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Antimicrobial Activity of Tebipenem (SPR859) against a Global Challenge Set of *Enterobacteriaceae* Isolates

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Introduction

- β-lactamase enzymes constitute the main mechanism of resistance against β-lactam agents in *Enterobacteriaceae*
- The increasing prevalence of potent β-lactamases challenges current antimicrobial therapy
- Extended-spectrum β-lactamases (ESBLs) are encoded by acquired genes and these enzymes are capable of hydrolyzing penicillins, cephalosporins, and monobactams
  - Organisms that produce ESBLs are, thus, resistant to most broad-spectrum β-lactam agents, except for carbapenems
- *Enterobacteriaceae*-producing CTX-M enzymes are currently responsible for a series of nosocomial and community infections and have significantly contributed to the rapid global increase in the cephalosporin resistance rates
- Tebipenem is a broad-spectrum agent introduced in Japan in 2009 for the treatment of pediatric pneumonia, otitis media, and sinusitis
- Tebipenem is under development by Spero Therapeutics as the first oral carbapenem, which would be an alternative drug to combat bacteria that had developed resistance to antimicrobial agents
- This study assessed the *in vitro* activity of SPR859, the microbiologically active form of the orally available tebipenem-pivoxil prodrug SPR994, against a challenge set of *Enterobacteriaceae*

Materials and Methods

Bacterial isolates

- A total of 33 *Enterobacteriaceae* isolates displaying susceptible phenotypes to several agents, including broad-spectrum β-lactam agents, were selected as wild-type control strains
  - *Escherichia coli* (12); *Klebsiella pneumoniae* (11); and *Proteus* spp. (10), including *P. mirabilis* (8) and *P. penneri* (2)
- A resistant subset of *Enterobacteriaceae* composed of the same species listed above was selected and molecularly characterized for the presence of genes encoding ESBL, plasmid AmpC, and/or carbapenemase enzymes (121)
  - *E. coli* (48)
  - *K. pneumoniae* (40)
  - *Proteus* spp. (33)
- Identification of bacterial isolates was confirmed by standard algorithms supported by matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany)

Antimicrobial susceptibility testing

- Isolates were tested for susceptibility by broth microdilution following guidelines in the CLSI M07 (2018) document
- Testing used reference 96-well panels prepared by JMI Laboratories
- Quality assurance was performed by concurrently testing CLSI-recommended quality control reference strains (*E. coli* ATCC 25922 and 35218; *Pseudomonas aeruginosa* ATCC 27853)
- Breakpoint criteria for comparator agents were from the CLSI M100 (2018) and EUCAST (2018) documents

Results

- Tebipenem (MIC_{50}, 0.03-0.06 µg/mL) showed similar MIC_{50} results when tested against wild-type and AmpC- and/or ESBL-producing *Enterobacteriaceae*, as did meropenem (MIC_{50}, 0.03-0.06 µg/mL) and ertapenem (MIC_{50}, ≤0.015-0.03 µg/mL) (Table 1)
- All carbapenem compounds tested herein had elevated MIC values against a challenge set of *Enterobacteriaceae* producing carbapenemase enzymes (MIC_{50}, 16-32 µg/mL) (Table 1)
- When tested against AmpC- and/or ESBL-producing *E. coli*, equivalent MIC_{50} values (MIC_{50}, 0.03 µg/mL) were obtained for all carbapenem compounds (Table 2)
  - In addition, similar MIC_{90} results were obtained for tebipenem and meropenem (MIC_{90}, 0.06 µg/mL for both), while an 8-fold higher MIC_{90} value was documented for ertapenem (MIC_{90}, 0.5 µg/mL) (Table 2)
- Equivalent tebipenem MIC_{90} values (MIC_{50}, 0.03 µg/mL) were obtained against wild-type *K. pneumoniae* isolates and those with confirmed production of ESBL and/or pAmpC enzymes (Table 3)
  - Similar observations were documented for meropenem against wild-type *K. pneumoniae* isolates and those with confirmed production of ESBL and/or pAmpC enzymes (MIC_{50}, 0.03 µg/mL against both groups) (Table 3)
  - The ertapenem MIC_{50} values obtained against wild-type *K. pneumoniae* (MIC_{50}, ≤0.015 µg/mL) was at least 4-fold lower than that observed against the group of isolates with ESBL and/or pAmpC enzymes (MIC_{50}, 0.06 µg/mL) (Table 3)
- Tebipenem demonstrated MIC_{50} results against wild-type isolates of *Proteus* spp. (MIC_{50}, 0.25 µg/mL) 8-fold higher than those obtained against *E. coli* or *K. pneumoniae* isolates (MIC_{50}, 0.03 µg/mL for both species) (Tables 2, 3, and 4)
  - A similar pattern was documented for meropenem, while ertapenem demonstrated consistent MIC_{50} results (MIC_{50}, ≤0.015 µg/mL) against wild-type strains, regardless of species tested (Tables 2, 3, and 4)
- Tebipenem MIC results ($MIC_{50/90}$, 0.5/2 µg/mL) obtained against nonwild-type *Proteus* spp. were slightly (2-fold) higher than those recorded against the wild-type subset ($MIC_{50/90}$, 0.25/1 µg/mL) (Table 4)

Conclusions

- Overall, tebipenem was highly potent against a current challenge set of *Enterobacteriaceae* that caused clinical infections in patients seen/hospitalized in US and European medical centers
- The production of ESBL and/or pAmpC enzymes did not adversely affect tebipenem *in vitro* activity against *E. coli*, *K. pneumoniae,* or *Proteus* spp.
  - As expected, all agents tested were less active against a challenge set of *Enterobacteriaceae* producing carbapenemase enzymes
- These *in vitro* results obtained for tebipenem warrant further clinical development as an oral option for treating infections caused by common *Enterobacteriaceae* species producing ESBL and/or AmpC enzymes

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Table 1 Antimicrobial activity of carbapenem agents tested against *Enterobacteriaceae* clinical isolates included in the study

Genotype / Antimicrobial agent	No. of isolates and cumulative % inhibited at MIC (µg/mL) of: ≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32	MIC (µg/mL) 50%	90%
Wild type															
Tebipenem (33)	4 12.1	15 57.6	5 72.7	1 75.8	4 87.9	1 90.9	3 100.0							0.03	0.5
Meropenem (33)	9 27.3	16 75.8	2 81.8	2 87.9	3 97.0	1 100.0								0.03	0.25
Ertapenem (33)	27 81.8	3 90.9	1 93.9	2 100.0										≤0.015	0.03
AmpC/ESBL															
Tebipenem (77)	2 2.6	31 42.9	8 53.2	6 61.0	4 66.2	13 83.1	8 93.5	3 97.4	2 100.0					0.06	1
Meropenem (77)	3 3.9	34 48.1	17 70.1	9 81.8	6 89.6	6 97.4	0 97.4	0 97.4	2 100.0					0.06	0.5
Ertapenem (77)	19 24.7	26 58.4	13 75.3	9 87.0	4 92.2	3 96.1	1 97.4	0 97.4	1 98.7	0 98.7	0 98.7	1 100.0		0.03	0.25
Carbapenemase															
Tebipenem (44)				1 2.3	0 2.3	0 2.3	0 2.3	0 2.3	3 9.1	3 15.9	7 31.8	10 54.5	20 100.0	32	>32
Meropenem (44)			1 2.3	0 2.3	0 2.3	0 2.3	1 4.5	3 11.4	8 29.5	7 45.5	8 63.6	4 72.7	12 100.0	16	>32
Ertapenem (44)					1 2.3	0 2.3	0 2.3	3 9.1	3 15.9	9 36.4	4 45.5	7 61.4	17 100.0	32	>32

Table 2 Antimicrobial activity of carbapenem agents tested against *E. coli* clinical isolates included in the study

Genotype / Antimicrobial agent	No. of isolates and cumulative % inhibited at MIC (µg/mL) of: ≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	MIC (µg/mL) 50%	90%
Wild type														
Tebipenem (12)	3 25.0	8 91.7	1 100.0										0.03	0.03
Meropenem (12)	7 58.3	5 100.0											≤0.015	0.03
Ertapenem (12)	11 91.7	1 100.0											≤0.015	≤0.015
AmpC/ESBL														
Tebipenem (38)	2 5.3	26 73.7	7 92.1	1 94.7	0 94.7	1 97.4	0 97.4	0 97.4	1 100.0				0.03	0.06
Meropenem (38)	3 7.9	28 81.6	5 94.7	1 97.4	0 97.4	0 97.4	0 97.4	0 97.4	1 100.0				0.03	0.06
Ertapenem (38)	7 18.4	15 57.9	5 71.1	4 81.6	2 86.8	3 94.7	1 97.4	0 97.4	0 97.4	0 97.4	0 97.4	1 100.0	0.03	0.5

Table 3 Antimicrobial activity of carbapenem agents tested against *K. pneumoniae* clinical isolates included in the study

Genotype / Antimicrobial agent	No. of isolates and cumulative % inhibited at MIC (µg/mL) of: ≤0.015	0.03	0.06	0.12	0.25	0.5	MIC (µg/mL) 50%	90%
Wild type								
Tebipenem (11)	1 9.1	7 72.7	3 100.0				0.03	0.06
Meropenem (11)	2 18.2	9 100.0					0.03	0.03
Ertapenem (11)	11 100.0						≤0.015	≤0.015
AmpC/ESBL								
Tebipenem (8)		5 62.5	1 75.0	1 87.5	1 100.0		0.03	
Meropenem (8)		5 62.5	3 100.0				0.03	
Ertapenem (8)	1 12.5	2 37.5	1 50.0	3 87.5	1 100.0		0.06	

Table 4 Antimicrobial activity of carbapenem agents tested against *Proteus* spp. clinical isolates included in the study

Genotype / Antimicrobial agent	No. of isolates and cumulative % inhibited at MIC (µg/mL) of: ≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	MIC (µg/mL) 50%	90%
Wild type[a]											
Tebipenem (10)			1 10.0	1 20.0	4 60.0	1 70.0	3 100.0			0.25	1
Meropenem (10)		2 20.0	2 40.0	2 60.0	3 90.0	1 100.0				0.12	0.25
Ertapenem (10)	5 50.0	2 70.0	1 80.0	2 100.0						≤0.015	0.12
AmpC/ESBL[b]											
Tebipenem (31)				4 12.9	3 22.6	12 61.3	8 87.1	3 96.8	1 100.0	0.5	2
Meropenem (31)		1 3.2	9 32.3	8 58.1	6 77.4	6 96.8	0 96.8	0 96.8	1 100.0	0.12	0.5
Ertapenem (31)	11 35.5	9 64.5	7 87.1	2 93.5	1 96.8	0 96.8	0 96.8	0 96.8	1 100.0	0.03	0.12

[a] *P. mirabilis* (8) and *P. penneri* (2)
[b] *P. mirabilis*

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