In vitro Activity of Tebipenem, an Orally Available Carbapenem Agent, against a Collection of Surveillance Gram-positive Clinical Isolates

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Introduction

- Tebipenem is an orally bioavailable carbapenem administered as a pro-drug.
- It completed a Phase 3 clinical trial evaluating its safety and efficacy for the treatment of complicated urinary tract infection and acute pyelonephritis.
- The purpose of this study was to investigate the *in vitro* activity of tebipenem and comparator agents, including ertapenem and meropenem, against a recent collection of Gram-positive isolates associated with clinical infections.

Materials and Methods

- The susceptibility of 580 Gram-positive organisms were tested, including:
  - Methicillin-susceptible *Staphylococcus aureus* (MSSA, 489 isolates),
  - Methicillin-susceptible *Staphylococcus epidermidis* (MSSE, 31),
  - Other methicillin-susceptible coagulase-negative staphylococci (MSCoNS, 29), and
  - Vancomycin-susceptible *Enterococcus faecalis* (31).
- Bacterial species were identified by JMI Laboratories using standard microbiology methods and matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany).
- The isolates were collected in 2018 and 2019 as part of the SENTRY surveillance program and selected to be representative of these species with 45.0% from the United States, 44.3% from Europe, 5.3% from the Asia-Pacific region, and 5.3% from Latin America.
- Isolates are primarily from pneumonia in hospitalized patients (498 isolates; 85.9%), urinary tract infections (42 isolates; 7.2%), and bloodstream infections (38 isolates; 6.6%).
- Isolates were tested in a central laboratory (JMI Laboratories) for antimicrobial susceptibility using the CLSI M07 (2018) reference broth microdilution method.
- JMI Laboratories produced frozen-form 96-well panels and used cation-adjusted Mueller-Hinton broth (CA-MHB) as the testing medium.
- All categorical interpretations used CLSI M100 (2021) and EUCAST v10.0 (2021) breakpoint criteria, where published.
- QC organisms: *Escherichia coli* ATCC 25922, *Escherichia coli* ATCC 35218, *Enterococcus faecalis* ATCC 29212, *Pseudomonas aeruginosa* ATCC 27853, and *Staphylococcus aureus* ATCC 29213 were tested concurrently with clinical isolates.

Results

- Activity against MSSA isolates
  - Tebipenem had an $MIC_{50/90}$ value of 0.015/0.03 mg/L (Table 1).
  - Tebipenem had the lowest $MIC_{50/90}$ results of all antimicrobial agents tested (Table 2).
  - Tebipenem MIC_{90} value was 8-fold lower than ertapenem (MIC_{90}, 0.25 mg/L) against MSSA.
  - Most comparator agents tested showed susceptibility rates ≥90.0% against MSSA isolates, except for erythromycin, which was 65.6% susceptible.
- Activity against MSSE isolates
  - Tebipenem had an $MIC_{50/90}$ value of 0.008/0.015 mg/L (Table 1).
  - Tebipenem had the lowest $MIC_{50/90}$ results of all antimicrobial agents tested (Table 2).
  - Tebipenem MIC_{90} value was 32-fold lower than ertapenem (MIC_{90}, 0.5 mg/L) against MSSE.
  - Most comparator agents tested showed susceptibility rates ≥90.0% against MSSE isolates, except for erythromycin, which was 54.8% susceptible.
- Activity against MSCoNS species other than *S. epidermidis*
  - Tebipenem had an $MIC_{50/90}$ value of 0.015/0.03 mg/L (Table 1).
  - Tebipenem had the lowest $MIC_{50/90}$ results of all antimicrobial agents tested (Table 2).
  - Tebipenem MIC_{90} value was 32-fold lower than ertapenem (MIC_{90}, 1 mg/L) against other MSCoNS.
  - All other MSCoNS isolates were susceptible to ertapenem and amoxicillin-clavulanic acid whereas susceptibilities to trimethoprim-sulfamethoxazole (83.9% S) and erythromycin (54.8% S) were lower.
- Activity against *E. faecalis*
  - Tebipenem inhibited all *E. faecalis* isolates at ≤1 mg/L (MIC_{90}, 1 mg/L; Table 3).
  - This MIC_{90} value was at least 2-fold lower than meropenem (MIC_{90}, >1 mg/L) and 16-fold lower than ertapenem (MIC_{90}, >8 mg/L).
  - Susceptibility rates of 80.6% and 100.0% were observed for levofloxacin and ampicillin, respectively, against *E. faecalis* isolates.

Conclusions

- Tebipenem displayed potent activity against methicillin-susceptible staphylococci, including MSSA, MSSE, and other MSCoNS.
- Tebipenem MIC_{50} and MIC_{90} values for these species and species groups ranged from 0.015-0.03 mg/L and the activity observed was 16- to 32- fold greater than ertapenem.
- The *in vitro* activity of tebipenem (all isolates with MIC values ≤1 mg/L) was greater than meropenem and ertapenem against *E. faecalis* isolates.
- These data indicate that tebipenem may be an option for treating urinary tract infections caused by these organisms or as an empiric option to provide broader coverage against Gram-negative and -positive organisms

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Table 1. Antimicrobial activity of tebipenem tested against the main organisms and organism groups

Organism/organism group (no. of isolates)	No. and cumulative % of isolates inhibited at MIC (mg/L) of:									MIC_{50}	MIC_{90}
	≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1		
Methicillin-susceptible *Staphylococcus aureus* (489)	0 0.0	9 1.8	325 68.3	151 99.2	4 100.0					0.015	0.03
Methicillin-susceptible *Staphylococcus epidermidis* (31)	1 3.2	22 74.2	8 100.0							0.008	0.015
Other methicillin-susceptible coagulase-negative staphylococci (29)	4 13.8	4 27.6	17 86.2	4 100.0						0.015	0.03
Enterococcus faecalis (31)						0 0.0	4 12.9	20 77.4	7 100.0	0.5	1

Table 2. Antimicrobial activity of tebipenem and comparator agents tested against methicillin-susceptible *Staphylococcus*

Organism Antimicrobial agent	mg/L			CLSI[a]			EUCAST[a]		
	MIC_{50}	MIC_{90}	MIC range	%S	%I	%R	%S	%I	%R
Methicillin-susceptible *Staphylococcus aureus* (n=489)									
Tebipenem	0.015	0.03	0.008 to 0.06						
Ertapenem	0.25	0.25	0.06 to 0.5	100.0 [b,c]		0.0			
Trimethoprim-sulfamethoxazole	0.06	0.06	≤0.03 to 2	100.0		0.0	100.0	0.0	0.0
Levofloxacin	0.25	1	0.06 to >4	91.2 [d]	0.0	8.8	[e]	91.2	8.8
Tetracycline	≤0.5	≤0.5	≤0.5 to >8	95.5 [f,g]	0.0	4.5	94.3	0.8	4.9
Erythromycin	0.25	>8	≤0.06 to >8	65.6 [g]	5.5	28.8	66.5	2.5	31.1
Gentamicin	≤1	≤1	≤1 to >8	95.7 [b,g]	0.2	4.1	95.7 [h]		4.3
Methicillin-susceptible *Staphylococcus epidermidis* (n=31)									
Tebipenem	0.008	0.015	≤0.004 to 0.015						
Ertapenem	0.25	0.5	0.12 to 0.5	100.0		0.0			
Trimethoprim-sulfamethoxazole	0.12	4	≤0.03 to 8	83.9		16.1	83.9	6.5	9.7
Levofloxacin	0.25	0.5	0.12 to >4	90.3	3.2	6.5	[d]	90.3	9.7
Amoxicillin-clavulanic acid	≤0.25	≤0.25	≤0.25 to ≤0.25	100.0		0.0			
Tetracycline	≤0.5	2	≤0.5 to >8	93.5	0.0	6.5	87.1	6.5	6.5
Erythromycin	0.12	>8	≤0.06 to >8	54.8	0.0	45.2	54.8	0.0	45.2
Gentamicin	≤1	≤1	≤1 to 8	96.8	3.2	0.0	96.8 [g]		3.2
Other methicillin-susceptible coagulase-negative staphylococci (n=29)[i]									
Tebipenem	0.008	0.03	≤0.004 to 0.03						
Ertapenem	0.5	1	0.25 to 1	100.0 [b,c]		0.0			
Trimethoprim-sulfamethoxazole	0.12	4	≤0.03 to 0.5	100.0		0.0	100	0.0	0.0
Levofloxacin	0.12	0.5	0.06 to >4	96.6		3.4	[d]	96.6	3.4
Amoxicillin-clavulanic acid	≤0.25	≤0.25	≤0.25 to ≤0.25	100.0		0.0			
Tetracycline	≤0.5	4	≤0.5 to >8	93.1 [e,f]	0.0	6.9	89.7	3.5	6.9
Erythromycin	0.12	>8	≤0.06 to >8	58.6 [f]	10.4	31.0	58.6	0.0	41.4
Gentamicin	≤1	≤1	≤1 to ≤1	100.0 [b,f]	0.0	0.0	100 [g]		0.0

[a] Criteria as published by CLSI (2021), EUCAST (2021), and the US FDA (2021).
[d] US FDA breakpoints were applied to all *S. aureus*, but they are only approved for MSSA isolates.
[e] An arbitrary susceptible breakpoint of ≤0.001 mg/L and/or >50 mm has been published by EUCAST indicating that susceptible should not be reported for this organism-agent combination and intermediate should be interpreted as susceptible increased exposure.
[f] Using oral breakpoints.
[h] For systemic infections, aminoglycosides must be used in combination with other active therapy.
[i] Organisms include: *Staphylococcus capitis* (6), *S. haemolyticus* (2), *S. hominis* (10), *S. lugdunensis* (5), *S. saprophyticus* (2), *S. simulans* (2), and *S. warneri* (2).

Table 3. Antimicrobial activity of tebipenem and comparator agents tested against 31 *Enterococcus faecalis* isolates

Antimicrobial agent	No. of isolates	mg/L			CLSI[a]			EUCAST[a]		
		MIC_{50}	MIC_{90}	MIC range	%S	%I	%R	%S	%I	%R
Tebipenem	31	0.5	1	0.25 to 1						
Ertapenem	31	>8	>8	8 to >8						
Meropenem	31	>1	>1	>1 to >1						
Trimethoprim-sulfamethoxazole	31	0.06	0.12	≤0.03 to 0.12						
Levofloxacin	31	1	>4	0.5 to >4	80.6	0.0	19.4	80.6 [b]		19.4
Ampicillin	31	1	1	0.5 to 1	100.0		0.0	100.0	0.0	0.0
Amoxicillin-clavulanic acid	31	0.5	0.5	0.5 to 1						
Tetracycline	31	>16	>16	≤0.12 to >16	22.6	0.0	77.4			

[a] Criteria as published by CLSI (2021), EUCAST (2021), and the US FDA (2021).
[b] Uncomplicated UTI only.

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