Diagnostic Microbiology and Infectious Disease 93 (2019) 258–260

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

In vitro evaluation of meropenem-vaborbactam against clinical CRE isolates at a tertiary care center with low KPC-mediated carbapenem resistance

Patrick M. Kinn [d], Derrick J. Chen [c,b], Thomas M. Gihring [c], Lucas T. Schulz [d], Barry C. Fox [a], Erin K. McCreary [d], Alexander J. Lepak [a,*]

[a] Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA
[b] Department of Pharmacy, UW Health, Madison, WI, USA
[c] Clinical Labs - Microbiology, UW Health, Madison, WI, USA
[d] Department of Pathology and Laboratory Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

ARTICLE INFO

Article history:
Received 6 August 2018
Received in revised form 26 September 2018
Accepted 30 September 2018
Available online 4 October 2018

Keywords:
Meropenem-vaborbactam
CRE
KPC
Antimicrobial stewardship

ABSTRACT

The *in vitro* activity of meropenem-vaborbactam was examined against clinical carbapenem-resistant *Enterobacteriaceae* isolates collected over 3 years at our medical center. Only 3 KPC-producers were identified. Susceptibility to meropenem-vaborbactam was noted in 15/16 (94%) isolates (MIC_{90} 2 mg/L) that were nonsusceptible to meropenem. Meropenem-vaborbactam may have utility at centers where non–KPC-producers are more frequent.

Carbapenem-resistant *Enterobacteriaceae* (CRE) are a significant global threat with substantially poorer outcomes and limited treatment options (Bassetti et al., 2016; Doi et al., 2017; Duin and Doi, 2017; Logan and Weinstein, 2017). Meropenem-vaborbactam was FDA-approved in 2017 for use in adult patients with complicated urinary tract infections (Drugs@FDA). Vaborbactam is a cyclic boronic acid derivative with potent activity against Ambler class A and class C β-lactamases (Lomovskaya et al., 2017). Its major utility has been demonstrable potency *in vitro* and efficacy in clinical trials against Ambler class A carbapenemase-producing *Enterobacteriaceae*, specifically isolates with KPC-mediated resistance (Castanheira et al., 2016, 2017; Hackel et al., 2018; Kaye et al., 2017; Lomovskaya et al., 2017; Pfaller et al., 2018). While these results were particularly encouraging, there is still considerable variation in KPC prevalence between medical centers even in similar geographical locations. At the University of Wisconsin Hospitals and Clinics, we have had approximately 1 KPC-producing clinical isolate per year (0.3 per 100 000 patient days and 0.007% of all *Enterobacteriaceae* isolates processed annually at our clinical laboratory). In contrast, non–KPC-producing CRE isolates are much more common, numbering 15–20 per year. Given the very low incidence of KPC-producing isolates, we sought to answer whether meropenem-vaborbactam could have potential benefit in our patient population by evaluating its *in vitro* potency against CRE clinical isolates from our institution.

Retrospective review of the clinical microbiology database at the University of Wisconsin Hospitals and Clinics from 1/1/2015 to 12/30/2017 was performed. Over this period, it was standard practice to test and report ertapenem and meropenem susceptibility results on all *Enterobacteriaceae* isolates. A clinical isolate had to be resistant by CLSI interpretive criteria to at least 1 carbapenem to be included in analysis. Forty-six CRE isolates were identified from unique clinical encounters; 44 were able to be recovered from frozen stocks and included in the analysis. These isolates included *E. cloacae* complex ($n = 19$), *E. coli* ($n = 10$), *K. pneumoniae* ($n = 8$), *S. marcescens* ($n = 5$), *Klebsiella* (formerly *Enterobacter*) *aerogenes* ($n = 1$), and *K. oxytoca* ($n = 1$). Isolates were most commonly recovered from urine ($n = 21$), followed by intraabdominal source ($n = 9$), lung ($n = 6$), blood ($n = 3$), skin and soft tissue ($n = 3$), bone ($n = 1$), and sinus ($n = 1$). Antimicrobial susceptibility testing performed by CLSI broth microdilution techniques (MicroScan, Beckman Coulter, Indianapolis, IN) at the time of isolation (CLSI, 2018a, 2018b) from the clinical specimen revealed 2 distinct groups of isolates: 1) resistant to ertapenem but susceptible to meropenem ($n = 28$, 64%) and 2) resistant to ertapenem and nonsusceptible (intermediate $n = 2$, resistant $n = 14$) to meropenem

* Corresponding author. Tel.: +1-608-263-1545; fax: +1-608-263-4464.
E-mail address: ajlepak@medicine.wisc.edu (A.J. Lepak).

https://doi.org/10.1016/j.diagmicrobio.2018.09.017
0732-8893/

Table 1
In vitro susceptibility of clinical CRE isolates to meropenem-vaborbactam[a] and select comparator antibiotics (University of Wisconsin Hospitals and Clinics, 2015–2017).

CRE phenotype	*N* (%)	Meropenem-vaborbactam MIC_{50} (mg/L)	Meropenem-vaborbactam MIC_{90} (mg/L)	Number (%) susceptible to meropenem-vaborbactamb[b]	Number (%) susceptible to ciprofloxacin[c]	Number (%) susceptible to piperacillin/tazobactam[c]	Number (%) susceptible to tobramycin[c]
Ertapenem resistant, meropenem susceptible[d]	28 (64)	0.125	0.5	28 (100)	18 (64)	5 (18)	23 (82)
Ertapenem resistant, meropenem nonsusceptible[d]	16 (36)	0.125	2	15 (94)	8 (50)	7 (44)	10 (63)

[a] Meropenem-vaborbactam MIC testing is performed with fixed vaborbactam concentration of 8 mg/L per manufacturer instructions.
[b] 2018 US FDA MIC interpretative criteria for meropenem-vaborbactam as follows: susceptible ≤4/8 mg/L, intermediate 8/8 mg/L, and resistant ≥16/8 mg/L.
[c] Approved CLSI breakpoints at the time of testing were used for determining susceptibility to ciprofloxacin, piperacillin/tazobactam, and tobramycin.
[d] Ertapenem resistance was determined based on CLSI breakpoints (MIC ≤0.5 mg/L). Meropenem nonsusceptible includes intermediate ($n = 2$) and resistant ($n = 14$) organisms based on CLSI interpretive criteria. MIC_{50} and MIC_{90} were not able to be calculated for meropenem alone as the data included truncated MICs for those isolates that were ≤1 mg/L.

(total $n = 16$, 36%). Each isolate was sent to the Wisconsin State Laboratory of Hygiene for molecular detection of carbapenemase genes for KPC, NDM-1, and OXA-48-like *via* real-time PCR. Only 3 were positive, and all were KPC-producing *K. pneumoniae* isolates.

Each isolate recovered from stock underwent additional antimicrobial susceptibility testing against meropenem-vaborbactam by antimicrobial gradient diffusion (Liofilchem Inc., Waltham, MA) and disk diffusion (Mast Group Ltd., Bootle, UK) per manufacturer instructions with a fixed vaborbactam concentration of 8 mg/L (CLSI, 2015, 2018a). Quality control testing was performed with ATCC reference strains using CLSI performance guidelines, and all values were in range (CLSI, 2018b). Breakpoints established by the FDA and included in the package insert were used for interpretation (The Medicines Company, 2017). As expected, the combination of meropenem-vaborbactam against isolates that were resistant to ertapenem but susceptible to meropenem was highly efficacious with all 28 isolates demonstrating susceptibility to the combination with an MIC_{50} of 0.125 mg/L and MIC_{90} of 0.5 mg/L (Table 1). In the group resistant to ertapenem and nonsusceptible to meropenem, meropenem-vaborbactam continued to demonstrate efficacy with an MIC_{50} of 0.125 mg/L and MIC_{90} of 2 mg/L (Table 1). Susceptibility to meropenem-vaborbactam was noted in 15 of 16 (94%) isolates in this group (Table 2). Notably, 11 of 16 isolates had a ≥4-fold decrease and 9 of 16 had a ≥16-fold decrease in MIC for meropenem-vaborbactam compared to meropenem alone. On average, the meropenem-vaborbactam MIC decreased by almost 128-fold compared with meropenem alone. There were no discrepancies between susceptibility interpretation using gradient diffusion and disk diffusion.

This study demonstrates a number of important findings. First, we found that a majority (64%) of the CRE isolates at our center are resistant to ertapenem but are susceptible to other carbapenems such as meropenem. This has been reported as due to the combination of ESBL or AmpC β-lactamase production with contribution of active efflux pumps and/or porin loss (Woodford et al., 2007), and other carbapenems usually maintain activity against these isolates. Secondly, for CRE isolates that were resistant to ertapenem and nonsusceptible to meropenem, non–KPC-producers are much more frequently encountered at our center than KPC-producing isolates (81% *vs.* 19%). Nonetheless, we found that vaborbactam significantly decreased the meropenem MIC in most isolates compared to meropenem alone for this group. Previously published large *in vitro* studies have demonstrated a relative decrease in potency for meropenem-vaborbactam against non–KPC-producing CRE (Castanheira et al., 2017; Lomovskaya et al., 2017; Pfaller et al., 2018). For example, Pfaller et al. (2018)

Table 2
In vitro susceptibility results for meropenem-vaborbactam[a] by gradient diffusion and disk diffusion for CRE clinical isolates that were resistant to ertapenem and nonsusceptible to meropenem (University of Wisconsin Hospitals and Clinics, 2015–2017).

Organism	Meropenem MIC (mg/L)[b]	Meropenem-vaborbactam MIC (mg/L)[c]	Meropenem-vaborbactam inhibition zone diameter (nearest whole mm)[c]	Carbapenemase detected[d]
Enterobacter cloacae complex	2	2	21	
Enterobacter cloacae complex	2	0.5	28	
Enterobacter cloacae complex	4	2	20	
Escherichia coli	8	8	14	
Escherichia coli	>8	0.03	27	
Escherichia coli	4	0.06	30	
Escherichia coli	4	2	18	
Klebsiella (formerly *Enterobacter*) *aerogenes*	4	4	17	
Klebsiella oxytoca	4	0.03	29	
Klebsiella pneumoniae	>8	0.125	20	KPC
Klebsiella pneumoniae	8	0.06	23	KPC
Klebsiella pneumoniae	>8	0.125	21	KPC
Serratia marcescens	>8	0.06	28	
Serratia marcescens	4	0.06	26	
Serratia marcescens	4	0.125	27	
Serratia marcescens	>8	0.06	29	

[a] Meropenem-vaborbactam MIC testing was performed with fixed vaborbactam concentration of 8 mg/L per manufacturer instructions.
[b] 2018 CLSI M100 interpretative criteria for meropenem as follows: susceptible ≤1 mg/L, intermediate 2 mg/L, and resistant ≥4 mg/L.
[c] 2018 US FDA MIC interpretative criteria for meropenem-vaborbactam as follows: susceptible ≤4/8 mg/L or ≥17 mm, intermediate 8/8 mg/L or 14–16 mm, and resistant ≥16/8 mg/L or ≤13 mm.
[d] Isolates were tested for KPC, NDM-1, and OXA-48–like carbapenemases *via* real-time PCR.

recently published meropenem-vaborbactam activity against 330 CRE isolates from a worldwide collection during 2015 In this comprehensive study, meropenem-vaborbactam demonstrated an MIC_{50} and MIC_{90} against non–KPC-producers of 16 mg/L and 32 mg/L, respectively, due to the large number of MBL (52/121; 43%) and OXA-48 (40/121; 33%) producing isolates in this subset. Against the 16 isolates that were resistant to ertapenem and nonsusceptible to meropenem in our study, the MIC_{50} was 0.125 mg/L and MIC_{90} only 2 mg/L. Thus, we noted relatively preserved effectiveness despite the vast majority of our isolates in this group being non–KPC-producers. We believe this retained activity noted in our study can be explained by a relatively higher comparative incidence of other class A carbapenemase resistance mechanisms and lack of NDM and OXA-48–like isolates. The data presented in Table 2 demonstrate that most of the enhanced potency in our non–KPC-producing CRE was noted in 4 *S. marcescens* isolates, 2 *E. coli,* and a single *K. oxytoca* isolate. The *S. marcescens* isolates mimicked phenotypically a classic SME pattern, a class A carbapenemase. Based on the dramatic decrease in MIC in the presence of vaborbactam, it is possible that the *E. coli* and *K. oxytoca* isolates may have other less common class A carbapenemase genes present. Unfortunately, we were not able to assess for other serine Ambler class A carbapenemases (e.g., SME, IMI, GES, NMC, etc.) in these isolates. In general, these are considered relatively uncommon at many health care centers; however, our data suggest that these mechanisms may be as common as or more common than KPC-mediated resistance at some centers.

In conclusion, our study demonstrates that meropenem-vaborbactam activity is highly dependent on local epidemiology, may have retained *in vitro* potency against non–KPC-producers, and could be an important treatment option for patients with CRE at our institution despite a very low incidence of KPC-mediated resistance. Our *in vitro* evaluation serves as a template for other institutions to assess the activity of novel antimicrobial agents in the context of the local epidemiological distribution of resistance mechanisms circulating at their centers to best inform clinicians, guide antimicrobial stewardship efforts, and ensure their patients have access to optimized therapies.

Acknowledgments

Meropenem-vaborbactam gradient test strips and disk diffusion test disks were provided by The Medicines Company (Parsippany, NJ).

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

Bassetti M, Peghin M, Pecori D. The management of multidrug-resistant Enterobacteriaceae. Curr Opin Infect Dis 2016;29:583–94.

Castanheira M, Rhomberg PR, Flamm RK, Jones RN. Effect of the beta-lactamase inhibitor vaborbactam combined with meropenem against serine carbapenemase-producing Enterobacteriaceae. Antimicrob Agents Chemother 2016;60:5454–8.

Castanheira M, Huband MD, Mendes RE, Flamm RK. Meropenem-vaborbactam tested against contemporary gram-negative isolates collected worldwide during 2014, including carbapenem-resistant, KPC-producing, multidrug-resistant, and extensively drug-resistant Enterobacteriaceae. Antimicrob Agents Chemother 2017;61.

Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicrobial disk susceptibility tests — 12th edition. CLSI document M02-A12. Wayne, PA: Clinical and Laboratory Standards Institute; 2015.

Clinical and Laboratory Standards Institute (CLSI). Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard — 11th edition. CLSI document M07-A11. Wayne, PA: Clinical and Laboratory Standards Institute; 2018a.

Clinical and Laboratory Standards Institute (CLSI). Perfomance standards for antimicrobial suscpetibility testing — 28th edition. CLSI document M100. Wayne, PA: Clinical and Laboratory Standards Institute; 2018b.

Doi Y, Bonomo RA, Hooper DC, Kaye KS, Johnson JR, Clancy CJ, et al. Gram-negative bacterial infections: research priorities, accomplishments, and future directions of the antibacterial resistance leadership group. Clin Infect Dis 2017;64:S30–5.

Drugs@FDA. FDA approved drug products. www.accessdata.fda/gov.

Hackel MA, Lomovskaya O, Dudley MN, Karlowsky JA, Sahm DF. In vitro activity of meropenem-vaborbactam against clinical isolates of KPC-positive Enterobacteriaceae. Antimicrob Agents Chemother 2018;62.

Kaye KS, Vazquez J, Mathers A, et al. Meropenem–vaborbactam (vabomere) vs best available therapy for carbapenem-resistant Enterobacteriaceae infections in TANGO II: pooled population analysis across infection types. Presented at: ID Week. San Diego, CA, USA, 4–8 October 2017; 2017.

Logan LK, Weinstein RA. The epidemiology of carbapenem-resistant Enterobacteriaceae: the impact and evolution of a global menace. J Infect Dis 2017;215:S28–36.

Lomovskaya O, Sun D, Rubio-Aparicio D, Nelson K, Tsivkovski R, Griffith DC, et al. Vaborbactam: spectrum of beta-lactamase inhibition and impact of resistance mechanisms on activity in Enterobacteriaceae. Antimicrob Agents Chemother 2017;61.

Pfaller MA, Huband MD, Mendes RE, Flamm RK, Castanheira M. In vitro activity of meropenem-vaborbactam and characterization of carbapenem resistance mechanisms among carbapenem-resistant Enterobacteriaceae from the 2015 meropenem-vaborbactam surveillance program. Int J Antimicrob Agents 2018. https://doi.org/10.1016/j.ijantimicag.2018.02.021.

The Medicines Company. Vabomere™ (meropenem and vaborbactam) for injection, for intravenous use, prescribing information. Revised august. Parsippany, NJ: The medicines company; 2017.

van Duin D, Doi Y. The global epidemiology of carbapenemase-producing Enterobacteriaceae. Virulence 2017;8:460–9.

Woodford N, Dallow JW, Hill RL, Palepou MF, Pike R, Ward ME, et al. Ertapenem resistance among Klebsiella and Enterobacter submitted in the UK to a reference laboratory. Int J Antimicrob Agents 2007;29:456–9.