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Meropenem-Vaborbactam Activity against *Enterobacteriaceae* Isolates Collected during 2014-2015 from European Countries

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Abstract

Background: Vaborbactam (formerly RPX7009) is a cyclic boronic acid beta-lactamase inhibitor with activity against Ambler class A, including KPC and C enzymes. We evaluated the activity of meropenem-vaborbactam against *Enterobacteriaceae*, including 152 isolates carrying bla_{KPC}, collected in 20 European and surrounding countries during 2014-2015.
Materials/methods: *Enterobacteriaceae* clinical isolates (n=10,476) collected in 36 hospitals were tested for susceptibility against meropenem ± vaborbactam at fixed 8 mg/L and comparators using CLSI broth microdilution method. Carbapenem-resistant *Enterobacteriaceae* (CRE) isolates were screened for carbapenemase genes using PCR/sequencing.
Results: Meropenem-vaborbactam ($MIC_{50/90}$, 0.03/0.06 mg/L) inhibited 98.5% at ≤1 mg/L and 98.7% at ≤2 mg/L (EUCAST and CLSI susceptible breakpoints for meropenem used for comparison; Abstract Table). Meropenem inhibited 96.6% and 96.9% of these isolates at the same concentrations. Against CRE, meropenem-vaborbactam ($MIC_{50/90}$, 1/32 mg/L) was considerably more active than meropenem ($MIC_{50/90}$, 16/>32 mg/L). Carbapenemases were detected among 238 (69.2%) CRE and included 103 KPC-3 (mostly from Italy), 49 KPC-2 (Greece, Italy, and Poland), 66 OXA-48-like (12 countries; 32 isolates from Turkey), and 59 metallo-beta-lactamases (41 NDM-1, 8 countries, and 18 VIM-like, 4 types). Three *Klebsiella pneumoniae* isolates from Italy carried bla_{OXA-48} and bla_{KPC-3}. Meropenem-vaborbactam ($MIC_{50/90}$, 0.25/1 mg/L) inhibited 91.9%, 96.6%, and 99.3% of the isolates carrying bla_{KPC} at ≤1 mg/L, ≤2 mg/L, and ≤8 mg/L, respectively. Meropenem activity was limited against these isolates, and this carbapenem inhibited only 0.7% and 3.3% of the isolates at ≤1 mg/L and ≤2 mg/L, respectively. CRE isolates that did not carry bla_{KPC} displayed higher MIC results for meropenem-vaborbactam, and this combination inhibited 35.4% of the isolates at ≤2 mg/L. These 192 isolates carrying other carbapenemase genes or other resistance mechanisms displayed elevated meropenem MIC results, and only 8.9% of the isolates were inhibited at ≤2 mg/L.
Conclusions: Meropenem and meropenem-vaborbactam were very active against *Enterobacteriaceae* isolates, but meropenem-vaborbactam displayed greater activity against KPC isolates that usually display resistance to carbapenems and other agents. The prevalence of carbapenemase genes varies in European countries, but the dissemination of KPC-producing organisms has been documented in several countries of this region, and meropenem-vaborbactam displayed good activity against these isolates.

Introduction

- Carbapenems often have been considered the last resource to treat serious infections caused by multidrug-resistant (MDR) gram-negative organisms or isolates producing β-lactamases
- Carbapenems are hydrolyzed by carbapenemases that include KPC serine-carbapenemases, OXA-48, and class B metallo-β-lactamases (MBLs)
- Among carbapenemase genes, bla_{KPC} variants are the most widespread, and isolates carrying these genes have been detected in many European countries
- KPC enzymes hydrolyze and encode resistance to virtually all β-lactams, and isolates producing these enzymes are often MDR
- Vaborbactam (formerly RPX7009) is a cyclic boronic acid β-lactamase inhibitor that has activity against Ambler class A (including KPC) and C enzymes
- This inhibitor has been combined with meropenem to enhance the activity of this carbapenem against KPC-producing isolates when compared to the β-lactam tested alone
- In this study, we evaluated the activity of meropenem-vaborbactam against *Enterobacteriaceae*, including 152 isolates carrying bla_{KPC}, collected in 20 European and surrounding countries during 2014-2015

Materials and Methods

- *Enterobacteriaceae* clinical isolates (n=10,476) collected during 2014-2015 from 36 hospitals located in 20 European countries were included in the study
- Isolates were limited to 1 per patient episode and were collected from bloodstream infections (n=3,133), intra-abdominal infections (n=940), pneumonia in hospitalized patients (n=2,184), skin and skin structure infections (n=1,973), urinary tract infections (n=2,095), and other sources (n=151)
- Species identification was confirmed, when necessary, by matrix-assisted laser desorption ionization-time of flight mass spectrometry
- Isolates were susceptibility tested against meropenem-vaborbactam (inhibitor at fixed 8 mg/L) and comparator agents using the reference broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI)
  - Quality control (QC) was performed according to CLSI guidelines (M100-S27) and all QC MIC results were within acceptable ranges as published in CLSI documents
  - Categorical interpretations for all comparator agents were those found in CLSI criteria in M100-S27 (2017), EUCAST breakpoint tables (version 7.0, January 2017), and/or United States Food and Drug Administration (US FDA) package inserts
- Extended spectrum β-lactamase (ESBL)-phenotype criterion was applied for *Escherichia coli*, *Klebsiella pneumoniae*, *K. oxytoca*, and *P. mirabilis* displaying an MIC value at ≥2 mg/L for ceftriaxone, ceftazidime, and/or aztreonam (M100-S27)
- Carbapenem-resistant *Enterobacteriaceae* (CRE) was defined as any isolate exhibiting doripenem, imipenem, and/or meropenem MIC values at ≥2 mg/L (*Proteus mirabilis* and indole-positive Proteeae used only meropenem due to intrinsically elevated imipenem MIC values)
  - CRE isolates were screened for acquired carbapenemase-encoding genes by PCR using custom primers
  - Amplicons were sequenced on both strands, and nucleotide sequences obtained were analyzed using the Lasergene® software package (DNAStar; Madison, Wisconsin, USA) and compared to available sequences via NCBI BLAST search (http://www.ncbi.nlm.nih.gov/blast/)

Results

- Meropenem-vaborbactam activity ($MIC_{50/90}$, 0.03/0.06 mg/L) against *Enterobacteriaceae* isolates tested was identical to meropenem activity alone ($MIC_{50/90}$, 0.03/0.06 mg/L) against these isolates (Table 1)
- Meropenem-vaborbactam ($MIC_{50/90}$, 0.03/0.06 mg/L) was slightly more active than meropenem ($MIC_{50/90}$, 0.03/0.12 mg/L) against isolates displaying an ESBL phenotype without resistance to carbapenems (ESBL non-CRE; Table 1)
- Overall, carbapenem resistance was observed among 3.3% of the *Enterobacteriaceae* isolates (344/10,476)
  - CRE rates were very high in Belarus (60.0%) and Poland (30.0%), but were also elevated in Italy (8.8%), Ukraine (8.6%), and Russia (8.1%; Figure 1)
- Against CRE isolates, meropenem-vaborbactam ($MIC_{50/90}$, 1/32 mg/L) was 8-fold more active than meropenem alone ($MIC_{50/90}$, 16/>32 mg/L; Table 1)
- CRE isolates displayed higher MIC values against comparator agents tested when compared to all *Enterobacteriaceae* isolates, and meropenem-vaborbactam, colistin ($MIC_{50/90}$, ≤0.5/>8 mg/L), and tigecycline ($MIC_{50/90}$, 0.5/1 mg/L) were the antimicrobial agents retaining some activity against these isolates (Table 1)
- Meropenem-vaborbactam and meropenem ($MIC_{50/90}$, ≤0.015/0.03 mg/L) displayed the same activity against *E. coli* isolates (n=4,636); however, this combination was more active against *K. pneumoniae* ($MIC_{50/90}$, 0.03/0.5 mg/L) isolates when compared to the carbapenem tested alone ($MIC_{50/90}$, 0.03/16 mg/L; Table 1)
- Carbapenemase-producing isolates were detected in 19/20 countries surveyed (Figure 2), and Hungary was the only country with no CRE or carbapenemase-producing isolates
- Among 344 CRE isolates, 271 (78.8%) carried genes encoding carbapenemases that included 49 bla_{KPC-2}, 103 bla_{KPC-3}, 41 bla_{NDM-1}, 2 $bla_{OXA-232}$, 59 bla_{OXA-48}, 12 bla_{VIM-1}, 1 bla_{VIM-2}, 4 bla_{VIM-4}, and 1 bla_{VIM-5}
- The majority of CRE isolates were *K. pneumoniae* (n=291), and 231 harboured carbapenemase-encoding genes, including 3 isolates from Italy carrying bla_{OXA-48} and bla_{KPC-3}
- A total of 149 carried only bla_{KPC} genes (1.4% overall and 43.3% of CRE), and meropenem-vaborbactam ($MIC_{50/90}$, 0.25/1 mg/L) inhibited 91.9%, 96.6%, and 99.3% of these isolates at ≤1 mg/L, ≤2 mg/L, and ≤8 mg/L, respectively
  - Meropenem alone ($MIC_{50/90}$, >32/>32 mg/L) inhibited 0.7%, 3.4%, and 18.8% of the isolates carrying bla_{KPC} at the same concentrations (Figure 2)
  - The activity of meropenem-vaborbactam was similar for isolates carrying bla_{KPC-2} ($MIC_{50/90}$, 0.5/2 mg/L) or bla_{KPC-3} ($MIC_{50/90}$, 0.25/1 mg/L)
- Meropenem ± vaborbactam displayed limited activity against isolates carrying genes encoding OXA-48-like enzymes or MBLs ($MIC_{50/90}$, ≥16/>32 mg/L) and these isolates corresponded to 0.59% of all isolates tested and 17.2% of the CREs

Abstract Table

Organism/group (no. tested)	Cumulative % inhibited at MIC (mg/L):					MIC_{50}	MIC_{90}
	≤0.5	1	2	4	8		
Enterobacteriaceae (10,476)							
Meropenem-vaborbactam	97.8	98.5	98.7	99.0	99.2	0.03	0.06
Meropenem	96.0	96.6	96.9	97.5	97.9	0.03	0.06
KPC-producers (149)[a]							
Meropenem-vaborbactam	81.9	91.9	96.6	99.3	99.3	0.25	1
Meropenem		0.7	3.4	10.1	18.8	>32	>32
OXA-48-like-producers (58)[b]							
Meropenem-vaborbactam	6.9	10.3	12.1	22.4	34.5	16	>32
Meropenem	1.7	3.4	5.2	13.8	27.6	16	>32
Metallo-beta-lactamase-producers (59)							
Meropenem-vaborbactam		3.4	10.2	18.6	25.4	32	>32
Meropenem		1.7	8.5	20.3	25.4	32	>32

[a] Does not include 3 isolates that also carry bla_{OXA-48}
[b] Does not include 3 isolates that also carry bla_{KPC} and another 5 also carrying bla_{NDM-1}

Table 1 Meropenem-vaborbactam activity (inhibitor at fixed 8 mg/L) and comparator antimicrobial agents tested against *Enterobacteriaceae* isolates collected in European and surrounding countries

Antimicrobial agent	MIC_{50}/MIC_{90} (mg/L)				
	Enterobacteriaceae (10,476)	ESBL non-CRE (1,764)	CRE (344)	*Klebsiella pneumoniae* (1,978)	*Escherichia coli* (4,636)
Meropenem-vaborbactam	0.03 / 0.06	0.03 / 0.06	1 / 32	0.03 / 0.5	≤0.015 / 0.03
Meropenem	0.03 / 0.06	0.03 / 0.12	16 / >32	0.03 / 16	≤0.015 / 0.03
Amikacin	2 / 4	2 / 16	16 / >32	1 / 32	2 / 4
Aztreonam	≤0.12 / >16	>16 / >16	>16 / >16	0.25 / >16	≤0.12 / >16
Cefepime	≤0.5 / >16	>16 / >16	>16 / >16	≤0.5 / >16	≤0.5 / >16
Ceftazidime	0.25 / >32	16 / >32	>32 / >32	1 / >32	0.25 / 16
Colistin	≤0.5 / >8	≤0.5 / 1	≤0.5 / >8	≤0.5 / 1	≤0.5 / ≤0.5
Levofloxacin	≤0.12 / >4	>4 / >4	>4 / >4	0.5 / >4	≤0.12 / >4
Piperacillin-tazobactam	2 / 64	8 / >64	>64 / >64	8 / >64	2 / 16
Minocycline	2 / >8	2 / >8	4 / >8	2 / >8	1 / 8
Tigecycline	0.25 / 1	0.25 / 1	0.5 / 1	0.25 / 1	0.12 / 0.25

Figure 1 CRE rates and distribution of carbapenemase-encoding genes among *Enterobacteriaceae* isolates collected from European and surrounding countries

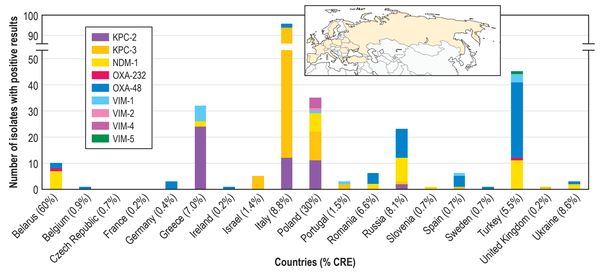
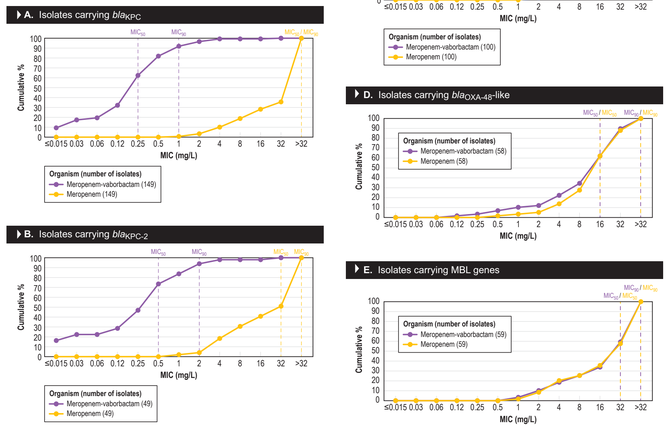


Figure 2 Activity of meropenem-vaborbactam (inhibitor at fixed 8 mg/L) and meropenem tested against carbapenemase-producing *Enterobacteriaceae* isolates collected in European and surrounding countries[a]

[a] Isolates carrying multiple carbapenemase genes were excluded from the analysis



Conclusions

- Meropenem-vaborbactam was active against contemporary *Enterobacteriaceae* isolates collected from European hospitals
- This combination displayed activity against most CRE isolates and strains carrying bla_{KPC} genes that are often MDR and prevalent in various European countries
- Similar to other β-lactam-β-lactamase inhibitor combinations clinically available and in late stage of development, meropenem-vaborbactam has limited activity against isolates harbouring genes encoding OXA-48-like enzymes and MBLs
- The worldwide spread of CREs and KPC-producing organisms is a matter of great concern and the development of treatment options active against these organisms is warranted

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