

In Vitro Activity of Doripenem Relative to Meropenem and Imipenem against Enterobacteriaceae and *P. aeruginosa* Isolates from Europe (2006-2007)

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ABSTRACT

Objective: Carbapenems are widely used to treat infections involving resistant Gram-negative pathogens due to their potent activity against extended spectrum beta-lactamase (ESBL)-producing enteric bacilli and *P. aeruginosa* (PA). Doripenem (DOR), a 1-beta-methyl carbapenem, is approved to treat complicated urinary tract infections (cUTI) and intra-abdominal infections (IAI) in the US, and is currently undergoing regulatory review for the treatment of cUTI and IAI in Europe (EU) and nosocomial pneumonia both in the US and EU. This study examined the *in vitro* activity of DOR relative to other currently available carbapenems against Gram-negative pathogens recently isolated from EU.

Methods: During 2006 and 2007, Enterobacteriaceae (EN) and PA isolates from patient specimens were collected from 28 laboratories in 11 EU countries. All isolates were centrally tested by broth microdilution against DOR, imipenem (IPM), and meropenem (MER) at Eurofins Medinet, Inc. (CLSI; M7-A7). Data were interpreted according to CLSI M100-S17 for IPM and MER. For DOR, there are no CLSI approved breakpoints.

Results:

Organism	Phenotype	Total n	DOR			IPM			MER			
			Mode	MIC ₅₀	MIC ₉₀	Mode	MIC ₅₀	MIC ₉₀	%S	Mode	MIC ₅₀	MIC ₉₀
EN	All	1,912	0.03	0.03	0.25	0.25	2	99.8	0.03	0.03	0.12	100
	CAZ S	1,656	0.03	0.03	0.12	0.25	2	99.9	0.03	0.03	0.06	100
	CAZ NS	256	0.03	0.06	0.25	0.5	2	99.2	0.03	0.06	0.25	100
PA	All	533	0.25	0.5	8	2	32	76.0	0.25	0.5	8	85.0
	CAZ S	421	0.25	0.25	2	2	8	85.3	0.25	0.5	4	92.4
	CAZ NS	112	8	4	32	32	32	41.1	4	4	32	57.1

CAZ, ceftazidime; S, susceptible; NS, nonsusceptible

By MIC_{50/90}, DOR and MER were similar in activity against the tested isolates and were superior to IPM, regardless of CAZ susceptibility. The MICs of DOR and MER were lower than IPM against the EN and PA tested.

Conclusions: EN from EU were highly susceptible (>99%) to the carbapenems tested, while susceptibility of PA ranged from 76% for IPM to 85% for MER, respectively. MICs of IPM were higher against both PA and EN than MICs of either DOR or MER, which were of similar activity by MIC_{50/90}. The increasing prevalence of carbapenemases among EN and the high-level resistance commonly encountered among PA highlight the importance of continued surveillance of carbapenem activity against these organisms.

BACKGROUND AND OBJECTIVE

Doripenem is a broad-spectrum 1-beta-methyl carbapenem with activity against *Pseudomonas aeruginosa* and ESBL-producing Enterobacteriaceae. It is indicated in the United States for adults requiring treatment of complicated intra-abdominal infections (IAI) and complicated urinary tract infections (cUTI), including pyelonephritis. Phase 3 studies have been completed for nosocomial pneumonia, including ventilator-associated pneumonia, and are under review by the Food and Drug Administration. To support the ongoing clinical development of doripenem in Europe, where it is currently under review by the EMEA for the aforementioned indications, and to detect any change in its activity profile against target pathogens, the current surveillance examined the activity of doripenem and comparator carbapenems against recent clinical isolates of Enterobacteriaceae and *P. aeruginosa* from Europe.

METHODS

In 2006 and 2007, Gram-negative clinical isolates were collected from 28 hospital laboratories in 11 European countries (France, Italy, Spain, the United Kingdom, Germany, Belgium, Czech Republic, Hungary, the Netherlands, Poland, and Sweden). A total of 1,912 Enterobacteriaceae (547 *Escherichia coli*, 412 *Klebsiella pneumoniae*, 254 *Proteus mirabilis*, 213 *Citrobacter* spp., 246 *Enterobacter* spp., and 240 *Serratia marcescens*) and 533 *P. aeruginosa* isolates were centrally tested by broth microdilution against doripenem, imipenem, and meropenem at Eurofins Medinet, Inc., according to CLSI M7-A7 guidelines. Data were analyzed according to resistant phenotypes and interpreted according to CLSI M100-S17 for imipenem and meropenem. Currently, there are no CLSI or EUCAST approved breakpoints for doripenem.

RESULTS

- Against all Enterobacteriaceae, doripenem was more potent by MIC₅₀ and MIC₉₀ than imipenem and exhibited comparable MIC activity to that of meropenem. Doripenem had an overall MIC₉₀ of 0.25 mg/L (Table 1, Figure 1a).
- For both ceftazidime-susceptible and nonsusceptible Enterobacteriaceae overall, the MIC₅₀ and MIC₉₀ of doripenem were identical or differed by only one doubling dilution (Table 1, Figure 1b-c).
- Doripenem was active against ESBL screen-positive isolates of *E. coli* (MIC₉₀ of 0.06 mg/L), *K. pneumoniae* (MIC₉₀ of 0.12 mg/L), and *P. mirabilis* (MIC₉₀ of 0.5 mg/L) (Table 1).

Table 1. MIC (mg/L) activity of doripenem and comparator carbapenems against Enterobacteriaceae

Organism	Agent	Phenotype ^a	Total n	MIC (mg/L)							
				Range	Mode	MIC ₅₀	MIC ₉₀	nS (%S)	nl (%)	nR (%R)	
Enterobacteriaceae	Doripenem	All	1,912	≤0.015-4	0.03	0.03	0.25	— ^b	—	—	
		CAZ S	1,656	≤0.015-4	0.03	0.03	0.12	—	—	—	
		CAZ NS	256	≤0.015-1	0.03	0.06	0.25	—	—	—	
	Imipenem	All	1,912	≤0.015-32	0.25	0.25	2	1,908 (99.8)	3 (0.2)	1 (0.1)	
		CAZ S	1,656	≤0.015-32	0.25	0.25	2	1,654 (99.9)	1 (0.1)	1 (0.1)	
		CAZ NS	256	0.12-8	0.25	0.5	2	254 (99.2)	2 (0.8)	0 (0)	
Meropenem	All	1,912	≤0.015-4	0.03	0.03	0.12	1,912 (100)	0 (0)	0 (0)		
	CAZ S	1,656	≤0.015-4	0.03	0.03	0.06	1,656 (100)	0 (0)	0 (0)		
	CAZ NS	256	≤0.015-4	0.03	0.06	0.25	256 (100)	0 (0)	0 (0)		
<i>E. coli</i>	Doripenem	All	547	≤0.015-0.25	0.03	0.03	0.06	—	—	—	
		CAZ S	511	≤0.015-0.25	0.03	0.03	0.06	—	—	—	
		CAZ NS	36	≤0.015-0.12	0.03	0.03	0.06	—	—	—	
	Imipenem	All	547	≤0.015-4	0.25	0.25	0.25	547 (100)	0 (0)	0 (0)	
		CAZ S	511	≤0.015-4	0.25	0.25	0.25	511 (100)	0 (0)	0 (0)	
		CAZ NS	36	0.12-0.5	0.25	0.25	0.5	36 (100)	0 (0)	0 (0)	
	Meropenem	All	547	≤0.015-0.12	≤0.015	≤0.015	0.03	547 (100)	0 (0)	0 (0)	
		CAZ S	511	≤0.015-0.12	≤0.015	≤0.015	0.03	511 (100)	0 (0)	0 (0)	
		CAZ NS	36	≤0.015-0.06	0.03	0.03	0.06	36 (100)	0 (0)	0 (0)	
	<i>K. pneumoniae</i>	Doripenem	All	412	≤0.015-1	0.03	0.03	0.12	—	—	—
			CAZ S	346	≤0.015-0.25	0.03	0.03	0.06	—	—	—
			CAZ NS	66	0.03-1	0.03	0.06	0.12	—	—	—
Imipenem		All	412	≤0.015-2	0.25	0.25	0.5	412 (100)	0 (0)	0 (0)	
		CAZ S	346	≤0.015-2	0.25	0.25	0.5	346 (100)	0 (0)	0 (0)	
		CAZ NS	66	0.12-2	0.25	0.25	0.5	66 (100)	0 (0)	0 (0)	
Meropenem	All	412	0.12-2	0.25	0.25	0.5	71 (100)	0 (0)	0 (0)		
	CAZ S	346	≤0.015-0.12	0.03	0.03	0.03	346 (100)	0 (0)	0 (0)		
	CAZ NS	66	≤0.015-0.12	0.03	0.03	0.06	66 (100)	0 (0)	0 (0)		
<i>P. mirabilis</i>	Doripenem	All	254	≤0.015-4	0.25	0.25	0.5	—	—	—	
		CAZ S	242	≤0.015-4	0.25	0.25	0.5	—	—	—	
		CAZ NS	12	0.12-1	0.25	0.25	1	—	—	—	
	Imipenem	All	254	≤0.015-32	2	2	4	250 (98.4)	3 (1.2)	1 (0.4)	
		CAZ S	242	≤0.015-32	2	2	4	240 (99.2)	1 (0.4)	1 (0.4)	
		CAZ NS	12	2-8	4	4	8	10 (83.3)	2 (16.7)	0 (0)	
Meropenem	All	254	0.5-4	2	2	4	10 (100)	0 (0)	0 (0)		
	CAZ S	242	0.03-4	0.12	0.12	0.25	254 (100)	0 (0)	0 (0)		
	CAZ NS	12	0.06-4	0.12	0.12	2	12 (100)	0 (0)	0 (0)		
<i>Citrobacter</i> spp.	Doripenem	All	213	≤0.015-0.12	0.03	0.03	0.06	—	—	—	
		CAZ S	182	≤0.015-0.12	0.03	0.03	0.03	—	—	—	
		CAZ NS	31	0.03-0.12	0.03	0.06	0.12	—	—	—	
	Imipenem	All	213	0.12-4	0.25	0.5	1	213 (100)	0 (0)	0 (0)	
		CAZ S	182	0.12-4	0.25	0.25	1	182 (100)	0 (0)	0 (0)	
		CAZ NS	31	0.25-2	0.5	0.5	1	31 (100)	0 (0)	0 (0)	
Meropenem	All	213	≤0.015-0.25	0.03	0.03	0.06	213 (100)	0 (0)	0 (0)		
	CAZ S	182	≤0.015-0.06	0.03	0.03	0.03	182 (100)	0 (0)	0 (0)		
	CAZ NS	31	0.03-0.25	0.06	0.06	0.12	31 (100)	0 (0)	0 (0)		
<i>E. cloacae</i>	Doripenem	All	246	≤0.015-1	0.03	0.06	0.25	—	—	—	
		CAZ S	149	≤0.015-0.25	0.03	0.03	0.06	—	—	—	
		CAZ NS	97	0.03-1	0.06	0.12	0.5	—	—	—	
	Imipenem	All	246	0.12-4	0.5	0.5	1	246 (100)	0 (0)	0 (0)	
		CAZ S	149	0.12-4	0.5	0.5	1	149 (100)	0 (0)	0 (0)	
		CAZ NS	97	0.12-4	0.5	0.5	2	97 (100)	0 (0)	0 (0)	
Meropenem	All	246	≤0.015-1	0.03	0.03	0.25	246 (100)	0 (0)	0 (0)		
	CAZ S	149	≤0.015-0.12	0.03	0.03	0.06	149 (100)	0 (0)	0 (0)		
	CAZ NS	97	≤0.015-1	0.06	0.12	0.25	97 (100)	0 (0)	0 (0)		
<i>S. marcescens</i>	Doripenem	All	240	0.03-1	0.12	0.12	0.25	—	—	—	
		CAZ S	226	0.03-0.5	0.12	0.12	0.12	—	—	—	
		CAZ NS	14	0.03-1	0.25	0.12	0.5	—	—	—	
	Imipenem	All	240	0.25-4	1	1	2	240 (100)	0 (0)	0 (0)	
		CAZ S	226	0.25-4	1	1	2	226 (100)	0 (0)	0 (0)	
		CAZ NS	14	0.5-4	2	2	2	14 (100)	0 (0)	0 (0)	
Meropenem	All	240	≤0.015-2	0.06	0.06	0.12	240 (100)	0 (0)	0 (0)		
	CAZ S	226	≤0.015-2	0.06	0.06	0.12	226 (100)	0 (0)	0 (0)		
	CAZ NS	14	0.03-1	0.06	0.06	0.5	14 (100)	0 (0)	0 (0)		

^aCAZ, ceftazidime; S, susceptible; NS, nonsusceptible. ^bDashes indicate that CLSI and EUCAST interpretive breakpoints for susceptible (S), intermediate (I), and/or resistant (R) are not available. ^cESBL screen positive by CLSI criteria (MICs of ceftazidime or cefotaxime affected by clavulanate).

- Doripenem activity against ESBL-positive Enterobacteriaceae isolates was superior to that of imipenem and comparable to that of meropenem (Figure 1d).
- Against *P. aeruginosa*, doripenem had an overall MIC₅₀ of 0.5 mg/L and an MIC₉₀ of 8 mg/L.
- Doripenem had an MIC₉₀ of 2 mg/L against ceftazidime-susceptible *P. aeruginosa*, and an MIC₉₀ of 32 mg/L against ceftazidime-nonsusceptible and imipenem-nonsusceptible isolates (Table 2).
- Doripenem activity against *P. aeruginosa* was greater than that of imipenem and similar to that of meropenem, regardless of ceftazidime phenotype (Figure 2a-c).

Figure 1a-d. Cumulative percent of doripenem and comparator agent MICs against Enterobacteriaceae

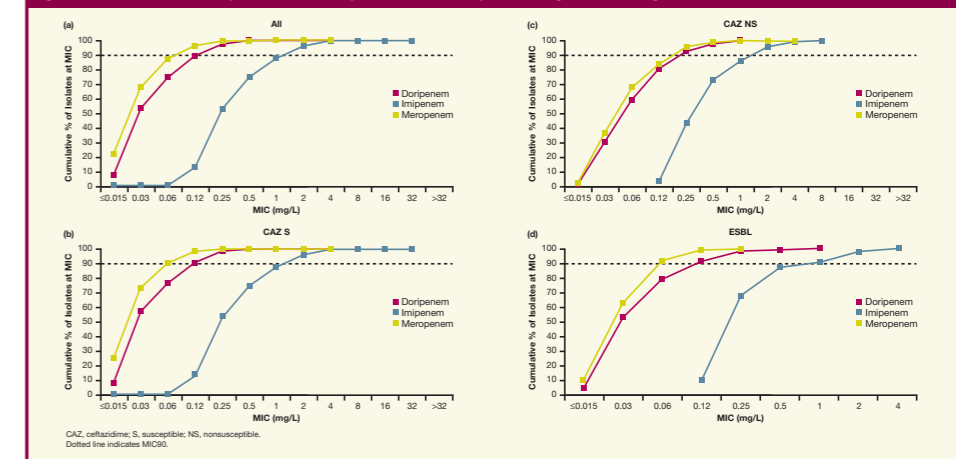
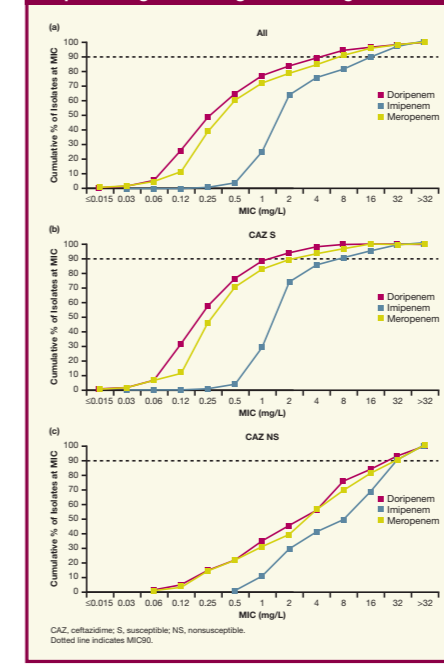


Table 2. MIC (mg/L) activity of doripenem and comparator carbapenems against *P. aeruginosa*

Organism	Agent	Phenotype ^a	Total n	MIC (mg/L)						
				Range	Mode	MIC ₅₀	MIC ₉₀	nS (%S)	nl (%)	nR (%R)
<i>P. aeruginosa</i>	Doripenem	All	533	≤0.015->32	0.25	0.5	8	— ^b	—	—
		CAZ S	421	≤0.015->32	0.25	0.25	2	—	—	—
		CAZ NS	112	0.06->32	8	4	32	—	—	—
	Imipenem	All	533	0.03->32	2	2	32	405 (76.0)	30 (5.6)	98 (18.4)
		CAZ S	421	0.03->32	2	2	8	359 (85.3)	21 (5.0)	41 (9.7)
		CAZ NS	112	0.5->32	32	16	32	46 (41.1)	9 (8.0)	57 (50.9)
Meropenem	All	533	8->32	16	16	>32	0 (0)	30 (23.4)	98 (76.6)	
	CAZ S	421	≤0.015->32	0.25	0.5	4	453 (85.0)	29 (5.4)	51 (9.6)	
	CAZ NS	112	0.06->32	4	4	32	389 (92.4)	15 (3.6)	17 (4.0)	
IPM NS	All	128	0.25->32	4	8	32	64 (57.1)	14 (12.5)	34 (30.4)	
	CAZ S	128	0.25->32	4	8	32	49 (38.3)	29 (22.7)	50 (39.1)	

^aCAZ, ceftazidime; IPM, imipenem; S, susceptible; NS, nonsusceptible. ^bDashes indicate that CLSI and EUCAST interpretive breakpoints for susceptible (S), intermediate (I), and/or resistant (R) are not available.

Figure 2a-c. Cumulative percent of doripenem and comparator agent MICs against *P. aeruginosa*



CONCLUSIONS

- The *in vitro* activity profile of doripenem was similar to that of meropenem and superior to that of imipenem against the tested Enterobacteriaceae and *P. aeruginosa*, regardless of resistance phenotype.
- Doripenem activity against ESBL isolates was not notably altered (MIC₅₀ and MIC₉₀ were equivalent or within one