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

Amit Bhalla¹

¹Uniza 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.

Introduction

Antimicrobial resistance is a huge barrier to the effective prevention and treatment of infectious diseases worldwide. Antimicrobial 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.
ESBL remains a major healthcare challenge


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. Alarming, the resistance of MRSA isolates to co-trimoxazole was 55.6%, to erythromycin was 70.8% and to ciprofloxacin was 79.3%. Indian 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. Carbapenems: past, present, and future. Antimicrob Agents Chemother 2011; 55: 4943–60. 10.1128/AAC.00296-11

Therapeutic options for treating severe and resistant bacterial infections


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.


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.


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. 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.

Figure 1: Faropenem mechanism of bactericidal effect.

Spectrum activity of faropenem:

**Gram-positive bacteria**: Faropenem is highly potent against S. pneumoniae, 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. Faropenem is as active as metronidazole and clindamycin. Faropenem also has activity against Peptostreptococci and B. fragilis.

**Anaerobes**: Against Clostridium perfringens, faropenem is as active as metronidazole and clindamycin. As depicted in Table 1, faropenem exhibited better inhibitory potential compared to other antimicrobials like cefuroxime and 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**


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 MICs 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. Fujino, 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.**


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.


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


*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 sinussitis and duration of signs and symptoms >7 days but <28 days. Patients were randomly assigned in a 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). Upchurch J, Rosemore M, Tosio M, 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 sinussitis. 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.