (82.18%)	2 (1.98%)	16 (15.84%)	0.081[1]
	Cephalexin (LEX)	101	52 (51.49%)	0	49 (48.51%)	0.033[2]*
	Cefuroxime (CXM)	101	59 (58.42%)	0	42 (41.58%)	0.049[2]*
	Ceftazidime (CAZ)	14	9 (64.26%)	0	5 (35.71%)	0.794[2]
	Cefotaxime (CTX)	101	55 (54.46%)	1 (0.99%)	45 (44.55%)	0.037[1]*
	Cefepime (FEP)	51	37 (72.55%)	1 (1.96%)	13 (25.49%)	<0.001[1]*
	Co-amoxiclav (AMC)	101	54 (53.47%)	6 (5.94%)	41 (40.59%)	0.310[1]
	Piperacillin/ tazobactam (TZP)	92	62 (67.39%)	3 (3.26%)	27 (29.34%)	0.005[1]*
	Ticarcillin/ clavulanic acid (TIM)	7	5 (71.43%)	1 (14.29%)	1 (14.29%)	0.046[1]
	Imipenem (IPM)	72	64 (88.89%)	0	8 (11.11%)	0.009[2]*
	Meropenem (MEM)	50	48 (96.00%)	0	2 (4.00%)	<0.001[2]*
Fosfomycins	Fosfomycin (FOF)	101	101 (100%)	0	0	-

*A statistically significant difference was noted. [1]Kruskal-Wallis test; [2]Mann-Whitney U test.

antibiotics available for the treatment are also limited. Fosfomycin is a feasible first line antibiotic that can be used to treat antibiotic-resistant UTIs caused by *E. coli*. Although fosfomycin is used in many other countries, it is still not used in the Sri Lankan clinical setting. This study was performed to determine the susceptibility to fosfomycin by the disc diffusion method, among *E. coli* isolated from patients with UTI, with an aim to explore a potential oral option for the treatment of UTIs in the context of high antibiotic resistance. Additionally, the antibiotic resistance rates for currently used antibiotics were also considered.

Only the *E. coli* isolates (n=101) were tested, as the uropathogenic *E. coli* is the main causative organism for UTIs.[14-16] The majority of the *E. coli* isolates were from the oncology patients (52.5%). Disparity among genders highlights the importance of guiding females on UTI prevention as the majority of the UTI patients were females (66.3%, n=67). Emergence of antibiotic resistance is a concern, as more than 30% of the sample had a previous exposure to antibiotics. The causative mechanisms for the resistance development should be fully discovered to understand the association between previous antibiotic usage and current resistance patterns. Furthermore, when considering the AST patterns of all isolates, higher resistance rates were observed for first line antibiotics than for the second line antibiotics. Statistically significant differences were observed among the susceptibility patterns of antibiotics like norfloxacin, cefuroxime, cephalexin, netilmicin, trimethoprim-sulfamethoxazole, ciprofloxacin, cefotaxime, cefepime, piperacillin-tazobactam, imipenem and meropenem. These findings alarm the issue of antibiotic resistance, which complicates the treatment of UTIs and the value of antibiotic susceptibility testing in identifying the best medications to treat uropathogenic *E. coli*. Therefore, antibiotic susceptibility patterns should be reviewed from time to time as resistance rates are increasing. However, the major finding of this study was that fosfomycin showed the highest susceptibility rates (100%). Moreover, this alarming situation emphasizes the need of discovering more efficient antibiotics or re-evaluation of 'older', and 'forgotten' antibacterial drugs. Fosfomycin is one such drug which was used in the past and is currently not used in many parts of the world.

In the current study, performed in Western Province Sri Lanka, fosfomycin showed the highest susceptibility rate (100%) for all of the tested isolates, which is in agreement with the only research study published from Southern Province Sri Lanka[6] on community acquired UTI patients and elsewhere.[8,17] Although 3 years have passed from 2019 to 2021, still fosfomycin is unavailable in the Sri-Lankan clinical setting. The reason for this should be discovered by the surveillance teams and the necessary steps should be taken to introduce fosfomycin to treat uropathogenic *E. coli*.

According to the standard guidelines, to be used as empirical treatment, an antibiotic should show more than 90% sensitivity for the causative organism, in this case *E. coli* from that community.[18] Based on our results, only netilmicin, meropenem and fosfomycin meet these criteria, which is also supported by another study.[19] Fosfomycin can be used for the treatment of uncomplicated cystitis while meropenem can be used to treat complicated UTIs.[19] In contrast to the present study, a Sri-Lankan study in 2019[6] has proposed only mecillinam, nitrofurantoin and fosfomycin as empirical antibiotics for patients with community-acquired UTI in Sri-Lanka but a gradual increase in resistance rates for the other antibiotics was also observed. However, some antibiotics were not tested for all the isolates, which might have a significant impact on resistance trends, due to the unavailability of supplies during the study period. However, a low rate of fosfomycin resistance was also reported in other countries.[20]

We categorized isolates of MDR and CRO as these would be the primary interest for the treatment with fosfomycin, in order to spare the use of second line antibiotics like carbapenems and 3rd and 4th generation cephalosporins. Intravenous fosfomycin is currently being clinically evaluated as an alternative to meropenem for bacteremia caused by ESBL-positive *E. coli*.[21] However, in the present study, fosfomycin showed 100% effectiveness against MDR and CR isolates from patients with UTI, which is in line with several other studies.[17,20]

The major concern with the initiation of the treatment with fosfomycin is the possibility to develop resistance during the treatment. The spread of resistance is linked with the increase of consumption of the particular drug. However, the rate of resistance is less frequent in *E. coli* than in *Klebsiella* spp.[22] To eliminate fosfomycin resistance and to overcome emergence of antimicrobial resistance, its use should be limited and well managed.

This study had several limitations. Although agar dilution method was the gold standard for AST, we performed disc diffusion method due to the limitation of sophisticated laboratory facilities. Further studies should be performed in multiple centers from different provinces, including patients from different units with different age categories, using larger sample sizes. To determine a more precise dosing regimen, it would be better to determine the MICs of all isolates, in addition to the results given by the disc diffusion method.

Conclusions

Antibiotic resistance in frequently isolated uropathogenic *E. coli* is on the rise due to overuse and misuse of antibiotics. Fosfomycin has shown 100% in vitro susceptibility against all of the tested *E. coli*, including MDR and CR organisms. Currently, fosfomycin is not used in Sri Lanka but it could be used as an empiric antibiotic in areas where high antibiotic resistance is reported. Due to its excellent susceptibility rate, it should be used with caution to reduce the emergence of resistance. Further studies with multiple centers and larger sample size should be conducted to assess the feasibility to use fosfomycin in clinical settings.

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