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Monitoring the *In Vitro* Activity of Tebipenem, an Orally Available Carbapenem Agent, against a Current Collection of Surveillance *Enterobacterales* Clinical Isolates (2018)

Rodrigo E. Mendes, Helio S. Sader, Paul R. Rhomberg, Jill Lindley, Holly K. Huynh, Robert K. Flamm

JMI Laboratories, North Liberty, Iowa, USA

Introduction

- Complicated and uncomplicated urinary tract infections (UTIs) are frequent in any given population
- Current guidelines recommend that empiric antibiotic therapy for UTIs should be based on local resistance data, drug availability, drug intolerance/allergy, and patient history
  - Nitrofurantoin or trimethoprim-sulfamethoxazole (TMP-SMX), if local resistance ≤20% can be used empirically for uncomplicated cystitis, while fluoroquinolones, ceftriaxone, aminoglycosides, and carbapenems are appropriate for pyelonephritis and complicated UTIs
- However, managing such infections is challenged by the dissemination of isolates producing extended-spectrum β-lactamases (ESBLs) and displaying cross-resistance to fluoroquinolones, aminoglycosides, and folate pathway inhibitors in the hospital and community settings
- Carbapenem agents represent good options for treating these patients with UTIs, who usually have a spectrum of illness severity, comorbidities, and clinical histories, and an oral carbapenem option would provide additional benefits
- Tebipenem, the active metabolite of tebipenem-pivoxil (SPR859), is an oral carbapenem introduced in Japan (2009) for pediatric respiratory and otolaryngologic infections
- SPR994 is a novel tebipenem formulation (tebipenem-pivoxil hydrobromide) that is under clinical development for treatment of UTIs
- This study evaluated the tebipenem activity and spectrum against targeted *Enterobacterales* species

Materials and Methods

Surveillance isolates

- *Enterobacterales* isolates included in this study were collected as part of the SENTRY Antimicrobial Surveillance Program
- A total of 1,031 isolates composed of target numbers of randomly selected species recovered from documented infections during 2018 were included (Table 1)
- Preference was given to isolates recovered from urinary tract samples (669 isolates; 64.9%), but those recovered from bloodstream infections (186 isolates; 18.0%) and lower respiratory tract of patients with pneumonia (176 isolates; 17.1%) were included, as well
- Isolates were collected in 113 medical centers located in 26 countries and 9 US census divisions: the United States (674 isolates [65.4%] from 62 medical centers), Europe (262 isolates [25.4%] from 32 medical centers), Latin America (44 isolates [4.3%] from 8 medical centers), and the Asia-Pacific region (51 isolates [4.9%] from 11 medical centers)
- Bacterial species were initially identified by the submitting laboratories and confirmed by JMI Laboratories using standard microbiology methods and matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany)

Antimicrobial susceptibility testing

- Susceptibility testing was performed for tebipenem and comparator agents by reference broth microdilution method
  - 96-well frozen-form broth microdilution panels with cation-adjusted Mueller-Hinton broth (CAMHB) were manufactured by JMI Laboratories (North Liberty, Iowa, USA) per the Clinical and Laboratory Standards Institute (CLSI) specifications described in the M07 (2018) document
  - Quality control strains were tested before and concomitantly with selected isolates, and bacterial inoculum density was monitored by counting the number of colony-forming units present in the inoculum material
  - Interpretations of MIC values obtained from clinical isolates used CLSI M100 (2019) breakpoint criteria, as available
- The ESBL phenotype was defined for *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Proteus mirabilis* as an isolate that displayed MIC values ≥2 µg/mL for ceftriaxone, ceftazidime, and/or aztreonam

Results

- Overall, tebipenem showed MIC_{50} and MIC_{90} results of 0.06 µg/mL and 0.25 µg/mL, respectively, against all isolates in the study (Table 1)
  - These tebipenem ($MIC_{50/90}$, 0.06/0.25 µg/mL) MIC results were similar to meropenem ($MIC_{50/90}$, 0.06/0.12 µg/mL)
  - Isolates displaying tebipenem MIC values of >2 µg/mL were meropenem-nonsusceptible (Table 1)
- The lowest tebipenem MIC_{50} values (0.008 µg/mL) were obtained against *Citrobacter koseri* and *E. coli*, followed by *Citrobacter freundii*, *K. pneumoniae*, and *K. oxytoca* (MIC_{50}, 0.015 µg/mL) (Table 1)
- A tebipenem MIC_{50} value of 0.03 µg/mL was obtained against *Enterobacter cloacae* and *Enterobacter aerogenes* (Table 1), while the MIC_{50} value of 0.12 µg/mL was observed for other species tested (*Proteus* spp., *Morganella morganii*, *Providencia* spp., and *Serratia marcescens*)
- Agents other than carbapenems did not show high activity against *Enterobacterales*, except for piperacillin-tazobactam (91.0% susceptible) and the aminoglycosides (92.5–99.2% susceptible) (Figure 1)
- Carbapenems, amikacin, and tigecycline showed susceptibility rates >80% when tested against *Enterobacterales* isolates, meeting the MIC criteria for ESBL phenotype (Figure 2)
- Tebipenem MIC_{50} values within ±1 doubling dilution were obtained against the respective species of isolates with and without an ESBL phenotype (Table 2)
- Similar MIC_{50} results were observed for tebipenem when tested against *Enterobacterales* isolates showing nonsusceptible or susceptible phenotypes for levofloxacin or trimethoprim-sulfamethoxazole (Table 2)

Conclusions

- Tebipenem showed broad-spectrum and potent activity against this current and targeted collection of *Enterobacterales* clinical isolates and inhibited all but 14 isolates (98.6%) at ≤0.5 µg/mL
- Tebipenem was most active against *E. coli*, *K. pneumoniae*, *K. oxytoca*, *C. koseri*, and *C. freundii* (MIC_{50}, 0.008–0.015 µg/mL) followed by *Enterobacter* spp., *Proteus* spp., *M. morganii*, *Providencia* spp., and *S. marcescens* (MIC_{50}, 0.03–0.12 µg/mL)
- ESBL phenotype and/or nonsusceptibility to levofloxacin and/or trimethoprim-sulfamethoxazole did not adversely affect tebipenem activity
- These data suggest that tebipenem may be a convenient oral option for treating UTIs caused by carbapenem-susceptible *Enterobacterales* isolates and warrant its clinical development

Table 1 MIC distributions of tebipenem tested against surveillance *Enterobacterales* isolates

Species (no. of isolates)	No. and cumulative % of isolates inhibited at MIC (µg/mL) of:													MIC_{50}	MIC_{90}
	≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4[a]	8[a]	>8[a]		
Enterobacterales (1,031)	2 0.2	113 11.2	174 28.0	161 43.6	195 62.6	229 84.8	125 96.9	18 98.6	0 98.6	1 98.7	3 99.0	2 99.2	8 100.0	0.06	0.25
E. coli (102)	1 1.0	67 66.7	30 96.1	4 100.0										0.008	0.015
C. koseri (55)	1 1.8	36 67.3	17 98.2	1 100.0										0.008	0.015
C. freundii (50)		4 8.0	32 72.0	11 94.0	2 98.0	0 98.0	0 98.0	0 98.0	0 98.0	0 98.0	0 98.0	0 98.0	1 100.0	0.015	0.03
K. pneumoniae (85)		1 1.2	42 50.6	34 90.6	4 95.3	1 96.5	0 96.5	0 96.5	0 96.5	0 96.5	0 96.5	0 96.5	3 100.0	0.015	0.03
K. oxytoca (16)			10 62.5	6 100.0										0.015	0.03
E. aerogenes (105)			15 14.3	44 56.2	35 89.5	9 98.1	2 100.0							0.03	0.12
E. cloacae (103)		5 4.9	27 31.1	25 55.3	26 80.6	9 89.3	5 94.2	0 94.2	0 94.2	0 94.2	2 96.1	0 96.1	4 100.0	0.03	0.25
M. morganii (107)				2 1.9	7 8.4	45 50.5	47 94.4	6 100.0						0.12	0.25
P. mirabilis (103)				5 4.9	15 19.4	39 57.3	38 94.2	6 100.0						0.12	0.25
P. rettgeri (49)				1 2.0	19 40.8	23 87.8	4 95.9	1 98.0	0 98.0	1 100.0				0.12	0.25
P. stuartii (50)				2 4.0	15 34.0	25 84.0	8 100.0							0.12	0.25
S. marcescens (103)			1 1.0	8 8.7	42 49.5	35 83.5	10 93.2	4 97.1	0 97.1	0 97.1	1 98.1	1 99.0	1 100.0	0.12	0.25

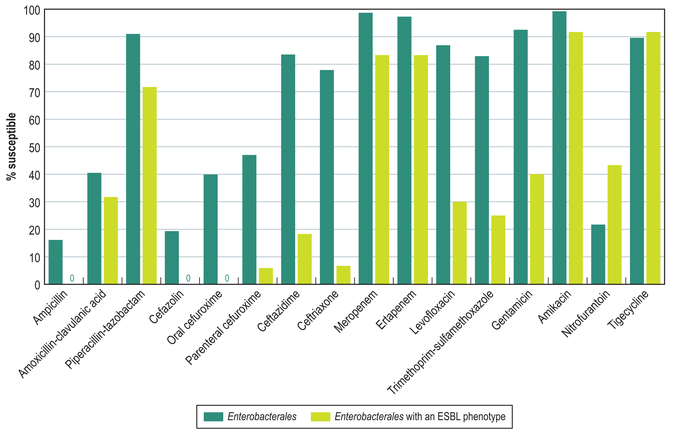
[a] Meropenem-nonsusceptible.

Table 2 MIC distributions of tebipenem tested against specific phenotypes

Phenotypic organism group (no. of isolates)	No. and cumulative % of isolates inhibited at MIC (µg/mL) of:													MIC_{50}	MIC_{90}
	≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4[a]	8[a]	>8[a]		
ESBL-phenotype *E. coli* (20)[b]		6 30.0	10 80.0	4 100.0										0.015	0.03
Non-ESBL-phenotype *E. coli* (82)	1 1.2	61 75.6	20 100.0											0.008	0.015
ESBL-phenotype *Klebsiella* spp. (25)[b]			12 48.0	10 88.0	0 88.0	0 88.0	0 88.0	0 88.0	0 88.0	0 88.0	0 88.0	0 88.0	3 100.0	0.03	>8
ESBL-phenotype carbapenem-susceptible *Klebsiella* spp. (22)[b]			12 54.5	10 100.0										0.015	0.03
Non-ESBL-phenotype *Klebsiella* spp. (76)		1 1.3	40 53.9	30 93.4	4 98.7	1 100.0								0.015	0.03
ESBL-phenotype *P. mirabilis* (7)[b]				1 14.3	1 28.6	3 71.4	2 100.0							0.12	
Non-ESBL-phenotype *P. mirabilis* (96)				4 4.2	14 18.8	36 56.2	36 93.8	6 100.0						0.12	0.25
Levofloxacin-susceptible *Enterobacterales* (894)[c]	1 0.1	93 10.5	157 28.1	148 44.6	179 64.7	191 86.0	103 97.5	16 99.3	0 99.3	1 99.4	1 99.6	0 99.6	4 100.0	0.06	0.25
Levofloxacin-non-susceptible *Enterobacterales* (135)	1 0.7	20 15.6	17 28.1	13 37.8	15 48.9	37 76.3	22 92.6	2 94.1	0 94.1	0 94.1	2 95.6	2 97.0	4 100.0	0.12	0.25
Trimethoprim-sulfamethoxazole-susceptible *Enterobacterales* (855)[d]	1 0.1	88 10.4	141 26.9	141 43.4	180 64.4	190 86.7	98 98.1	14 99.8	0 99.8	0 99.8	1 99.9	0 99.9	1 100.0	0.06	0.25
Trimethoprim-sulfamethoxazole-resistant *Enterobacterales* (176)	1 0.6	25 14.8	33 33.5	20 44.9	15 53.4	39 75.6	27 90.9	4 93.2	0 93.2	1 93.8	2 94.9	2 96.0	7 100.0	0.06	0.25

ESBL, extended-spectrum β-lactamase
[a] Meropenem-nonsusceptible.
[b] The ESBL phenotype was defined for *E. coli*, *K. pneumoniae*, *K. oxytoca*, and *P. mirabilis* as isolates that displayed MIC values of ≥2 µg/mL for ceftriaxone, ceftazidime, and/or aztreonam.
[c] Isolates with MIC results of ≤2 µg/mL.
[d] Isolates with MIC results of ≤2/38 µg/mL.

Figure 1 Antimicrobial activity of comparator agents tested against *Enterobacterales* and *Enterobacterales* displaying an extended-spectrum β-lactamase phenotype



Acknowledgements

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Contact

Rodrigo E Mendes, PhD
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, IA 52317
Phone: (319) 665-3370
Fax: (319) 665-3371
Email: rodrigo-mendes@jmilabs.com

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