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Original Research Article

Fosfomycin for treating *Escherichia coli* UTIs: Results from a tertiary hospital

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ABSTRACT

Background: Urinary tract infections (UTIs) arise due to the infiltration of microorganisms into the urinary system. The rising incidence of antibiotic resistance among UTI pathogens has narrowed the range of effective treatment options. Fosfomycin has been recognized as a potential alternative in the face of increasing resistance.

Aim and Objective: This research focuses on evaluating the in vitro effectiveness of Fosfomycin against gram-negative bacteria isolated from urinary tract infections (UTIs)

Materials and Methods: This retrospective study was carried out at the tertiary care hospital in Vadodara, Gujarat from 1^{st} Jan 2022 to 31^{st} Oct 2022. Out of 256 urine cultures that tested positive for microorganisms, 125 isolates (62.8%) were identified as *Escherichia coli* and were included in the study. Standard laboratory techniques were used for bacterial identification, and the VITEK 2 compact system was employed for antimicrobial sensitivity testing. The sensitivity of Fosfomycin was assessed using the disc diffusion technique with a 200 μg disc (Himedia), and the results were interpreted by measuring the zone of inhibition.

Results: Fosfomycin showed a sensitivity rate of 96% against *Escherichia coli*. Among extended-spectrum beta-lactamase (ESBL)-producing strains, Fosfomycin demonstrated a sensitivity rate of 91.4%.

Conclusion: Fosfomycin presents a valuable option for treating UTIs, particularly those caused by *Escherichia coli*, including strains that produce ESBLs.

1. Introduction

Each year, roughly 150 million urinary tract infection (UTI) cases are reported globally.[1] The inappropriate use of antibiotics in treating UTIs, combined with their significant socioeconomic impact, has contributed to the rise of antimicrobial-resistant strains among UTI-causing pathogens.[2] The occurrence of multidrug-resistant (MDR) strains in UTI isolates makes selecting suitable antimicrobial therapies more challenging. Moreover, the development of ESBL producing strains and AmpC-producing strains, as well as methicillin-resistant Staphylococcus aureus (MRSA), has further reduced the number of effective antibiotic options.[3,4]

Fosfomycin, with its broad-spectrum antibacterial activity against both gram-positive and gram-negative organisms, offers a promising alternative for treating UTIs, including complicated infections and acute pyelonephritis. It is an orally administered drug that is generally well-tolerated. This study aimed to evaluate the in vitro activity

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of Fosfomycin against gram-negative bacteria isolated from UTIs, in comparison to other antimicrobial agents."

1.1. History and mechanism

Fosfomycin was first identified in Spain in 1969 as an antimicrobial agent.[5] It acts as a bactericidal drug by inhibiting cell wall synthesis and demonstrates extensive antibacterial activity against both gram-positive and gram-negative bacteria. Historically, Fosfomycin has been used effectively in hospitals for treating both uncomplicated and more severe urinary tract infections (UTIs). However, its use declined with the advent of newer antibiotics such as β-lactams and fluoroquinolones. Recently, the rise of resistant bacterial strains, including those producing extended-spectrum beta-lactamases (ESBL), carbapenem-resistant Klebsiella pneumoniae, multidrug-resistant Pseudomonas aeruginosa, vancomycin-resistant enterococci (VRE), and methicillin-resistant Staphylococcus aureus (MRSA), has spurred renewed interest in older antibiotics like Fosfomycin.[6,7]

Given the limited number of effective antibiotics available for these cases, older antibiotics, including Fosfomycin, have been re-evaluated for their efficacy against multi-resistant bacteria. Fosfomycin has shown good in vitro sensitivity against these resistant strains.[8] This evidence has led to renewed interest in Fosfomycin in the past five years. Combining Fosfomycin with other active antimicrobial agents, such as aminoglycosides, Carbapenem, Cephalosporin, Daptomycin, and Oritavancin, has been found to produce an additive effect, potentially decreasing resistance development and improving the effectiveness of the drugs.[9–11]

2. Materials and Methods

2.1. Study setting and participants

The study was conducted in the at a tertiary care hospital in Vadodara, Gujarat, between 1^{st} Jan 2022 to 31st Oct 2022. It included patients from both outpatient and inpatient departments who were clinically diagnosed with a urinary tract infection (UTI).

2.1.1. Sample collection

Patients were instructed to collect mid-stream urine samples using sterile containers provided by the laboratory and then send them to the laboratory for testing.

2.2. Microbiological techniques

2.2.1. Culture and incubation

Urine samples were transferred onto sheep blood agar and MacConkey agar plates using a sterile, calibrated loop. These plates were incubated at 37°C for 18 to 24 hours in an aerobic environment.

1. Assessment of growth: After incubation, the Petri dishes were examined for bacterial growth. Significant growth was defined as a colony count exceeding 10^5 CFU/ml for a single bacterial isolate, as determined by the Kass count method.
2. Identification of bacteria
   (a) Colony characteristics: Initial identification was performed by examining the colony morphology on sheep blood agar and MacConkey agar plates.
   (b) Biochemical tests: The isolates were tested using standard biochemical methods, including Gram staining, indole production, methyl red, Voges-Proskauer, and citrate utilization assays.
   (c) Identification of *Escherichia coli*: The specific identification of *Escherichia coli* was validated with the VITEK 2 compact system (bioMérieux), utilizing the VITEK® 2 GN card to accurately determine *E. coli* based on its biochemical characteristics.[12,13]
3. Antimicrobial sensitivity testing
   (a) ESBL screening: The production of ESBL was assessed using antibiotic discs with cefotaxime, ceftazidime, and ceftriaxone on Mueller Hinton Agar. After incubating the plates at 37°C for 24 hours, the inhibition zones were measured according to CLSI guidelines.[14]
   (b) Confirmatory testing: Isolates that tested positive in the initial screening were subjected to further testing with discs of ceftazidime and a ceftazidime/clavulanic acid combination. The results were interpreted in accordance with CLSI guidelines.[14]
   (c) VITEK 2 testing: ESBL detection was additionally performed using the VITEK 2 compact system with AST N235 cards.
   (d) Fosfomycin sensitivity: Fosfomycin susceptibility was evaluated using the disc diffusion technique on Mueller-Hinton Agar. A 0.5 McFarland suspension of each isolate was prepared, and a Fosfomycin 200 μg disc was applied to the agar. Isolates with an inhibition zone of ≥16 mm were considered susceptible. Results were cross-checked with CLSI standards to confirm accuracy.

3. Result

Out of 256 urine samples analyzed, 199 (77.8%) were gram-negative and 57 (22.2%) were gram-positive. Among the gram-negative isolates, 37 (18.6%) were from outpatients and 162 (81.4%) from inpatients, with 118 (59.3%) from general wards and 44 (22.1%) from the ICU. Notably, 178 (89.2%) of the gram-negative isolates were Enterobacteriaceae, with 125 (62.8%) identified as

Table 1: Pattern and distribution of *E. coli* by patient setting

Gram –Ve Isolates	No. of Isolates	OPD	Ward	ICU
E. coli	125 (62.8%)	26	76	23
Total	199	37	118	44

Table 2: Antibiotic sensitivity pattern in *E. coli i*solates

Antibiotics	Ampicillin	Ceftriazone	Ciprofloxacin	Amikacin	Gentamicin	Nitrofurantoin	Fosfomycin	Piperacillin tazobactam
E.coli (n=125)	7 (5.6%)	67 (53.6%)	37 (29.6%)	94 (75.2)	71 (56.8%)	98 (78.4%)	120 (96%)	59 (47.2%)

Table 3: Prevalence of ESBL production in *E. coli*

***E. coli* (n=125)**	**Number of Isolates**	**Percentage (%)**
ESBL-Producing *E. coli*	58	46.4
Non-ESBL *E. coli*	67	53.6
Total	**125**	**100**

Table 4: Fosfomycin sensitivity in ESBL-producing *E. coli*

Fosfomycin Sensitivity	***E. coli* (n=58)**	**Percentage (%)**
Sensitive	53	91.4
Resistant	5	8.6

Escherichia coli (Table 1).

The antibiotic sensitivity profile for the 125 *E. coli* isolates is summarized in (Table 2). Fosfomycin exhibited a high efficacy, with 120 isolates (96%) demonstrating sensitivity to this agent. A comparative analysis of other antibiotics, such as ampicillin, ceftriaxone, ciprofloxacin, amikacin, gentamicin, nitrofurantoin, and piperacillin-tazobactam, showed varied effectiveness, with Fosfomycin outperforming most of these drugs in terms of sensitivity rates.

Out of the 125 *E. coli* isolates tested, 58 (46.4%) were identified as ESBL producers, while 67 (53.6%) were non-ESBL producers (Table 3). Fosfomycin demonstrated significant activity against both ESBL-producing and non-ESBL *E. coli* strains. Specifically, Fosfomycin was effective in 53 of the 58 ESBL-producing isolates (91.4%) and in all 67 non-ESBL isolates (100%) (Table 4).

4. Discussion

This study assessed the efficacy of Fosfomycin against UTI pathogens, particularly *Escherichia coli,* the most common causative agent. The findings highlight Fosfomycin's significant antibacterial activity against *E. coli* isolates, including ESBL-producing strains. These results are consistent with previous studies, which have also reported more sensitivity of *E. coli* to Fosfomycin. [15,16]

A comparative analysis with other antimicrobials demonstrated Fosfomycin's superior efficacy, particularly against MDR and ESBL-producing *E. coli*. These findings align with previous research that has identified Fosfomycin as a potent alternative for treating UTIs caused by resistant pathogens. [17]

Given the increasing prevalence of antimicrobial resistance, Fosfomycin appears to be a valuable alternative, especially for treating complicated UTIs caused by multidrug-resistant organisms. Its oral formulation makes it convenient for outpatient treatment, reducing the need for hospitalization. [18] Continued monitoring and responsible use are crucial to avert the potential development of resistance to Fosfomycin.

5. Conclusion

Fosfomycin demonstrates high in vitro efficacy against *Escherichia coli* isolates from UTI patients, including those producing ESBLs. This study supports the inclusion of Fosfomycin as a first-line or alternative treatment option in the management of UTIs, particularly in cases where multidrug-resistant strains are involved. Comparative studies have highlighted Fosfomycin superior effectiveness against *E. coli* compared to other commonly used antibiotics, reinforcing its potential role in treating complicated infections. Additional studies should aim to assess the clinical outcomes of Fosfomycin treatment across various patient groups.

6. Ethical Approval

This study was conducted under approval of Sumandeep Vidhyapeeth stitutional Ethics Committee (SVIEC/ON/Medi/RP/Jan/23/2024).

7. Conflict of Interest

None.

8. Sources of Funding

None.

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