C-152 Activity of Meropenem/RPX7009 and Comparator Agents Tested Against Contemporary Enterobacteriaceae Isolates Collected from Bloodstream Infections in USA Hospitals

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Amended Abstract

Background: Increasing reports of carbapenem-resistant Enterobacteriaceae (CRE) highlight the need for treatment options effective against these organisms. We evaluated the activity of meropenem/RPX7009 (MER/RPX) and comparators tested against bloodstream infections (BSI) isolates collected as part of a surveillance program in USA hospitals.

Methods: 854 Enterobacteriaceae (ENT) clinical isolates were consecutively collected from BSI during 2014 at 29 USA hospitals. Isolates were susceptibility (S) tested by reference broth microdilution methods for MER ± RPX (at fixed 8 µg/ml) and comparators. CRE was defined as an isolate resistant (CLSI criteria) to imipenem and/or meropenem. CLSI and EUCAST interpretative criteria were applied.

Results: MER/RPX inhibited 99.9% of the ENT at ≤1 µg/ml (MER CLSI S breakpoint for comparison) and MER alone inhibited 98.1% of the isolates at the same concentration. MER ($MIC_{50/90}$, ≤0.015/0.06 µg/ml) and MER/RPX ($MIC_{50/90}$, ≤0.015/0.03 µg/ml) were the most active agents among comparators tested (see table). All *E. coli* isolates (n=374) had MER/RPX MIC at ≤1 µg/ml. MER/RPX inhibited 186/187 (99.5%) of the *K. pneumoniae* isolates at ≤1 µg/ml, and the remaining isolate had MER/RPX MIC at 2 µg/ml. MER alone inhibited 92.0% of the *K. pneumoniae* isolates at ≤1 µg/ml. All *Enterobacter* spp. (n=113), *Citrobacter* spp. (n=23), *P. mirabilis* (n=35) and indole-positive Proteae (n=19) were inhibited by MER/RPX at ≤1 µg/ml. MER/RPX inhibited all *Serratia* spp. isolates (n=52) at ≤0.5 µg/ml. 14/15 CRE isolates were inhibited by MER/RPX at ≤1 µg/ml and one isolate (*K. pneumoniae*) had a MER/RPX MIC at 2 µg/ml. Among comparators, CRE strains were most susceptible to colistin (COL; 73.3% S, EUCAST criteria) and tigecycline (100.0% S, CLSI /86.7% S, EUCAST criteria).

Conclusions: MER/RPX was active against ENT and RPX enhanced MER activity against CRE isolates that were cause of BSI in USA hospitals. MER/RPX could become an important option for the treatment of severe infections in hospitals with elevated CRE rates.

Organism/group (no. tested)	Antimicrobial agent MIC_{50}/MIC_{90} (µg/ml)					
	MER/RPX[a]	MER[b]	P/T[c]	AMK	COL[d]	CEP[e]
Enterobacteriaceae (854)	≤0.015/0.03	≤0.015/0.06	2/16	1/4	≤0.5/>8	≤0.5/4
E. coli (374)	≤0.015/≤0.015	≤0.015/0.03	2/8	2/4	≤0.5/≤0.5	≤0.5/8
K. pneumoniae (187)	0.03/0.03	0.03/0.06	4/32	1/2	≤0.5/1	≤0.5/16
CRE (15)	0.06/1	32/>32	>64/>64	8/32	≤0.5/>8	>16/>16

a. MER/RPX= meropenem/RPX7009
b. MER= meropenem
c. P/T= piperacillin/tazobactam
d. COL= colistin
e. CEP= cefepime

Background

Carbapenem-resistant Enterobacteriaceae (CRE) isolates have been detected worldwide, and their elevated prevalence is mainly due to the dissemination of isolates producing carbapenemases, such as *Klebsiella pneumoniae* carbapenemase (KPC) and metallo-β-lactamases, largely NDM, IMP and VIM. Infections caused by carbapenemase-producing Enterobacteriaceae (CPE) became a serious clinical concern among infectious disease and clinical microbiology professionals since these infections are difficult to manage using currently available antimicrobials. CPE isolates are resistant to all or nearly all β-lactam agents, and these organisms are usually resistant to other antimicrobial classes.

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. The increasing prevalence of multidrug-resistant (MDR) organisms producing KPC enzymes and other β-lactamases that are poorly inhibited by clinically available inhibitors, suggests the need for new treatment alternatives.

In this study, we evaluated the activity of meropenem combined with the β-lactamase inhibitor RPX7009 when tested at a fixed 8 µg/ml concentration and comparators tested against bloodstream infection (BSI) isolates collected as part of a surveillance program in USA hospitals.

Methods

Bacterial isolates. A total of 854 Enterobacteriaceae clinical isolates were consecutively collected from BSI at 29 USA hospitals during 2014. 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 RPX7009 at a fixed concentration of 8 µg/ml. Categorical interpretations for all comparator agents were those found in CLSI document M100-S25 (2015), EUCAST website (2015) and US-FDA package insert (tigecyline). Quality control (QC) was performed using *Escherichia coli* ATCC 25922 and 35218 and KPC-producing *Klebsiella pneumoniae* BAA-1705. 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, K. oxytoca*) and *P. mirabilis* displaying a MIC at ≥2 µg/ml for ceftriaxone or ceftazidime or aztreonam (CLSI, 2015). CRE was defined as any isolate exhibiting an imipenem (*Proteus mirabilis* and indole-positive *Proteae* were not included due to the intrinsically elevated MIC values) and/or meropenem MIC values at ≥2 µg/ml.

Results

- Meropenem/RPX7009 (MIC_{50} and MIC_{90}, ≤0.015 and 0.03 µg/ml) inhibited all Enterobacteriaceae isolates collected from BSI at ≤2 µg/ml, and all but one of the isolates (99.9%) at ≤1 µg/ml (EUCAST and CLSI susceptibility breakpoint for meropenem when tested alone, respectively [used for comparison purposes only]; Table 1).
- Against 99 Enterobacteriaceae isolates displaying an ESBL-phenotype, including 62 *E. coli*, 33 *K. pneumoniae* and three *K. oxytoca*, meropenem/RPX7009 (MIC_{50} and MIC_{90}, ≤0.015 and 0.12 µg/ml) inhibited 99.0 and 100.0% of the isolates at ≤1 and ≤2 µg/ml, respectively (Table 1).
- Meropenem/RPX7009 (MIC_{50} and MIC_{90}, 0.06 and 1 µg/ml) inhibited 93.3 and 100.0% of the 15 CRE isolates (14 *K. pneumoniae* and one *E. coli*) at ≤1 and ≤2 µg/ml, respectively (Table 1).
- Although meropenem (MIC_{50} and MIC_{90}, ≤0.015 and 0.06 µg/ml) was only slightly less active when compared to meropenem/RPX7009 against all Enterobacteriaceae isolates; this combination displayed 128- and >32-fold lower MIC_{90} values when compared to meropenem alone against ESBL-phenotype and CRE isolate subsets, respectively (Figure 1).
- Meropenem/RPX7009 inhibited all *E. coli* isolates (n=374) at ≤1 µg/ml and 99.5% of the *K. pneumoniae* isolates at the same concentration (Table 1). Only one *K. pneumoniae* strain displayed a meropenem/RPX7009 MIC at 2 µg/ml and meropenem alone at 8 µg/ml. All *K. oxytoca* (n=35) isolates were inhibited by meropenem/RPX7009 at ≤0.03 µg/ml.
- *Enterobacter cloacae* (n=84), *E. aerogenes* (n=28) and *Citrobacter freundii* (n=17) isolates were inhibited by meropenem/RPX7009 at ≤0.06 µg/ml, whereas *P. mirabilis* (n=35), indole-positive Proteae (n=19) and *Serratia* spp. (n=52) isolates were inhibited by this combination at ≤0.25 µg/ml (Table 1).
- Selected comparator antimicrobial agents were also very active against Enterobacteriaceae isolates with susceptibility rates ranging from 77.4 to 99.1% and 75.8 to 98.7% applying the CLSI and EUCAST breakpoints, respectively. The lowest susceptibility rates were noted for levofloxacin and the highest for amikacin (Table 2).
- As expected, ESBL-phenotype isolates displayed diminished susceptibility rates to β-lactam agents, levofloxacin (22.2-23.2% susceptible), and slightly lower rates for amikacin (90.9 to 91.9% susceptible; Table 2) when compared to the overall Enterobacteriaceae collection.
- CRE strains were highly resistant to comparator agents and the highest susceptibility rates were observed for amikacin (53.3 and 53.3% susceptible; CLSI and EUCAST criteria, respectively), colistin (73.3%; EUCAST criteria), and tigecycline (100.0 and 86.7%, USA-FDA and EUCAST criteria; Table 2). Meropenem/RPX7009 displayed the highest activity among tested agents against these isolates.

Table 1. Activity of meropenem/RPX7009 when tested at fixed 8 µg/ml against 854 Enterobacteriaceae isolates collected from BSI in USA hospitals during 2014.

Organism/Subsets	No. of isolates	No. of isolates inhibited by meropenem/RPX7009 (cumulative %; µg/ml)									MIC (µg/ml)	
		≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	≥4	50%	90%
Enterobacteriaceae	854	534 (62.5)	251 (91.9)	48 (97.5)	10 (98.7)	4 (99.2)	4 (99.6)	2 (99.9)	1 (100.0)		≤0.015	0.03
ESBL-phenotype	99	69 (69.7)	17 (86.9)	2 (88.9)	2 (90.9)	2 (92.9)	4 (97.0)	2 (99.0)	1 (100.0)		≤0.015	0.12
CRE	15	1 (6.7)	6 (46.7)	1 (53.3)	1 (60.0)	0 (60.0)	3 (80.0)	2 (93.3)	1 (100.0)		0.06	1
Escherichia coli	374	345 (92.2)	24 (98.7)	3 (99.5)	0 (99.5)	1 (99.7)	0 (99.7)	1 (100.0)			≤0.015	≤0.015
ESBL-phenotype *E. coli*	62	54 (87.1)	5 (95.2)	1 (96.8)	0 (96.8)	1 (98.4)	0 (98.4)	1 (100.0)			≤0.015	0.03
Klebsiella pneumoniae	187	88 (47.1)	88 (94.1)	2 (95.2)	2 (96.3)	1 (96.8)	4 (98.9)	1 (99.5)	1 (100.0)		0.03	0.03
ESBL-phenotype *K. pneumoniae*	33	12 (36.4)	11 (69.7)	1 (72.7)	2 (78.8)	1 (81.8)	4 (93.9)	1 (97.0)	1 (100.0)		0.03	0.5
Klebsiella oxytoca	35	16 (45.7)	19 (100.0)								0.03	0.03
Enterobacter cloacae species complex	84	55 (65.5)	27 (97.6)	2 (100.0)							≤0.015	0.03
Enterobacter aerogenes	28	8 (28.6)	19 (96.4)	1 (100.0)							0.03	0.03
Citrobacter freundii species complex	17	10 (58.8)	6 (94.1)	1 (100.0)							≤0.015	0.03
Proteus mirabilis	35		15 (42.9)	12 (77.1)	6 (94.3)	2 (100.0)					0.06	0.12
Indole-positive *Proteus* spp.	19		7 (36.8)	11 (94.7)	1 (100.0)						0.06	0.06
Serratia spp.	52	1 (1.9)	34 (67.3)	16 (98.1)	1 (100.0)						0.03	0.06

Figure 1. Comparative activity of meropenem and meropenem/RPX7009 (using inhibitor at fixed 8 µg/ml) when tested against Enterobacteriaceae isolates and resistant subsets.

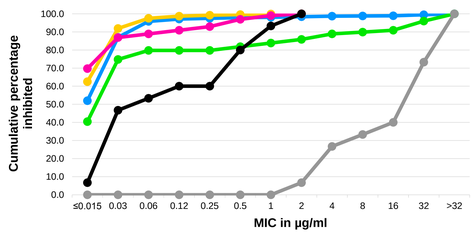

Table 2. Activity of meropenem/RPX7009 and comparator antimicrobial agents when tested against 854 isolates of Enterobacteriaceae collected from bloodstream infections during 2014 in USA hospitals.

Organism (no. tested)/ Antimicrobial Agent	MIC (µg/ml)			CLSI[a]			EUCAST[a]		
	50%	90%	Range	%S	%I	%R	%S	%I	%R
All Enterobacteriaceae (n=854)									
Meropenem/RPX7009	≤0.015	0.03	≤0.015 — 2	-	-	-	-	-	-
Meropenem	≤0.015	0.06	≤0.015 — >32	98.1	0.2	1.6	98.4	0.5	1.2
Imipenem	≤0.12	1	≤0.12 — >8	95.2	2.7	2.1	97.9	1.1	1.1
Cefepime	≤0.5	4	≤0.5 — >16	89.6	3.0[b]	7.4	88.4	2.8	8.8
Ceftazidime	0.25	16	0.03 — >32	87.1	1.9	11.0	85.0	2.1	12.9
Piperacillin/tazobactam	2	16	≤0.5 — >64	92.5	3.4	4.1	88.8	3.7	7.5
Amikacin	1	4	≤0.25 — >32	98.9	0.8	0.2	98.7	0.2	1.1
Colistin	≤0.5	>8	≤0.5 — >8	-	-	-	85.8	-	14.2
Levofloxacin	≤0.12	>4	≤0.12 — >4	77.4	0.6	22.0	75.8	1.5	22.6
Tigecycline	0.12	0.5	0.03 — 4	99.1[c]	0.9[c]	0.0[c]	96.1	2.9	0.9
***Escherichia coli* (n=374)**									
Meropenem/RPX7009	≤0.015	≤0.015	≤0.015 — 1	-	-	-	-	-	-
Meropenem	≤0.015	0.03	≤0.015 — 4	99.7	0.0	0.3	99.7	0.3	0.0
Imipenem	≤0.12	≤0.12	≤0.12 — 1	100.0	0.0	0.0	100.0	0.0	0.0
Cefepime	≤0.5	8	≤0.5 — >16	86.6	3.7[b]	9.6	85.8	2.9	11.2
Ceftazidime	0.25	16	0.03 — >32	86.9	2.7	10.4	84.0	2.9	13.1
Piperacillin/tazobactam	2	8	≤0.5 — >64	94.7	2.9	2.4	91.2	3.5	5.3
Amikacin	2	4	≤0.25 — >32	99.5	0.3	0.3	99.5	0.0	0.5
Colistin	≤0.5	≤0.5	≤0.5 — 2	-	-	-	100.0	-	0.0
Levofloxacin	≤0.12	>4	≤0.12 — >4	62.0	0.3	37.7	61.2	0.8	38.0
Tigecycline	0.06	0.12	0.03 — 1	100.0[c]	0.0[c]	0.0[c]	100.0	0.0	0.0
***Klebsiella pneumoniae* (n=187)**									
Meropenem/RPX7009	0.03	0.03	≤0.015 — 2	-	-	-	-	-	-
Meropenem	0.03	0.06	≤0.015 — >32	92.0	1.1	7.0	93.0	1.6	5.3
Imipenem	≤0.12	0.5	≤0.12 — >8	92.5	0.5	7.0	93.0	2.1	4.8
Cefepime	≤0.5	16	≤0.5 — >16	85.6	2.7[b]	11.8	84.5	1.6	13.9
Ceftazidime	0.12	32	0.03 — >32	84.5	0.5	15.0	84.0	0.5	15.5
Piperacillin/tazobactam	4	32	≤0.5 — >64	88.2	3.7	8.0	80.7	7.5	11.8
Amikacin	1	2	≤0.25 — 32	96.8	3.2	0.0	96.3	0.5	3.2
Colistin	≤0.5	1	≤0.5 — >8	-	-	-	97.3	-	2.7
Levofloxacin	≤0.12	>4	≤0.12 — >4	87.6	0.0	12.4	86.0	1.6	12.4
Tigecycline	0.25	0.5	0.06 — 2	100.0[c]	0.0[c]	0.0[c]	96.8	3.2	0.0
ESBL-phenotype (n=99)									
Meropenem/RPX7009	≤0.015	0.12	≤0.015 — 2	-	-	-	-	-	-
Meropenem	0.03	16	≤0.015 — >32	83.8	2.0	14.1	85.9	4.0	10.1
Imipenem	≤0.12	8	≤0.12 — >8	85.9	1.0	13.1	86.9	4.0	9.1
Cefepime	16	>16	≤0.5 — >16	23.2	18.2[b]	58.6	19.2	13.1	67.7
Ceftazidime	16	>32	0.12 — >32	19.2	11.1	69.7	7.1	12.1	80.8
Piperacillin/tazobactam	8	>64	1 — >64	65.7	12.1	22.2	50.5	15.2	34.3
Amikacin	2	8	0.5 — >32	91.9	7.1	1.0	90.9	1.0	8.1
Colistin	≤0.5	≤0.5	≤0.5 — >8	-	-	-	95.9	-	4.1
Levofloxacin	>4	>4	≤0.12 — >4	23.2	0.0	76.8	22.2	1.0	76.8
Tigecycline	0.12	1	0.06 — 2	100.0[c]	0.0[c]	0.0[c]	94.9	5.1	0.0
CRE (n=15)									
Meropenem/RPX7009	0.06	1	≤0.015 — 2	-	-	-	-	-	-
Meropenem	32	>32	2 — >32	0.0	6.7	93.3	6.7	26.7	66.7
Imipenem	>8	>8	1 — >8	13.3	0.0	86.7	13.3	26.7	60.0
Cefepime	>16	>16	1 — >16	6.7	6.7[b]	86.7	6.7	0.0	93.3
Ceftazidime	>32	>32	16 — >32	0.0	0.0	100.0	0.0	0.0	100.0
Piperacillin/tazobactam	>64	>64	64 — >64	0.0	6.7	93.3	0.0	0.0	100.0
Amikacin	8	32	0.5 — >32	53.3	40.0	6.7	53.3	0.0	46.7
Colistin	≤0.5	>8	≤0.5 — >8	-	-	-	73.3	-	26.7
Levofloxacin	>4	>4	≤0.12 — >4	13.3	0.0	86.7	13.3	0.0	86.7
Tigecycline	0.5	2	0.12 — 2	100.0[c]	0.0[c]	0.0[c]	86.7	13.3	0.0

a. Criteria as published by CLSI [2015] and EUCAST [2015].
b. Intermediate interpreted as susceptible-dose dependent (SDD).
c. Breakpoints from FDA Package Insert revised 12/2014.
d. "-" = criteria not available.

Conclusions

- Meropenem/RPX7009 was active against contemporary Enterobacteriaceae isolates collected from BSI in USA hospitals. Additionally, this compound displayed good activity against ESBL-phenotype and CRE isolates with MIC_{50} and MIC_{90} values that were lower than comparator agents.
- The dissemination of KPC-producing isolates in USA hospitals has been well documented. These CRE isolates are usually resistant to several available antimicrobial agents and recent case reports of colistin and/or tigecycline resistant KPC-producing isolates highlight the need for additional therapeutic options to treat infections caused by these isolates. Meropenem/RPX7009 demonstrated good activity against CRE BSI isolates collected in USA hospitals during 2014, and its further development appears warranted.

Disclosures

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