Uniformly Enhanced Activity of Doripenem Compared to Other Carbapenems (Imipenem, Meropenem) When Testing *P. aeruginosa* Isolates: Results From Three Continents

RN JONES, MG STILWELL, HS SADER, TR FRITSCHE • JMI LABORATORIES, NORTH LIBERTY, IOWA, USA

JMI Laboratories
North Liberty, Iowa, USA
www.jmilabs.com
319.665.3370
fax 319.665.3371
ronald-jones@jmilabs.com

ABSTRACT

Background: Doripenem (DORI), an investigational parenteral carbapenem, inhibits a great number of Gram-positive and -negative pathogens, as well as *P. aeruginosa* (PSA), among non-fermentative bacilli with acquired and intrinsic resistances (R). DORI was compared to imipenem (IMP) and meropenem (MERO) tested against contemporary (2003-2005) PSA isolated from patients in North America (NA), Latin America (LA), and Europe (EU) using a central laboratory and 1 strain per patient surveillance design.

Methods: A total of 3330 PSA were tested from NA (34 laboratory sites, 1199 strains), LA (12, 788) and EU (29, 1343), each processed by the CLSI broth microdilution method in cation-adjusted Mueller-Hinton broth. QC was assured by use of PSA ATCC 27853 with all results within published ranges. CLSI breakpoints for IMP and MERO were used for DORI for comparison purposes because of nearly identical PK/PD characteristics.

Results: DORI MIC_{50} and MIC_{90} results versus PSA ranged from ≤0.5-1 mg/L and 4-8 mg/L across all continents, respectively, a potency ≥2-fold greater than IMP or MERO. PSA from NA were most susceptible (S) to all 3 carbapenems, with a rank order of activity (%S) favoring DORI > MERO > IMP.

	Cumulative % Inhibited at MIC (mg/L)				
Continent/carbapenem (no.)	**≤0.5**	**1**	**2**	**4**	**8**
North America/DORI (1199)	66	80	87	95	99
MERO	62	76	84	89	94
IMP	22	71	83	86	94
Europe/DORI (1343)	53	67	75	84	91
MERO	50	64	71	79	86
IMP	14	59	71	76	86
Latin America/DORI (788)	46	61	70	80	90
MERO	41	56	64	73	83
IMP 15	15	56	67	70	83

Using a ≤4 mg/L S breakpoint, DORI inhibited 8-10% and 5-7% more PSA isolates across all regions compared to IMP or MERO, respectively. Individual site analyses in NA demonstrated a uniformly greater %S for DORI, while at 15% of sites, IMP %S was higher than for MERO, with DORI remaining 4-15% higher in the %S than IMP at these locations.

Conclusions: DORI, a novel carbapenem in late phase III clinical trials, demonstrated remarkably consistent advantages in %S against PSA when directly compared to MERO or IMP. Results indicate that DORI was least influenced by contemporary carbapenem R mechanisms, regardless of geographic isolation (continent) or endemic institutional/clonal R patterns. Further development clearly appears warranted.

INTRODUCTION

Pseudonomas aeruginosa can be difficult to treat because of intrinsic resistance caused by efflux systems and chromosomal β-lactamase, or emergent multidrug-resistance (MDR) patterns. Combination therapy has long been applied when treating patients with this pathogen, and early studies documented in vitro synergistic and additive effects when various antimicrobial agents were tested in combination. β-Lactams used in combination with aminoglycosides can be synergistic against Gram-negative organisms, including *P. aeruginosa*, and patients have improved clinically on such regimens. More recently, carbapenems have been prescribed for patients with *P. aeruginosa* infections, because of the high rates of resistance to other antimicrobial classes often encountered. However, rapid development of resistance to carbapenems, even with combination therapies, has been documented, and some studies suggest that antipseudomonal penicillins may inactivate aminoglycosides.

Doripenem (formerly S-4661 [Shionogi]) is a broad-spectrum parenteral carbapenem being developed by Johnson & Johnson that is in the late stages of clinical development. The microbiological and pharmacokinetic/pharmacodynamic features of doripenem have been described previously, and clinical success in human trials has been reported in Japan. Several recent studies have shown that doripenem incorporates the most favorable characteristics of the carbapenem class by combining the superior in vitro activities of imipenem against Gram-positive cocci and of meropenem against Gram-negative pathogens. In a study of MDR pathogens, doripenem retained the greatest potency among carbapenems against extended-spectrum β-lactamase (ESBL)- and AmpC-producing enteric bacilli, as well as against penicillin-resistant *Streptococcus pneumoniae*. Also, a greater proportion of carbapenem-resistant *P. aeruginosa* and *Acinetobacter* spp. isolates were inhibited by doripenem at ≤4 mg/L. When compared with several other antipseudomonal agents, including other carbapenems, doripenem was associated with the lowest rate of spontaneously occurring resistance.

The aim of the present study was to characterize the global antibiogram for doripenem, directly compared with other parenteral carbapenems (imipenem and meropenem), using a large collection of *P. aeruginosa* isolates from Europe, North America, and Latin America.

MATERIALS AND METHODS

A total of 3330 non-duplicate *P. aeruginosa* strains were collected from significant infections in patients hospitalized in Europe (29 sites, 1343 strains), North America (34 sites, 1199 strains), and Latin America (12 sites, 788 strains). Organisms were identified locally and forwarded to a central monitoring laboratory (JMI Laboratories, North Liberty, IA, USA), where the identification was confirmed and reference susceptibility testing performed.

Doripenem, imipenem, and meropenem were tested in validated microdilution trays in cation-adjusted Mueller-Hinton broth using the Clinical and Laboratory Standards Institute (CLSI) methods (M7-A7, 2006). All interpretations were by CLSI M100-S16 breakpoint criteria. Doripenem was assigned the same susceptible breakpoint MIC (≤4 mg/L) for comparison purposes and because of similar pharmacokinetic and pharmacodynamic features with short infusion times (≤1 hour). The results were analyzed by geographic region (continents) due to initially recognized differences in resistance rates. Also, variations occurring in the resistance rates for imipenem and meropenem in specific North American sites were assessed as to their impact on doripenem's spectrum of activity and potency versus *P. aeruginosa*.

RESULTS

- The rank order of the 3 carbapenems tested against *P. aeruginosa* strains from 3 continents at the breakpoint MIC was consistent: doripenem (80-95% susceptible) > meropenem (73-89% susceptible) > imipenem (70-86% susceptible) (Table 1).

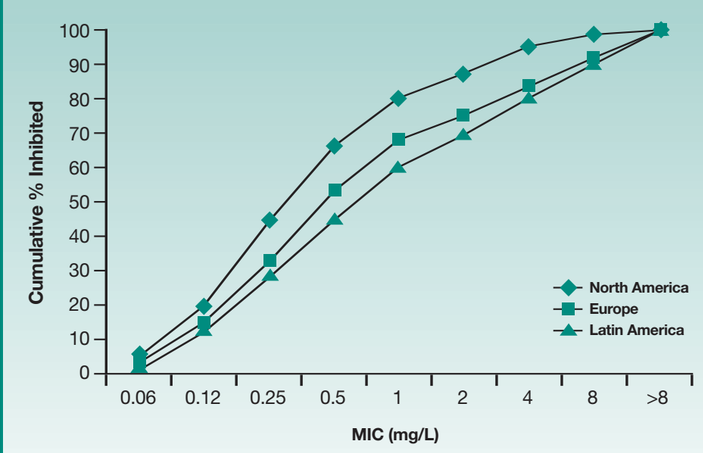
Table 1. Comparisons of 3 carbapenems tested against recent clinical isolates of *P. aeruginosa* cultured from 3 continents

Continent Sample (no. tested)	Cumulative % Inhibited at MIC (mg/L)				
Carbapenem	**≤0.5**	**1**	**2**	**4**	**8**
Europe (1343)					
Doripenem	53	67	75	84	91
Imipenem	14	59	71	76*	86
Meropenem	50	64	71	79*	86
North America (1199)					
Doripenem	66	80	87	95	99
Imipenem	22	71	83	86*	94
Meropenem	62	76	84	89*	94
Latin America (788)					
Doripenem	46	61	70	80	90
Imipenem	15	56	67	70*	83
Meropenem	41	56	64	73*	83

*CLSI breakpoint for susceptibility of the comparison carbapenem is ≤4 mg/L.

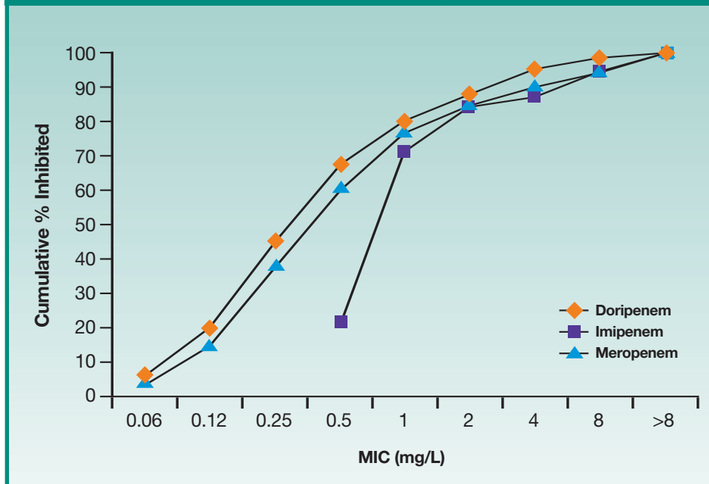
- Important differences were noted in the susceptibility rates for the 3 carbapenems between regions, with greatest susceptibility for *P. aeruginosa* isolated in North America (86-95%) > Europe (76-84%) > Latin America (73-80%) (Table 1 and Figure 1).

Figure 1. Doripenem activity against 3330 *P. aeruginosa* listed by geographic region



- In all 3 regions, the inhibition of *P. aeruginosa* at 8 mg/L was equal for imipenem and meropenem (Figures 2-4).

Figure 2. Comparisons of 3 carbapenems for activity against North American isolates of *P. aeruginosa* (1199 strains)



- In Latin America, imipenem had 3% greater coverage at 2 mg/L than meropenem, whereas meropenem had 3% greater coverage at 4 mg/L than imipenem (Table 1 and Figure 3).

Figure 3. Comparisons of 3 carbapenems for activity against Latin American isolates of *P. aeruginosa* (788 strains)

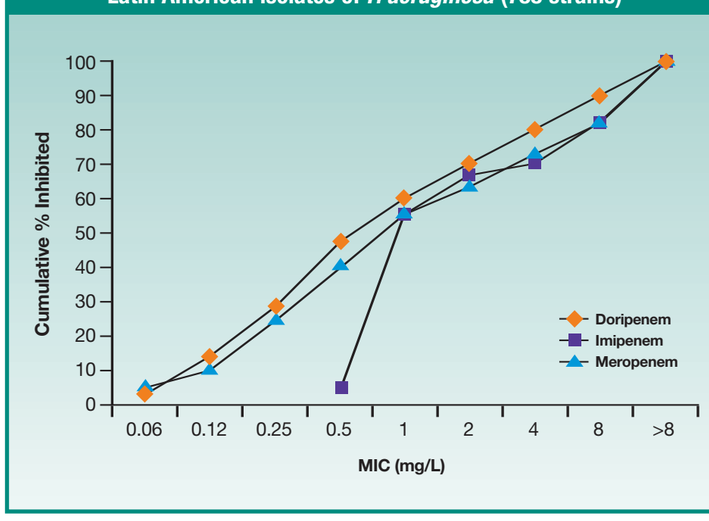
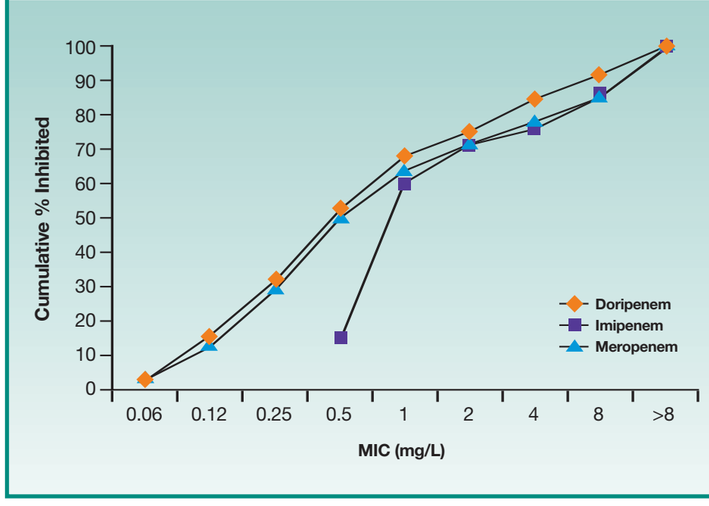


Figure 4. Comparisons of 3 carbapenems for activity against European isolates of *P. aeruginosa* (1343 strains)



- In some North American medical centers (15%), imipenem had a greater susceptibility rate than meropenem (data not shown). However, susceptibility to doripenem remained 4-15% greater than imipenem in these institutions. The cause of these variations appears to be varied, endemic resistance mechanisms (efflux, OMP alterations, chromosomal AmpC expression).

CONCLUSIONS

- High volume, reference method surveillance studies of doripenem confirmed the uniformly broader coverage of *P. aeruginosa* strains compared with imipenem or meropenem.
- The enhanced doripenem activity was not altered by site or geographic variations in resistance mechanisms.

SELECTED REFERENCES

1. Andes DR, Kiem S, Craig WA. In vivo pharmacodynamic activity of a new carbapenem, doripenem (DOR), against multiple bacteria in a murine thigh infection model. In: Program and abstracts of the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy; September 14-17, 2003; Chicago, Ill. Abstr. A-308.
2. Bhavnani SM, Hammel JP, Cirincioni BB, et al. PK-PD target attainment with Monte Carlo simulation (MCS) as decision support of Phase 2/3 dosing strategies for clinical development of doripenem (DOR). In: Program and abstracts of the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy; September 14-17, 2003; Chicago, Ill. Abstr. A-11.
3. Clinical and Laboratory Standards Institute. *Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically,* 7th ed. *Approved Standard M7-A7.* Wayne, PA: CLSI, 2006.
4. Clinical and Laboratory Standards Institute. *Performance standards for antimicrobial susceptibility testing, 16th informational supplement M100-S16.* Wayne, PA: CLSI, 2006.
5. Fritsche TR, Stilwell MG, Jones RN. Antimicrobial activity of doripenem (S-4661): a global surveillance report (2003). *Clin Microbiol Infect.* 2005;11:974-984.
6. Jones RN, Huynh HK, Biedenbach DJ. Activities of doripenem (S-4661) against drug-resistant clinical pathogens. *Antimicrob Agents Chemother.* 2004;48:3136-3140.
7. Jones RN, Huynh HK, Biedenbach DJ, Fritsche TR, Sader HS. Doripenem (S-4661), a novel carbapenem: comparative activity against contemporary pathogens including bactericidal action and preliminary in vitro methods evaluations. *J Antimicrob Chemother.* 2004;54:144-154.
8. Jones RN, Sader HS, Fritsche TR. Comparative activity of doripenem and three other carbapenems tested against Gram-negative bacilli with various β-lactamase resistance mechanisms. *Diagn Microbiol Infect Dis.* 2005;52: 71-74.
9. Mushtaq S, Ge Y, Livermore DM. Doripenem versus *Pseudomonas aeruginosa* in vitro: activity against characterized isolates, mutants, and transconjugants and resistance selection potential. *Antimicrob Agents Chemother.* 2004;48:3086-3092.