Oral Carbapenem Antibiotics

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Carbapenem[1-3]

- Antibacterial antibiotics in the Beta-Lactam group
- In the U.S., all carbapenems are available for IV infusion only
- **Broad spectrum of antibacterial activities**
  - *Streptococcus, MSSA*
  - *Escherichia coli, Klebsiella pneumoniae*
  - *Pseudomonas, Acinetobacter* (selected carbapenems)
  - *Bacteroides*
- Generally lower MIC against susceptible bacteria
- Can withstand activities against many extended-spectrum beta-lactamases (ESBL), but are inactivated by carbapenemase

The need for Oral Carbapenems

- More urinary tract pathogens are showing ESBL and other drug resistance (e.g., fluoroquinolone, TMP/SMX) in U.S.
- Oral carbapenems, such as faropenem, already available in other countries (e.g., Japan)
- Two oral carbapenems, sulopenem and tebipenem, have recently been undergoing clinical trials in the U.S.

Pharmacology & Pharmacokinetics[1-3]

- Similar to all beta-lactams, INHIBIT the bacterial transpeptidase (penicillin-binding proteins) in susceptible bacteria, especially gram negative isolates
- Bactericidal activities, time-dependent mode activity
- Safe and well-tolerated in most patients; risk of penicillin anaphylaxis is relatively low
- Well-Distributed to many tissues; minimal drug metabolism
- Unique drug interaction with valproic acid (FDA warning)

Table 1: Oral carbapenems – A comparison of pharmacokinetics

ORAL Forms	Faropenem	Sulopenem	Tebipenem
Pro-drug (esters)	Faropenem daloxate	Sulopenem etzadroxil	Tebipenem pivoxil
Bioavailability	70-80%	60%	50%
Elimination	RENAL 20%	RENAL ~65%	RENAL ~60%
Protein Binding	95%	10%	60%-70%
Serum Half-life	~ 1 hour	~ 1 hours	~ 1 hour
Food-AUC Effect	Not reported	↑ AUC by 24%	AUC no change
Probenacid Effects	↓ absorption AUC no change	↑ AUC by 63%	↓ AUC by 50-80%
Dosing (CrCl >60 ml/min)	BID	BID (with probenecid)	TID

Chemistry[1,3]

Figure 1: Comparison of the chemical structures of β-lactams

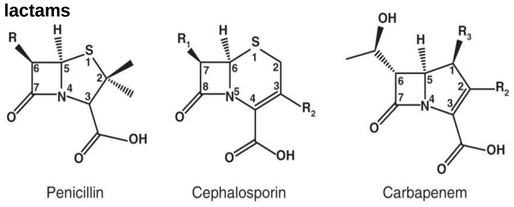
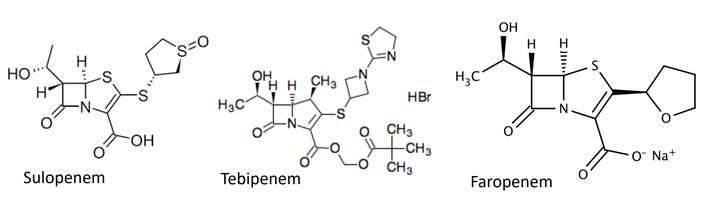


Figure 2: Chemical structures of oral carbapenems



Unique features to further resist bacterial beta lactamase

- A double bond between the C2-C3 carbons
- The *trans*-1-hydroxyethyl substituent at C6 carbon

Other functional features:

- The side chain or sulfur atom at C2 bolster their pharmacokinetic properties, including resistance to DHP-1 degradation in the kidneys (also determine classification of the antibiotic)

Microbiology[1-5]

Table 2: MIC values of oral carbapenems compared to ertapenem against common gram positive, gram negative, and anaerobic bacteria

Gram Negative Bacteria	Tebipenem (PO)		Sulopenem (PO)		Faropenem (PO)		Ertapenem (IV)	
	MIC50	MIC90	MIC50	MIC90	MIC50	MIC90	MIC50	MIC90
Acinetobacter spp.	NR	2	0.5	1	NR	NR	4	>8
E. coli	NR	0.05	0.03	0.06	0.25	1	0.008	0.03
H. influenzae (Amp^S)	NR	0.12	0.25	0.25	0.5	1	0.06	0.12
H. influenzae (Amp^R)	NR	1	0.5	0.5	0.5	1	0.12	0.3
Klebsiella pneumoniae	NR	0.05	0.03	0.12	0.13	0.3	0.008	0.06
Proteus mirabilis	NR	0.39	0.25	0.5	NR	NR	0.016	0.03
P. aeruginosa	NR	32	32	64	>256	>256	8	8
Gram Positive Bacteria								
S. aureus ($Meth^S$)	NR	0.06	0.06	0.12	0.13	0.13	0.12	0.25
S. pneumoniae	NR	0.002	0.008	0.06	0.016	0.03	0.016	0.016
Anaerobes								
Bacteroides fragilis	NR	0.06	0.06	0.5	1	4	NR	NR

- Over 90% of ESBL-producing, AmpC-producing and MDR (not susceptible to ≥1 antimicrobial from ≥3 classes) *E. coli* were inhibited by ≤0.25 mg/L of sulopenem and tebipenem. [6,7]
- Sulopenem and tebipenem had very similar MIC_{90} to meropenem for ESBL-producing and MDR *E. coli*.[6,7]

Clinical Developments[8-12]

- Sulopenem
  - In phase 3 clinical trials
  - Recently investigated for complicated UTI (cUTI) and uncomplicated UTI (uUTI) indications in the U.S.
  - Also investigated for complicated intra-abdominal infection (cIAI)
- Tebipenem
  - Tebipenem Pivoxil HBr is approved in Japan marketed as Orapenem® (oral fine granules)
    - For use in pediatric pneumonia, otitis media, and sinusitis
  - Recently investigated for cUTI
- Faropenem
  - Approved in Japan and India for use in uUTI, respiratory tract infections, and skin and skin structure infections
  - No trials currently being performed in the U.S.

Conclusion

- The mechanism of action and adverse drug reaction profiles are expected to be similar to other carbapanems
- Oral bioavailability improvements in sulopenem and tebipenem are promising with their prodrug-structural alterations
- Food and probenacid increase the area under the curve for sulopenem but not tebipenem
- The microbiologic MICs of tebipenem & sulopenem demonstrated feasible use against beta-lactamases, including ESBL, AmpC, and other drug-resistant isolates

- Oral carbapenems show potentials for further clinical development and trial evaluation
  - Both sulopenem and tebipenem have undergone Phase 1, 2 and 3 clinical trials

Please visit our accompanying posters on tebipenem and sulopenem for clinical data discussion

References
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