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Meropenem-vaborbactam activity against Enterobacteriaceae isolates collected during 2014-2015 from European countries

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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.

Material/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 and 98.7% at ≤1 and ≤2 mg/L (EUCAST and CLSI susceptible breakpoints for meropenem used for comparison; 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, four types). Three *Klebsiella pneumoniae* 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, ≤2 and ≤8 mg/L, respectively. Meropenem activity was limited against these isolates, and this carbapenem inhibited only 0.7 and 3.4% of the isolates at ≤1 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 vary 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.

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 three isolates that also carry *bla*_{OXA-48}

^b Does not include three isolates that also carry *bla*_{KPC} and other five also carrying *bla*_{NDM-1}