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Doripenem (DOR) International Surveillance: Antimicrobial Activity Against 16,008 Contemporary Pathogens

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AMENDED ABSTRACT

Background: DOR is a broad-spectrum parenteral carbapenem with promising potency and pharmacokinetic characteristics that is in clinical trials. We summarize the results of testing DOR and comparators against contemporary isolates originating from North America, Europe and Latin America.

Methods: The collection included 16,008 non-duplicate clinical isolates submitted to the international DOR surveillance program (2003). MIC values for > 10 antimicrobials were determined using reference methods. A tentative DOR breakpoint of ≤ 4 µg/ml (0.25 µg/ml for S. pneumoniae [SPN]) was used for comparative purposes against other carbapenems.

Results: Antimicrobial activities of DOR and other carbapenems vs. selected isolates are in the table:

	MIC$_{90}$ (% susceptible; S)		
Organism (no.)	**DOR**	**Meropenem**	**Imipenem**
S. aureus Oxacillin-S (2,705)	0.06(100.0)	0.12(100.0)	≤0.5(100.0)
CoNS Oxacillin-S (297)	0.06(99.7)	0.12(99.7)	≤0.5(100.0)
SPN (885)	0.5(82.1)	0.5(81.4)	≤0.5(-)[a]
H. influenzae (1,853)	0.25(100.0)	0.12(100.0)	1(100.0)
E. coli (3,023)	0.03(100.0)	0.03(100.0)	≤0.5(100.0)
Klebsiella spp. (1,107)	0.06(99.5)	0.03(99.6)	≤0.5(99.7)
Enterobacter spp. (601)	0.12(100.0)	0.12(99.6)	1(99.7)
P. aeruginosa (829)	8(86.7)	16(83.5)	>8(80.7)
Acinetobacter spp. (155)	4(90.3)	8(89.7)	2(92.3)

a. Susceptible breakpoint not tested.

Conclusions: DOR is a potent carbapenem with a spectrum resembling currently marketed anti-pseudomonal carbapenems, but with documented enhanced activity against some non-fermentative Gram-negative bacilli. Like other carbapenems, DOR displays excellent activity against contemporary clinical isolates.

BACKGROUND

Doripenem (formerly S-4661) is a parenteral carbapenem with the chemical formula of (+)-(4R,5S,6S)-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-3[[3S,5S)-S-(sulfamoylaminomethyl) pyrrolidin-3-yl]thio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate that confers ß-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). A particular feature, attributed to the side chain at position 2, is greater activity among non-fermentative Gram-negative bacilli having multi-drug resistances. However, this new 1ß-methylcarbapenem like other carbapenems, remains unstable to the L1 enzyme produced by *Stenotrophomonas maltophilia* and metallo-ß-lactamases.

In this report, we summarize the results of an international (North America, Europe, and Latin America) surveillance testing program comparing the activity of doripenem and currently marketed carbapenems with other antimicrobial agents against contemporary, clinical isolates (2003). A total of 16,008 bacterial strains were tested by reference NCCLS [2003] methods with susceptibilities to comparator agents interpreted by NCCLS breakpoint criteria [2004].

MATERIALS AND METHODS

A total of 16,008 non-duplicate consecutive clinical isolates were submitted from greater than 70 medical centers located in the Americas and Europe as part of a global surveillance program. Isolates originated from patients with documented bloodstream, respiratory, skin and soft tissue, and urinary tract infections. The distribution of species and strains was as follows: Enterobacteriaceae (6,240 strains); *Pseudomonas aeruginosa* (829 strains); *Acinetobacter* spp., (155 strains); *Stenotrophomonas maltophilia* (80 strains); *Burkholderia cepacia* (20 strains); *Aeromonas* spp. (44 strains); *Haemophilus influenzae* (1,853 strains), *Moraxella catarrhalis* (108 strains); *Staphylococcus* spp. (3,711 strains; 3,002 oxacillin susceptible); *Enterococcus* spp. (1,474 strains); streptococci (1,435 strains; four groups); and other Gram-positives (59 strains).

All strains were tested by the reference broth microdilution method (NCCLS, 2003) in Mueller-Hinton broth (with 5% lysed horse blood added for testing of streptococci and Haemophilus Test Medium for testing of *H. 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. Dry-form microdilution panels and broth reagents were purchased from TREK Diagnostics (Cleveland, OH). Interpretation of quantitative MIC results was in accordance with NCCLS (2004) criteria. Enterobacteriaceae with elevated MICs (≥ 2 µg/ml) for ceftazidime and/or ceftriaxone and/or aztreonam were considered as extended-spectrum ß-lactamase-producing phenotypes according to NCCLS (2004) criteria; confirmatory disk-approximation tests were subsequently performed. 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 strains of Enterobacteriaceae (MIC$_{90}$s, 0.03 – 0.5; median MIC$_{90}$, 0.06 µg/ml), (Table 1).
- Against confirmed ESBL-producing *E. coli* (121 strains) and *Klebsiella* spp. (155 strains), doripenem and meropenem had identical MIC$_{90}$ values of 0.06 µg/ml (*E. coli*) and 0.12 µg/ml (*Klebsiella* spp.), which were lower than either ertapenem or imipenem and only two-fold higher then ESBL negative strains (data not shown). The inhibitor combination piperacillin/tazobactam had markedly reduced activity in these subsets.
- Against Gram-positive cocci, doripenem was potent against methicillin-susceptible *S. aureus* (MIC$_{90}$, 0.06 µg/ml) and methicillin-susceptible CoNS (MIC$_{90}$, 0.06 µg/ml). In contrast, *E. faecalis* were marginally inhibited by doripenem (MIC$_{50/90}$ at 4 and 8 µg/ml, respectively; Table 2).
- Doripenem was very active against *S. pneumoniae* (MIC$_{50}$, 0.016 µg/ml and MIC$_{90}$, 0.5 µg/ml), viridans group streptococci (MIC$_{50}$, 0.03 µg/ml and MIC$_{90}$, 0.5 µg/ml), and ß-haemolytic streptococci (MIC$_{50}$, ≤ 0.008 µg/ml and MIC$_{90}$, 0.03 µg/ml). Increased resistance to penicillin among *S. pneumoniae* and viridans group streptococci resulted in somewhat elevated doripenem results, but all MIC$_{90}$ values remained ≤ 0.5 µg/ml (Table 2).
- Several other organisms were also susceptible (MIC, ≤ 4 µg/ml) to doripenem including *Aeromonas* spp. (MIC$_{50}$, 0.5 µg/ml), *Micrococcus* spp. (MIC$_{90}$, 0.12 µg/ml), *Listeria* spp. (MIC$_{90}$, 0.25 µg/ml) and *Bacillus* spp. (MIC$_{50}$, 0.06 µg/ml), but not *Corynebacterium* spp. (MIC$_{90}$, > 16 µg/ml; data not shown).
- Doripenem exhibited excellent activity against non-fermentative Gram-negative bacilli (MIC$_{50}$, 0.5 µg/ml), *H. influenzae* (MIC$_{90}$, 0.25 µg/ml) and *M. catarrhalis* (MIC$_{90}$, 0.03 µg/ml). All of these pathogens had doripenem MIC results at ≤ 2 µg/ml, except a subset of multi-drug resistant *Acinetobacter* spp. and *Pseudomonas* spp. (Table 3).
- Meropenem and doripenem were the most active carbapenems against *B. cepacia* with MIC$_{50/90}$, of 2 and 4 µg/ml, and 2 and 8 µg/ml, respectively, followed by imipenem (4 and 8 µg/ml); *S. maltophilia* were very resistant to tested agents and particularly refractory to carbapenems (data not shown).

Table 1. Antimicrobial activity of doripenem (S-4661) and five other broad-spectrum ß-lactams tested against contemporary wild-type strains of Enterobacteriaceae.

		MIC (µg/ml)			% by category[a]	
Organism (no. tested)	**Antimicrobial agent**	**50%**	**90%**	**Range**	**Susceptible**	**Resistant**
E. coli (3,023)	Doripenem	0.03	0.03	≤0.008-1	-[b]	-
	Ertapenem	≤0.06	≤0.06	≤0.06-4	99.9	0.0
	Imipenem	≤0.5	≤0.5	≤0.5->8	>99.9	<0.1
	Meropenem	0.016	0.03	≤0.008-2	100.0	0.0
	Cefepime	≤0.12	≤0.12	≤0.12->16	97.6	2.0
	Piperacillin/Tazobactam	2	4	≤0.12->256	97.3	1.4
Klebsiella spp. (1,107)	Doripenem	0.03	0.06	0.016->16	-	-
	Ertapenem	≤0.06	≤0.06	≤0.06->8	98.8	0.8
	Imipenem	≤0.5	≤0.5	≤0.5->8	99.7	0.3
	Meropenem	0.03	0.03	≤0.008->16	99.6	0.2
	Cefepime	≤0.12	4	≤0.12->16	92.3	6.1
	Piperacillin/Tazobactam	2	32	≤0.12->256	88.2	8.6
P. mirabilis (307)	Doripenem	0.12	0.25	0.016-0.5	-	-
	Ertapenem	≤0.06	≤0.06	≤0.06-4	99.6	0.0
	Imipenem	1	2	≤0.5-8	99.7	0.0
	Meropenem	0.06	0.06	0.016-1	100.0	0.0
	Cefepime	≤0.12	≤0.12	≤0.12->16	98.0	1.6
	Piperacillin/Tazobactam	0.25	1	≤0.12-64	98.4	0.0
Citrobacter spp. (136)	Doripenem	0.03	0.06	≤0.008-2	-	-
	Ertapenem	≤0.06	0.12	≤0.06-4	99.2	0.0
	Imipenem	≤0.5	1	≤0.5->8	99.3	0.7
	Meropenem	0.03	0.06	≤0.008-4	100.0	0.0
	Cefepime	≤0.12	1	≤0.12->16	97.8	2.2
	Piperacillin/Tazobactam	2	32	0.5->256	88.2	4.4
Enterobacter spp. (601)	Doripenem	0.06	0.12	≤0.008-4	-	-
	Ertapenem	≤0.06	1	≤0.06->8	96.8	1.3
	Imipenem	≤0.5	1	≤0.5->8	99.7	0.2
	Meropenem	0.03	0.12	≤0.008-8	99.8	0.0
	Cefepime	≤0.12	4	≤0.12->16	95.7	3.2
	Piperacillin/Tazobactam	2	64	≤0.12->256	81.4	8.7
Serratia spp. (187)	Doripenem	0.12	0.25	0.03-1	-	-
	Ertapenem	≤0.06	0.12	≤0.06-0.5	100.0	0.0
	Imipenem	≤0.5	1	≤0.5-8	99.5	0.0
	Meropenem	0.03	0.06	0.016-0.25	100.0	0.0
	Cefepime	≤0.12	0.5	≤0.12->16	95.7	4.3
	Piperacillin/Tazobactam	2	32	0.5->256	89.8	1.6
Indole-positive *Proteae* (148)	Doripenem	0.12	0.5	0.03-1	-	-
	Ertapenem	≤0.06	≤0.06	≤0.06-0.12	100.0	0.0
	Imipenem	2	4	≤0.5-4	100.0	0.0
	Meropenem	0.06	0.12	0.016-0.5	100.0	0.0
	Cefepime	≤0.12	0.25	≤0.12->16	99.3	0.7
	Piperacillin/Tazobactam	0.5	4	≤0.12-64	99.3	0.0
Salmonella spp. (530)	Doripenem	0.06	0.06	0.016-0.25	-	-
	Ertapenem	≤0.06	≤0.06	≤0.06-0.12	100.0	0.0
	Imipenem	≤0.5	≤0.5	≤0.5-2	100.0	0.0
	Meropenem	0.03	0.03	0.016-0.5	100.0	0.0
	Cefepime	≤0.12	≤0.12	≤0.12->16	97.4	0.6
	Piperacillin/Tazobactam	4	4	0.5->256	96.0	3.6
Shigella spp. (161)	Doripenem	0.03	0.06	0.016-0.06	-	-
	Ertapenem	≤0.06	≤0.06	≤0.06	100.0	0.0
	Imipenem	≤0.5	≤0.5	≤0.5	100.0	0.0
	Meropenem	0.03	0.03	0.016-0.03	100.0	0.0
	Cefepime	0.25	0.5	≤0.12-1	100.0	0.0
	Piperacillin/Tazobactam	2	4	0.25-8	100.0	0.0

a. Susceptibility criteria of the NCCLS [2004].
b. - = No breakpoints have been established by the NCCLS [2004].

Table 2. Antimicrobial activity of doripenem (S-4661) tested against Gram-positive organisms, compared to selected ß-lactam agents.

		MIC (µg/ml)			% by category[a]	
Organism (no. tested)	**Antimicrobial agent**	**50%**	**90%**	**Range**	**Susceptible**	**Resistant**
Staphylococcus aureus oxacillin-susceptible (2,705)	Doripenem	0.06	0.06	≤0.008-4	-[b]	-
	Ertapenem	0.12	0.25	≤0.06->8	>99.9	0.0
	Imipenem	≤0.5	≤0.5	≤0.5-4	100.0	0.0
	Meropenem	0.12	0.12	0.016-4	100.0	0.0
	Piperacillin/Tazobactam	1	2	≤0.12-64	99.8	0.2
	Ceftriaxone	4	4	0.5->32	98.9	0.3
	Cefepime	2	4	≤0.12->16	99.0	0.5
Coag.-neg. staphylococci oxacillin-susceptible (297)	Doripenem	0.03	0.06	≤0.008-8	-	-
	Ertapenem	0.25	0.5	≤0.06->8	99.3	0.3
	Imipenem	≤0.5	≤0.5	≤0.5-1	100.0	0.0
	Meropenem	0.12	0.12	0.016-8	99.7	0.0
	Piperacillin/Tazobactam	0.25	1	≤0.12-4	100.0	0.0
	Ceftriaxone	2	4	≤0.25-32	98.3	0.0
	Cefepime	1	2	≤0.12-8	100.0	0.0
E. faecalis (1,206) and other non-*faecium* spp. (70)	Doripenem	4	8	≤0.008->16	-	-
	Ertapenem	8	>8	≤0.06->8	-	-
	Imipenem	1	4	≤0.5->8	-	-
	Meropenem	8	16	≤0.008->16	-	-
	Ampicillin	2	4	≤1->16	97.6	2.4
	Levofloxacin	1	>4	0.12->4	61.1	37.6
	Vancomycin	1	2	0.25->16	92.9	5.5
E. faecium (198)	Doripenem	>16	>16	0.03->16	-	-
	Ertapenem	>8	>8	8->8	-	-
	Imipenem	>8	>8	1->8	-	-
	Meropenem	>16	>16	4->16	-	-
	Ampicillin	>16	>16	≤1->16	8.6	90.4
	Levofloxacin	>4	>4	1->4	7.1	87.3
	Vancomycin	>16	>16	0.5->16	28.4	70.6
S. pneumoniae (885)	Doripenem	0.016	0.5	≤0.008-1	-	-
	Ertapenem	≤0.06	0.5	≤0.06->8	99.7	0.3
	Imipenem	≤0.5	≤0.5	≤0.5-1	-[c]	0.6
	Meropenem	0.016	0.5	≤0.008-2	81.4	5.1
	Penicillin	≤0.03	2	≤0.03->4	67.9	16.1
	Ceftriaxone	≤0.25	1	≤0.25-8	97.5	0.8
	Cefepime	≤0.12	1	≤0.12-4	94.9	0.5
viridans gr. streptococci (140)	Doripenem	0.03	0.5	≤0.008->16	-	-
	Ertapenem	0.12	1	≤0.06-4	-	-
	Imipenem	≤0.5	≤0.5	≤0.5-4	-	-
	Meropenem	0.06	0.5	≤0.008->16	90.7	-
	Penicillin	0.06	2	≤0.016-32	65.7	7.9
	Ceftriaxone	≤0.25	1	≤0.25-8	90.7	2.9
	Cefepime	0.25	1	≤0.12-8	90.7	1.4
ß-haemolytic streptococci (397)	Doripenem	≤0.008	0.03	≤0.008-0.25	-	-
	Ertapenem	≤0.06	≤0.06	≤0.06-1	100.0	-
	Imipenem	≤0.5	≤0.5	≤0.5-1	-	-
	Meropenem	≤0.008	0.06	≤0.008-0.5	100.0	-
	Penicillin	≤0.016	0.06	≤0.016-1	99.7	-
	Ceftriaxone	≤0.25	≤0.25	≤0.25-16	99.2	-
	Cefepime	≤0.12	≤0.12	≤0.12-16	99.5	-

a. Susceptibility criteria of the NCCLS [2004].
b. - = No breakpoints have been established by the NCCLS [2004].
c. Susceptible breakpoint not tested.

Table 3. Comparative antimicrobial activity of doripenem (S-4661) tested against non-fermentative Gram-negative bacilli, *H. influenzae* and *M. catarrhalis* strains.

		MIC (µg/ml)			% by category[a]	
Organism (no. tested)	**Antimicrobial agent**	**50%**	**90%**	**Range**	**Susceptible**	**Resistant**
Acinetobacter spp. (155)	Doripenem	0.5	4	0.016->16	-[b]	-
	Ertapenem	4	>8	≤0.06->8	-	-
	Imipenem	≤0.5	2	≤0.5->8	92.3	7.1
	Meropenem	1	8	≤0.016->16	89.7	7.7
	Cefepime	8	>16	≤0.12->16	57.4	29.7
	Piperacillin/Tazobactam	32	>256	≤0.12->256	49.7	43.9
P. aeruginosa (829)	Doripenem	0.5	8	0.03->16	-	-
	Ertapenem	8	>8	0.12->8	-	-
	Imipenem	1	>8	≤0.5->8	80.7	13.5
	Meropenem	0.5	16	0.016->16	83.5	11.7
	Cefepime	4	>16	≤0.12->16	76.6	11.6
	Piperacillin/Tazobactam	8	256	≤0.12->256	81.8	18.2
Haemophilus influenzae ß-lactamase-negative (1,426)	Doripenem	0.06	0.25	≤0.008-2	-	-
	Meropenem	0.03	0.12	≤0.008-0.25	100.0	-
	Ceftriaxone	≤0.008	0.016	≤0.008->16	99.9	-
	Cefepime	≤0.06	0.12	≤0.06->8	99.8	-
	Levofloxacin	≤0.03	≤0.03	≤0.03-0.12	100.0	-
Haemophilus influenzae ß-lactamase-positive (398)	Doripenem	0.12	0.25	≤0.008-1	-	-
	Meropenem	0.03	0.12	≤0.008-0.25	100.0	-
	Ceftriaxone	≤0.008	≤0.008	≤0.008-2	100.0	-
	Cefepime	≤0.06	0.12	≤0.06-1	100.0	-
	Levofloxacin	≤0.03	≤0.03	≤0.03-0.06	100.0	-
Moraxella catarrhalis (108)	Doripenem	0.016	0.03	≤0.008-0.5	-	-
	Meropenem	≤0.008	≤0.008	≤0.008-0.12	-	-
	Ceftriaxone	0.12	0.5	≤0.008-1	-	-
	Cefepime	0.5	1	≤0.06-4	-	-
	Levofloxacin	≤0.03	0.06	≤0.03-0.12	-	-

a. Susceptibility criteria of the NCCLS [2004].
b. - = No breakpoints have been established by the NCCLS [2004].

CONCLUSIONS

- Results of this 2003 international surveillance program identified doripenem as a potent carbapenem with a spectrum of activity resembling currently marketed, *Pseudomonas*-active carbapenems such as imipenem and meropenem.
- Doripenem's potency was superior overall to other carbapenems primarily versus many non-fermentative Gram-negative bacillus isolates and some Gram-positive cocci (streptococci).
- Doripenem was active against ESBL-producing *E. coli* and *Klebsiella* spp.; unlike ertapenem, MIC values for doripenem and meropenem only increased two-fold against these resistant strains.
- In summary, doripenem appears to offer advantages in potency, spectrum and stability to ß-lactamases when compared to currently marketed carbapenems and other extended spectrum ß-lactam agents. Continued development in human clinical trials appears warranted.

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