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Doripenem European Surveillance: Antimicrobial Activity Against 6,480 Contemporary Pathogens (2004)

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AMENDED ABSTRACT

Objective: To characterize the spectrum of activity and potency of doripenem (DOR) (formerly S-4661) and comparator agents against contemporary wild-type bacterial isolates from medical centers in Europe and the Middle East in 2004. DOR is a novel parenteral 1-β-methyl carbapenem in late-stage clinical development whose molecular structure confers stability to β-lactamases and resistance to renal dehydropeptidases.
Methods: The collection included 6,480 non-duplicate, consecutive clinical isolates from patients in 24 medical centers in Europe (21), Turkey (2), and Israel (1) that were submitted to the DOR surveillance program (2004) for identification, confirmation, and susceptibility testing. MIC values for >30 antimicrobials were determined using NCCLS broth microdilution methods (2003). A tentative DOR susceptible break point of ≤4 mg/L (≤0.25 mg/L for *S. pneumoniae*) was used for comparative purposes; CLSI (2005) criteria were used for other tested agents.
Results: Antimicrobial activities of DOR and other carbapenems versus selected isolates.

	MIC_{90} mg/L (% susceptible)		
Organism (no. tested)	**DOR**	**Meropenem**	**Imipenem**
S. aureus oxacillin-S (1,231)	0.06 (100)	0.12 (100)	≤0.12 (100)
CoNS oxacillin-S (528)	0.06 (99.1)	0.12 (100)	≤0.12 (100)
S. pneumoniae (603)	0.5 (82.4)	0.5 (81.8)	0.25 (82.9)*
H. influenzae (459)	0.25 (100)	0.06 (100)	1 (100)
Enterobacter spp. (215)	0.25 (98.1)	0.12 (98.1)	1 (97.2)
P. aeruginosa (491)	16 (82.7)	>8 (76.4)	>8 (72.7)
Acinetobacter spp. (149)	16 (54.4)	>8 (49.0)	>8 (51.0)

*Results for 70 isolates only.

DOR consistently displayed activity against staphylococci and streptococci (MIC_{90}, 0.06 and 0.5 mg/L) most similar to that of imipenem, and against *E. coli* and *Klebsiella* spp. (MIC_{90}, 0.06 and 0.5 mg/L, respectively, including 8.3% and 26.9% of strains that met ESBL screening criteria) most similar to that of meropenem. *Enterobacter* spp. isolates, including 35.8% that were ceftazidime-resistant (indicative of AmpC production), were also highly susceptible to DOR and other carbapenems (0.5 to 1.4% resistant). DOR also provided slightly enhanced coverage against *P. aeruginosa* (82.7% susceptible) and *Acinetobacter* spp. (54.4% susceptible) compared to other carbapenems. Carbapenem resistance among these latter strains is, however, a particularly worrisome development.
Conclusions: DOR is a new carbapenem with a competitive profile that incorporates both potent Gram-negative and Gram-positive activity, with enhanced activity against the commonly occurring non-fermentative gram-negative bacilli. Carbapenems are assuming a greater therapeutic role in many nations as multidrug resistance (including emergence of Ambler class A, C, and D β-lactamases) spreads, necessitating their accelerated development.

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 extended-spectrum β-lactamase [ESBL]-producing and AmpC overproducing isolates), anaerobes, *Pseudomonas aeruginosa,* and *Acinetobacter* spp. Only recently have β-lactamases been detected that are variably able to hydrolyze carbapenem agents, including—and most importantly—enzymes in Ambler class B (metallo-β-lactamase [MβL]; IMP, VIM, SPM, GIM, SIM series) but also 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 MβLs 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 on 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 (e.g., 2- to 4-fold greater than imipenem). 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 contemporary (2004) clinical isolates from medical centers in Europe and the Middle East. A total of 6,480 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.

MATERIALS AND METHODS

Bacterial Strain Collection. A total of 6,480 non-duplicate consecutive clinical isolates were submitted from 24 medical centers located in Europe (21 sites), Turkey (2 sites) and Israel (1 site) 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 species and groups is shown in Table 1.

Table 1. Distribution of species and groups.

Species	Strains
Enterobacteriaceae	1,813
Pseudomonas aeruginosa	491
Acinetobacter spp.	149
Stenotrophomonas maltophilia	61
Aeromonas spp.	19
Haemophilus influenzae	459
Staphylococcus aureus (25.1% oxacillin-resistant)	1,643
Coagulase-negative staphylococci (79.9% oxacillin-resistant)	528
Streptococci (3 groups)	830
Enterococcus spp.	389
Others	98

Susceptibility Test Methods. All strains were tested by the reference broth microdilution method in Mueller-Hinton broth (with 5% lysed horse blood added for testing of streptococci and Haemophilus Test Medium for testing of *Hemophilus 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 minimum inhibitory concentration (MIC) results was in accordance with CLSI criteria. Enterobacteriaceae with elevated MICs (≥2 mg/L) 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, *Streptococcus pneumoniae* ATCC 49619, and *Enterococcus faecalis* ATCC 29212.

RESULTS

- Doripenem was very active against the most common species of Enterobacteriaceae isolated (MIC_{90} values, 0.03 – 0.25; median MIC_{90}, 0.12 mg/L). Among the approved carbapenems, ≥95.8% of each species or group studied were susceptible (Table 2).
- At a break point of 4 mg/L (equivalent to that of peer agents), ≥97.5% of each Enterobacteriaceae spp. or group was inhibited by doripenem. This included the 8.3% and 26.9% of *E. coli* and *Klebsiella* spp., respectively, that met ESBL screening criteria (ceftazidime or ceftriaxone or aztreonam MIC values ≥2 mg/L).

Table 2. Antimicrobial activity of doripenem and five other broad-spectrum β-lactams tested against contemporary wild-type strains of Enterobacteriaceae.

		MIC (mg/L)			% by category[a]	
Organism (no. tested)	**Antimicrobial agent**	**50%**	**90%**	**Range**	**Susceptible**	**Resistant**
Escherichia coli (916)	Doripenem	0.03	0.03	≤0.008-0.25	100.0[b]	0.0
	Ertapenem	≤0.008	0.016	≤0.008-1	100.0	0.0
	Imipenem	≤0.12	≤0.12	≤0.12-1	100.0	0.0
	Meropenem	≤0.06	≤0.06	≤0.06-0.5	100.0	0.0
	Cefepime	≤0.12	0.25	≤0.12->16	96.5	2.9
	Piperacillin/ tazobactam	2	8	≤0.5->64	92.7	3.4
Klebsiella spp. (321)	Doripenem	0.03	0.06	0.016-16	99.7	0.3
	Ertapenem	≤0.008	0.12	≤0.008->16	98.8	0.3
	Imipenem	≤0.12	0.25	≤0.12-8	99.4	0.0
	Meropenem	≤0.06	≤0.06	≤0.06-8	99.4	0.0
	Cefepime	≤0.12	>16	≤0.12->16	86.3	12.1
	Piperacillin/ tazobactam	4	>64	≤0.5->64	79.8	15.9
Proteus mirabilis (107)	Doripenem	0.12	0.25	0.03-1	100.0	0.0
	Ertapenem	≤0.008	0.016	≤0.008-4	99.1	0.0
	Imipenem	1	2	≤0.12-4	100.0	0.0
	Meropenem	≤0.06	≤0.06	≤0.06-0.5	100.0	0.0
	Cefepime	≤0.02	0.25	≤0.12->16	96.3	3.7
	Piperacillin/ tazobactam	≤0.5	1	≤0.5-8	100.0	0.0
Citrobacter spp. (39)	Doripenem	0.03	0.12	0.03-4	100.0	0.0
	Ertapenem	≤0.008	0.25	≤0.008-4	97.4	0.0
	Imipenem	0.5	1	≤0.12-2	100.0	0.0
	Meropenem	≤0.06	≤0.06	≤0.06-2	100.0	0.0
	Cefepime	≤0.12	2	≤0.12->16	97.4	2.6
	Piperacillin/ tazobactam	4	>64	1->64	79.5	13.4
Enterobacter spp. (215)	Doripenem	0.06	0.25	0.016-16	98.1	1.4
	Ertapenem	0.06	1	≤0.008->16	95.8	2.8
	Imipenem	0.25	1	≤0.12->8	97.2	0.5
	Meropenem	≤0.06	0.12	≤0.06->8	98.1	1.4
	Cefepime	≤0.12	4	≤0.12->16	95.8	2.8
	Piperacillin/ tazobactam	4	>64	≤0.5->64	69.8	12.6
Serratia spp. (80)	Doripenem	0.12	0.25	0.06->16	97.5	2.5
	Ertapenem	0.03	0.06	0.016->16	97.5	2.5
	Imipenem	0.5	1	≤0.12->8	97.5	2.5
	Meropenem	≤0.06	≤0.06	≤0.06->8	97.5	2.5
	Cefepime	≤0.12	1	≤0.12->16	98.8	1.2
	Piperacillin/ tazobactam	2	64	1->64	78.8	8.7
Indole-positive *Proteae* (69)	Doripenem	0.12	0.25	0.03-2	100.0	0.0
	Ertapenem	0.016	0.03	≤0.008-2	100.0	0.0
	Imipenem	1	2	≤0.12-8	98.6	0.0
	Meropenem	≤0.06	0.12	≤0.06-1	100.0	0.0
	Cefepime	≤0.12	2	≤0.12->16	94.2	4.3
	Piperacillin/ tazobactam	≤0.5	2	≤0.5-16	100.0	0.0
Salmonella spp. (48)	Doripenem	0.06	0.06	0.016-0.12	100.0	0.0
	Ertapenem	≤0.008	≤0.008	≤0.008-0.016	100.0	0.0
	Imipenem	0.25	0.25	≤0.12-0.5	100.0	0.0
	Meropenem	≤0.06	≤0.06	≤0.06	100.0	0.0
	Cefepime	≤0.12	≤0.12	≤0.12	100.0	0.0
	Piperacillin/ tazobactam	4	4	1-8	100.0	0.0

a. Susceptibility criteria of the CLSI (2005).
b. Break points for doripenem (≤4/8/≥16 mg/L for S/I/R) are for comparative purposes only and based upon those for peer agents.

- Against Gram-positive cocci, doripenem was highly potent against oxacillin-susceptible *S. aureus* and oxacillin-susceptible CoNS (MIC_{90} values for both, 0.06 mg/L). In contrast, *E. faecalis* was marginally inhibited by doripenem ($MIC_{50/90}$ at 4 and 8 mg/L, respectively); none of the carbapenems displayed activity against *E. faecium* ($MIC_{50/90}$ at ≥16 mg/L) (Table 3).
- Doripenem was very active against *S. pneumoniae* (MIC_{50}, ≤0.008 mg/L and MIC_{90}, 0.5 mg/L), viridans group streptococci (MIC_{50}, 0.06 mg/L and MIC_{90}, 1 mg/L), and β-hemolytic streptococci (MIC_{50}, ≤0.008 mg/L and MIC_{90}, 0.03 mg/L). Despite resistance to penicillin among *S. pneumoniae* and viridans group streptococci (17.6% and 14.7%, respectively), no doripenem MIC value exceeded 4 mg/L.

Table 3. Antimicrobial activity of doripenem tested against Gram-positive organisms, compared to selected β-lactam agents.

		MIC (mg/L)			% by category[a]	
Organism (no. tested)	**Antimicrobial agent**	**50%**	**90%**	**Range**	**Susceptible**	**Resistant**
Staphylococcus aureus oxacillin-susceptible (1,231)	Doripenem	0.06	0.06	0.016-2	100.0[b]	0.0
	Ertapenem	0.12	0.25	0.016-8	99.9	0.1
	Imipenem	≤0.12	≤0.12	≤0.12-0.5	100.0	0.0
	Meropenem	0.12	0.12	≤0.06-2	100.0	0.0
	Piperacillin/ tazobactam	2	2	≤0.5-16	99.8	0.2
	Ceftriaxone	4	4	≤0.25-16	99.8	0.0
	Cefepime	2	4	0.25-8	100.0	0.0
Coagulase-negative staphylococci oxacillin-susceptible (106)	Doripenem	0.03	0.06	0.016->16	99.1	0.9
	Ertapenem	0.12	0.25	0.016->16	99.1	0.9
	Imipenem	≤0.12	≤0.12	≤0.12-0.25	100.0	0.0
	Meropenem	0.12	0.12	≤0.06-0.25	100.0	0.0
	Piperacillin/ tazobactam	≤0.5	1	≤0.5-2	100.0	0.0
	Ceftriaxone	2	4	0.5-8	100.0	0.0
	Cefepime	1	2	0.25-2	100.0	0.0
Enterococcus faecalis (263)	Doripenem	4	8	0.03->16	-	-
	Ertapenem	8	16	0.12->16	-	-
	Imipenem	1	4	≤0.12->8	-	-
	Meropenem	8	>8	0.12->8	-	-
	Ampicillin	2	4	1->16	99.2	0.8
	Levofloxacin	1	>4	0.06->4	71.1	28.9
	Vancomycin	1	2	0.25->16	98.9	1.1
E. faecium (126)	Doripenem	>16	>16	1->16	-	-
	Ertapenem	>16	>16	2->16	-	-
	Imipenem	>8	>8	0.5->8	-	-
	Meropenem	>8	>8	1->8	-	-
	Ampicillin	>16	>16	≤1->16	13.5	86.5
	Levofloxacin	>4	>4	0.5->4	21.4	71.4
	Vancomycin	1	>16	0.25->16	86.5	12.7
S. pneumoniae (603)	Doripenem	≤0.008	0.5	≤0.008-2	-	-
	Ertapenem	0.016	0.5	≤0.008-2	99.8	0.0
	Imipenem	≤0.12	0.25	≤0.12-0.5	82.9	0.0
	Meropenem	≤0.03	0.5	≤0.03-1	81.8	3.2
	Penicillin	≤0.016	2	≤0.016->4	67.7	17.6
	Ceftriaxone	0.03	1	≤0.008-2	83.1[c]	1.0
	Cefepime	≤0.06	1	≤0.06-2	79.4[c]	3.0
Viridans group streptococci (68)	Doripenem	0.06	1	≤0.008-4	-	-
	Ertapenem	0.12	2	≤0.008-8	-	-
	Imipenem	≤0.12	0.5	<0.12-2	-	-
	Meropenem	0.12	1	≤0.06-4	88.2	-
	Penicillin	0.12	4	≤0.016-8	54.4	14.7
	Ceftriaxone	≤0.25	4	≤0.25-16	85.3	10.3
	Cefepime	0.5	2	≤0.12-16	79.4	7.4
β-hemolytic streptococci (159)	Doripenem	≤0.008	0.03	≤0.008-0.06	-	-
	Ertapenem	0.016	0.03	≤0.008-0.06	100.0	-
	Imipenem	≤0.12	≤0.12	≤0.12	-	-
	Meropenem	≤0.06	≤0.06	≤0.06-0.12	100.0	-
	Penicillin	≤0.016	0.06	≤0.016-0.12	100.0	-
	Ceftriaxone	≤0.25	≤0.25	≤0.25-0.5	100.0	-
	Cefepime	≤0.12	≤0.12	≤0.12-0.25	100.0	-

a. Susceptibility criteria of the CLSI (2005); - = No break points have been established by the CLSI (2005).
b. Break points for doripenem (≤4/8/≥16 mg/L for S/I/R) are for comparative purposes only and based upon those for peer agents.
c. Meningitis break points.

- Doripenem exhibited enhanced potency (two-fold; MIC_{50}, 0.5 mg/L) among indicated carbapenems tested against *P. aeruginosa,* and was similar in potency to imipenem and meropenem against *Acinetobacter* spp. (Table 4).
  — Among imipenem- and meropenem-resistant *P. aeruginosa,* 21.5 and 13.6%, respectively, had doripenem MIC values of ≤4 mg/L.
- All agents tested were highly active against *H. influenzae* isolates (MIC_{90} values, ≤0.5 mg/L), regardless of β-lactamase production (100% susceptible).

Table 4. Comparative antimicrobial activity of doripenem tested against non-fermentative Gram-negative bacilli, and *H. influenzae* strains.

		MIC (mg/L)			% by category[a]	
Organism (no. tested)	**Antimicrobial agent**	**50%**	**90%**	**Range**	**Susceptible**	**Resistant**
Acinetobacter spp. (149)	Doripenem	4	16	0.03->16	54.4[b]	24.8
	Ertapenem	16	>16	≤0.008->16	-	-
	Imipenem	4	>8	≤0.12->8	51.0	44.3
	Meropenem	8	>8	≤0.06->8	49.0	33.6
	Cefepime	16	>16	≤0.12>16	34.9	45.6
	Piperacillin/ tazobactam	>64	>16	≤0.5->64	24.2	69.8
Pseudonomas aeruginosa (491)	Doripenem	0.5	16	0.03->16	82.7	10.6
	Ertapenem	8	>16	0.06->16	-	-
	Imipenem	1	>8	≤0.12->8	72.7	13.2
	Meropenem	1	>8	≤0.06->8	76.4	16.5
	Cefepime	4	>16	0.25->16	71.9	15.1
	Piperacillin/ tazobactam	8	>64	≤0.5->64	77.6	22.4
Haemophilus influenzae β-lactamase-negative (384)	Doripenem	0.06	0.25	≤0.008-1	-	-
	Meropenem	<0.03	0.12	≤0.03-0.25	100.0	-
	Ceftriaxone	≤0.008	≤0.008	≤0.008-0.5	100.0	-
	Cefepime	≤0.06	0.12	≤0.06-0.25	100.0	-
	Levofloxacin	≤0.03	≤0.03	≤0.03-0.06	100.0	-
β-lactamase-positive (75)	Doripenem	0.06	0.5	≤0.008-0.5	-	-
	Meropenem	≤0.03	0.06	≤0.03-0.25	100.0	-
	Ceftriaxone	≤0.008	≤0.008	≤0.008-0.03	100.0	-
	Cefepime	≤0.06	0.12	≤0.06-0.25	100.0	-
	Levofloxacin	≤0.03	≤0.03	≤0.03-0.06	100.0	-

a. Susceptibility criteria of the CLSI (2005);- = No break points have been established by the CLSI (2005).
b. Break points for doripenem (≤4/8/≥16 mg/L for S/I/R) are for comparative purposes only and based upon those for peer agents.

CONCLUSIONS

- Carbapenems are assuming a greater therapeutic role in many nations, as multidrug resistance (including emergence of Ambler class A, C, and D β-lactamases) spreads.
- Results of this European surveillance program identified doripenem as a promising broad-spectrum agent with certain potency advantages against *P. aeruginosa* and some Gram-positive cocci (streptococci), compared with other class agents.
- Doripenem appears to offer advantages in potency when compared with currently marketed carbapenems and other extended-spectrum β-lactams. Continued, accelerated, development in human clinical trials appears warranted.

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