Section: Microbiology

Original Research Article

FOSFOMYCIN SUSCEPTIBILITY IN MULTI DRUG RESISTANT UROPATHOGENIC ISOLATES OF ESCHERICHIA COLI

Seema Gupta[1], Abha Gupta[2], Ankur Goyal[3], Rajiv Kumar[4]

[1]Associate Professor, Department of Microbiology, S.N. Medical College, Agra, Uttar Pradesh, India
[2]Assistant Professor, Department of Chemistry, D.S. College, Aligarh, UP, India
[3]Professor, Department of Microbiology, S.N. Medical College, Agra, Uttar Pradesh, India
[4]Professor, Department of Pharmacology, Government Medical College and Hospital, Chandigarh, India

Received : 05/11/2023
Received in revised form : 18/12/2023
Accepted : 02/01/2024

Keywords:
Urinary tract infection, Multidrug resistance, Escherichia coli.

Corresponding Author:
Dr. Rajiv Kumar,
Email: drrajiv.08@gmail.com

DOI: 10.47009/jamp.2024.6.1.171

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2024; 6 (1); 872-875

Abstract

Background: Urinary tract infection (UTI) is a common and widespread human infection caused primarily by Escherichia coli (E. coli). The emergence of multidrug-resistant E. coli strains poses a significant challenge as treatment options are limited. Fosfomycin emerged as a novel therapeutic option for the treatment of UTI. This study was conducted with the aim of evaluating the in vitro susceptibility of fosfomycin against multidrug-resistant (MDR) uropathogenic isolates of E. coli. **Materials and Methods:** This cross-sectional study was conducted from April 2022 to December 2022 in the Department of Microbiology at SNMC, Agra, UP, India. A total of 2875 urine samples from individuals with suspected urinary tract infections (UTI) were collected, processed, and analyzed. A total of 401 E. coli were isolated and identified through routine biochemical testing. Their susceptibility to antibiotics was determined by the Kirby Bauer disk diffusion test in accordance with CLSI guidelines. **Result:** A total of 401 E. coli isolates were obtained, of which 48% of the isolates were identified as multidrug-resistant (MDR) and 62% of the isolates were identified as extended-spectrum beta-lactamase (ESBL) producers. Fosfomycin sensitivity was 95.76%. Of the MDR isolates, 92% were sensitive to fosfomycin, while 96% of ESBL producers were sensitive to fosfomycin. **Conclusion:** In the current situation with challenging treatment of urinary tract infections (UTI) due to multidrug-resistant (MDR) isolates of E.coli and limited options for antibiotics, fosfomycin may be the preferable antibiotic.

INTRODUCTION

Urinary tract infections (UTIs) are most common and prevalent bacterial infection requiring medical attention. Uropathogenic Escherichia coli (E. coli) is the primary cause of UTIs, responsible for 80-90% of outpatient and 30-50% of inpatient cases.[1] Adult women are more susceptible to UTIs than adult men, and certain human populations are at increased risk of developing urinary tract infection (UTI). These groups comprise children, pregnant individuals, older adults, postmenopausal women, patients who have spinal cord injuries and/or catheters, patients who have diabetes, multiple sclerosis patients, patients with HIV, and patients who have previously had urological abnormalities.[2]

Urinary tract infections are not only common, but also recurrent. The increasing resistance of uropathogenic bacteria to antibiotics has led to a growing need for alternative therapeutic procedures. The antimicrobial resistance of Gram-negative bacteria, especially E. coli, is on the rise. The acquisition of antimicrobial resistance (AMR) genes is particularly crucial in the case of Enterobacterales, as they have the potential to cause multidrug resistance (MDR) by conferring cross- or co-resistance to multiple drug classes.[3] Among the various MDR phenotypes, the production of extended-spectrum beta-lactamases (ESBLs) is one of the most clinically significant phenotypes.[4] The increasing prevalence of ESBL-producing (ESBL+) E. coli, which are often co-resistant to TMP-SMX and FQ, has become a worldwide concern and has implications for the empiric treatment of community-onset UTI.[5,6] High rates of AMR and MDR E. coli limit the effective empiric options for the treatment of UTI.

With inappropriate and inadvertent use of potent antibiotics has resulted in an increase resistance to antimicrobials commonly used to treat E.coli

ISSN (O): 2687-5365; ISSN (P): 2753-6556

associated UTI, including penicillins, cephalosporins, and fluoroquinolones.[7] In addition, the emergence of bacteria producing ESBL, CR, and MDR strains further restricts the available antimicrobial treatment options for physicians.[8]

Fosfomycin may be an alternative to the currently used treatment of UTI. Its effectiveness in treating UTIs has been demonstrated in clinical studies, but further research is necessary to confirm its safety and efficacy. This antibacterial drug is well tolerated and has broad activity against both gram-positive and gram-negative bacteria.

The phosphonic acid derivative fosfomycin was discovered in Spain back in 1969 from cultures of Streptomyces species.[9] It inhibits bacterial cell wall formation by binding to the enzyme UDP-N-acetylglucosamine enolpyruvyl transferase (MURA), which inhibits the formation of the cell wall precursor N-acetylmuramic acid. It is available both orally and systemically. When given orally, it is best absorbed if given before food intake. Most of the drug is excreted unchanged in the urine and very high concentration levels (2000 µg/mL) are achieved in urine after a single oral dose. Urine levels remain elevated for a long period of time (more than 24 hours) which makes it a suitable drug in the treatment of UTI. Resistance rates is low and are often acquired by chromosomal mutations that do not spread easily. Due to its unique chemical structure and mechanism of action, fosfomycin lacks cross-resistance with other antimicrobial agents and can be safely administered in combination with many other antibiotics.[10,11]

Fosfomycin is reported to achieve high concentrations in the urinary tract, with a minimal impact on gastrointestinal flora and a low propensity for resistance. Fosfomycin and tromethamine have been approved as oral single-dose treatment for acute uncomplicated cystitis in many countries, making it now the first-line treatment option for uncomplicated urinary tract infections in women.[12]

According to guidelines published by the Infectious Diseases Society of America (IDSA) and the European Society for Clinical Microbiology and Infectious Diseases (ESCMID), first-line agents recommended for the treatment of acute uncomplicated urinary tract infections (UTI) in adult women include fosfomycin, nitrofurantoin, and trimethoprim-sulfamethoxazole (TMP-SMX). To treat acute uncomplicated UTI in adult women, fluoro-quinolones, amoxicillin-clavulanate, and other beta-lactams have been reserved as second-line agents.[13]

This study was conducted with the aim to assess the in-vitro fosfomycin susceptibility of extended-spectrum beta-lactamase (ESBL), carbapenem-resistant (CR), and multidrug-resistant (MDR) isolates of E. coli.

MATERIALS AND METHODS

This prospective cross-sectional study was conducted from April 2022 to December 2022 at the Department of Microbiology, Sarojini Naidu Medical College, Agra. The study was approved by the institutional ethics committee.

Study Population

Urine samples of all patients (both IPD and OPD) collected during the study period were processed and analyzed at the Department of Microbiology, Sarojini Naidu Medical College, Agra. Urine isolates other than E. coli were excluded from the study.

Sample Collection and Analysis

Urine samples obtained from both inpatients and outpatients were processed immediately in the microbiology laboratory. Direct microscopy of uncentrifuged urine sample was performed to examine pus cells and bacteria. Samples were cultured using a semi-quantitative method on Cysteine Lysine Electrolyte Deficient (CLED) agar.

A wire loop with a volume of 0.001 mL was used to inoculate CLED agar plates with urine. The plates were then incubated aerobically at 37°C overnight. The organisms' growth and colony count were determined. Further processing of isolates obtained from samples with significant bacteriuria and the presence of significant pus cells on direct microscopy was conducted in accordance with standard guidelines.[14] Bacterial species were identified by standard biochemical methods. Antimicrobial susceptibility testing was conducted on Mueller-Hinton agar plates using the Kirby-Bauer disk diffusion method and the results were interpreted according to Clinical and Laboratory Standards Institute guidelines.[6-8]

The study examined several antimicrobial agents, such as amoxiclave (20/10ug), ciprofloxacin (5 µg), ceftazidime (30 µg), trimethoprim / sulphamethoxazole (1.25 / 23.75 µg), amikacin (30 µg), nitrofurantoin (300 µg), cefapirazone/sulbactam (75/10µg), piperacillin-tazobactam (100 / 10 µg), meropenem (30 µg), Fosfomycin (200µg). To test ESBL production in E. coli, we applied the disk diffusion method with the combination of ceftazidime (30 µg) and ceftazidime/clavulanate (30/10 µg).[8]

Multi drug resistant (MDR) pathogens were defined as organisms resistant to three or more agents in different antimicrobial classes according to the standard definition. All the isolates identified as multidrug resistant were tested with fosfomycin (200 µg).

RESULTS

A total of 401 E. coli isolates were collected from 2875 urine samples and tested for antibiotic susceptibility. Of these isolates, 69% (276) were from female patients and 31% (125) were from male patients. Out of 401 isolates of E.coli, 192 (48%)

ISSN (O): 2687-5365; ISSN (P): 2753-6556

isolates were MDR, while 62% (249) were ESBL producers. The result showed high resistance rates to trimethoprim-sulfamethoxazole, amoxiclav, fluoroquinolones, cephalosporins, and aminoglycosides among the 401 E. coli isolates.

In the present study, 384 (95.76%) out of 401 isolates were found to be susceptible to fosfomycin. Of the 192 multidrug-resistant (MDR) isolates, 176 (92%) showed susceptibility to fosfomycin. Additionally, 240 (96%) out of 249 ESBL-producing isolates were susceptible to fosfomycin.

The resistance pattern of all antibiotics is as follows – amoxiclav 84% (337), cotrimoxazole 84.28% (338), ciprofloxacin 71.07% (285), ceftazidime 68.07% (273), amikacin 48.37% (194), cefoperazone-sulbactam 23.94% (96), piperacillin-tazobactam 15.7 0% (63), nitrofurantoin 10.22% (41), meropenem 9.22% (37), and fosfomycin 4.2% (17).

Table 1: Antibiotics Resistance and Sensitivity pattern of isolates of E.coli

Antibiotics	Resistance % (n=401)	Sensitive %(n=401)
Amoxiclav	84.03%(337)	15.97%(64)
Cotrimoxazole	84.28% (338)	15.71% (63)
Ciprofloxacin	71.07% (285)	28.92% (116)
Ceftazidime	68.07%(273)	31.92% (128)
Amikacin	48.37% (194)	51.6% (207)
Cefoperazone –sulbactam	23.94%(96),	76.05% (305)
Piperacillin –tazobactem	15.71%(63)	84.28% (338)
Nitrofurantoin	10.22% (41)	89.77% (360)
Meropenem	9.22% (37)	90.77% (364)
Fosfomycin	4.2% (17)	95.76% (384)

The present study showed the highest resistance to amoxiclav, cotrimoxazole, ciprofloxacin, ceftazidime and amikacin.

DISCUSSION

Urinary tract infection (UTI) is a common and widespread infection that affects many people across the world. Effective treatment of UTI depends on the identification of pathogenic microorganisms and their antibiotic sensitivity patterns. While E.coli is the most common organism that causes UTI, it is also a important organism that is sensitive to many antibiotics. However, the rise of multidrug-resistant E. coli strains has become a great challenge. Therefore new and highly potent antibiotics should be discovered or revive the use of old antibiotics, such as fosfomycin. The present study found high antibiotic resistance to commonly used antibiotics amoxiclav, cotrimoxazole, fluoroquinolones and cephalosporins.

Fosfomycin is an oral phosphonic acid derivative that was first isolated from Streptomyces in 1969, and is now produced synthetically.[9,10] Fosfomycin inhibits the synthesis of peptidoglycan one step earlier than beta-lactam or glycopeptide antibiotics and has a broad spectrum of activities against various Gram-positive and Gram-negative bacteria, including methicillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococci.[10,11]

During its early development, the drug's in vitro testing failed to confirm in vivo results, which led to underutilization. However, fosfomycin has recently gained attention as an agent against MDR and is now being actively researched.[10,11]

It has been shown to have benefits in treating UTIs due to its high concentrations in the urinary tract, exceeding 2,000 mg/liter after initial administration that last for a longer period than 24 hours.[8,10] Research has shown that fosfomycin is well tolerated with minimal adverse effects, affecting only 1–10% of patients.[10,12]

In our study, we found that 384 out of 401 isolates (95.76%) were found to be susceptible to fosfomycin. Susceptibility to fosfomycin was observed in 176 (92%) of 192 multidrug-resistant (MDR) isolates. These results are consistent with a previous study by Banerjee et al, which showed that 95.18% of the total isolates were found to be susceptible to fosfomycin and 95.93% of the MDR isolates were found to be susceptible to Fosfomycin.[15] Studies by Sultan et al, and Dasharaju Rajesh et al, have shown that MDR isolates of E. coli have 100% susceptibility to Fosfomycin.[16,17]

In the present study, 62% (249) of the isolates were ESBL producing and 96% (240) of the ESBL producing isolates were found to be sensitive to fosfomycin.

Another study by V Gupta et al, showed that 52.6% were ESBL producing and all ESBL producers were susceptible to Fosfomycin.[18] Nitrofurantoin also demonstrated significant susceptibility in this study, out of 401 E. coli isolates, 89.77% (360) isolates were susceptible to nitrofurantoin.

The findings of our study on the antibacterial activity of fosfomycin against uropathogenic E. coli align with previous research conducted globally.[15-20]

CONCLUSION

In the current situation with challenging treatment of urinary tract infections (UTI) due to multidrug-resistant (MDR) isolates of E.coli and limited options for antibiotics, fosfomycin may be the preferable antibiotic.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

REFERENCES

1. Ejrnæs K. Bacterial characteristics of importance for recurrent urinary tract infections caused by Escherichia coli. Dan Med Bull. 2011 April; 58(4).1
2. Jepson RG, Williams G, Craig JC. Cranberries for preventing urinary tract infections (updated review). Prescriber. 2013; 24(4): 20.
3. Nikaido H. Multidrug resistance in bacteria. Annu Rev Biochem 2009; 78:119–46.
4. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States. Atlanta, GA: U.S. Department of Health and Human Services, CDC, 2019
5. Critchley IA, Cotroneo N, Pucci MJ, Mendes RE. The burden of antimicrobial resistance among urinary tract isolates of Escherichia coli in the United States in 2017. PLoS One 2019; 14:e0220265
6. Payne DJ, Cramp R, Winstanley DJ, Knowles DJ. Comparative activities of clavulanic acid, sulbactam, and tazobactam against clinically important beta-lactamases. Antimicrob Agents Chemother 1994;38:767-72.
7. Leekha S, Terrell CL, Edson RS. General principles of antimicrobial therapy. Mayo Clin Proc. 2011;86(2):156-67.
8. Gupta K, Scholes D, Stamm WE. Increasing prevalence of antimicrobial resistance among uropathogens causing acute uncomplicated cystitis in women. JAMA. 1999;281(8):736-38.
9. Hendlin D, Stapley EO, Jackson M, Wallick H, Miller AK, Wolf FJ, et al. Phosphonomycin, a new antibiotic produced by strains of Streptomyces. Science. 1969;166:122-23.
10. Falagas ME, Kastoris AC, Kapaskelis AM, Karageorgopoulos DE. Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum beta-lactamase producing, Enterobacteriaceae infections: A systematic review. Lancet Infect Dis. 2010;10:43-50
11. Michalopoulos AS, Livaditis IG, Gougoutas V. The revival of fosfomycin. Int J Infect Dis 2011;15(11):e732-9.
12. Qiao LD, Zheng B, Chen S, et al. Evaluation of three-dose fosfomycin tromethamine in the treatment of patients with urinary tract infections: an uncontrolled, open-label, multicentre study. BMJ Open 2013;3(12):e004157.
13. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncom-plicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011;52(5):e103-20.
14. Clinical and Laboratory Standards Institute: performance standards for antimicrobial susceptibility testing; 27th Informational Supplement, CLSI M100-S27. Wayne PA, USA: Clinical and Laboratory Standards Institute 2017.
15. Banerjee S, Sengupta M, Sarker TK. Fosfomycin susceptibility among multidrug resistant, extended-spectrum beta-lactamase-producing, carbapenem-resistant uropathogens. Indian J Urol 2017;33(2):149–54.
16. Sultan A, Rizvi M, Khan F, Sami H, Shukla I, Khan HM. Increasing antimicrobial resistance among uropathogens: Is fosfomycin the answer? Urol Ann 2015;7:26-30.
17. Dasaraju R, Pothireddy S, Kavoori P. Fosfomycin in Multidrug-Resistant E. coli National Journal of Laboratory Medicine. 2021 Jan, Vol-10(1): MO09-MO12
18. Gupta V, Rani H, Singla N, Kaistha N, Chander J. Determination of extended-spectrum β-lactamases and ampc production in uropathogenic isolates of Escherichia coli and susceptibility to fosfomycin. J Lab Physicians 2013;5:90-3.
19. Kothari A, Sagar V. Antibiotic resistance in pathogens causing community-acquired urinary tract infections in India: A multicenter study. J Infect Dev Ctries 2008;2:354-8.
20. Maraki S, Samonis G, Rafailidis PI, Vouloumanou EK, Mavromanolakis E, Falagas ME. Susceptibility of urinary tract bacteria to fosfomycin. Antimicrob Agents Chemother 2009;53:4508-10.

ISSN (O): 2687-5365; ISSN (P): 2753-6556