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In Vitro Activity of a Novel Carbapenem, Doripenem, Tested Against Bacterial Pathogens Recovered From Patients Hospitalized With Pneumonia (North America; 2004-2005)

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AMENDED ABSTRACT[a]

Background: Hospital-acquired pneumonia (HAP) is a leading cause of morbidity and mortality in hospitalized patients, and emerging resistance (R) further compromises management. This report summarizes the activity of doripenem (DOR; formerly S-4661), an investigational parenteral carbapenem (CARB) in late-stage clinical development, against leading bacterial pathogens recovered from patients with HAP.

Methods: A total of 1,696 consecutive, non-duplicate isolates determined as the cause of pneumonia were submitted from patients in ≥25 US medical centers (2004-2005). Included HAP pathogens are summarized in the table. Susceptibility (S) testing of DOR and comparator agents was performed using CLSI methods and interpretive criteria, including those for ESBL phenotypes.

Results: Results for DOR are in the table.

Organism (no. tested)	DOR MIC (μg/mL) 50%	90%	Range	% ≤2/≤4
S. aureus (SA; oxacillin [OXA]-S; 168)	≤0.06	≤0.06	≤0.06-0.5	100/100
P. aeruginosa (PSA; 401)	0.5	4	≤0.06->8	80/91
Klebsiella spp. (KSP; 160)	≤0.06	≤0.06	≤0.06->8	95/96
Enterobacter spp. (ESP; 127)	≤0.06	0.12	≤0.06-1	100/100
Acinetobacter spp. (ASP; 97)	1	>8	≤0.06->8	66/80
Serratia spp. (SER; 91)	0.12	0.25	≤0.06-0.5	100/100
E. coli (EC; 84)	≤0.06	≤0.06	≤0.06-0.25	100/100

Ranking of the top 8 occurring HAP isolates and key R characteristics were (see table): SA (413 isolates; 40.7% OXA-R) > PSA > KSP (16.9% ESBL) > ESP (26% ceftazidime-R) > ASP > SER > EC (7.1% ESBL) > *S. maltophilia* (SM; 63 isolates). OXA-R SA and SM are inherently R to CARB and are not presented further. Overall, DOR inhibited 94.8% of the 7 top-ranked pathogens within its spectrum of activity using break points equivalent to peer agents (≤4 μg/mL). Elevated MICs were detected among PSA (MIC_{90}, 4 μg/mL) and ASP (MIC_{90}, >8 μg/mL). Strains of KSP expressing Bush group 2f carbapenemases (primarily KPC) were also detected in the United States.

Conclusions: DOR has potential for targeting HAP pathogens expressing rapidly increasing and problematic R phenotypes.

a. Updated to modify the geographic region sampled.

INTRODUCTION

Nosocomial respiratory tract infections are significant causes of morbidity and mortality and have become much more difficult to manage with the escalating resistances being seen among all usual pathogen groups, including *Staphylococcus aureus*, Enterobacteriaceae, and non-fermentative Gram-negative bacilli. The decrease in utility of many penicillins, cephalosporins, β-lactamase inhibitor combinations, aminoglycosides, and fluoroquinolones, among other classes of antimicrobials, has created a critical need for new agents. The search for compounds with greater potency, stability to common resistance mechanisms, favorable pharmacokinetic/pharmacodynamic features, and lower potential to select for resistance is essential in addressing this situation.

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 over-expressing isolates), anaerobes, *Pseudomonas aeruginosa*, and *Acinetobacter* spp. Only recently have β-lactamases within Ambler classes A (serine carbapenemases), B (metallo-β-lactamases), and D (oxacillinases) been detected sporadically in global surveillance programs that are able to variably hydrolyze carbapenem agents.

Doripenem (formerly S-4661) is currently undergoing clinical development by Johnson & Johnson. It is a potent parenteral carbapenem in late-stage clinical trials known 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).[1-10] The microbiologic and pharmacokinetic/pharmacodynamic features of doripenem have been described previously, and clinical success in human trials has been reported from Japan.[11] The agent is highly β-lactamase stable, is resistant to inactivation by renal dehydropeptidases, and when compared with several other antipseudomonal agents, including other carbapenems, has the lowest rate of spontaneously occurring resistance.

This report summarizes the activity of doripenem and selected comparator compounds when tested against a regional (USA) collection of the leading bacterial agents recovered from patients hospitalized with pneumonia.

MATERIALS AND METHODS

Bacterial Strain Collection

A total of 1,696 non-duplicate, consecutive clinical isolates recovered from hospitalized patients with documented pneumonia were submitted from ≥25 medical centers located in North America as part of a larger international surveillance program (2004 to 2005). The distribution of ranking species and strains included *S. aureus* (413 isolates), *P. aeruginosa* (401), *Klebsiella* spp. (160), *Enterobacter* spp. (127), *Acinetobacter* spp. (97), *Serratia* spp. (91), and *Escherichia coli* (84).

Susceptibility Test Methods

All strains were tested by the Clinical and Laboratory Standards Institute (CLSI; formerly NCCLS [2006])[12,13] broth microdilution method using validated commercially prepared panels (TREK Diagnostics, Cleveland, Ohio) in cation-adjusted Mueller-Hinton broth 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 CLSI published criteria; break points for doripenem have not been established. Enterobacteriaceae with elevated MICs (≥2 μg/mL) for ceftazidime and/or ceftriaxone and/or aztreonam were considered as ESBL-producing phenotypes. Quality control (QC) strains utilized included *E. coli* ATCC 25922 and 35218, *P. aeruginosa* ATCC 27853, and *S. aureus* ATCC 29213. All QC results were within CLSI-specified ranges (2006).

RESULTS

- Ranking pathogens producing >84% of hospital-acquired pneumonia in North America for 2004 to 2005 included *S. aureus* (413 total isolates; 24.3%), *P. aeruginosa* (23.6%), *Klebsiella* spp. (9.4%), *Enterobacter* spp. (7.5%), *Acinetobacter* spp. (5.7%), *Serratia* spp. (5.4%), *E. coli* (4.9%), and *Stenotrophomonas maltophilia* (3.7%) (Table 1).

Table 1. Summary of In Vitro Activity of Doripenem Against Leading Gram-positive and Gram-negative Pathogens Producing Hospital-acquired Pneumonia Collected as Part of a Regional (USA) Surveillance Program (2004 to 2005)

Organism (no. tested)	MIC (μg/mL) 50%	90 %	Cum. % Inhibited at MIC (μg/mL) ≤1	2	4	8
S. aureus (oxacillin-susceptible; 168)	≤0.06	≤0.06	100.0			
P. aeruginosa (401)	0.5	4	71.8	80.3	91.5	97.5
Klebsiella spp. (160)	≤0.06	≤0.06	95.0	95.6	96.3	98.1
Enterobacter spp. (127)	≤0.06	0.12	100.0			
Acinetobacter spp. (97)	1	>8	51.5	66.0	80.4	85.6
Serratia spp. (91)	0.12	0.25	100.0			
E. coli (84)	≤0.06	≤0.06	100.0			

- Key resistance characteristics included (Table 2): *S. aureus* (40.7% oxacillin-resistant), *E. coli* (7.1% ESBL-phenotype positive), *Klebsiella* spp. (16.9% ESBL-phenotype positive), and *Enterobacter* spp. (26% ceftazidime-resistant).
- Oxacillin-resistant staphylococci and *S. maltophilia* are outside the spectrum of carbapenems and are not discussed further.
- Doripenem was broadly active against this collection, inhibiting 94.8% of the 7 top-ranked pathogens within its spectrum of activity at a concentration of ≤4 μg/mL, the equivalent break point of peer agents.
- All ESBL-screen–positive *E. coli* (6.0% to 7.1%) and *Klebsiella* spp. (14.4% to 15.0%) were inhibited by ≤4 μg/mL of doripenem.
- Six strains of *Klebsiella* spp. (3.7%) with elevated carbapenem MIC values (>4 μg/mL) were found to express Bush group 2f carbapenemases (KPC enzymes) and originated from the east coast of the United States (New York state) (Table 2).
- *Enterobacter* spp. isolates constitutively expressing chromosomal AmpC (ceftazidime-resistance; 26%) were all inhibited by 1 μg/mL of doripenem and 2 μg/mL of meropenem and imipenem (Table 2).
- Doripenem ($MIC_{50/90}$, 0.5/4 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 (91.5%, 82.8%, and 79.8%, respectively) (Table 2).
- Only amikacin (94.5% susceptible) and polymyxin B (100%) provided greater coverage of *P. aeruginosa*.
- Polymyxin B (100% susceptible) and the carbapenems (77.3% to 87.6%) were the most active agents against *Acinetobacter* spp., whereas high levels of resistance were noted with levofloxacin (64.9%), ceftazidime (60.8%), cefepime (48.5%), and piperacillin/tazobactam (41.2%) (Table 2).

Table 2. In vitro Activity of Doripenem in Comparison With Selected Antimicrobial Agents Tested Against the 7 Most Prevalent Isolates Producing Hospital-acquired Pneumonia Collected as Part of a Regional (USA) Surveillance Program (2004 to 2005)

Organism (no. tested)/ Antimicrobial Agent	MIC (μg/mL) 50%	90%	Range	% by Category[a] Susceptible	Resistant
S. aureus (168)					
Doripenem	≤0.06	≤0.06	≤0.06-0.5	–	–
Imipenem	≤0.12	≤0.12	≤0.12-0.25	100.0	0.0
Ceftriaxone	4	4	0.5-8	100.0	0.0
Ceftazidime	8	16	≤1-16	85.7	0.0
Cefepime	2	4	1-8	100.0	0.0
Piperacillin/tazobactam	1	2	≤0.5-16	99.4	0.6
Levofloxacin	0.12	2	0.06->4	89.9	8.9
Gentamicin	≤2	≤2	≤2->8	98.8	1.2
Daptomycin	0.25	0.5	0.12-1	100.0	–
Linezolid	2	2	0.5-2	100.0	–
Vancomycin	1	1	0.5-2	100.0	0.0
P. aeruginosa (401)					
Doripenem	0.5	4	0.03-16	–	–
Meropenem	0.5	8	≤0.06->8	82.8	8.5
Imipenem	1	8	≤0.12->8	79.8	8.0
Piperacillin/tazobactam	8	>64	≤0.5->64	83.0	17.0
Ceftazidime	4	>16	≤1->16	78.1	16.7
Cefepime	4	16	≤0.12->16	78.1	7.2
Levofloxacin	1	>4	0.06->4	69.0	22.0
Tobramycin	0.5	8	≤0.12->16	89.5	9.5
Amikacin	4	16	≤0.25->32	94.5	3.2
Polymyxin B	0.5	1	≤0.12-2	100.0	0.0
Klebsiella spp. (160)					
Doripenem	≤0.06	≤0.06	≤0.06->16	–	–
Meropenem	≤0.06	≤0.06	≤0.06->8	95.0	4.4
Imipenem	≤0.12	0.25	≤0.12->8	95.0	3.8
Ertapenem	≤0.06	≤0.06	≤0.06->16	95.0	5.0
Piperacillin/tazobactam	4	64	≤0.5->64	86.9	10.0
Ceftriaxone	≤0.25	16	≤0.25->32	88.8	7.5
Ceftazidime	≤1	>16	≤1->16	88.1	10.6
Cefepime	≤0.12	2	≤0.12->16	94.4	4.4
Levofloxacin	≤0.5	2	≤0.5->4	90.6	8.8
Gentamicin	≤2	8	≤2->8	87.5	10.0
Enterobacter spp. (127)					
Doripenem	0.06	0.12	0.03-1	–	–
Meropenem	≤0.06	0.12	≤0.06-2	100.0	0.0
Imipenem	0.5	1	≤0.12-2	100.0	0.0
Ertapenem	≤0.06	0.5	≤0.06-2	100.0	0.0
Piperacillin/tazobactam	4	>64	≤0.5->64	77.2	12.6
Ceftriaxone	≤0.25	>32	≤0.25->32	75.6	17.3
Ceftazidime	≤1	>16	≤1->16	72.4	26.0
Cefepime	≤0.12	4	≤0.12->16	96.1	2.4
Levofloxacin	≤0.5	2	≤0.5->4	92.1	3.9
Gentamicin	≤2	>8	≤2->8	86.6	10.2
Acinetobacter spp. (97)					
Doripenem	1	16	0.03->16	–	–
Meropenem	2	>8	0.12->8	77.3	15.5
Imipenem	0.5	8	≤0.12->8	87.6	7.2
Ampicillin/sulbactam	8	>32	1->32	57.7	30.9
Piperacillin/tazobactam	64	>64	≤0.5->64	35.1	41.2
Ceftazidime	>16	>16	≤1->16	29.9	60.8
Cefepime	16	>16	0.25->16	34.0	48.5
Levofloxacin	>4	>4	0.06->4	29.9	64.9
Tobramycin	2	>16	≤0.25->16	69.1	29.9
Amikacin	8	>32	1->32	72.2	22.7
Polymyxin B	0.5	0.5	0.25-2	100.0	0.0

Table 2. *continued*

Organism (no. tested)/ Antimicrobial Agent	MIC (μg/mL) 50%	90%	Range	% by Category[a] Susceptible	Resistant
Serratia spp. (91)					
Doripenem	0.12	0.25	0.03-0.5	–	–
Meropenem	≤0.06	≤0.06	≤0.06-0.12	100.0	0.0
Imipenem	0.5	1	0.25-2	100.0	0.0
Ertapenem	≤0.06	≤0.06	≤0.06-2	100.0	0.0
Piperacillin/tazobactam	2	8	≤0.5-64	95.6	0.0
Ceftriaxone	≤0.25	1	≤0.25-32	98.9	0.0
Ceftazidime	≤1	≤1	≤1-16	98.9	0.0
Cefepime	≤0.12	0.25	≤0.12-1	100.0	0.0
Levofloxacin	≤0.5	2	≤0.5->4	94.5	2.2
Gentamicin	≤2	≤2	≤2->8	95.6	4.4
E. coli (84)					
Doripenem	≤0.06	≤0.06	≤0.06-0.25	–	–
Meropenem	≤0.06	≤0.06	≤0.06-0.12	100.0	0.0
Imipenem	≤0.12	0.25	≤0.12-1	100.0	0.0
Ertapenem	≤0.06	≤0.06	≤0.06-0.12	100.0	0.0
Piperacillin/tazobactam	2	8	≤0.5->64	96.4	3.6
Ceftriaxone	≤0.25	≤0.25	≤0.25->32	96.4	2.4
Ceftazidime	≤1	≤1	≤1->16	95.2	1.2
Cefepime	≤0.12	0.25	≤0.12->16	98.8	1.2
Levofloxacin	≤0.5	>4	≤0.5->4	71.4	28.6
Gentamicin	≤2	>8	≤2->8	81.0	19.0

a. Break point criteria are those of CLSI M100-S16 (2006). – = no break points established.

CONCLUSIONS

- Pathogens producing >84% of hospital-acquired pneumonia in North American patients for 2004 to 2005 included *S. aureus* (24.3%), *P. aeruginosa* (23.6%), *Klebsiella* spp. (9.4%), *Enterobacter* spp. (7.5%), *Acinetobacter* spp. (5.7%), *Serratia* spp. (5.4%), *E. coli* (4.9%), and *S. maltophilia* (3.7%).
- Doripenem was broadly active against this collection (exceptions, oxacillin-resistant *S. aureus* and *S. maltophilia)*, inhibiting 94.8% of the 7 top-ranked pathogens within its spectrum of activity at a concentration of ≤4 μg/mL, the equivalent break point of peer agents.
- Among Enterobacteriaceae, doripenem inhibited 98.7% of all isolates at ≤4 μg/mL. Non-susceptible strains (6; 3.7%) were all KPC-producing *Klebsiella* spp.
- For the *P. aeruginosa* isolates tested here, doripenem inhibited 91.5% at ≤4 μg/mL compared with 82.8% for meropenem and only 79.8% for imipenem.
- Doripenem has potential for treatment of hospital-acquired pneumonia targeting those pathogens expressing rapidly increasing and problematic resistant phenotypes.

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