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Meropenem-vaborbactam (MER-VAB) Tested Against Contemporary Enterobacteriaceae Isolates from USA Hospitals

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Amended Abstract

Background: Carbapenem-resistant ENT (CRE) have been detected in various USA hospitals and most of these isolates produce KPC enzymes. We evaluated the activity of MER-VAB (formerly RPX7009), that has enhanced activity against KPC-producing isolates, and comparators tested against Enterobacteriaceae (ENT) isolates collected during 2015 in 30 USA hospitals.

Methods: 5039 ENT clinical isolates consecutively collected were susceptibility (S) tested by reference broth microdilution methods for MER ± VAB (at fixed 8 µg/ml) and comparators. CRE was defined as an isolate resistant (CLSI criteria) to imipenem and/or meropenem. CLSI, US-FDA (tigecycline) and EUCAST interpretative criteria were applied.

Results: MER-VAB ($MIC_{50/90}$, 0.03/0.06 µg/ml) was very active against ENT isolates and 99.7% of the isolates were inhibited at ≤1 µg/ml (MER S CLSI breakpoint) and only four isolates had a MER-VAB MIC >4 µg/ml. MER alone inhibited 98.0% of the isolates at the same concentration. Among 1,049 *K. pneumoniae* (KPN) tested, 94.3% were S to MER and 99.3% of the isolates were inhibited by MER-VAB at ≤1 µg/ml. MER-VAB was very active against other ENT species and inhibited 1979/1981 (99.9%) *E. coli*, 487/488 (99.8%) *E. cloacae* and 300/301 (99.7%) *P. mirabilis* isolates tested at ≤1 µg/ml. MER-VAB inhibited all 272 *Citrobacter* spp. at ≤0.06 µg/ml and all indole-positive Proteeae at ≤1 µg/ml. One S. *marcescens* isolate displayed a MER-VAB MIC result at 2 µg/ml, but the other 244 isolates tested had MIC results at ≤0.5 µg/ml and 96.7% were S to MER using the CLSI criteria. MER-VAB was very active against isolates displaying an ESBL-phenotype without CR (n=530 [10.5% overall]; $MIC_{50/90}$, 0.03/0.03 µg/ml) and CRE isolates (n=96 [1.9% overall]; $MIC_{50/90}$, 0.03/2 µg/ml) that included 55 KPN and 8 other species. MER alone inhibited 98.0% of the ESBL non-CRE, but only 3.1% of CRE isolates using CLSI breakpoints. CRE isolates were non-S to β-lactams (S rates ranged from 0.0 to 5.2%) and more resistant to other antimicrobial classes when compared to overall ENT isolates. Minocycline, colistin and tigecycline displayed the highest S rates (79.2, 77.7 and 100.0% S by CLSI, EUCAST and US-FDA criteria) against CRE.

Conclusions: MER-VAB was very active against ENT isolates recently collected in USA hospitals and the advantage of this combination over MER alone was demonstrated in CRE isolates that are less susceptible to other clinically available antimicrobials.

Background

Carbapenems were often considered to be the antibiotic of last resort to treat serious infections caused by multidrug-resistant (MDR) organisms or isolates producing β-lactamases, but these agents are hydrolyzed by carbapenemases which include KPC serine-carbapenemases, OXA-48 and class B metallo-β-lactamases (MBLs) that have become disseminated worldwide.

The use of β-lactamase inhibitors combined with a β-lactam agent has been a successful strategy for overcoming β-lactamase-mediated resistance; however, older inhibitors such as tazobactam, sulbactam and clavulanate are generally not active against isolates producing various contemporary β-lactamases, including KPC enzymes. Vaborbactam (formerly known as RPX7009) is a cyclic boronic acid β-lactamase inhibitor that has potent activity against Ambler class A, including KPC, and C enzymes. This inhibitor has been combined with meropenem, enhancing the activity of this carbapenem against KPC-producing isolates when compared to meropenem tested alone.

In this study, we evaluated the activity of meropenem-vaborbactam and comparator antimicrobial agents against 5,039 Enterobacteriaceae isolates collected in 30 USA hospitals during 2015.

Methods

Bacterial isolates. A total of 5,039 Enterobacteriaceae clinical isolates collected in 30 USA hospitals during 2015 were tested. Isolates were consecutively collected according to standardized protocols from bloodstream infections (1,352 isolates), intra-abdominal infections (431), pneumonia in hospitalized patients (1,112), skin/soft tissue infection (731), urinary tract infection (1,362) and other sites (51). Only clinically significant isolates were included in the study (one per patient episode). Species identification was confirmed when necessary by Matrix-Assisted Laser Desorption Ionization-Time Of Flight Mass Spectrometry (MALDI-TOF MS) using the Bruker Daltonics MALDI Biotyper (Billerica, Massachusetts, USA), following manufacturer instructions.

Antimicrobial susceptibility testing. All isolates were susceptibility tested using the reference broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI). Meropenem was combined with vaborbactam at a fixed concentration of 8 µg/ml. Categorical interpretations for all comparator agents were those found in CLSI document M100-S26, EUCAST website or United States Food and Drug Administration (US-FDA) package inserts. Quality control (QC) was performed using *Escherichia coli* ATCC 25922 and 35218, *K. pneumoniae* ATCC 700603 and BAA-1705 and *P. aeruginosa* ATCC 27853 reference strains. All QC MIC results were within acceptable ranges as published in CLSI documents.

Definitions. ESBL-phenotype criteria were applied for *E. coli*, *Klebsiella* spp. (including *K. pneumoniae* and *K. oxytoca*) and *Proteus mirabilis* displaying a MIC of ≥2 µg/ml for ceftriaxone and/or ceftazidime and/or aztreonam. Carbapenem-resistant Enterobacteriaceae (CRE) was defined as any isolate exhibiting an imipenem (*Proteus mirabilis* and indole-positive Proteeae were not included due to their intrinsically elevated MIC values) and/or meropenem MIC value at ≥4 µg/ml.

Results

- Meropenem-vaborbactam (MIC_{50} and MIC_{90}, 0.03 and 0.06 µg/ml) inhibited 99.7% of the Enterobacteriaceae isolates tested at ≤1 µg/ml and all but four isolates (99.9%) were inhibited by this combination at ≤4 µg/ml (Table 1).
- Meropenem alone inhibited 98.0% of the Enterobacteriaceae isolates at the CLSI susceptible breakpoint (≤1 µg/ml; Table 2). Among comparator antimicrobial agents, susceptibility rates ranged from 80.9 to 99.2% (CLSI interpretative criteria), being lowest for levofloxacin and highest for amikacin, respectively.
- A total of 96 (1.9% overall) CRE isolates were identified in this collection, including 55 *K. pneumoniae* isolates. CRE isolates displayed high resistance rates to other antimicrobial agents and susceptibility rates for comparator β-lactams ranged from 0.0 to 5.2% (Table 2). Among non-β-lactams, minocycline, colistin and tigecycline displayed the highest susceptibility rates (79.2, 77.7 and 100.0% susceptible, respectively)
- Meropenem-vaborbactam (MIC_{50} and MIC_{90}, 0.03 and 2 µg/ml) inhibited 86.5% of the CRE isolates at ≤1 µg/ml and all but four (95.8%) of these isolates at ≤4 µg/ml (Table 1 and Figure 1). Meropenem alone was only active against 3.1 and 10.4% of the CRE isolates, respectively.
- Isolates displaying an ESBL-phenotype without resistance to carbapenems (non-CRE) were all inhibited by meropenem-vaborbactam (MIC_{50} and MIC_{90}, 0.03 and 0.03 µg/ml) at ≤2 µg/ml (Table 1).

Results

- Meropenem-vaborbactam (MIC_{50} and MIC_{90}, ≤0.015 and 0.03 µg/ml) inhibited 1,979 of 1,981 (99.9%) of *E. coli* isolates at ≤1 µg/ml. Two isolates displayed MIC values for meropenem-vaborbactam at ≥32 µg/ml.
- Meropenem was active against 94.3% of the 1,049 *K. pneumoniae* isolates tested at the CLSI breakpoint, and meropenem-vaborbactam inhibited 99.3% of these isolates at the same concentration. Only four *K. pneumoniae* isolates displayed meropenem-vaborbactam MIC values >2 µg/ml and only one at >4 µg/ml (Table 1).
- Meropenem-vaborbactam inhibited all *K. oxytoca* (278 isolates; MIC_{50}, 0.03 µg/ml), *E. cloacae* (488; MIC_{90}, 0.03 µg/ml), *Citrobacter* spp. (272; MIC_{90}, ≤0.03 µg/ml), indole-positive Proteeae spp. (179; MIC_{90}, 0.12 µg/ml) and *Serratia* spp. (245; MIC_{90}, 0.06 µg/ml) at ≤2 µg/ml. This combination inhibited 300/301 *P. mirabilis* at ≤0.25 µg/ml (MIC_{90}, 0.12 µg/ml; Table 1).

Table 1. Activity of meropenem-vaborbactam (inhibitor at fixed 8 µg/ml) tested against 5,039 Enterobacteriaceae isolates collected in USA hospitals during 2015.

Organisms / Organism Groups	No. of isolates at MIC (µg/ml; cumulative %)														MIC_{50}	MIC_{90}
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32			
Enterobacteriaceae (5,039)	2037 (40.4)	2337 (86.8)	522 (97.2)	99 (99.1)	16 (99.4)	8 (99.6)	5 (99.7)	8 (99.9)	3 (99.9)	0 (99.9)	1 (99.9)	1 (>99.9)	2 (100.0)		0.03	0.06
CRE (96)	17 (17.7)	33 (52.1)	14 (66.7)	6 (72.9)	6 (79.2)	4 (83.3)	3 (86.5)	6 (92.7)	3 (95.8)	0 (95.8)	1 (96.9)	1 (97.9)	2 (100.0)		0.03	2
ESBL non-CRE (530)	237 (44.7)	252 (92.3)	18 (95.7)	11 (97.7)	7 (99.1)	3 (99.6)	1 (99.8)	1 (100.0)							0.03	0.03
***Escherichia coli* (1,981)**	1401 (70.7)	563 (99.1)	14 (99.8)	0 (99.8)	0 (99.8)	0 (99.8)	1 (99.9)	0 (99.9)	0 (99.9)	0 (99.9)	0 (99.9)	1 (99.9)	1 (100.0)		≤0.015	0.03
***Klebsiella pneumoniae* (1,049)**	210 (20.0)	770 (93.4)	36 (96.9)	8 (97.6)	10 (98.6)	6 (99.1)	2 (99.3)	3 (99.6)	3 (99.9)	0 (99.9)	0 (99.9)	0 (99.9)	1 (100.0)		0.03	0.03
***Klebsiella oxytoca* (278)**	48 (17.3)	226 (98.6)	3 (99.6)	0 (99.6)	0 (99.6)	0 (99.6)	0 (99.6)	1 (100.0)							0.03	0.03
***Enterobacter cloacae* species complex (488)**	187 (38.3)	280 (95.7)	17 (99.2)	3 (99.8)	0 (99.8)	0 (99.8)	0 (99.8)	1 (100.0)							0.03	0.03
***Citrobacter* spp. (272)**	148 (54.4)	122 (99.3)	2 (100.0)												≤0.015	0.03
***Proteus mirabilis* (301)**		68 (22.6)	172 (79.7)	58 (99.0)	2 (99.7)	0 (99.7)	0 (99.7)	0 (99.7)	0 (99.7)	0 (99.7)	1 (100.0)				0.06	0.12
Indole-positive Proteeae spp. (179)		31 (17.3)	123 (86.0)	23 (98.9)	1 (99.4)	0 (99.4)	1 (100.0)								0.06	0.12
***Serratia* spp. (245)**	2 (0.8)	90 (37.6)	142 (95.5)	7 (98.4)	2 (99.2)	1 (99.6)	0 (99.6)	1 (100.0)							0.06	0.06

Figure 1. Activity of meropenem alone and meropenem-vaborbactam against 96 CRE isolates collected from USA hospitals during 2015.

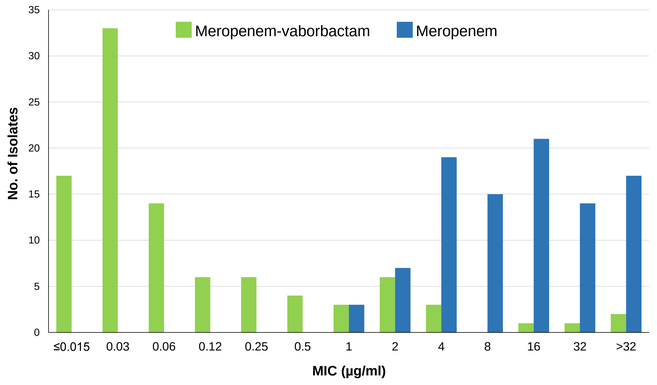

Table 2. Activity of meropenem-vaborbactam and comparator antimicrobial agents when tested against 5,039 isolates of Enterobacteriaceae collected during 2015 in USA hospitals.

Organism/group (no. tested) / 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 (5,039)									
Meropenem-vaborbactam	0.03	0.06	≤0.015 — >32	-	-	-	-	-	-
Meropenem	≤0.015	0.06	≤0.015 — >32	98.0	0.3	1.7	98.3	0.7	1.0
Amikacin	2	4	≤0.25 — >32	99.2	0.6	0.2	98.3	0.9	0.8
Aztreonam	≤0.12	>16	≤0.12 — >16	85.7	1.6	12.7	84.0	1.7	14.3
Cefepime	≤0.03	4	≤0.03 — >64	89.6	2.4	8.1[b]	88.2	2.5	9.3
Ceftazidime	0.25	32	≤0.015 — >32	86.4	1.0	12.6	83.7	2.7	13.6
Colistin	0.12	>8	≤0.06 — >8	-	-	-	82.3	-	17.7
Levofloxacin	0.06	>4	≤0.03 — >4	80.9	1.8	17.3	79.5	1.4	19.1
Piperacillin-tazobactam	2	16	≤0.06 — >128	92.0	3.5	4.5	89.0	2.9	8.0
Minocycline	1	8	≤0.06 — >8	84.1	7.2	8.7	-	-	-
Tigecycline	0.25	1	≤0.06 — >8	98.0	2.0	0.1[c]	92.6	5.4	2.0
CRE (96)									
Meropenem-vaborbactam	0.03	2	≤0.015 — >32	-	-	-	-	-	-
Meropenem	16	>32	1 — >32	3.1	7.3	89.6	10.4	35.4	54.2
Amikacin	8	32	0.5 — >32	74.0	19.8	6.2	58.3	15.6	26.0
Aztreonam	>16	>16	>16 — >16	0.0	0.0	100.0	0.0	0.0	100.0
Cefepime	32	>64	1 — >64	5.2	16.7	78.1[b]	1.0	9.4	89.6
Ceftazidime	>32	>32	2 — >32	2.1	0.0	97.9	0.0	2.1	97.9
Colistin	0.12	>8	≤0.06 — >8	-	-	-	77.7	-	22.3
Doripenem	8	>8	1 — >8	1.0	17.7	81.2	1.0	17.7	81.2
Levofloxacin	>4	>4	≤0.03 — >4	24.0	4.2	71.9	16.7	7.3	76.0
Piperacillin-tazobactam	>128	>128	0.25 — >128	1.0	7.3	91.7	1.0	0.0	99.0
Minocycline	2	8	0.5 — >8	79.2	13.5	7.3	-	-	-
Tigecycline	0.5	2	0.12 — 2	100.0	0.0	0.0[c]	89.6	10.4	0.0
ESBL non-CRE (530)									
Meropenem-vaborbactam	0.03	0.03	≤0.015 — 2	-	-	-	-	-	-
Meropenem	0.03	0.06	≤0.015 — 2	98.9	1.1	0.0	100.0	0.0	0.0
Amikacin	2	8	≤0.25 — >32	97.5	1.9	0.6	93.4	4.2	2.5
Aztreonam	>16	>16	≤0.12 — >16	18.5	12.3	69.2	7.0	11.5	81.5
Cefepime	32	>64	≤0.03 — >64	27.7	14.9	57.4[b]	23.0	11.9	65.1
Ceftazidime	32	>32	0.06 — >32	25.8	7.9	66.2	7.9	17.9	74.2
Colistin	0.12	0.25	≤0.06 — >8	-	-	-	95.1	-	4.9
Doripenem	≤0.06	0.12	≤0.06 — 2	99.1	0.9	0.0	99.1	0.9	0.0
Levofloxacin	>4	>4	≤0.03 — >4	30.9	3.8	65.3	27.9	3.0	69.1
Piperacillin-tazobactam	4	128	0.25 — >128	78.9	9.6	11.5	67.0	11.9	21.1
Minocycline	2	>8	0.12 — >8	72.1	9.8	18.1	-	-	-
Tigecycline	0.25	1	≤0.06 — 8	97.4	2.5	0.2[c]	90.9	6.4	2.6
***E. coli* (1,981)**									
Meropenem-vaborbactam	≤0.015	0.03	≤0.015 — >32	-	-	-	-	-	-
Meropenem	≤0.015	0.03	≤0.015 — >32	99.7	0.0	0.3	99.7	0.1	0.2
Amikacin	2	4	≤0.25 — >32	99.8	0.2	0.1	98.7	1.1	0.2
Aztreonam	≤0.12	16	≤0.12 — >16	85.0	2.9	12.1	82.5	2.5	15.0
Cefepime	≤0.03	16	≤0.03 — >64	86.8	2.5	10.7[b]	86.0	2.1	12.0
Ceftazidime	0.25	16	0.03 — >32	86.7	1.5	11.9	83.4	3.2	13.3
Colistin	0.12	0.25	≤0.06 — >8	-	-	-	99.8	-	0.2
Levofloxacin	0.06	>4	≤0.03 — >4	68.0	1.5	30.5	67.6	0.4	32.0
Piperacillin-tazobactam	2	8	≤0.06 — >128	95.7	2.2	2.2	93.3	2.3	4.3
Minocycline	0.5	4	≤0.06 — >8	91.0	5.3	3.7	-[d]	-	-
Tigecycline	0.12	0.25	≤0.06 — 2	100.0	0.0	0.0[c]	99.9	0.1	0.0
***K. pneumoniae* (1,049)**									
Meropenem-vaborbactam	0.03	0.03	≤0.015 — >32	-	-	-	-	-	-
Meropenem	0.03	0.03	≤0.015 — >32	94.3	0.8	5.0	95.0	1.6	3.3
Amikacin	1	2	≤0.25 — >32	96.9	2.3	0.8	95.1	1.8	3.1
Aztreonam	≤0.12	>16	≤0.12 — >16	83.4	0.5	16.1	82.8	0.6	16.6
Cefepime	≤0.03	32	≤0.03 — >64	84.6	3.0	12.5[b]	83.9	1.8	14.3
Ceftazidime	0.12	>32	0.03 — >32	83.3	0.9	15.8	81.5	1.8	16.7
Colistin	0.12	0.25	≤0.06 — >8	-	-	-	97.7	-	2.3
Levofloxacin	0.06	>4	≤0.03 — >4	86.0	1.6	12.4	84.7	1.2	14.0
Piperacillin-tazobactam	2	64	≤0.06 — >128	88.0	3.3	8.7	82.4	5.6	12.0
Minocycline	1	>8	≤0.06 — >8	84.2	5.1	10.8	-	-	-
Tigecycline	0.25	1	≤0.06 — 8	99.0	1.0	0.1[c]	93.1	5.8	1.0

a. Criteria as published by CLSI [2016] and EUCAST [2016].
b. Intermediate interpreted as susceptible-dose dependent (SDD).
c. Breakpoints from FDA Package Insert revised 12/2014.

Conclusions

- Meropenem-vaborbactam was as active as meropenem alone against wild-type isolates; however, this combination was >32-fold more active when compared to meropenem alone against CRE isolates from USA hospitals collected in 2015.
- CRE isolates are a matter of great concern in the USA and other regions worldwide. These isolates are resistant to β-lactams and often to other antimicrobial classes, which limits the therapeutic options available to treat infections caused by these organisms. Meropenem-vaborbactam is currently in a final Phase 3 clinical trial for complicated urinary tract infections; a clinical trial study in patients with CRE infections is ongoing.

Disclosures

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