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Potency of Meropenem-Vaborbactam in Lung Surfactant

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ABSTRACT This study investigated whether pulmonary surfactant has an effect on the *in vitro* antibacterial activity of either meropenem alone or meropenem in combination with vaborbactam at a fixed concentration of 8 μg/ml against several *Klebsiella pneumoniae* carbapenemase (KPC)-producing strains of Gram-negative bacteria. Results showed that the potency of meropenem alone and that of meropenem-vaborbactam were not affected when tested with pulmonary surfactant.

KEYWORDS meropenem, vaborbactam, pulmonary surfactant

The effect of body fluids on the efficacy of an antibiotic is an important consideration in the treatment of infections in the lower respiratory tract (1). Pulmonary surfactant is a primary component of the epithelial lining fluid (ELF) of the lower respiratory tract (2). Importantly, pulmonary surfactant can bind antibiotics in the ELF, which can impede the antibacterial activity of the drug. Daptomycin efficacy in clinical trials for community-associated pneumonia (CAP) was unexpectedly low, and it was subsequently demonstrated that pulmonary surfactant reduced its antibacterial activity, providing a mechanistic explanation for its clinical failure (1).

Meropenem is a broad-spectrum carbapenem antibiotic used to treat a wide variety of serious infections, including lower respiratory tract infections. Vaborbactam is a novel beta-lactamase inhibitor with potent activity against class A carbapenemases, such as *Klebsiella pneumoniae* carbapenemases (KPC) (3). It has been shown to penetrate into pulmonary ELF (4). The purpose of this study was to determine the effect of pulmonary surfactant on the *in vitro* antibacterial activity of either meropenem alone or meropenem in combination with vaborbactam (meropenem-vaborbactam).

The effect of surfactant was assessed with the use of 9 KPC-producing strains of *Enterobacteriaceae*, including 7 *Klebsiella pneumoniae* isolates, 1 *Enterobacter cloacae* isolate, and 1 *Serratia marcescens* isolate; 2 KPC-producing strains of *Pseudomonas aeruginosa*; and 1 KPC-producing strain of *Acinetobacter baumannii*, containing either KPC-2 or KPC-3 carbapenemase with a broad range of meropenem alone and meropenem-vaborbactam MICs (Table 1). *Staphylococcus aureus* strain SAM1001 (ATCC 29213) was used as the control for daptomycin and ceftriaxone testing.

Cation-adjusted Mueller-Hinton broth (CAMHB) was used as the test medium. Meropenem (Sandoz) was used at a concentration range of 0.015 to 256 μg/ml alone and in combination with vaborbactam; the vaborbactam concentration was fixed at 8 μg/ml. Daptomycin (Sequoia Research) (concentration range, 0.125 to 128 μg/ml) and ceftriaxone (Sigma-Aldrich) (concentration range, 0.125 to 128 μg/ml) served as controls for surfactant effects. Beractant (Survanta; Abbott Laboratories) served as the pulmonary surfactant. Beractant is a bovine-derived surfactant containing 25 mg/ml phospholipids. Although its composition differs slightly from that of human surfactant, it is functionally equivalent. For testing with the control agent daptomycin, the CAMHB was supplemented with calcium to a final concentration of 50 μg/ml.

MIC and minimum bactericidal concentration (MBC) values were determined as recommended by the Clinical and Laboratory Standards Institute (5–7). For surfactant

Received 16 August 2017 **Returned for modification** 3 September 2017 **Accepted** 6 October 2017

Accepted manuscript posted online 16 October 2017

Citation Rubio-Aparicio D, Loutit J, Dudley M, Lomovskaya O. 2018. Potency of meropenem-vaborbactam in lung surfactant. Antimicrob Agents Chemother 62:e01702-17. https://doi.org/10.1128/AAC.01702-17.

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TABLE 1 Antibacterial activity of meropenem and meropenem-vaborbactam against KPC-producing strains of Gram-negative bacteria in CAMHB alone and in CAMHB with surfactant

Strain	Organism	Description	Meropenem-vaborbactam[a]				Meropenem			
			MIC		MBC		MIC		MBC	
			CAMHB alone	CAMHB with surfactant[b]	CAMHB alone	CAMHB with surfactant	CAMHB alone	CAMHB with surfactant	CAMHB alone	CAMHB with surfactant
KPM1123 (BAA-1705)	*K. pneumoniae*	KPC-2, TEM, SHV	0.015	0.015	0.015	0.015	32	32	32	32
KP1004	*K. pneumoniae*	KPC-2, TEM-1, SHV-11	0.06	0.06	0.06	0.06	64	64	32	32
KP1095	*K. pneumoniae*	KPC-2, TEM-1, SHV-1	0.03	0.03	0.03	0.03	16	16	16	16
KP1074 (BAA-2814)	*K. pneumoniae*	KPC-3, TEM-1, SHV-11	0.5	0.5	0.5	1	128	128	128	128
KP1093	*K. pneumoniae*	KPC-3, TEM-1, SHV-11	0.5	0.5	0.5	0.5	>256	>256	>256	>256
KP1099	*K. pneumoniae*	KPC-2, SHV-11, SHV-12, CTX-M-14	1	2	1	1	>256	ND[c]	ND	ND
KP1094	*K. pneumoniae*	KPC-2, TEM-1, LEN-17	4	4	4	8	>256	ND	ND	ND
ECL1079	*E. cloacae*	KPC, TEM	8	8	8	8	>256	>256	>256	>256
SM1040	*S. marcescens*	KPC-2, TEM-1	1	2	2	2	256	256	256	256
PA5261	*P. aeruginosa*	KPC-3	2	2	2	2	64	64	64	64
PA5258	*P. aeruginosa*	KPC-3	4	4	4	4	128	256	128	256
AB1291	*A. baumannii*	KPC-2	4	4	4	4	256	128	256	128

[a]Vaborbactam concentration was fixed at 8 μg/ml.
[b]Bovine pulmonary surfactant at 2.5 mg/ml (10%).
[c]ND, not done.

testing, the test medium was supplemented with beractant at 7 different fixed percentages ranging from 0.125 to 10% or 0.03 to 2.5 mg/ml.

The MIC and MBC testing of daptomycin and ceftriaxone for *Staphylococcus aureus* strain ATCC 29213 confirmed the findings of Silverman et al. (1); daptomycin activity was significantly inhibited by the inclusion of even small amounts of surfactant in the test medium, with a 16- to 32-fold loss of potency in 1% surfactant and a >100-fold loss in 10% surfactant, while ceftriaxone activity was unaffected by surfactant.

The MICs and MBCs of meropenem alone and meropenem-vaborbactam at a fixed concentration of 8 μg/ml were determined for KPC-producing strains of *Enterobacteriaceae* (9 strains), *P. aeruginosa* (3 strains), and *A. baumannii* (1 strain), with increasing concentrations of surfactant in the test medium. Antibacterial activities of both meropenem alone and meropenem-vaborbactam were not affected even when tested with the highest concentrations of surfactant (2.5 mg/ml, 10%) (Table 1). MICs and MBCs for meropenem alone and meropenem-vaborbactam ranged from 16 to >256 μg/ml and from 0.015 to 8 μg/ml, respectively, depending on the bacterial strain. As expected, meropenem alone and meropenem-vaborbactam activity against the strain of *P. aeruginosa* overexpressing AmpC (MIC and MBC 1 μg/ml) also was not affected by surfactant (data not shown).

The therapeutic options for treating pulmonary infections caused by Gram-negative pathogens, including KPC-producing strains, are limited. *In vitro* studies show that meropenem-vaborbactam is highly active against Gram-negative pathogens, including KPC-producing carbapenem-resistant *Enterobacteriaceae* (CRE) (8). Vaborbactam restores the activity of meropenem *in vitro* and in animal models of infections, including a mouse pneumonia model (9).

In this study, pulmonary surfactant from a bovine source had no significant effect on meropenem or meropenem-vaborbactam MICs and MBCs. The limitations of this study are those inherent to an *in vitro* study as opposed to an *in vivo* one (including closer to 100% of surfactant *in vivo*) and the use of bovine versus human surfactant. Studies of meropenem-vaborbactam in the treatment of patients with documented CRE infections, including those in patients with hospital-acquired and ventilator-associated bacterial pneumonia, are in progress (ClincalTrials.gov identifier NCT02168946).

ACKNOWLEDGMENTS

This work, including the efforts of Debora Rubio-Aparicio and Olga Lomovskaya, was funded in part by the Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority (BARDA), under contract HHSO100201400002C.

Writing and editorial assistance was provided by Laurel Ranger and Health and Wellness Partners, LLC, of Upper Saddle River, NJ, funded by The Medicines Company.

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