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Antimicrobial Activity Assessment of Tebipenem (SPR859) against an Isolate Collection Causing Urinary Tract Infections

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Introduction

- Urinary tract infections (UTIs) are among the most frequent infectious diseases affecting humans and represent an important public health problem with a substantial economic burden
- UTIs are primarily caused by gram-negative bacteria, and *Escherichia coli* remains the main pathogen responsible for uncomplicated cystitis and pyelonephritis, followed by other species, such as *Klebsiella pneumoniae* and *Proteus mirabilis*
- These isolates commonly responsible for nosocomial UTIs have become resistant to several antimicrobial agents in hospitals around the world since the late 1980s
  - A group of β-lactamases distinct from the historically common TEM and SHV enzymes, specifically CTX-M-15, emerged during the mid-2000s
  - The nosocomial emergence and dissemination of such resistant isolates was followed by their emergence in the community
- The spread of a specific clone defined as belonging to phylogenetic group B2, serotype O25:H4, and multilocus sequence typing (MLST) 131, has been identified as an important contributor to the epidemic of antimicrobial resistance in *E. coli* in the hospital and community settings, especially for first-line agents such as fluoroquinolones and extended-spectrum cephalosporins
- This epidemiologic shift has great implications for the empiric management of community-acquired UTIs; therefore, oral agents to treat outpatients with high risk for extended-spectrum β-lactamase (ESBL) infections or to be used as a stepdown therapy would become valuable assets in the antimicrobial armamentarium
- 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 as an alternative drug to combat bacteria that had developed resistance to usually used antimicrobial agents
- This study evaluated the antimicrobial activity of carbapenem compounds tested against contemporary *Enterobacteriaceae* responsible for UTI

Materials and Methods

Bacterial isolates

- A total of 412 bacterial clinical isolates collected through the SENTRY Antimicrobial Surveillance Program during 2016 were tested; isolates were selected to contain the most prevalent UTI pathogens and to reflect the current antimicrobial susceptibility trends occurring in United States (US) and European hospitals. Species included were as follows:
  - *E. coli* (101 isolates)
  - *K. pneumoniae* (208 isolates)
  - *P. mirabilis* (103 isolates)
- Isolates were determined to be clinically significant based on local guidelines and submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa)
- Bacterial isolate identification was confirmed by standard algorithms supported by matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany)
- Isolates displaying ceftriaxone and/or ceftazidime MIC results of ≥2 μg/mL were selected for further characterization of β-lactamase content. In addition, those displaying a carbapenem resistance phenotype (CRE; MIC results for imipenem [imipenem was not applied to *P. mirabilis* or to indole-positive Proteeae], meropenem, or doripenem ≥4 μg/mL) were selected for molecular characterization.
- These isolates were molecularly characterized for the presence of genes encoding ESBL, plasmid AmpC, and/or carbapenemase enzymes by genome sequencing and screening (Table 1)

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 manufactured 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 M100 CLSI (2018) and EUCAST (2018) documents

Results

- Tebipenem showed MIC_{50} and MIC_{90} values of 0.03 and 0.12 μg/mL, respectively, when tested against all *Enterobacteriaceae* isolates or the wild-type subset (Tables 2 and 3)
  - Similar tebipenem MIC values were obtained against isolates with confirmed ESBL and/or pAmpC enzyme production ($MIC_{50/90}$, 0.03/0.25 μg/mL) (Table 2)
- Tebipenem ($MIC_{50/90}$, 0.03/0.12 μg/mL) and ertapenem ($MIC_{50/90}$, ≤0.015/0.06 μg/mL) showed similar MIC results when tested against all *Enterobacteriaceae* isolates included in the study (Table 2)
  - Tebipenem MIC values obtained against all *Enterobacteriaceae* isolates were 4- to 8-fold lower than imipenem ($MIC_{50/90}$, 0.12/1 μg/mL)
- When tested against isolates with confirmed ESBL and/or pAmpC enzyme production, tebipenem ($MIC_{50/90}$, 0.03/0.25 μg/mL) displayed MIC_{90} values 4-fold lower than imipenem ($MIC_{50/90}$, 0.12/1 μg/mL) and 16-fold lower than ertapenem ($MIC_{50/90}$, 0.06/4 μg/mL) (Table 2)
- All penem and carbapenem agents were less active (MIC_{50}, ≥32 μg/mL) when tested against isolates with confirmed carbapenemase enzyme production (*K. pneumoniae* carbapenemase [KPC] or OXA-48) (Table 2)

Table 1 Genes encoding β-lactamases detected among uropathogen isolates included in this study

Main class Genes encoding for:	Number of isolates
Carbapenemase	
KPC-2, SHV-11, TEM-1	1
KPC-2, SHV-12	1
KPC-2, SHV-12, TEM-1	1
KPC-3, OXA-9, SHV-11, TEM-1	1
KPC-3, SHV-11, TEM-1	1
KPC-2, CTX-M-15, OXA-1, SHV-28, TEM-1	1
KPC-2, CTX-M-15, OXA-1, SHV-76, TEM-1	1
OXA-48, CTX-M-15, OXA-1, SHV-76, TEM-1	1
ESBL	
CTX-M-14	1
CTX-M-14, OXA-1	1
CTX-M-14, SHV-11	1
CTX-M-15, SHV-11, TEM-1	2
CTX-M-15, SHV-28	2
CTX-M-15, TEM-1	1
CTX-M-15, TEM-40	1
CTX-M-15, OXA-1, SHV-28, TEM-1	3
CTX-M-15, OXA-1, SHV-11, TEM-1	5
CTX-M-15, OXA-1, SHV-1	3
CTX-M-15, OXA-1	3
CTX-M-15, OXA-1, SHV-76, TEM-1	1
CTX-M-15, OXA-1, TEM-1	1
CTX-M-15, OXA-1, SHV-2, TEM-1	1
CTX-M-15, PSE-1, SHV-11	1
CTX-M-15, OXA-1, SHV-11	1
CTX-M-15, OXA-1, SHV-28	1
CTX-M-15, OXA-1, SHV-27, TEM-1	1
CTX-M-27	1
CTX-M-55	1
SHV-12	1
SHV-27	1
ESBL and/or AmpC	
CMY-2, TEM-1	2
CTX-M-15, DHA-1, OXA-1, SHV-11	1
CTX-M-15, DHA-1, OXA-1, OXA-9, SHV-11, TEM-1	1
Total	46

Table 2 Antimicrobial activity of carbapenem agents tested against all *Enterobacteriaceae* clinical isolates included in the study

Organism group (no. of isolates) 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_{50}	MIC_{90}
Enterobacteriaceae (412)															
Tebipenem	91 22.1	185 67.0	73 84.7	42 94.9	9 97.1	1 97.3	1 97.6	1 97.8	1 98.1	1 98.3	0 98.3	1 98.5	6 100.0	0.03	0.12
Imipenem		1 0.2	34 8.5	208 59.0	58 73.1	30 80.3	58 94.4	12 97.3	3 98.1	3 98.8	0 98.8	2 99.3	3 100.0	0.12	1
Ertapenem	339 82.3	19 86.9	16 90.8	12 93.7	6 95.1	3 95.9	3 96.6	2 97.1	1 97.3	1 97.6	1 97.8	2 98.3	7 100.0	≤0.015	0.06
ESBL and pAmpC (38)															
Tebipenem	5 13.2	20 65.8	5 78.9	3 86.8	2 92.1	0 92.1	0 92.1	1 94.7	1 97.4	1 100.0				0.03	0.25
Imipenem			2 5.3	25 71.1	5 84.2	2 89.5	3 97.4	0 97.4	0 97.4	1 100.0				0.12	1
Ertapenem	6 15.8	7 34.2	7 52.6	6 68.4	5 81.6	2 86.8	1 89.5	0 89.5	1 92.1	0 92.1	0 92.1	1 94.7	2 100.0	0.06	4
KPC or OXA-48 (8)															
Tebipenem							1 12.5	0 12.5	0 12.5	0 12.5	0 12.5	1 25.0	6 100.0	>32	
Imipenem									1 12.5	2 37.5	0 37.5	2 62.5	3 100.0	32	
Ertapenem										1 12.5	1 25.0	1 37.5	5 100.0	>32	
Wild type (366)															
Tebipenem	86 23.5	165 68.6	68 87.2	39 97.8	7 99.7	1 100.0								0.03	0.12
Imipenem		1 0.3	32 9.0	183 59.0	53 73.5	28 81.1	55 96.2	12 99.5	2 100.0					0.12	1
Ertapenem	333 91.0	12 94.3	9 96.7	6 98.4	1 98.6	1 98.9	2 99.5	2 100.0						≤0.015	≤0.015

Table 3 Activity of tebipenem and comparator antimicrobial agents when tested against *Enterobacteriaceae* uropathogens

Organism group (no. of isolates) Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a] %S	CLSI[a] %I	CLSI[a] %R	EUCAST[a] %S	EUCAST[a] %I	EUCAST[a] %R
Enterobacteriaceae (412)									
Tebipenem	0.03	0.12	≤0.015 — >32						
Imipenem	0.12	1	0.03 — >32	94.4	2.9	2.7	97.3	1.5	1.2
Ertapenem	≤0.015	0.06	≤0.015 — >32	95.9	0.7	3.4	95.9	0.7	3.4
Amoxicillin-clavulanate	2	16	≤1 — >256	84.2	8.0	7.8	84.2		15.8[b]
							96.4		3.6[c]
Piperacillin-tazobactam	2	16	≤0.5 — >64	93.7	2.2	4.1	88.8	4.9	6.3
Cefazolin	4	>16	1 — >16	29.9	22.8	47.3[d]			
				77.2		22.8[e]			
Ceftriaxone	≤0.25	>64	≤0.25 — >64	80.3	0.2	19.4	80.3	0.2	19.4
Levofloxacin	0.06	>4	≤0.03 — >4	80.1	2.2	17.7	73.8	5.1	21.1
Trimethoprim-sulfamethoxazole	≤0.25	>8	≤0.25 — >8	68.9		31.1	68.9	0.7	30.3
E. coli (101)									
Tebipenem	≤0.015	0.03	≤0.015 — 0.12						
Imipenem	0.12	0.25	0.06 — 0.5	100.0	0.0	0.0	100.0	0.0	0.0
Ertapenem	≤0.015	0.03	≤0.015 — 0.5	100.0	0.0	0.0	100.0	0.0	0.0
Amoxicillin-clavulanate	4	16	≤1 — 64	87.1	5.9	6.9	87.1		12.9[b]
							97.0		3.0[c]
Piperacillin-tazobactam	2	8	≤0.5 — 64	97.0	3.0	0.0	95.0	2.0	3.0
Cefazolin	4	>16	2 — >16	23.8	39.6	36.6[d]			
				76.2		23.8[e]			
Ceftriaxone	≤0.25	>64	≤0.25 — >64	79.2	0.0	20.8	79.2	0.0	20.8
Levofloxacin	≤0.03	>4	≤0.03 — >4	68.3	2.0	29.7	68.3	0.0	31.7
Trimethoprim-sulfamethoxazole	≤0.25	>8	≤0.25 — >8	61.4		38.6	61.4	1.0	37.6
Fosfomycin	0.5	0.5	≤0.25 — >128	99.0	0.0	1.0	98.0		2.0
K. pneumoniae (208)									
Tebipenem	0.03	0.06	≤0.015 — >32						
Imipenem	0.12	0.5	0.03 — >32	95.2	0.5	4.3	95.7	1.9	2.4
Ertapenem	≤0.015	0.25	≤0.015 — >32	91.8	1.4	6.7	91.8	1.4	6.7
Amoxicillin-clavulanate	2	16	≤1 — >256	78.4	12.5	9.1	78.4		21.6[b]
							95.2		4.8[c]
Piperacillin-tazobactam	4	32	≤0.5 — >64	88.9	2.9	8.2	80.3	8.7	11.1
Cefazolin	4	>16	1 — >16	47.6	19.2	33.2[d]			
				75.0		25.0[e]			
Ceftriaxone	≤0.25	>64	≤0.25 — >64	76.0	0.0	24.0	76.0	0.0	24.0
Levofloxacin	0.06	>4	≤0.03 — >4	84.1	1.9	13.9	77.9	5.3	16.8
Trimethoprim-sulfamethoxazole	≤0.25	>8	≤0.25 — >8	72.1		27.9	72.1	1.0	26.9
P. mirabilis (103)									
Tebipenem	0.06	0.12	0.03 — 0.5						
Imipenem	1	2	0.06 — 4	87.4	10.7	1.9	98.1	1.9	0.0
Ertapenem	≤0.015	≤0.015	≤0.015 — 0.06	100.0	0.0	0.0	100.0	0.0	0.0
Amoxicillin-clavulanate	≤1	8	≤1 — 64	93.2	1.0	5.8	93.2		6.8[b]
							98.1		1.9[c]
Piperacillin-tazobactam	≤0.5	1	≤0.5 — 8	100.0	0.0	0.0	100.0	0.0	0.0
Cefazolin	8	>16	4 — >16	0.0	13.6	86.4[d]			
				82.5		17.5[e]			
Ceftriaxone	≤0.25	1	≤0.25 — >64	90.3	1.0	8.7	90.3	1.0	8.7
Levofloxacin	0.06	>4	≤0.03 — >4	83.5	2.9	13.6	70.9	9.7	19.4
Trimethoprim-sulfamethoxazole	≤0.25	>8	≤0.25 — >8	69.9		30.1	69.9	0.0	30.1

[a] Criteria as published by CLSI 2018 and EUCAST 2018
[b] Using other than uncomplicated UTI breakpoints.
[c] Using uncomplicated UTI breakpoints.
[d] Using parenteral, complicated UTI breakpoints.
[e] Using parenteral, uncomplicated UTI-only breakpoints.

- Tebipenem ($MIC_{50/90}$, ≤0.015/0.03 μg/mL) and ertapenem ($MIC_{50/90}$ ≤0.015/0.03 μg/mL; 100.0% susceptible) showed equivalent MIC values against *E. coli* isolates; MIC_{90} values were 8-fold lower than imipenem ($MIC_{50/90}$, 0.12/0.25 μg/mL; Table 3)
- A total of 20.8%–38.6% of *E. coli* isolates were resistant to parenteral cephalosporins (cefazolin and ceftriaxone), levofloxacin, and trimethoprim-sulfamethoxazole (Table 3)
- The oral agents amoxicillin-clavulanate and fosfomycin, showed susceptibility rates of 87.1% and 99.0%, respectively (CLSI criteria) against *E. coli* (Table 3)
- Tebipenem ($MIC_{50/90}$, 0.03/0.06 μg/mL) had MIC results 4- to 8-fold lower than imipenem ($MIC_{50/90}$, 0.12/0.5 μg/mL; 95.2%–95.7% susceptible) against *K. pneumoniae* (Table 3)
  - While ertapenem (91.8% susceptible) demonstrated *in vitro* activity against *K. pneumoniae*, other agents tested had marginal coverage (47.6%–88.9% susceptible) when applying the CLSI criteria (Table 3)
- Ertapenem ($MIC_{50/90}$, ≤0.015/≤0.015 μg/mL; 100.0% susceptible) showed the lowest MIC_{50} and MIC_{90} results against *P. mirabilis*, followed by tebipenem ($MIC_{50/90}$, 0.06/0.12 μg/mL) (Table 3)
- Piperacillin-tazobactam (100.0% susceptible), amoxicillin-clavulanate (93.2%–98.1% susceptible), and ceftriaxone (90.3% susceptible) were active against *P. mirabilis* (Table 3)

Conclusions

- Overall, tebipenem was highly potent against a current collection of *Enterobacteriaceae* causing UTIs in patients seen/hospitalized in US and European medical centers
- ESBL and/or pAmpC enzyme production did not adversely affect tebipenem *in vitro* activity against *E. coli*, *K. pneumoniae,* or *P. mirabilis* uropathogens
- These *in vitro* results obtained for tebipenem warrant further clinical development as an oral option for treating complicated/uncomplicated UTIs

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