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Worldwide Summary of Doripenem Spectrum and Activity: Potencies Against Non-fermentative and Fastidious Gram-negative Pathogens

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Amended Abstract

Background: Doripenem (DOR) is a carbapenem approved in many countries for the treatment of nosocomial pneumonia, ventilator-associated pneumonia, complicated intra-abdominal infections, and complicated urinary tract infections. We report the in vitro antimicrobial activity of DOR tested against prevalent non-fermentative (NF) and fastidious Gram-negative (GN) pathogens isolated worldwide.

Methods: During 2003-2009, a total of 31,608 consecutive, non-duplicate isolates from a variety of infections were collected from the following regions (n countries; n isolates): Asia Pacific (13; 7,139), Europe (15; 10,010), Latin America (5; 5,049), and North America (2; 9,410). Susceptibility (S) testing was performed using CLSI methods (M07-A8, M100-S20-U) and EUCAST (2010) clinical breakpoints were used for susceptibility interpretation.

Results: DOR MIC_{50} (%susceptible/%resistant) against *Pseudomonas aeruginosa* (PA) and *Acinetobacter* spp. (ACIN) were 0.5 µg/ml (69%/14%) and 2 µg/ml (43%/40%), respectively. DOR was not active against *Stenotorphomonas maltophilia* (SMALT). DOR demonstrated high potency against *Haemophilus influenzae* (HI; $MIC_{50/90}$, ≤0.06/0.5 µg/ml) and *Moraxella catarrhalis* (MCAT; $MIC_{50/90}$, ≤0.06/≤0.06 µg/ml).

Conclusion: Against this very large global population of geographically and temporally (including contemporary [2009]) diverse collection of isolates, DOR exhibited moderate potency against many PA and ACIN, but not against SMALT, and high potency against HI and MCAT.

Introduction

Empiric antimicrobial therapy in healthcare settings that deal with a high proportion of seriously ill patients is becoming progressively more compromised by dramatic increases in the prevalence of extended spectrum β-lactamase (ESBL)-producing Enterobacteriaceae (primarily *Escherichia coli* and *Klebsiella* spp.), constitutively-expressed chromosomal AmpC (Bush group 1 enzymes in *Enterobacter* spp., *Citrobacter* spp and *Serratia* spp.), serine carbapenemases (primarily KPC in *Klebsiella* spp.), and multidrug-resistant (MDR) nonfermentative Gram-negative bacilli. Resistances to "third"- and "fourth-generation" cephalosporins, β-lactam/β-lactamase inhibitor combinations, fluoroquinolones and aminoglycosides have also become commonplace in various geographic regions, requiring the utilization of carbapenems, glycylcyclines, combination therapies or 'agents of last resort' such as the polymyxins.

As an antimicrobial class, carbapenems are innately stable to most β-lactamases of Ambler class A, C and D, and are widely used for serious infections involving resistant Enterobacteriaceae (including ESBL-producing and AmpC over-expressing isolates), anaerobes, *Pseudomonas aeruginosa* and *Acinetobacter* spp. Doripenem was recently approved in Europe and United States (USA) for treatment of complicated intraabdominal infections (cIAI), complicated urinary tract infections (cUTI) and in Europe and other countries including Turkey for hospital-acquired bacterial pneumonia (HABP) – including ventilator-associated bacterial pneumonia (VABP). The agent has a spectrum and potency versus Gram-positive cocci most similar to that of imipenem, and Gram-negative activity like that of meropenem (e.g. two- to four-fold greater than imipenem). The agent is highly β-lactamase stable, is resistant to inactivation by renal dehydropeptidases and, when compared with several other anti-pseudomonal agents, including other carbapenems, has the lowest rate of spontaneously occurring resistance.

In this study, we report *in vitro* testing results from a very large global collection of non-fermentative (NF) and fastidious Gram-negative (GN) pathogens collected between 2003-2009 in the SENTRY Antimicrobial Surveillance Program. Doripenem activity was also compared with that of other β-lactam agents and members of several antimicrobial classes used in the empiric or directed therapy of cIAI, cUTI and HABP (including VABP).

Materials and Methods

Bacterial Strain Collection. During 2003-2009, a total of 31,608 consecutive, non-duplicate non-fermentative (NF) and fastidious Gram-negative (GN) pathogens isolates from a variety of infections (including HABP, VABP, cIAI, and cUTI) were collected from 181 medical centers (35 countries) in four geographic regions (Table 1). Species identifications were performed by the submitting laboratories with confirmation performed by the central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA).

Susceptibility Test Methods. All isolates were tested for susceptibility by reference broth microdilution methods using the Clinical Laboratory Standards Institute recommendations (CLSI; M07-A8, 2009). Susceptibility testing was performed by using validated broth microdilution panels manufactured by TREK Diagnostics Systems/Sensititre (Cleveland, Ohio, USA) with cation-adjusted Mueller-Hinton broth or Haemophilus Test Medium. Validation of the minimum inhibitory concentration (MIC) values was performed by concurrent testing of CLSI-recommended (M100-S20-U, 2010) quality control (QC) strains, including *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, and *Haemophilus influenzae* ATCC 49247 and 49677. Categorical interpretation of comparator MIC values was performed according to CLSI (M100-S20-U, 2010) criteria, when available.

Results

- Polymyxin B was the most active antimicrobial agent tested against 13,168 *P. aeruginosa* ($MIC_{50/90}$, ≤1/≤1 µg/ml; 99.9% susceptible; Table 3). Doripenem ($MIC_{50/90}$, 0.5/8 µg/ml; Tables 2 and 3) was the second most active compound tested, being slightly more active than meropenem ($MIC_{50/90}$, 0.5/>8 µg/ml) and four-fold more active than imipenem ($MIC_{50/90}$, 2/>8 µg/ml). Resistance to the other compounds tested ranged from 9.6% for amikacin to 32.8% for ticarcillin/clavulanate; levofloxacin resistance was 27.6% (Table 3).
- Doripenem demonstrated identical activity to imipenem and meropenem against 5,949 *Acinetobacter* spp. ($MIC_{50/90}$, 2/>8 µg/ml; Tables 2 and 3). Polymyxin B was the most active compound tested against this pathogen group ($MIC_{50/90}$, ≤1/≤1 µg/ml; 99.3% susceptible). Resistance was high against the other compounds tested ranging from 45.0% for tobramycin to 60.9% for ceftazidime; levofloxacin resistance was 57.4% (Table 3).
- As observed with meropenem and imipenem, doripenem was not active against most strains of *S. maltophilia* (Table 2 and 3). Susceptibility was highest for trimethoprim/sulfamethoxazole (96.5%) followed by levofloxacin (83.2%).
- Doripenem demonstrated high potency against *H. influenzae* ($MIC_{50/90}$, ≤0.06/0.5 µg/ml) and *M. catarrhalis* (MCAT; $MIC_{50/90}$, ≤0.06/≤0.06 µg/ml; Table 3).

Table 1. Distribution of 31,608 non-fermentative and fastidious Gram-negative isolates and medical centers by geographic region and country

Region and country	Number of medical centers	Number of isolates
Asia Western Pacific (12 countries)	79	7139
Latin America (4 countries)	12	5049
Europe (14 countries)	34	10010
North America (2 countries)	56	9410

Table 2. Cumulative percent distribution of doripenem MIC values for non-fermentative and fastidious Gram-negative isolates

	Cumulative % inhibited at doripenem MIC (µg/ml):							
Organism (no. of strains)	≤0.06	0.12	0.25	0.5	1	2	4	8
All NF-GN (22,575)[a]	4	14	30	44	56	64	72	78
P. aeruginosa (13,168)	3	17	36	55	69	77	86	93
Acinetobacter spp. (5,949)	3	10	23	34	43	54	60	67
S. maltophilia (1,888)	-	<1	<1	<1	<1	1	2	3
H. influenzae (8,046)	52	81	89	97	99.6	99.9	99.9	100
M. catarrhalis (987)	99.5	99.9	100	-	-	-	-	-

a. Includes 1,570 isolates other than *P. aeruginosa, Acinetobacter* spp. and *S. maltophilia*.

Table 3. Antimicrobial activity of doripenem and comparator agents when tested against non-fermentative and fastidious Gram-negative isolates (2003-2009)

Organism (no. tested)/ Antimicrobial agent	MIC in µg/ml MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
P. aeruginosa (13,168)					
Doripenem	0.5	8	≤0.06 – >8	- / -[b]	69.1 / 14.4
Imipenem	2	>8	≤0.5 – >8	75.4 / 17.2	75.4 / 17.2
Meropenem	0.5	>8	≤0.12 – >8	79.5 / 12.8	73.0 / 12.8
Piperacillin/tazobactam	8	>64	≤0.5 – >64	81.7 / 18.3	68.6 / 31.4
Ticarcillin/clavulanate	32	>128	≤16 – >128	67.2 / 32.8	16.4 / 83.6
Aztreonam	8	>16	≤0.12 – >16	63.7 / 22.2	3.4 / 22.2
Cefepime	4	>16	≤0.12 – >16	75.7 / 12.7	75.7 / 24.3
Ceftazidime	4	>16	≤1 – >16	73.6 / 20.9	73.6 / 26.4
Amikacin	≤4	32	≤4 – >32	87.5 / 9.6	83.4 / 12.5
Tobramycin	0.5	>16	≤0.25 – >16	79.9 / 19.2	79.9 / 20.1
Levofloxacin	1	>4	≤0.5 – >4	67.5 / 27.6	60.0 / 32.5
Polymyxin B	≤1	≤1	≤1 – >4	99.8 / 0.1	- / -
Acinetobacter spp. (5,949)					
Doripenem	2	>8	≤0.06 – >8	- / -	43.4 / 40.4
Imipenem	2	>8	≤0.5 – >8	60.7 / 35.5	55.8 / 35.5
Meropenem	2	>8	≤0.12 – >8	58.6 / 35.9	53.2 / 35.9
Piperacillin/tazobactam	>64	>64	≤0.5 – >64	39.5 / 60.5	- / -
Ticarcillin/clavulanate	>128	>128	≤16 – >128	29.8 / 58.6	- / -
Cefepime	>16	>16	≤0.12 – >16	37.1 / 51.9	- / -
Ceftazidime	>16	>16	≤1 – >16	33.4 / 60.9	- / -
Amikacin	32	>32	≤4 – >32	46.5 / 49.5	43.8 / 53.5
Tobramycin	4	>16	≤0.25 – >16	52.3 / 45.0	52.3 / 47.7
Levofloxacin	>4	>4	≤0.5 – >4	35.6 / 57.4	34.4 / 64.4
Polymyxin B	≤1	≤1	≤1 – >4	99.3 / 0.7	- / -
Trimethoprim/sulfamethoxazole	>2	>2	≤0.5 – >2	39.5 / 60.5	39.5 / 0.0
Stenotrophomonas maltophilia (1,888)					
Doripenem	>8	>8	0.12 – >8	- / -	- / -
Imipenem	>8	>8	0.5 – >8	- / -	- / -
Meropenem	>8	>8	≤0.12 – >8	- / -	- / -
Ticarcillin/clavulanate	32	>128	≤16 – >128	38.7 / 25.0	- / -
Ceftazidime	16	>16	≤1 – >16	44.7 / 42.1	- / -
Levofloxacin	1	4	≤0.5 – >4	83.2 / 8.2	- / -
Polymyxin B	≤1	>4	≤1 – >4	- / -	- / -
Trimethoprim/sulfamethoxazole	≤0.5	1	≤0.5 – >2	96.5 / 3.5	100.0 / 0.0
Haemophilus influenzae (8,046)					
Doripenem	≤0.06	0.5	≤0.06 – 8	- / -	99.6 / 0.4
Imipenem	≤0.5	1	≤0.5 – 8	99.9 / -	99.3 / 0.7
Ampicillin	≤1	>4	≤1 – >4	77.7 / 21.1	77.7 / 22.3
Amoxicillin/clavulanate	≤1	≤1	≤1 – >8	99.7 / 0.3	90.8 / 9.2
Cefepime	≤0.12	≤0.12	≤0.12 – 4	>99.9 / -	99.1 / 0.9
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 1	100.0 / -	99.6 / 0.4
Azithromycin	1	2	≤0.5 – >4	99.5 / -	13.9 / 0.5
Clarithromycin	8	16	≤0.25 – >32	83.0 / 2.0	1.2 / 0.5
Tetracycline	≤2	≤2	≤2 – >8	97.7 / 2.0	97.6 / 2.3
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	99.9 / -	99.9 / 0.1
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5 – >2	77.3 / 20.0	77.3 / 21.6
Moraxella catarrhalis (987)					
Doripenem	≤0.06	≤0.06	≤0.06 – 0.25	- / -	100.0 / 0.0
Imipenem	≤0.5	≤0.5	≤0.5	- / -	100.0 / 0.0
Amoxicillin/clavulanate	≤1	≤1	≤1 – 2	- / -	99.8 / 0.2
Ceftriaxone	≤0.25	1	≤0.25 – 4	- / -	98.6 / 0.3
Azithromycin	≤0.5	≤0.5	≤0.5	- / -	100.0 / 0.0
Clarithromycin	≤0.25	≤0.25	≤0.25 – 0.5	- / -	98.1 / 0.0
Tetracycline	≤2	≤2	≤2 – >8	- / -	98.3 / 1.7
Levofloxacin	≤0.5	≤0.5	≤0.5 – 4	- / -	99.8 / 0.2
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	- / -	94.2 / 3.5

a. Criteria as published by the CLSI [2010] and EUCAST [2010].
b. - = No breakpoint has been established.

Conclusions

- Against a very large (n=31,608), geographically diverse collection of contemporary (2003-2009) isolates, doripenem exhibited moderate activity against many *P. aeruginosa* and *Acinetobacter* spp., but not against *S. maltophilia*.
- Doripenem demonstrated high potency (MIC_{90}, ≤0.5 µg/ml) against 9,033 *H. influenzae* and *M. catarrhalis* isolates.

Selected References

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