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Geographic Variations in the Activity of Doripenem and Other Broad-spectrum Agents: Results From an International Surveillance Program (2003-2005)

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AMENDED ABSTRACT[a]

Background: Doripenem (DOR) is a parenteral carbapenem (CARB) in late-stage clinical development; regional data assessing resistance is needed. We summarize the results of an international surveillance program comparing activity of DOR and other agents against contemporary pathogens.

Methods: Non-duplicate bacterial isolates (51,042; 57.2% bloodstream; 18.9% respiratory tract; 10.2% skin and skin structure; 13.7% other) were collected from >60 medical centers in North America (NA), Latin America (LA), and Europe (EU) during 2003-2005. Identifications were confirmed and all isolates were susceptibility (S) tested using CLSI methods against DOR, meropenem (MEM), imipenem (IPM), and comparators.

Results:

Organism (no. tested)	MIC (μg/mL) 50%	MIC (μg/mL) 90%	Cum. % inhibited at MIC (μg/mL) ≤1	2	4	8
S. aureus (OXA-S; 7,607)	≤0.06	≤0.06	>99	>99	100	100
CoNS* (OXA-S; 815)	≤0.06	≤0.06	>99	>99	100	100
BHS* (1,336)	≤0.06	≤0.06	100			
S. pneumoniae (SPN; 3,554)	≤0.06	0.5	>99	100		
H. influenzae (2,985)	0.06	0.25	>99	100		
E. coli (EC; 8,528)	≤0.06	≤0.06	100			
Klebsiella spp. (KSP; 3,837)	≤0.06	≤0.06	97	98	98	>99
Enterobacter spp. (2,211)	≤0.06	0.12	98	>99	>99	>99
P. aeruginosa (PSA; 3,874)	0.5	8	70	77	87	93
Acinetobacter spp. (1,204)	1	>8	54	68	77	87

*CoNS = coagulase-negative staphylococci; BHS = beta-hemolytic streptococci.

At MIC values of 0.25 μg/mL for SPN, 0.5 μg/mL for BHS, and 4 μg/mL for all others (equivalent to peer agents), DOR inhibited >95% of the top 10 pathogens recovered from all sources. DOR was broadly active against staphylococci and streptococci, and at least 2-fold more potent against PSA than either MEM or IPM (MIC_{90}/% ≤4 μg/mL: 8/87, >8/81, and >8/78, respectively) with PSA coverage in NA (94%) > EUR (85%) > LA (79%). Only polymyxin B (>99% S) and amikacin (88%) provided greater PSA coverage. While inter-regional increases in ESBL-screen rates were apparent (EC 2003/2005 [%]: NA 1.5/4.1, EU 4.9/7.1, and LA 11.1/15.7; KSP: NA 8.6/16.7, EU 19/26.5, and LA 33.5/48.6), DOR inhibited >99.9% of strains.

Conclusions: Emergence of resistance has created a critical need for accelerated drug development. DOR is a new CARB in clinical development showing a promising broad-spectrum profile, especially against non-fermentative bacilli and Enterobacteriaceae.

a. Amended to reflect a change in the number of isolates investigated.

INTRODUCTION

As an antimicrobial class, carbapenems are innately stable to most β-lactamases of Ambler classes A, C, and D and are widely used for serious infections involving resistant Enterobacteriaceae (including ESBL-producing and AmpC-overproducing isolates), anaerobes, *Pseudomonas aeruginosa,* and *Acinetobacter* spp. Only recently have plasmid-encoded β-lactamases been detected that are variably able to hydrolyze carbapenem agents, including—and most importantly—enzymes in Ambler class B (metallo-β-lactamase [MBL]; IMP, VIM, SPM, GIM, SIM series), class A (SME, NMC-A, IMI-1, KPC), and class D (OXA series). While often detected as part of clonal outbreaks, the situation has been gradually changing with the established presence of MBLs in areas such as Japan, South America, and Italy.

Doripenem (formerly S-4661), a parenteral carbapenem in late-stage clinical trials, confers β-lactamase stability and resistance to inactivation by renal dehydropeptidases. Earlier in vitro studies of this new carbapenem have shown the compound to have a spectrum and potency versus Gram-positive cocci most similar to imipenem, and a Gram-negative activity most like meropenem (eg, 2- to 4-fold greater than imipenem).[1-5]

While previous studies have focused on limited populations of targeted species, particularly resistant subsets or from specific anatomic sites of infection, current surveillance data assessing particular regional resistance characteristics are needed as the compound nears approval for clinical use. In this report, we summarize the results of an international surveillance testing program comparing the activity of doripenem and currently marketed carbapenems with other antimicrobial agents against clinical isolates submitted as part of a global (North America, South America, and Europe) protocol for the years 2003-2005. A total of 51,042 bacterial strains were tested by reference Clinical and Laboratory Standards Institute (CLSI; formerly NCCLS) methods, with susceptibilities to comparator agents interpreted by CLSI break point criteria (M100-S16, 2006).[6,7]

MATERIALS AND METHODS

Bacterial Strain Collection

A total of 51,042 non-duplicate consecutive clinical isolates were submitted from 59 to 64 medical centers located in North America, South America, and Europe as part of an international surveillance program. Isolates originated from patients with documented bloodstream, respiratory, skin and soft tissue, and urinary tract infections. The distribution of leading species and strains is presented in Table 1.

Table 1. Summary of the in vitro activity of doripenem against leading Gram-positive and -negative pathogens collected as part of a global surveillance program (2003 to 2005).

Organism (no. tested)	MIC (μg/mL) 50%	MIC (μg/mL) 90%	Cum. % inhibited at MIC (μg/mL) ≤1	2	4	8
S. aureus (oxacillin-susceptible; 7,607)	≤0.06	≤0.06	>99	>99	100	100
Coagulase-negative staphylococci (oxacillin-susceptible; 815)	≤0.06	≤0.06	>99	>99	100	100
β-Hemolytic streptococci (1,336)	≤0.06	≤0.06	100			
S. pneumoniae (3,554)	≤0.06	0.5	>99	100		
H. influenzae (2,985)	0.06	0.25	>99	100		
E. coli (8,528)	≤0.06	≤0.06	100			
Klebsiella spp. (3,837)	≤0.06	≤0.06	97	98	98	>99
Enterobacter spp. (2,211)	≤0.06	0.12	98	>99	>99	>99
P. aeruginosa (3,874)	0.5	8	70	77	87	93
Acinetobacter spp. (1,204)	1	>8	54	68	77	87

Susceptibility Test Methods

All strains were tested by the broth microdilution method using validated commercially prepared panels (TREK Diagnostics, Cleveland, Ohio) in cation-adjusted Mueller-Hinton broth (with 5% lysed horse blood added for testing of streptococci and Haemophilus Test Medium for testing of *Haemophilus influenzae*) against a variety of antimicrobial agents representing the most common classes and examples of drugs used in the empiric or directed treatment of the indicated pathogen. Interpretation of MIC results was in accordance with published CLSI criteria. Enterobacteriaceae with elevated MICs (≥2 μg/mL) for ceftazidime and/or ceftriaxone and/or aztreonam were considered as ESBL-producing phenotypes. Quality control strains utilized included *Escherichia coli* ATCC 25922 and 35218, *P. aeruginosa* ATCC 27853, *H. influenzae* ATCC 49247, *Staphylococcus aureus* ATCC 29213, and *Streptococcus pneumoniae* ATCC 49619.

RESULTS

- Doripenem was broadly active against oxacillin-susceptible staphylococci (*S. aureus* and coagulase-negative staphylococci, 100% at ≤4 μg/mL; Table 2). Among comparators, resistance was highest (5.6% to 9.1%) to levofloxacin.

Table 2. In vitro activity of doripenem in comparison with selected antimicrobial agents tested against isolates of staphylococci (oxacillin-susceptible) and streptococci.

Organism (no. tested)/ antimicrobial agent	MIC (μg/mL) 50%	MIC (μg/mL) 90%	MIC (μg/mL) Range	% by Category[a] Susceptible	% by Category[a] Resistant
S. aureus (7,607)					
Doripenem	≤0.06	≤0.06	≤0.06-4	-	-
Imipenem	≤0.5	≤0.5	≤0.5-4	100.0	0.0
Ceftriaxone	4	4	≤0.25->32	99.3	0.3
Ceftazidime	8	8	≤1->16	90.8	0.8
Cefepime	2	4	≤0.12->16	99.6	0.2
Piperacillin/tazobactam	1	2	≤0.12->256	99.7	0.3
Levofloxacin	≤0.5	≤0.5	≤0.5->4	94.0	5.6
Daptomycin	0.25	0.5	≤0.06-2	>99.9	-
Linezolid	2	2	0.12-2	100.0	-
Vancomycin	1	1	≤0.12-4	>99.9	0.0
CoNS (815)					
Doripenem	≤0.06	≤0.06	≤0.06-4	-	-
Imipenem	≤0.5	≤0.5	≤0.5-1	100.0	0.0
Ceftriaxone	2	4	≤0.25-32	98.7	0.0
Ceftazidime	4	8	≤1->16	95.7	0.7
Cefepime	1	2	≤0.12-8	100.0	0.0
Piperacillin/tazobactam	≤0.5	1	≤0.5-8	100.0	0.0
Levofloxacin	0.25	2	≤0.03->4	89.7	9.1
Daptomycin	0.25	0.5	≤0.06-4	99.8	-
Linezolid	1	1	0.12-2	100.0	-
Vancomycin	1	2	≤0.12-4	100.0	0.0
S. pneumoniae (3,554)					
Doripenem	≤0.06	0.5	≤0.06-2	-	-
Imipenem	≤0.5	≤0.5	≤0.5-1	67.7	1.5
Ertapenem	≤0.06	0.5	≤0.06->8	99.4	0.1
Penicillin	≤0.03	2	≤0.03->4	67.1	16.4
Ceftriaxone	≤0.25	1	≤0.25-8	97.6	0.6
Cefepime	≤0.12	1	≤0.12-4	95.7	0.3
Levofloxacin	1	1	≤0.03->4	99.0	0.9
Erythromycin	≤0.25	>8	≤0.25->8	71.4	27.9
Clindamycin	≤0.25	>2	≤0.25->2	84.4	15.0
Linezolid	1	1	≤0.12-2	100.0	-
Vancomycin	≤1	≤1	≤1	100.0	-
β-Hemolytic streptococci (1,336)					
Doripenem	≤0.06	≤0.06	≤0.06-0.25	-	-
Imipenem	≤0.5	≤0.5	≤0.5-1	-	-
Ertapenem	≤0.25	≤0.25	≤0.25-1	100.0	-
Penicillin	≤0.015	0.06	≤0.015-1	99.9	-
Ceftriaxone	≤0.25	≤0.25	≤0.25-16	99.5	-
Cefepime	≤0.12	≤0.12	≤0.12-16	99.7	-
Levofloxacin	0.5	1	0.06->4	99.6	0.4
Erythromycin	≤0.25	>2	≤0.25->2	78.2	21.4
Clindamycin	≤0.25	≤0.25	≤0.25->8	93.2	6.5
Daptomycin	≤0.06	0.25	≤0.06-0.5	100.0	-
Linezolid	1	1	0.25-2	100.0	-
Vancomycin	0.25	0.5	≤0.12-1	100.0	-

a. Break point criteria are those of CLSI M100-S16 [2006]; - = no break points established.

- Doripenem was also highly active against *S. pneumoniae* (MIC_{50}, ≤0.06 μg/mL and MIC_{90}, 0.5 μg/mL) and β-hemolytic streptococci ($MIC_{50/90}$, ≤0.06 μg/mL). Increased resistance to penicillin (16.4%) among *S. pneumoniae* resulted in elevated MIC_{90} results for most β-lactam antimicrobials (Table 2), most likely due to similarly targeted penicillin-binding proteins.
- Most *E. coli* (>99.9%), *Klebsiella* spp. (97.7%), and *Enterobacter* spp. (97.1%) isolates were inhibited by doripenem at concentrations ≤4 μg/mL (MIC_{90}, ≤0.06 to 0.12 μg/mL; Table 3). Rare isolates expressing KPC β-lactamases (eastern seaboard of the USA) or VIM MBLs (Europe) were discovered during the study period.
- Inter-regional increases in *E. coli* ESBL-screen positivity rates were apparent between 2003 and 2005.
  - — North America, 1.5% to 4.1%
  - — Europe, 4.9% to 7.1%
  - — Latin America, 11.1% to 15.7%
- Increases in ESBL rates for *Klebsiella* spp. were more problematic.
  - — North America, 8.6% to 16.7%
  - — Europe, 19.0% to 26.5%
  - — South America, 33.5% to 48.6%
- Doripenem inhibited >99% of these ESBL-screen–positive strains at ≤4 μg/mL.
- Doripenem ($MIC_{50/90}$, 0.5/8 μg/mL) was at least 2-fold more potent against *P. aeruginosa* than either meropenem or imipenem ($MIC_{50/90}$, 0.5/>8 and 1/>8 μg/mL, respectively) and inhibited a greater percentage of isolates at ≤4 μg/mL (87.0%, 81.1%, and 77.8%, respectively; Table 3).
  - — Breadth of coverage was
    - ▪ Greatest in North America (94%)
    - ▪ Less in Europe (85%) and South America (79%)
  - — Only polymyxin B (99.9% susceptible) and amikacin (88.4%) provided greater coverage of *P. aeruginosa*
- Against *Acinetobacter* spp. isolates, the carbapenems (73.4% to 79.3% susceptible) and polymyxin B (99.7%) were most active, whereas greatest resistance was noted with ceftazidime (57.1%), piperacillin/tazobactam (52.0%), and levofloxacin (49.5%).
- *H. influenzae* were readily inhibited by all tested β-lactamase–stable agents (≥99.9% susceptible); among carbapenems, ranking of potency was ertapenem (MIC_{90}, 0.06 μg/mL) > meropenem (0.12 μg/mL) > doripenem (0.25 μg/mL) > imipenem (1 μg/mL).

Table 3. In vitro activity of doripenem in comparison to selected antimicrobial agents tested against isolates of *Enterobacteriaceae*, non-fermentative Gram-negative bacilli, and *H. influenzae*.

Organism (no. tested)/ antimicrobial agent	MIC (μg/mL) 50%	MIC (μg/mL) 90%	MIC (μg/mL) Range	% by Category[a] Susceptible	% by Category[a] Resistant
E. coli (8,528)					
Doripenem	≤0.06	≤0.06	≤0.06-4	-	-
Meropenem	≤0.06	≤0.06	≤0.06-4	100.0	0.0
Imipenem	≤0.5	≤0.5	≤0.5->8	>99.9	<0.1
Ertapenem	≤0.06	≤0.06	≤0.06-4	>99.9	0.0
Piperacillin/tazobactam	2	4	≤0.12->256	95.6	2.1
Ceftriaxone	≤0.25	≤0.25	≤0.25->32	94.9	4.2
Ceftazidime	1	≤1	≤1->16	95.9	2.5
Cefepime	≤0.12	0.25	≤0.12->16	96.9	2.5
Levofloxacin	0.25	>4	≤0.03->4	83.0	14.8
Klebsiella spp. (3,835)					
Doripenem	≤0.06	≤0.06	≤0.06->16	-	-
Meropenem	≤0.06	≤0.06	≤0.06->16	98.6	0.9
Imipenem	≤0.5	≤0.5	≤0.5->8	98.7	0.9
Ertapenem	≤0.06	0.12	≤0.06->16	97.7	1.8
Piperacillin/tazobactam	2	>64	≤0.12->64	83.9	12.3
Ceftriaxone	≤0.25	>32	≤0.25->32	81.3	13.3
Ceftazidime	≤1	>16	≤1->16	83.5	13.6
Cefepime	≤0.12	16	≤0.12->16	88.7	8.7
Levofloxacin	≤0.5	>4	≤0.5->4	87.2	10.5
Enterobacter spp. (2,211)					
Doripenem	≤0.06	0.12	≤0.06-16	-	-
Meropenem	≤0.06	0.12	≤0.06->8	99.5	0.4
Imipenem	≤0.5	1	≤0.5->8	99.2	0.3
Ertapenem	≤0.06	1	≤0.06->16	97.1	1.5
Piperacillin/tazobactam	2	>64	≤0.12->64	78.2	10.5
Ceftriaxone	≤0.25	>32	≤0.25->32	75.5	15.1
Ceftazidime	≤1	>16	≤1->16	73.2	22.1
Cefepime	≤0.12	4	≤0.12->16	94.7	3.6
Levofloxacin	≤0.5	4	≤0.5->4	89.4	8.6
P. aeruginosa (3,875)					
Doripenem	0.5	8	0.015->16	-	-
Meropenem	0.5	>8	0.015->8	81.1	12.1
Imipenem	1	>8	≤0.12->8	77.8	12.0
Piperacillin/tazobactam	8	>64	≤0.12->64	82.1	17.9
Ceftazidime	4	>16	≤1->16	75.4	19.7
Cefepime	4	>16	≤0.12->16	76.2	11.5
Levofloxacin	0.5	>4	≤0.03->4	68.0	27.4
Tobramycin	0.5	>16	≤0.12->16	79.0	19.9
Amikacin	4	32	≤0.25->32	88.4	8.6
Polymyxin B	0.5	1	≤0.12->4	99.9	0.1
Acinetobacter spp. (1,204)					
Doripenem	1	>8	0.015->8	-	-
Meropenem	2	>8	0.015->8	73.4	16.8
Imipenem	1	>8	≤0.12->8	79.3	17.2
Ampicillin/sulbactam	8	32	≤0.25->32	51.8	34.9
Piperacillin/tazobactam	>64	>64	≤0.12->64	36.0	52.0
Ceftazidime	>16	>16	≤1->16	36.2	57.1
Cefepime	16	>16	≤0.12->16	43.6	40.6
Levofloxacin	4	>4	≤0.03->4	39.6	49.5
Tobramycin	2	>16	≤0.12->16	59.7	36.2
Amikacin	32	>32	≤0.25->32	49.4	46.1
Polymyxin B	≤0.5	≤0.5	≤0.5->4	99.7	0.3
H. influenzae (2,984)					
Doripenem	0.06	0.25	≤0.008-2	-	-
Meropenem	0.03	0.12	≤0.008-0.25	100.0	-
Imipenem	0.5	1	≤0.12-4	100.0	-
Ertapenem	0.03	0.06	≤0.008-0.25	100.0	-
Piperacillin/tazobactam	≤0.5	≤0.5	≤0.5-1	100.0	0.0
Ampicillin	≤0.5	>4	≤0.5->4	77.6	21.5
Amoxicillin/clavulanic acid	0.5	1	≤0.06-4	100.0	0.0
Ceftriaxone	≤0.008	0.015	≤0.008->16	>99.9	-
Cefepime	≤0.06	0.12	≤0.06->8	99.9	-
Levofloxacin	≤0.5	≤0.5	≤0.5	100.0	-

a. Break point criteria are those of CLSI M100-S16 [2006]; - = no break points established.

CONCLUSIONS

- At MIC values of 0.25 μg/mL for *S. pneumoniae*, 0.5 μg/mL for β-hemolytic streptococci, and 4 μg/mL for all other pathogens tested (equivalent to peer agents), doripenem inhibited >95% of the top 10 tested organisms (a total of 35,966 isolates) recovered from all sources in this international, multiyear collection (Table 1).
- Among Enterobacteriaceae, doripenem inhibited 99.6% of all isolates at ≤4 μg/mL.
- For the collection of *P. aeruginosa* tested here, doripenem inhibited 87.0% of isolates, compared with 81.1% for meropenem and only 77.8% for imipenem.
- Doripenem is a new carbapenem in clinical development showing a promising broad-spectrum profile, and displays particular strengths against non-fermentative bacilli and Enterobacteriaceae.

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