Faropenem, a stable and orally bioavailable β-lactam, to counteract resistant pathogens and infectious diseases. A narrative review

Amit Bhalla[1]

[1]Uniza Healthcare LLP

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Abstract

Antimicrobial resistance is a huge challenge for the effective prevention and treatment of infectious diseases worldwide. Community-onset infections with Extended-spectrum β-lactamases (ESBL) producing bacteria are a challenge. In various studies, ESBL-producing isolates were consistently susceptible only to carbapenems. When treatment with other antibiotics fails, carbapenems are used as the last-line antibiotics for treating severe and/or resistant bacterial infections. In this narrative review, we aim to present the pharmacology of Faropenem, which is an orally administered penem antibiotic with a broad-spectrum activity against many Gram-positive and Gram-negative aerobes, and anaerobes. Faropenem is effective in the treatment of uncomplicated cystitis and is a potential solution to combat the emergence of resistance among respiratory tract pathogens. It is an alternative to fluoroquinolones or macrolides/ketolides when there is a concern with resistant pathogens. Keywords: β-lactamases, Carbapenems, Faropenem.

Φαροπενεμ, α σταβλε ανδ οραλλψ βιοααιλαβλε β-λασταμ, το ζουντεραζτ ρεσισταντ πατηογενς ανδ ινφεζτιους δισεασες. Α ναρρατιε ρειεω

Authors: Dr Amit Bhalla; Affiliations: Uniza Healthcare LLP; email: amitbhll@yahoo.com

Abstract: Antimicrobial resistance is a huge challenge for the effective prevention and treatment of infectious diseases worldwide. Community-onset infections with Extended-spectrum β-lactamases (ESBL) producing bacteria are a challenge. In various studies, ESBL-producing isolates were consistently susceptible only to carbapenems. When treatment with other antibiotics fails, carbapenems are used as the last-line antibiotics for treating severe and/or resistant bacterial infections. In this narrative review, we aim to present the pharmacology of Faropenem, which is an orally administered penem antibiotic with a broad-spectrum activity against many Gram-positive and Gram-negative aerobes, and anaerobes. Faropenem is effective in the treatment of uncomplicated cystitis and is a potential solution to combat the emergence of resistance among respiratory tract pathogens. It is an alternative to fluoroquinolones or macrolides/ketolides when there is a concern with resistant pathogens. Keywords: β-lactamases, Carbapenems, Faropenem.

Introduction

Antimicrobial resistance is a huge barrier to the effective prevention and treatment of infectious diseases worldwide.11Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet 2022; 399: 629–55. 10.1016/S0140-6736(21)02724-0 [Europe PMC free article] Over time, infectious agents such as bacteria, viruses and fungi acquire resistance to anti-infectives, which is associated with disease progression, increased numbers of treatment cycles and hospital stays, negative impacts on health-related quality of life, and higher patient mortality.22Naylor NR, Atun R, Zhu

Net al. . Estimating the burden of antimicrobial resistance: a systematic literature review. Antimicrob Resist Infect Control 2018; 7: 58. 10.1186/s13756-018-0336-y

ESBL remains a major healthcare challenge

Previous research has demonstrated that community-onset infections with ESBL-producing bacteria are a challenge facing treatment protocols in clinical practice.33Mushtaq S, Hope R, Warner M, et al. Activity of faropenem against cephalosporin-resistant Enterobacteriaceae. J Antimicrob Chemother. 2007;59(5):1025–1030.

Studies from India suggest that with a high prevalence of >62% in E. coli and Klebsiella, ESBL remains a major healthcare challenge. The prevalence of Methicillin-resistant Staphylococcus aureus (MRSA) in India has been reported at 41% in a multicenter study.[4] Alarmingly, the resistance of MRSA isolates to co-trimoxazole was 55.6%, to erythromycin was 70.8% and to ciprofloxacin was 79.3%.44Indian Network for Surveillance of Antimicrobial Resistance (INSAR) group, India. Methicillin-resistant Staphylococcus aureus (MRSA) in India: Prevalence & susceptibility pattern. Indian J Med Res. 2013;137(2):363–369

In various studies, ESBL-producing isolates were consistently susceptible only to carbapenems.55Manoharan A, Premalatha K, Chatterjee S, *et al* . Correlation of TEM, SHV and CTX-M extended-spectrum beta-lactamases among Enterobacteriaceae with their*in vitro* antimicrobial susceptibility. Indian J Med Microbiol. 2011;29(2):161–164.

Therapeutic options for treating severe and resistant bacterial infections

Several hundred β-lactam antibiotics exist, but the carbapenems have the broadest spectrum of activity and greatest potency against Gram-positive and Gram-negative bacterial species.66Papp-Wallace KM, Endimiani A, Taracila MAet al. . Carbapenems: past, present, and future. Antimicrob Agents Chemother 2011; 55: 4943–60. 10.1128/AAC.00296-11

For this reason, when treatment with other antibiotics fails, carbapenems are used as the last-line antibiotics for treating severe and resistant bacterial infections that often are associated with high morbidity and mortality. Carbapenems as IV formulations are available in most countries for the treatment of severe, complicated and resistant bacterial infections, including those affecting the respiratory, abdominal and urinary tracts, and the skin. While faropenem demonstrates high oral bioavailability (around 70%–80% in its ester prodrug form), carbapenems must be administered parenterally. Efforts to improve the oral bioavailability of carbapenems are ongoing.77Veeraraghavan B, Bakthavatchalam YD, Sahni RD. Oral antibiotics in clinical development for community-acquired urinary tract infections. Infect Dis Ther 2021; 10: 1815–35. 10.1007/s40121-021-00509-4

An oral penem, faropenem, is available in Japan and India for the treatment of urinary tract infections (UTIs), respiratory tract infections, skin and skin structure infections and gynaecological infections.88Gandra S, Klein EY, Pant Set al. . Faropenem consumption is increasing in India. Clin Infect Dis 2016; 62: 1050–2. 10.1093/cid/ciw055,99Hatakeyama S, Ohama Y, Okazaki Met al. . Antimicrobial susceptibility testing of rapidly growing mycobacteria isolated in Japan. BMC Infect Dis 2017; 17: 197. 10.1186/s12879-017-2298-8

This narrative review aims to profile the only available oral penem that addresses the challenge of resistant infectious diseases.

Faropenem: Pharmacological profile

Faropenem is an orally administered penem antibiotic which demonstrates broad-spectrum antimicrobial activity against many Gram-positive and Gram-negative aerobes and anaerobes. Faropenem is resistant to hydrolysis by nearly all β-lactamases, including ESBLs and AmpC β-lactamases.11Schreuck KN, Wiebe R,

Karlowsky JA, *et al.* Faropenem: Review of a new oral penem. Expert Rev Anti Infect Ther. 2007;5(2):185–198. Faropenem medoxomil (the prodrug form) is inherently stable to most β-lactamases produced by *Haemophilus influenzae, Moraxella catarrhalis* and *S. aureus.*22Siegert R, Berg O, Gehanno P, *et al.* Comparison of the efficacy and safety of faropenem daloxate and cefuroxime axetil for the treatment of acute bacterial maxillary sinusitis in adults. Eur Arch Otorhinolaryngol. 2003;260(4):186–194.

Pharmacodynamics:

Faropenem is characterized by pronounced β-lactamase stability compared to other cephalosporins and imipenem. It is highly stable against hydrolysis by various β-lactamases from *Bacteroides fragilis*strains and the rate of faropenem hydrolysis by metallo-β-lactamases is 5 times lower than that for imipenem.33Dalhoff A, Nasu T, Okamoto K. Beta-lactamase stability of faropenem. Chemotherapy. 2003;49(5):229– 236. Faropenem, like other β-lactam antibiotics, interferes with penicillin-binding proteins (PBPs) activity involved in the final phase of peptidoglycan synthesis (Figure 1). PBPs catalyze a pentaglycine crosslink between alanine and lysine residues providing additional strength to the cell wall. Without a pentaglycine crosslink, the integrity of the cell wall is severely compromised and ultimately leads to cell lysis and death.44Faropenem sodium. Product data sheet. Available at www.toku-e.com/ConvertHtmlToPdf.and?product=643. Accessed on May 05, 2023

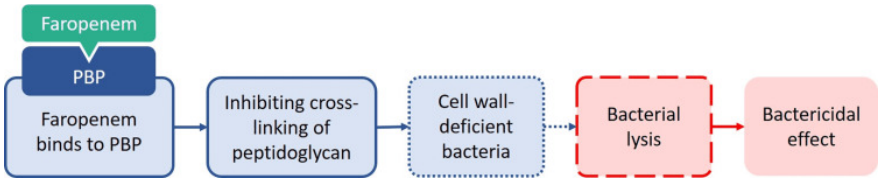

Figure 1: Faropenem mechanism of bactericidal effect.

Spectrum activity of faropenem:

Gram-positive bacteria : Faropenem is highly potent against*S. pneumoniae* ,11Upchurch J, Rosemore M, Tosiello R,*et al* . Randomized double-blind study comparing 7- and 10-day regimens of faropenem medoxomil with a 10-day cefuroxime axetil regimen for treatment of acute bacterial sinusitis. Otolaryngol Head Neck Surg. 2006;135(4):511–517. and in vitro activity has been noted against many methicillin-sensitive and methicillin-resistant strains of *S. aureus* and coagulase-negative Staphylococci.

Gram-negative bacteria : Faropenem has good in vitro activity against *E. coli* and *Klebsiella* spp. with ESBLs, including the CTX-M types.22Shazad Mushtaq and others, Activity of faropenem against cephalosporin-resistant Enterobacteriaceae, *Journal of Antimicrobial Chemotherapy* , Volume 59, Issue 5, May 2007, Pages 1025–1030, https://doi.org/10.1093/jac/dkm063 Furthermore, it has significant activity against the common respiratory pathogens,*H. influenzae* and *M. catarrhalis* .

Anaerobes : Against *Clostridium perfringens* , faropenem is as active as metronidazole and clindamycin. Faropenem also has activity against *Peptostreptococci* and *B. fragilis* .

As depicted in Table 1, faropenem exhibited better inhibitory potential compared to other antimicrobials like cefuroxime and Co-amoxiclav.

Table 1. The better activity of faropenem compared to other antimicrobials33Wexler HM, Molitoris D, St John S, *et al.In vitro* activities of faropenem against 579 strains of anaerobic bacteria. Antimicrob Agents Chemother. 2002;46(11):3669–3675,44Woodcock JM, Andrews JM, Brenwald NP, *et al.* The *in-vitro* activity of faropenem, a novel oral penem. J Antimicrob Chemother. 1997;39(1):35–43.

Pathogen	**MIC_{90} (mg/L)**		
	Faropenem	**Cefuroxime**	**Co-amoxiclav**

Streptococcus pneumoniae	**0.25**	4	1
MSSA	**0.12**	2	0.5
MRSA	**2**	>128	16
Haemophilus influenzae	**1**	2	2
Moraxella catarrhalis	**0.5**	2	0.25

MRSA: Methicillin-resistant *Staphylococcus aureus*; MSSA: Methicillin-sensitive *Staphylococcus aureus*

PHARMACOKINETICS

Orally administered faropenem medoxomil is readily absorbed. The addition of the medoxomil ester to the faropenem moiety improves bioavailability. The bioavailability of faropenem medoxomil is proposed to be 70–80%, which is approximately four times that of faropenem sodium.11https://m.chemicalbook.com/Article/Pharmacokinetics-of-Faropenem.htm [accessed May 18 2023] The half-life of faropenem medoxomil is estimated to be 0.9 hours. Administration of faropenem medoxomil under fasting and postprandial conditions resulted in no significant difference in Cmax and AUC.

Clinical Evidence for Faropenem

7-day regimen of faropenem for the treatment of cystitis 11Hamasuna R, Tanaka K, Hayami H, *et al* . Treatment of acute uncomplicated cystitis with faropenem for 3 days versus 7 days: Multicentre, randomized, open-label, controlled trial. J Antimicrob Chemother. 2014;69(6):1675–1680.

Acute uncomplicated cystitis is a common disease in women, and the increasing prevalence of resistant bacteria including ESBL-producing strains in pathogens causing acute uncomplicated cystitis has been of concern. Hamasuna, *et al* ., evaluated the efficacy of faropenem against cystitis, and compared 3- and 7-day administration regimens in a multicenter, randomized, controlled, open-label study. Women aged [?]20 years, with any cystitis symptoms, such as micturition pain, urinary frequency, urge to urinate, or lower abdominal pain with pyuria and bacteriuria were included in this study. The target bacteria were*Staphylococcus* spp., *Enterococcus faecalis* ,*Streptococcus agalactiae* and Enterobacteriaceae. Faropenem sodium was administered three times daily (600 mg/day) for 3 days (n=97) or 7 days (n=103).

Clinical efficacy in the two groups was not significantly different when evaluated at 5–9 days after treatment completion, and at 4–6 weeks after treatment completion. The microbiological non-recurrence rate was 80.8% (21/26) in the 3-day treatment group and 79.4% (27/34) in the 7-day treatment group (p=1.0). The MIC_{90} for *E. coli, K. pneumoniae, Staphylococcus and Enterococcus* was 1, 0.5, 1 and 0.03 mg/L, respectively. Adverse events (AEs) were reported in 9.5% of patients (19/200) and there was no significant difference between the 3- and 7-day treatment groups. The most common AE was diarrhea (7.5%, 15/200). AE severity was mild-to-moderate.

The 7-day regimen of faropenem showed a superior rate of microbiological response. E. coli strains were, in general, susceptible to faropenem, including fluoroquinolone- and cephalosporin-resistant strains.

Faropenem for patients with acute cystitis caused by ESBL-producing E.coli

Fujino et al retrospectively reviewed the medical charts of patients with acute cystitis caused by ESBL-producing E. coli who were treated with the oral antimicrobial agent faropenem (FRPM) in their institution

from June 2011 to May 2015.22Fujino, Keiko et al. The efficacy of faropenem for patients with acute cystitis caused by extended-spectrum β-lactamase producing Escherichia coli. Journal of Infection and Chemotherapy, Volume 23, Issue 5, 336 - 338 Ten patients with acute cystitis caused by ESBL-producing E.coli were treated with FRPM. Although a clinical cure was achieved in 9 of them, it reoccurred in 3. This study revealed that the treatment regimen with FRPM for patients with acute cystitis caused by ESBL-producing E.coli is promising. However, a non-negligible number of recurrences were caused by ESBL-producing E.coli

because of the nature of underlying diseases or pathologies in the urinary tract.

Faropenem for the management of urinary tract infection: Real-world experience from India. 33Shah A, Sharma S, Unnikrishnan TK. Experience of Faropenem for the management of urinary tract infection: Real-world experience from India. IP J Urol Nephrol Hepatol Sci 2020;3(4):

To record the real-world evidence on the use of faropenem in the management of UTIs, the responses of Indian urologists were obtained on the usage of faropenem in the management of complicated urinary tract infection (cUTI) after providing a set of eight questions having both multiple-choice responses and open-ended answers. **Results** : Responses from 391 participants were collected. In the majority of the urology clinics prevalence of cUTI was 5-10% whereas others found it to be 10-20%. A majority believed that faropenem was an effective pharmacotherapy for the management of UTIs (66.4%) including cUTI as a step-down therapy (66.4%). Faropenem 300 mg provided more compliance. The overall perception of the use of faropenem in their practice was that (out of 391 responses) the majority found it to be effective (72.7%) and 4.6% of participants have used faropenem as an alternative for cUTI. The majority found it safe (68.5) to be used in cUTI. It was shown that faropenem was preferred for the treatment of urinary tract infections due to its effectiveness, ability to cause less resistance and safety profile.

A faropenem regimen of 200–300 mg twice daily is recommended by Medindia for treating genitourinary infections.44Gandra S, Takahashi S, Mitrani-Gold FS, Mulgirigama A, Ferrinho DA. A systematic scoping review of faropenem and other oral penems: treatment of Enterobacterales infections, development of resistance and cross-resistance to carbapenems. JAC-Antimicrobial Resistance. 2022 Dec;4(6):dlac125.

Farpenem as an alternative to cefuroxime for the treatment of acute bacterial sinusitis

Siegert, *et al* ., compared the efficacy and safety of 7-day courses of faropenem medoxomil (300 mg twice daily; n=228) and cefuroxime axetil (250 mg twice daily; n=224) in adult patients with acute bacterial sinusitis in a prospective, multinational, multicenter, double-blind, comparative study.55Siegert R, Berg O, Gehanno P,*et al* . Comparison of the efficacy and safety of faropenem daloxate and cefuroxime axetil for the treatment of acute bacterial maxillary sinusitis in adults. Eur Arch Otorhinolaryngol. 2003;260(4):186–194.

S. pneumoniae , *H. influenzae* , *S. aureus* and*M. catarrhalis* were the most common organisms isolated at baseline. Four out of 36 *H. influenzae* , 9 out of 10 *M. catarrhalis* and 11 out of 19 *S. aureus* strains were β-lactamase producers. At 7–16 days post-therapy, clinical cure was reported in 89.0% of faropenem medoxomil- and 88.4% of cefuroxime axetil-treated patients, while the corresponding rates for bacteriological success were 91.5% and 90.8%. Eradication or presumed eradication (bacteriological response) is described in Figure 5. AEs were reported by 46 (16.8%) of the faropenem medoxomil-treated patients and 49 (17.9%) of the cefuroxime axetil-treated patients.

In a study by Upchurch, *et al* ., the efficacy and safety of faropenem medoxomil was compared with cefuroxime axetil in adults with acute bacterial sinusitis. This phase III, prospective, randomized, double-blind, multicenter trial included patients aged [?]18 years with a clinical diagnosis of acute sinusitis and duration of signs and symptoms >7 days but <28 days. Patients were randomly assigned in a 1:1:1 proportion to faropenem medoxomil 300 mg twice daily for 7 days (n=366) or 10 days (n=363) or cefuroxime axetil 250 mg twice daily for 10 days (n=370).66Upchurch J, Rosemore M, Tosiello R,*et al* . Randomized double-blind study comparing 7- and 10-day regimens of faropenem medoxomil with a 10-day cefuroxime axetil regimen for treatment of acute bacterial sinusitis. Otolaryngol Head Neck Surg. 2006;135(4):511–517.

Clinical cure rates for the 7-day and 10-day faropenem medoxomil regimens were non-inferior to that of the 10-day cefuroxime axetil regimen for the efficacy-valid population. The continued cure rates at the late follow-up visit showed that both faropenem medoxomil regimens had higher success rates than cefuroxime axetil. At least one AE was reported by 39%, 34% and 41% of patients in the faropenem medoxomil 7-day and 10-day groups and the cefuroxime axetil group, respectively. The majority of the AEs were mild or moderate in severity (87%) and improved or resolved after treatment.

Conclusions

Faropenem, a stable and orally bioavailable β-lactam, has broad-spectrum in vitro antimicrobial activity against many Gram-positive and Gram-negative aerobes and anaerobes and is resistant to hydrolysis by nearly all β-lactamases. A 7-day regimen of faropenem is effective in the treatment of uncomplicated cystitis. Faropenem is a potential solution to combat the emergence of resistance among respiratory tract pathogens. It is an alternative to fluoroquinolones or macrolides/ketolides when there is a concern with resistant pathogens.

Study limitations and directions for future

The limitation of our work is that we were unable to include a meta-analysis that could provide a larger sample size for making a more accurate status update of faropenem. For future research, larger prospective randomized clinical trials, especially in resistant urinary and respiratory infections will help to establish the definitive role in such patients.

Summary points:

- Carbapenems are used as the last-line antibiotics for treating severe and resistant bacterial infections.
- Carbapenems must be administered parenterally
- Oral penem, faropenem, is available in Japan and India for the treatment of urinary tract infections (UTIs), respiratory tract infections, skin and skin structure infections and gynaecological infections
- Faropenem demonstrates high oral bioavailability (around 70%–80% in its ester prodrug form).
- Faropenem is resistant to hydrolysis by nearly all β-lactamases, including ESBLs and AmpC β-lactamases.
- Faropenem is effective in the treatment of uncomplicated cystitis.
- Faropenem is a solution to combat the emergence of resistance among respiratory tract pathogens. It is an alternative to fluoroquinolones or macrolides/ketolides when there is a concern with resistant pathogens.