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Faropenem, a Stable and Orally Bioavailable β-Lactam, to Counteract Resistant Pathogens and Infectious Diseases

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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

Abbreviations: MRSA: Methicillin-Resistant *Staphylococcus aureus*; MSSA: Methicillin-Sensitive *Staphylococcus aureus.*

Introduction

Antimicrobial resistance is a huge barrier to the effective prevention and treatment of infectious diseases worldwide [1]. 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 [2].

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 [3].

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%. In various studies, ESBL-producing isolates were consistently susceptible only

to carbapenems [5].

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 [6].

- 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 [7].

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 [8,9]. 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 [10]. Faropenem medoxomil (the prodrug form) is inherently stable to most β-lactamases produced by *Haemophilus influenzae*, *Moraxella catarrhalis* and *S. aureus* [11].

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 [12]. Faropenem, like other β-lactam antibiotics, interferes with penicillin-binding proteins (PBPs) activity involved in the final phase of peptidoglycan synthesis. 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 [13].

Spectrum activity of faropenem:

- Gram-positive bacteria: Faropenem is highly potent against *S. pneumoniae*, [14] 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 [3]. 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.

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

Table 1: The better activity of faropenem compared to other antimicrobials [15,16].

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 [17]. 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: 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 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 [18]. 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 MIC90 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 retrospectively reviewed the medical charts of patients with acute cystitis caused by ESBL-producing *E. coli* who was treated with the oral antimicrobial agent faropenem (FRPM) in their institution from June 2011 to May 2015 [19] 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 [20]**:** 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 [21].

Faropenem 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 [11].

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%. 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) [14].

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 was mild or moderate in severity (~87%) and improved or resolved after treatment.

Conclusions

Faropenem is a stable and orally bioavailable β-lactam that 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.

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