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Antimicrobial Activities of Doripenem and Other Carbapenems Tested Against *Pseudomonas aeruginosa*, Other Non-fermentative Bacilli, and *Aeromonas* spp.

Thomas R. Fritsche, Helio S. Sader, Patricia A. Strabala, and Ronald N. Jones

JMI Laboratories, North Liberty, Iowa, USA

Thomas R. Fritsche, MD, PhD
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, IA 52317-9258
Tel: (319) 665-3370 • Fax: (319) 665-3371
E-mail: thomas-fritsche@jmilabs.com

ABSTRACT

Background: Doripenem (DOR), an investigational broad-spectrum parenteral carbapenem, is stable to most class A and C β-lactamases and to renal DHP-1. DOR displays a spectrum similar to meropenem (MEM) against Gram-negatives and to imipenem (IPM) against Gram-positives. This report summarizes DOR activity against prevalent non-fermentative bacilli (NFB) and *Aeromonas* spp. (AER), groups with heightened potential for rapid resistance emergence.

Methods: The collection included 5,968 non-duplicate clinical isolates submitted for the global DOR surveillance program (2003-2005; for species see Table). MIC results were determined using CLSI methods, and susceptibility (S) criteria (4 μg/mL used for DOR, equivalent to peer agents).

Results: Overall, DOR inhibited 85.0% of tested isolates, compared with 80.0% for MEM and 78.6% for IPM.

	MIC_{50} (μg/mL)/% at ≤4 μg/mL		
Organism (n)	**DOR**	**MEM**	**IPM**
P. aeruginosa (PSA; 3,875)	0.5/87.0	0.5/81.1	1/77.8
Other *Pseudomonas* spp. (PSP; 183)	0.5/91.3	1/83.1	1/84.2
Acinetobacter spp. (ASP; 1,204)	1/76.7	2/73.4	1/79.3
Achromobacter spp. (ACH; 36)	0.5/94.4	0.12/97.2	1/94.4
B. cepacia (BC; 64)	4/81.3	2/92.2	4/64.1
Aeromonas spp. (AER; 95)	0.5/97.9	0.25/98.9	1/92.6

DOR was 2-fold more potent than IPM and MEM against PSA and ASP, respectively, and 2-fold more potent than both against other PSP. DOR also inhibited 87% of PSA, compared with 81% for MEM and 78% for IPM. Among IPM- and MEM-resistant PSA, 26.9% and 28.5%, respectively, had DOR MIC values ≤4 μg/mL. MEM was 2-fold more potent than DOR against ACH (MIC_{90} values, 2 and 4 μg/mL, respectively) and BC (4 and 8 μg/mL). DOR and MEM provided similar and near-complete coverage against AER, both being superior to IPM.

Conclusions: Infections produced by PSA, other NFB, and AER often occur in the setting of severe patient debilitation and result in poor clinical outcomes. Given the limited therapy choices available for infections produced by these pathogens, DOR offers the potency and an enhanced spectrum worthy of continued, rapid development.

INTRODUCTION

Non-fermentative Gram-negative bacilli and others such as *Aeromonas* spp. can be found in moist environments and are ubiquitous around people, animals, plants, and water. These bacterial species are often recovered as nosocomial pathogens from patients with severe underlying medical conditions, and are frequent contaminants in hospital environments and therapeutic equipment. Nosocomial infections produced by these bacteria often occur in highly compromised patients and are associated with significant morbidity and mortality. Treatment of these infections has become more difficult due to the rising incidence of resistance to many of the commonly used therapeutic agents.

Doripenem (formerly S-4661 [Shionogi], currently a Johnson & Johnson product) is a broad-spectrum parenteral carbapenem in the late stages of clinical development. The microbiological and pharmacokinetic/pharmacodynamic features of doripenem have been described previously, and doripenem has been approved for use in Japan.[1] Several recent studies have shown that doripenem incorporates the most favorable characteristics of the carbapenem class by combining the superior in vitro activities of imipenem against Gram-positive cocci and of meropenem against Gram-negative pathogens.[2-8] In a study of multidrug-resistant pathogens, doripenem retained the greatest potency among carbapenems against ESBL- and AmpC-producing enteric bacilli, as well as against penicillin-resistant *Streptococcus pneumoniae*. Also, a greater proportion of carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter* spp. isolates have been shown to be inhibited by doripenem at ≤4 μg/mL. When compared with several other antipseudomonal agents, including other carbapenems, doripenem was associated with the lowest rate of spontaneously occurring resistance.[9]

This report summarizes the activity of doripenem and selected comparator compounds when tested against a collection of *P. aeruginosa*, other non-fermentative Gram-negative bacilli, and *Aeromonas* spp., a group of opportunistic pathogens with recognized resistance profiles to commonly used antimicrobial agents.

MATERIALS AND METHODS

Organism Collection

A total of 5,968 non-duplicate bacterial strains were collected from significant infections in patients hospitalized in Europe (29 sites), North America (34 sites), and South America (12 sites) during 2003 to 2005, and included *P. aeruginosa* (3,875 strains), other *Pseudomonas* spp. (183), *Acinetobacter* spp. (1,204), *Achromobacter* (formerly *Alcaligenes*) spp. (36), *Burkholderia cepacia* (64), and *Aeromonas* spp. (95). Organisms were identified locally and forwarded to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA), where the identification was confirmed and susceptibility testing performed.

Susceptibility Testing

Doripenem, imipenem, and meropenem were tested in validated microdilution trays in cation-adjusted Mueller-Hinton broth using the Clinical and Laboratory Standards Institute (CLSI) methods (M7-A7, 2006). All interpretations were by CLSI M100-S16 break point criteria or those of CLSI M45-A (for *Aeromonas* spp. only).[10-12] Quality control (QC) methods and recommended QC strains were those of CLSI M100-S16.

RESULTS

- For the entire collection of *P. aeruginosa*, other non-fermentative bacilli, and *Aeromonas* spp. tested (5,968 isolates), doripenem inhibited 85.0% at 4 μg/mL, compared with 80.0% for meropenem and 78.6% for imipenem (data not shown).
- Doripenem and meropenem (MIC_{50}, 0.5 μg/mL) were 2-fold more potent than imipenem against *P. aeruginosa*, and doripenem provided the broadest coverage by inhibiting 87.0% of isolates at 4 μg/mL, compared with 81.1% for meropenem and 77.8% for imipenem (Table 1).

Table 1. Summary of in vitro activity of doripenem, meropenem, and imipenem when tested against collections of non-fermentative bacilli and *Aeromonas* spp.

	MIC_{50} (μg/mL)/% at ≤4 μg/mL		
Organism (no. tested)	**Doripenem**	**Meropenem**	**Imipenem**
P. aeruginosa (3,875)	0.5/87.0	0.5/81.1	1/77.8
Other *Pseudomonas* spp. (183)	0.5/91.3	1/83.1	1/84.2
Acinetobacter spp. (1,204)	1/76.7	2/73.4	1/79.3
Achromobacter spp. (36)	0.5/94.4	0.12/97.2	1/94.4
B. cepacia (64)	4/81.3	2/92.2	4/64.1
Aeromonas spp. (95)	0.5/97.9	0.25/98.9	1/92.6

- Among tested comparators, only amikacin (88.4% susceptible) provided similar breadth of spectrum to that of doripenem against *P. aeruginosa* (Table 2).
- Among imipenem- and meropenem-resistant *P. aeruginosa*, 26.9% and 28.5%, respectively, had doripenem MIC values ≤4 μg/mL (data not shown).
- Doripenem and imipenem (MIC_{50}, 1 μg/mL) were 2-fold more potent than meropenem against *Acinetobacter* spp.; imipenem inhibited slightly more isolates at a concentration of ≤4 μg/mL (79.3% vs 76.7%). Only polymyxin B provided near-complete (99.7% susceptible) coverage of this organism group (Table 2).
- Against other *Pseudomonas* spp., doripenem was 2-fold more potent than either meropenem or imipenem (MIC_{50}, 0.5 μg/mL vs 1 μg/mL, respectively), and inhibited more isolates at a concentration of ≤4 μg/mL (91.3% vs 83.1% to 84.2%). Only amikacin provided equivalent coverage (91.8% susceptible; Table 2).
- The highest susceptibility rates for *Achromobacter* spp. were provided by the carbapenems (94.4% to 97.2% susceptible), piperacillin/tazobactam (100%), and trimethoprim/sulfamethoxazole (94.4%). Aminoglycosides and ciprofloxacin retained little activity (69.4% to 88.9% resistant) against this group.
- Meropenem, trimethoprim/sulfamethoxazole, and ceftazidime were the most active agents against *B. cepacia* (all >85% susceptible), followed by levofloxacin (82.8%) and doripenem (81.3% at ≤4 μg/mL).
- Doripenem and meropenem provided similar and near-complete inhibition (>97% inhibited at ≤4 μg/mL) against *Aeromonas* spp., both being superior to imipenem in potency and susceptibility rates (92.6%; Table 2). Other agents providing similar statistics included cefepime and aztreonam (96.8% susceptible) and amikacin (96.1%).

Table 2. In vitro activity of broad-spectrum antimicrobial agents when tested against *P. aeruginosa*, other non-fermentative bacilli, and *Aeromonas* spp.

	MIC (μg/mL)			% by Category[a]	
Organism (no. tested)/ antimicrobial agent	**50%**	**90%**	**Range**	**Susceptible**	**Resistant**
P. aeruginosa (3,875)					
Doripenem	0.5	8	≤0.06->8	-	-
Meropenem	0.5	>8	≤0.06->8	81.1	12.1
Imipenem	1	>8	≤0.5->8	77.8	12.0
Ceftazidime	4	>16	≤1->16	75.4	19.7
Cefepime	4	>16	≤0.12->16	76.2	11.5
Piperacillin/tazobactam	8	>64	≤0.5->64	82.1	17.9
Aztreonam	8	>16	≤0.12->16	65.6	20.3
Gentamicin	≤2	>8	≤2->8	76.4	20.4
Amikacin	4	32	≤0.25->32	88.4	8.6
Ciprofloxacin	0.25	>4	≤0.03->4	69.1	27.2
Trimethoprim/sulfamethoxazole	>2	>2	≤0.5->2	8.8	91.2
Polymyxin B	0.5	1	≤0.5->4	-	-
Other *Pseudomonas* spp. (183)					
Doripenem	0.5	4	≤0.06->8	-	-
Meropenem	1	8	≤0.06->8	83.1	6.6
Imipenem	1	8	≤0.12->8	84.2	8.2
Ceftazidime	2	>16	≤1->16	83.1	13.7
Cefepime	4	16	≤0.12->16	82.0	5.5
Piperacillin/tazobactam	8	>64	≤0.5->64	74.9	12.6
Aztreonam	8	>16	≤0.12->16	50.8	27.9
Gentamicin	≤2	>8	<2->8	84.2	15.3
Amikacin	2	16	≤0.25->32	91.8	4.9
Ciprofloxacin	0.12	>4	≤0.03->4	76.0	15.8
Trimethoprim/sulfamethoxazole	>2	>2	≤0.5->2	25.1	74.9
Polymyxin B	≤0.5	>4	≤0.5->4	-	-
Acinetobacter spp. (1,204)					
Doripenem	1	>8	≤0.06->8	-	-
Meropenem	2	>8	≤0.06->8	73.4	16.8
Imipenem	1	>8	≤0.5->8	79.3	17.2
Ceftazidime	>16	>16	≤1->16	36.2	57.1
Cefepime	16	>16	≤0.12->16	43.6	40.6
Piperacillin/tazobactam	>64	>64	≤0.5->64	36.0	52.0
Gentamicin	>8	>8	≤2->8	41.7	52.6
Amikacin	32	>32	≤0.25->32	49.4	46.1
Ciprofloxacin	>4	>4	≤0.03->4	34.1	65.3
Trimethoprim/sulfamethoxazole	>2	>2	≤0.5->2	38.5	61.5
Polymyxin B	≤0.5	0.5	≤0.5->4	99.7	0.3
Achromobacter spp. (36)					
Doripenem	0.5	4	0.12->16	-	-
Meropenem	0.12	2	≤0.06-8	97.2	0.0
Imipenem	1	4	0.5-8	94.4	0.0
Ceftazidime	4	16	≤1->16	86.1	2.8
Cefepime	16	>16	2->16	11.4	40.0
Piperacillin/tazobactam	1	1	≤0.5-8	100.0	0.0
Gentamicin	>8	>8	≤2->8	5.6	88.9
Amikacin	>32	>32	≤0.25->32	13.9	83.3
Ciprofloxacin	4	>4	≤0.06->4	8.3	69.4
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5->2	94.4	5.6
Polymyxin B	1	2	≤0.5-8	-	-
B. cepacia (64)					
Doripenem	4	8	0.12->8	-	-
Meropenem	2	4	0.06->8	92.2	6.2
Imipenem	4	8	<0.5->8	-	-
Ceftazidime	4	16	≤1->16	85.9	7.8
Cefepime	8	>16	≤0.12->16	-	-
Ticarcillin/clavulanate	>128	>128	≤0.16->128	9.1	81.8
Levofloxacin	2	>4	≤0.5->4	82.8	10.9
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5->2	88.6	11.4
Polymyxin B	>4	>4	≤0.5->4	-	-
Aeromonas spp. (95)					
Doripenem	0.5	2	≤0.06->8	-	-
Meropenem	0.25	1	≤0.06->8	98.9	1.1
Imipenem	1	4	≤0.5->8	92.6	5.3
Ceftazidime	≤1	4	≤1->16	92.6	4.3
Cefepime	≤0.12	0.5	≤0.12->16	96.8	3.2
Piperacillin/tazobactam	8	>64	1->64	55.3	14.9
Aztreonam	≤0.12	0.25	≤0.12->16	96.8	3.2
Gentamicin	<2	4	≤2->8	92.2	7.8
Amikacin	2	8	1->32	96.1	3.9
Ciprofloxacin	≤0.03	0.5	≤0.03->4	92.2	3.9
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5->2	82.4	17.6
Polymyxin B	1	>4	≤0.5->4	-	-

a. Break point criteria those of CLSI M100-S16 and CLSI M45-A (for *Aeromonas* spp. only) [2006]; - = no break points established.

CONCLUSIONS

- Infections produced by *P. aeruginosa*, other non-fermentative bacilli, and *Aeromonas* spp. occur in the setting of severe patient debilitation and can result in poor clinical outcomes, often due to concurrent multidrug resistance.
- In such circumstances, carbapenems are being increasingly used either as monotherapy or combination therapy, given their unique characteristics, which include broad spectrum, recognized safety profiles, potency, and β-lactamase stability.
- For the entire collection of *P. aeruginosa*, other non-fermentative bacilli, and *Aeromonas* spp. tested here, doripenem inhibited 85% at ≤4 μg/mL, compared with only 80% for meropenem and 78.6% for imipenem.
- Given the limited therapeutic choices available for infections produced by these pathogens, doripenem offers the potency and an enhanced spectrum worthy of continued, rapid development.

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