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Antimicrobial Activity of Doripenem Against Multi-drug Resistant *Pseudomonas aeruginosa* and *Streptococcus pneumoniae*

TR FRITSCHE, DM JOHNSON, RN JONES
The JONES Group/JMI Laboratories, North Liberty, IA

The JONES Group/JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
319.665.3370, fax 319.665.3371
ronald-jones@jmilabs.com

AMENDED ABSTRACT

Background:

DOR (formerly S-4661) is a potent parenteral carbapenem currently in clinical trials. The compound resembles marketed antipseudomonal carbapenems in spectrum but displays enhanced in vitro activity. We summarize results of testing DOR and comparators against MDR PSA and SPN.

Methods:

The collection included 79 PSA (resistant to ceftazidime, piperacillin/tazobactam, gentamicin and ciprofloxacin) and 57 SPN (R to penicillin, erythromycin, clindamycin, tetracycline and trimethoprim/sulfamethoxazole) originating from various contemporary international (Europe and the Americas) collections (2003). MIC values for DOR and comparator antimicrobials were determined by NCCLS reference broth microdilution methods. A tentative R DOR breakpoint of ≥ 16 µg/ml (≥ 1 µg/ml for SPN) was used for comparative purposes only.

Results:

	$MIC_{50/90}$ (% R) in µg/ml	
Antimicrobial	MDR-PSA	MDR-SPN
DOR	8/>16(31.6)	0.5/1(0.03-1)[a]
Meropenem	16/>16(54.4)	0.5/1(0.03-1)[a]
Imipenem (IMP)	>8/>8(57.0)	≤0.5/≤0.5(≤0.5-1)[a]
Cefepime	>16/>16(69.6)	1/2(5.3)[b]
Ceftriaxone	>32/>32(97.5)	1/4(10.5)[b]
Amikacin	>32/>32(53.2)	-
Tobramycin	>16/>16(93.7)	-
Vancomycin	-	0.25/0.5(0.0)
Linezolid	-	1/1(0.0)

a. Range.
b. Non-meningitis breakpoints [NCCLS, 2004].

DOR was ≥ 2-fold more potent and had the lowest % R when tested against MDR PSA. Among carbapenems, IMP displayed slightly greater activity against MDR-SPN. Cefepime had the lowest SPN R rate among ß-lactams.

Conclusions:

Based upon the in vitro data, DOR appears to offer advantages in potency and spectrum among currently available ß-lactams, especially against MDR non-fermentative bacilli and streptococci.

INTRODUCTION

Doripenem (formerly S-4661) is a novel parenteral carbapenem that represents the first new antipseudomonal drug in advanced development in nearly a decade. It has the favorable characteristics of the carbapenem class including ß-lactamase stability, resistance to inactivation by renal dehydropeptidases and low potential for CNS toxicity. Earlier in vitro studies of this 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. two- to four-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. These characteristics are especially important given the persistence and escalation of multi-drug resistance rates among both Gram-positive and –negative organisms.

In this report, we summarize the results of testing doripenem and comparator agents against multi-drug resistant *Pseudomonas aeruginosa* (resistant to ceftazidime, piperacillin/tazobactam, gentamicin and ciprofloxacin) and *Streptococcus pneumoniae* (resistant to penicillin, erythromycin, clindamycin, tetracycline and trimethoprim/sulfamethoxazole) originating from contemporary international surveillance collections. Bacterial strains were tested by reference NCCLS [2003] methods with susceptibilities to comparator agents interpreted by NCCLS breakpoint criteria [2004].

MATERIALS AND METHODS

The collection consisted of 79 strains (out of a total of 829 isolates collected during the study) of *P. aeruginosa* identified as being multi-drug resistant (resistant to ceftazidime, piperacillin/tazobactam, gentamicin and ciprofloxacin, among others) and 57 (out of a total of 885 isolates collected during the study) strains of *S. pneumoniae* (resistant to penicillin, erythromycin, clindamycin, tetracycline and trimethoprim/sulfamethoxazole). All isolates were non-duplicate consecutive clinical isolates submitted from numerous medical centers located in the Americas and Europe that contributed to various surveillance programs for the year 2003. The isolates originated from patients with documented bloodstream, respiratory, skin and soft tissue, and/or urinary tract infections.

All strains were tested by the reference broth microdilution method [NCCLS, 2003] in cation-adjusted Mueller-Hinton broth (with 2 - 5% lysed horse blood added for testing of streptococci) 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 (Ohio, USA). Interpretation of quantitative MIC results was in accordance with NCCLS [2004] criteria. A tentative doripenem resistance breakpoint of ≥ 16 µg/ml was used for comparative purposes only when testing *P. aeruginosa* (≥ 1 µg/ml for *S. pneumoniae*). Quality control strains utilized included *P. aeruginosa* ATCC 27853 and *S. pneumoniae* ATCC 49619.

RESULTS

- In vitro, doripenem was at least two-fold more potent than meropenem and imipenem (MIC_{50}, 8 versus ≥ 16 µg/ml) and displayed the lowest resistance rates (31.6%) among carbapenems and other anti-pseudomonal drugs tested (with the exception of polymyxin B; Table 1).
- Only polymyxin B was uniformly active against multi-drug resistant *P. aeruginosa* (MIC_{50} and MIC_{90}, ≤ 1 µg/ml).
- Among other antimicrobial agents, the resistance rates against MDR *P. aeruginosa* were greater than 50% (53.2 - 93.7%); amikacin was the only non-ß-lactam with some activity against these strains.
- Against multi-drug resistant *S. pneumoniae*, carbapenems were the most potent ß-lactams: MIC_{50} and MIC_{90} of doripenem and meropenem were 0.5 and 1 µg/ml, respectively; imipenem displayed a slightly greater activity (MIC_{90} value, ≤ 0.5 µg/ml). MIC_{50} and MIC_{90} of ceftriaxone and cefepime were 1 and 4 µg/ml, and 1 and 2 µg/ml, respectively.
- All multi-resistant *S. pneumoniae* isolates studied here remained susceptible to levofloxacin, linezolid and vancomycin.

Table 1. Antimicrobial activity of doripenem (S-4661) and comparator broad-spectrum agents tested against multi-drug resistant[a] *P. aeruginosa* (79 strains).

	MIC (µg/ml)			% by category	
Antimicrobial agent	50%	90%	Range	Susceptible	Resistant
Doripenem	8	>16	0.5->16	36.7[b]	31.6[b]
Meropenem	16	>16	0.5->16	30.4	54.4
Imipenem	>8	>8	≤0.5->8	31.6	57.0
Ceftriaxone	>32	>32	0.5->32	2.5	97.5
Cefepime	>16	>16	16->16	0.0	69.6
Aztreonam	>16	>16	8->16	1.3	92.4
Amikacin	>32	>32	2->32	34.2	53.2
Tobramycin	>16	>16	2->16	2.5	93.7
Polymyxin B	≤1	≤1	≤1->8	-[c]	-[c]

a. Resistant to ceftazidime, piperacillin/tazobactam, gentamicin and ciprofloxacin.
b. The breakpoints for meropenem and imipenem were used with doripenem for comparative purposes.
c. Breakpoints not established by NCCLS [2004].

Table 2. Antimicrobial activity of doripenem (S-4661) and comparator broad-spectrum agents tested against multi-drug resistant[a] *S. pneumoniae* (57 strains).

	MIC (µg/ml)			% by category	
Antimicrobial agent	50%	90%	Range	Susceptible	Resistant
Doripenem	0.5	1	0.03-1	-[b]	-[b]
Meropenem	0.5	1	0.03-1	-[b]	-[b]
Imipenem	≤0.5	≤0.5	≤0.5-1	-[b]	-[b]
Ceftriaxone	1	4	≤0.25-8	80.7[c]	10.5[c]
Cefepime	1	2	≤0.12-4	68.4[c]	5.3[c]
Levofloxacin	1	1	0.5-2	100.0	0.0
Linezolid	1	1	0.5-1	100.0	0.0
Vancomycin	0.25	0.5	0.12-0.5	100.0	0.0

a. Resistant to penicillin, erythromycin, clindamycin, tetracycline and trimethoprim/sulfamethoxazole.
b. Non-meningitis breakpoints are not established.
d. Non-meningitis breakpoints [NCCLS, 2004].

CONCLUSIONS

- Previous international surveillance results have identified doripenem as a potent carbapenem with a spectrum of activity resembling currently marketed, *Pseudomonas*-active carbapenems such as imipenem and meropenem.
- When tested against a collection of multi-resistant *P. aeruginosa*, doripenem was ≥ two-fold more potent than other carbapenems and anti-pseudomonal agents (with the exception of polymyxin B) and demonstrated the lowest percentage of resistant isolates.
- Against multidrug-resistant *S. pneumoniae* the MIC_{90} for doripenem and meropenem was 1 µg/ml; only imipenem (≤ 0.5 µg/ml) and vancomycin (0.5 µg/ml) were two-fold more potent.
- Doripenem appears to offer advantages in potency and spectrum among currently available ß-lactam agents in vitro, including some activity against multi-drug resistant non-fermentative bacilli; further clinical studies trial investigations should clarify the role of this agent in treatment of these infections.

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