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In vitro potency of doripenem tested against an international collection of rarely isolated bacterial pathogens

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Abstract

Doripenem, a new 1β-methyl parenteral carbapenem, has very broad-spectrum activity against Gram-positive and Gram-negative aerobic bacteria. As noted here, the spectrum and potency extended to many rarely isolated species sampled by the Doripenem Global Surveillance Program. Among the species or species groups with ≤0.14% prevalence (1959 strains tested), doripenem was active against 98.9% of Enterobacteriaceae at ≤0.5 μg/mL. Similarly, more than 90% of other rarely isolated Gram-negative species isolates (*Aeromonas* spp., *Delftia acidovorans*, *Haemophilus parainfluenzae*, *Neisseria meningitidis*, *Ochrobactrum anthropi*, *Pasteurella multocida*, *Pseudomonas oryzihabitans*, and *Pseudomonas stutzeri*) were inhibited by ≤2 μg/mL of doripenem. The low-prevalence Gram-positive pathogens were generally less doripenem susceptible with MIC_{90} results at >0.25 μg/mL for all tested species except *Lactococcus garvieae*, *Listeria monocytogenes*, and *Micrococcus* spp. In conclusion, doripenem exhibited a very wide spectrum but variable potencies against uncommonly cultured aerobic bacterial pathogens isolated in 2003 to 2007. These results confirm the potential use of this new carbapenem for broad-spectrum empiric or directed antimicrobial therapy.

Keywords: Doripenem; Unusual pathogens; Carbapenems; Broad-spectrum

1. Introduction

Doripenem (formerly S-4661; Shionogi, Osaka, Japan) is a novel parenteral 1β-methyl carbapenem with documented broad-spectrum activity against commonly isolated Gram-positive and Gram-negative pathogens (Keam, 2008; Lister, 2007; Shah, 2008). The potency of doripenem has been consistently among the best observed for the antipseudomonal carbapenems and appears to be sustained since early reports of activity by Japanese investigators (Nomura and Nagayama, 2002; Tsuji et al., 1998; Watanabe et al., 2000). Anaerobic bacterial genera and species are also inhibited by doripenem (Goldstein et al., 2008), as are multidrug-resistant (MDR) aerobic Gram-negative bacilli associated with infections in cystic fibrosis patients (Chen et al., 2005; Traczewski and Brown, 2006). This favorable breadth of spectrum and potency for doripenem have led to successful clinical trial results (Chastre et al., 2008; Lucasti et al., 2008; Merchant et al., 2008; Rea-Neto et al., 2008) for intra-abdominal infections, nosocomial pneumonias (including ventilator-associated cases), and complicated urinary tract infections (Doribax® Package Insert, 2008).

Although doripenem has been tested in vitro against an estimated 200 000 clinical isolates by various investigators and global surveillance networks (Fritsche et al., 2005; Ge et al., 2004; Jones et al., 2004a and b and 2005; Pillar et al., 2008), some species are only processed in small numbers and/or not reported by these earlier publications. Like special investigations of MDR organism subsets (Jones et al., 2004a and 2005; Mushtaq et al., 2004), uncommonly isolated pathogens could become candidates for doripenem treatment in an effort to initiate empiric therapy and to maximize favorable clinical outcomes (Kollef, 2008). In this review, we examined the Doripenem Global Surveillance Program (141 235 isolates; 2003–2007) results for doripenem activities against rarely cultured pathogens. These 1959 strains (1.4% of all organisms tested) have ≥10 isolates per species or species group affording a reasonable experience or

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sample size. All isolates were tested in central GLP reference laboratories (JMI Laboratories, North Liberty, IA; Women's and Children's Hospital, North Adelaide, Australia) by Clinical and Laboratory Standards Institute (CLSI, 2006 and 2008) (formerly National Committee for Clinical Laboratory Standards) methods.

2. Materials and methods

2.1. Organisms

More than 141 000 consecutive nonduplicate isolates have been processed in the Doripenem Global Surveillance Program (2003–2007), monitoring clinically important organisms from Europe, the Asia-Pacific region, and North and South America. Because of the high volume of this longitudinal trial, normally uncommon or rarely isolated species are found in sufficient numbers to allow the assessment of in vitro doripenem activity. All species or species groups having ≥10 strains (≥0.007% of all isolates) were tabulated, a total of 1959 isolates or 1.4% of all surveillance cultures over the initial 5 years of this resistance surveillance program (Tables 1–3). Major categories of these isolates were Enterobacteriaceae (744, 20 species), non-Enterobacteriaceae Gram-negative bacilli (701, 19 species), and unusual Gram-positive cocci or bacilli (514).

Species identifications were confirmed by the central coordinating laboratory (JMI Laboratories) using established biochemical or molecular algorithms, including the Vitek microbial identification systems (bioMerieux, Hazelwood, MO).

2.2. Susceptibility test methods

All isolates were tested by the CLSI (2006 and 2008) broth microdilution methods using validated commercially prepared panels (TREK Diagnostics, Cleveland, OH) in cation-adjusted Mueller–Hinton broth (with 5% lysed horse blood added or HTM for testing of streptococci and *Haemophilus* spp.) against a variety of antimicrobial agents including doripenem. Doripenem standard powder provided by Johnson & Johnson, Raritan, NJ, was tested over the range and ≤0.06 to 8 μg/mL. Testing was performed at JMI Laboratories or at Women's and Children's Hospital. Categoric interpretations of MIC results were in accordance with published CLSI (2008) criteria for comparison agents. Breakpoints for doripenem when testing staphylococci, enterococci, and streptococci (other than *Streptococcus anginosus* group) have not been established by either the USA Food and Drug Administration (USA-FDA) or by the CLSI (2008). However, the USA-FDA has recommended susceptible breakpoints for doripenem as follows: ≤0.5 μg/mL for

Table 1
Doripenem activity tested by reference broth microdilution method (CLSI, 2006) against 744 isolates of infrequently occurring Enterobacteriaceae

Organism (no. tested)	MIC (μg/mL)		Cumulative percentage inhibited at MIC (μg/mL)					Percentage by category[a]
	50%	90%	≤0.5	1	2	4	8	Susceptible/resistant
Citrobacter spp. (923)	≤0.06	≤0.06	99.5	99.8	100.0			99.5/–
C. amalonaticus (25)	≤0.06	≤0.06	100.0					100.0/–
C. braakii (31)	≤0.06	≤0.06	100.0					100.0/–
Enterobacter spp. (5098)	≤0.06	0.12	97.9	98.7	99.2	99.7	99.8	97.9/–
E. amnigenus (21)	≤0.06	≤0.06	95.2	100.0				95.2/–
E. asburiae (25)	≤0.06	0.12	96.0	100.0				96.0/–
E. cancerogenus (10)	≤0.06	≤0.06	100.0					100.0/–
E. gergoviae (13)	≤0.06	0.25	92.3	92.3	92.3	100.0		92.3/–
E. hormaechei (10)	≤0.06	≤0.06	100.0					100.0/–
E. sakazakii (23)	≤0.06	0.12	100.0					100.0/–
Hafnia alvei (48)	≤0.06	0.12	100.0					100.0/–
Klebsiella spp. (9228)	≤0.06	0.12	97.1	97.6	98.0	98.6	99.2	97.1/–
K. ozaenae (18)	≤0.06	0.25	94.4	94.4	94.4	100.0		94.4/–
Kluyvera spp. (13)	≤0.06	≤0.06	100.0					100.0/–
Pantoea spp. (160)	≤0.06	0.12	99.4	99.4	99.4	100.0		99.4/–
P. agglomerans (133)	≤0.06	0.12	99.3	99.3	99.3	100.0		99.3/–
Proteus penneri (20)	0.12	0.25	100.0					100.0/–
Providencia spp. (195)	0.12	0.25	98.0	100.0				98.0/–
P. rettgeri (57)	0.12	0.25	98.3	100.0				98.3/–
P. stuartii (96)	0.12	0.25	97.9	100.0				97.9/–
Raoultella ornithinolytica (25)	≤0.06	≤0.06	100.0					100.0/–
Serratia spp. (1993)	0.12	0.25	98.9	99.3	99.6	99.7	99.8	98.9/–
S. liquefaciens (48)	0.12	0.25	100.0					100.0/–
S. plymuthica (17)	≤0.06	0.12	100.0					100.0/–
S. rubidaea (13)	0.12	0.25	100.0					100.0/–
Yersinia enterocolitica (29)	≤0.06	≤0.06	100.0					100.0/–

[a] Susceptibility criteria of the USA-FDA (Doribax® Package Insert, 2008) for Enterobacteriaceae at ≤0.5 μg/mL.