Available online at www.sciencedirect.com
ScienceDirect
Diagnostic Microbiology and Infectious Disease 63 (2009) 440–446
DIAGNOSTIC MICROBIOLOGY AND INFECTIOUS DISEASE
www.elsevier.com/locate/diagmicrobio

Antimicrobial activity of doripenem tested against prevalent Gram-positive pathogens: results from a global surveillance study (2003–2007)☆

Thomas R. Fritsche[a,1], Helio S. Sader[a], Matthew G. Stillwell[a], Ronald N. Jones[a,b,*]

[a]JMI Laboratories, North Liberty, IA 52317, USA
[b]Tufts University School of Medicine, Boston, MA 02111, USA

Abstract

Doripenem is a broad-spectrum parenteral carbapenem recently approved in the United States for treatment of complicated urinary tract and intra-abdominal infections. Although pronounced doripenem antimicrobial activity against various Gram-negative pathogens, including anaerobes, has been confirmed, limited information has been forthcoming on the activity of this agent against leading Gram-positive species. We evaluated the activity of doripenem using reference broth microdilution procedures against a large collection of staphylococci, enterococci, and streptococci collected as part of a global (North America, 43.0%; Latin America, 11.7%; Europe, 31.3%; and Asia-Pacific, 14.0%) Doripenem Surveillance Program for the years 2003 to 2007. Doripenem was confirmed to be highly active against oxacillin-susceptible *Staphylococcus aureus* (22 389 isolates) and coagulase-negative staphylococci (2444 isolates; MIC_{90} values, ≤0.06 μg/mL), with no differences noted between geographic regions. Against *Enterococcus faecalis* (8714 isolates), doripenem displayed modest activity (MIC_{50}, 4 μg/mL) but was largely inactive against *Enterococcus faecium* (4233 isolates). Although not currently approved for treatment of respiratory tract infections in the United States, doripenem was highly active against *Streptococcus pneumoniae* (10 260 isolates; MIC_{90}, 0.5 μg/mL) and 2-fold more active than either ceftriaxone or cefepime. Doripenem activity was even more noteworthy against β-hemolytic streptococci (4598 isolates; MIC_{90}, ≤0.06 μg/mL, similar to that of penicillin) and viridans group streptococci (1887 isolates; MIC_{90}, 0.25 μg/mL). Doripenem appears broadly active in vitro against Gram-positive pathogens, a potency similar to that of other carbapenems, a distinct advantage that complements other attributes including β-lactamase and dehydropeptidase stability and activity against emerging multidrug-resistant Gram-negative pathogens.

Keywords: Doripenem; Carbapenems; Susceptibility; Gram-positive; Surveillance

1. Introduction

Broad-spectrum antimicrobial coverage is a standard management approach for dealing with the seriously ill hospitalized patient and often includes advanced generation β-lactams either singly or in combination with potentially synergistic codrugs (Kollef, 2008; Ibrahim et al., 2000). Therapeutic goals include minimizing patient morbidity and mortality, as well as limiting length of stay and emergence of resistance. In particular, the presence of extended-spectrum β-lactamases (ESBLs) and/or cephalosporinases in Enterobacteriaceae and the increasing prevalence of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in many centers have driven the increased empiric and directed use of the most potent β-lactam class, the carbapenems (Baldwin et al., 2008; Chen et al., 2005; Keam, 2008). Such therapy is often based upon the recognized spectrums of organisms inhibited by the agent, requiring precedent knowledge on the rates of resistance occurring within the institution and the geographic region. Although such Gram-negative species (including anaerobes) have become clearly problematic in the compromised patient population, the occurrence of Gram-positive infections (primarily staphylococcal, streptococcal, and enterococcal) offers additional therapeutic

☆ Presented in part at the 47th Annual ICAAC meeting held in Chicago. IL, September 17-20, 2007.

* Corresponding author. Tel.: +1-319-665-3370; fax: +1-319-665-3371.
E-mail address: ronald-jones@jmilabs.com (R.N. Jones).
[1] Current address: Marshfield Clinic, 1000 N Oak Ave, Marshfield, Wisconsin 54449, USA. Tel.: +1-715-221-6133; fax: +1-715-221-6128.

0732-8893/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.diagmicrobio.2009.01.019

Table 1
In vitro activity of doripenem and comparator antimicrobial agents tested against *S. aureus*, coagulase-negative staphylococci, and enterococci (Doripenem Surveillance Program, 2003–2007)

Organism (no. tested)/antimicrobial agent	MIC (μg/mL)		Cumulative percentage inhibited at MIC (μg/mL)					Percentage by category[a]
	50%	90%	≤0.5	1	2	4	8	Susceptible/resistant
S. aureus oxacillin susceptible (22 389)								
Doripenem	≤0.06	≤0.06	>99.9	>99.9	>99.9	100.0	–	–/–
Oxacillin	0.5	0.5	92.0	98.8	100.0	–	–	100.0/0.0
Cefepime	2	4	0.6	2.8	77.8	99.7	>99.9	>99.9/<0.1
Ceftazidime	8	8	–	0.1	0.3	14.1	94.4	94.4/0.3
Ceftriaxone	4	4	0.1	0.9	32.7	98.0	99.8	99.8/0.0
Daptomycin	0.25	0.5	99.3	>99.9	>99.9	100.0	–	>99.9/–
Imipenem	≤0.5	≤0.5	99.9	>99.9	>99.9	100.0	–	100.0/0.0
Levofloxacin	≤0.5	≤0.5	92.1	92.7	93.2	95.6	100.0	92.7/6.8
Linezolid	2	2	1.2	43.5	>99.9	100.0	–	100.0/–
Meropenem	0.12	0.12	99.9	>99.9	100.0	–	–	100.0/0.0
Piperacillin/tazobactam	≤1	2	12.1	66.3	98.8	99.7	99.9	99.9/0.1
Tetracycline	≤2	≤2	13.5	13.7	93.2	93.7	94.2	93.7/5.8
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	96.8	97.8	98.3	100.0	–	98.3/1.7
Vancomycin	1	1	18.3	98.5	>99.9	100.0	–	>99.9/0.0
CoNS oxacillin susceptible (2444)								
Doripenem	≤0.06	≤0.06	99.5	99.7	99.9	100.0	–	–/–
Oxacillin	0.25	0.25	100.0	–	–	–	–	100.0/0.0
Cefepime	0.5	2	55.4	88.3	98.7	99.8	>99.9	>99.9/0.0
Ceftazidime	4	8	–	0.9	5.4	61.6	96.2	96.2/0.6
Ceftriaxone	2	4	9.1	48.1	76.5	95.1	98.9	98.9/0.0
Daptomycin	0.25	0.5	95.1	99.8	99.9	100.0	–	99.8/–
Imipenem	≤0.5	≤0.5	99.7	100.0	–	–	–	100.0/0.0
Levofloxacin	≤0.5	4	86.7	87.6	89.0	92.3	100.0	87.6/11.0
Linezolid	1	1	36.6	98.1	99.8	99.8	99.9	99.8/–
Meropenem	≤0.06	0.12	99.0	99.3	99.6	100.0	–	100.0/0.0
Piperacillin/tazobactam	≤0.5	1	87.4	98.0	99.4	99.8	100.0	100.0/0.0
Tetracycline	≤2	>8	6.6	7.5	86.0	86.7	87.4	86.7/12.6
Trimethoprim/sulfamethoxazole	≤0.5	>2	84.7	85.8	87.9	100.0	–	87.9/12.1
Vancomycin	1	2	18.2	78.5	99.7	100.0	–	100.0/0.0
E. faecalis (8714)								
Doripenem	4	8	0.7	1.9	25.5	81.4	95.7	–/–
Ampicillin	≤1	2	–	68.1	94.3	98.4	99.5	99.5/0.5
Daptomycin	1	1	48.4	93.7	99.7	>99.9	100.0	>99.9/–
Gentamicin (high level)	≤500	>1000	–	–	–	–	–	67.2/32.8
Imipenem	2	4	4.7	44.7	88.5	97.1	99.3	99.5/–
Levofloxacin	1	>4	10.4	59.3	65.0	65.5	100.0	65.0/34.5
Linezolid	1	2	5.4	62.0	99.8	99.8	99.9	99.8/0.2
Meropenem	4	8	0.3	0.7	5.3	53.8	90.5	–/–
Piperacillin/tazobactam	4	8	0.1	0.7	6.1	74.0	92.3	99.5/–
Quinupristin/dalfopristin	>2	>2	0.6	0.8	4.8	100.0	–	0.8/95.2
Streptomycin (high level)	≤1000	>2000	–	–	–	–	–	69.5/30.5
Teicoplanin	≤2	≤2	11.2	11.2	97.5	97.6	97.6	97.6/2.3
Vancomycin	1	2	2.2	62.8	95.6	96.5	96.7	96.5/3.2
E. faecium (4233)								
Doripenem	>8	>8	0.4	0.6	1.0	1.9	5.3	–/–
Ampicillin	>16	>16	0.0	2.6	6.2	7.6	8.5	8.5/91.5
Daptomycin	2	4	6.8	36.4	86.9	99.8	>99.9	99.8/–
Gentamicin (high level)	≤500	>1000	–	–	–	–	–	62.3/37.7
Imipenem	>8	>8	0.7	1.5	2.4	5.7	7.2	–/–
Levofloxacin	>4	>4	0.8	3.9	11.0	14.7	100.0	11.0/85.3
Linezolid	1	2	1.3	59.7	98.6	98.9	99.6	98.6/1.1
Meropenem	>8	>8	0.5	0.6	0.8	1.4	3.0	–/–
Piperacillin/tazobactam	>64	>64	0.0	0.2	0.5	1.0	2.2	8.5/–
Quinupristin/dalfopristin	1	2	47.8	81.8	91.0	100.0	–	81.8/9.0
Streptomycin (high level)	2000	>2000	–	–	–	–	–	48.3/51.7
Teicoplanin	≤2	>16	5.0	5.5	56.2	56.4	57.3	57.3/38.0
Vancomycin	1	>16	18.0	51.0	53.2	53.8	54.3	53.8/45.2

CoNS = coagulase-negative staphylococci; – = no established breakpoint criteria.

[a] Interpretation criteria from M100-S18 (CLSI, 2008); β-lactam susceptibility, when testing staphylococci, should be directed by the oxacillin test results.