Activity of doripenem against extended-spectrum β-lactamase-producing Enterobacteriaceae and isolates

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Abstract: The in vitro activity of doripenem was evaluated against a recent collection of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae and Pseudomonas aeruginosa isolates (201 ESBL-producing Enterobacteriaceae [153 Escherichia coli and 48 Klebsiella pneumoniae] and 201 P. aeruginosa. Comparator agents included amikacin, tobramycin, ciprofloxacin, cefepime, cefotaxime, piperacillin-tazobactam, imipenem, and meropenem. Both doripenem and meropenem inhibited 100% of the ESBL-producing Enterobacteriaceae at ≤0.5 μg/mL. For these isolates, the MIC90 of doripenem (0.12 μmg/mL) was 4-fold lower than that of imipenem (0.5 μg/mL). Against P. aeruginosa, the MIC90 of doripenem and meropenem was 2 μg/mL, 4-fold lower than that of imipenem (8 μg/mL). At an MIC of ≤2 μg/mL, doripenem, meropenem, and impenem inhibited 90.5%, 89.6%, and 82.1% of P. aeruginosa isolates, respectively. Doripenem maintained activity against imipenem-nonsusceptible isolates of P. aeruginosa; at an MIC of ≤4 μg/mL, it inhibited 15 of the 25 isolates with MICs for imipenem of >4 μg/mL. Doripenem is active against ESBL-producing Enterobacteriaceae and P. aeruginosa isolates. Its activity is similar to that of meropenem and slightly better than that of imipenem. The results of this study suggest that doripenem could be an alternative therapeutic agent for infections caused by these organisms.

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Dr. Alex van Belkum
Editor-in-Chief
European Journal of Clinical Microbiology & Infectious Diseases

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Dear Dr. van Belkum,

Thank you for your e-mail dated April 30. We enclose a revised version of the manuscript.

Following the recommendations of the reviewer, we have addressed the following points:

1. MIC interpretations were made using EUCAST breakpoint criteria. We have therefore modified Table 1 (% Resistant strains) in accordance with these data. As we used the EUCAST breakpoints in Table 1, we have added a new comment in the text regarding the FDA susceptibility criteria applied to doripenem for Enterobacteriaceae and *P. aeruginosa* isolates. We have provided two references (nos. 11 and 12 in the revised manuscript) for the breakpoint concentrations.

2. A new Table showing the distribution of doripenem MICs for the organisms tested has been added.

3. The period during which the strains were isolated has been included in the new version of the manuscript.

4. When reviewing the original manuscript, we realized that the term “cefepime” (page 4, line 7) was incorrect. This has been changed in the new version to “ceftazidime”.

5. The Etest ESBL strips used for ESBL confirmatory test have been indicated in the revised manuscript. In the Results section we also indicate that all tested Enterobacteriaceae were confirmed to be ESBL-producing strains.

6. As requested, we have omitted the term “excellent” from the description of the activity of doripenem.

7. On Table 1, mg/L has been changed to µg/mL, as it appears in the rest of the manuscript.

8. We used two decimal places when describing MIC values for concentrations ≥ 0.03.

We hope that you will now find the manuscript suitable for publication in the Journal and we thank the reviewer for the suggestions.

Yours sincerely,

Carmen Betriu

ACTIVITY OF DORIPENEM AGAINST EXTENDED-SPECTRUM β-LACTAMASE-PRODUCING ENTEROBACTERIACEAE AND *Pseudomonas aeruginosa* ISOLATES

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Abstract

The in vitro activity of doripenem was evaluated against a recent collection of extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae and *Pseudomonas aeruginosa* isolates (201 ESBL-producing Enterobacteriaceae [153 *Escherichia coli* and 48 *Klebsiella pneumoniae*] and 201 *P. aeruginosa*. Comparator agents included amikacin, tobramycin, ciprofloxacin, cefepime, cefotaxime, piperacillin-tazobactam, imipenem, and meropenem. Both doripenem and meropenem inhibited 100% of the ESBL-producing Enterobacteriaceae at ≤0.5 µg/mL. For these isolates, the MIC_{90} of doripenem (0.12 µmg/mL) was 4-fold lower than that of imipenem (0.5 µg/mL). Against *P. aeruginosa*, the MIC_{90} of doripenem and meropenem was 2 µg/mL, 4-fold lower than that of imipenem (8 µg/mL). At an MIC of ≤2 µg/mL, doripenem, meropenem, and impenem inhibited 90.5%, 89.6%, and 82.1% of *P. aeruginosa* isolates, respectively. Doripenem maintained activity against imipenem-nonsusceptible isolates of *P. aeruginosa*; at an MIC of ≤4 µg/mL, it inhibited 15 of the 25 isolates with MICs for imipenem of >4 µg/mL. Doripenem is active against ESBL-producing Enterobacteriaceae and *P. aeruginosa* isolates. Its activity is similar to that of meropenem and slightly better than that of imipenem. The results of this study suggest that doripenem could be an alternative therapeutic agent for infections caused by these organisms.

Keywords: Doripenem, Susceptibility, Extended-spectrum β-lactamase-producing Enterobacteriaceae, *Pseudomonas aeruginosa*

Introduction

The incidence of extended-spectrum-β-lactamase (ESBL)-producing Enterobacteriaceae has been increasing worldwide to the extent that it is now an important cause of both hospital- and community-acquired infections [1]. *Pseudomonas aeruginosa* remains a major pathogen. Its intrinsic resistance to multiple antibiotics and its capability to develop mutational resistance to commonly used antimicrobials make treatment of this entity challenging [2, 3].

Doripenem is a new parenteral 1-β-methyl carbapenem with broad activity against gram-positive bacteria, Enterobacteriaceae, anaerobes, and non-fermentative bacilli such as *P. aeruginosa* [4-8]. Like other carbapenems, doripenem is stable against human renal dehydropeptidases and to many β-lactamases. The purpose of this study was to evaluate the in vitro activity of doripenem and comparator agents against a recent collection of ESBL–producing Enterobacteriaceae and *P. aeruginosa* isolates.

Materials and methods

A total of 402 isolates collected from 2006 to 2008 were processed. Identification was by ID 32 GN (bioMérieux, Marcy l'Etoile, France). The isolates tested comprised 201 ESBL-producing Enterobacteriaceae (153 *Escherichia coli* and 48 *Klebsiella pneumoniae*) and 201 *P. aeruginosa*. *E. coli* ATCC 25922, *E. coli* ATCC 35218, and *P. aeruginosa* ATCC 27853 were used as quality control strains

Isolates were tested using the reference broth microdilution method of the Clinical Laboratory Standards Institute (CLSI) [9]. Cation-adjusted Mueller-Hinton broth was used. The antibiotics evaluated were doripenem, tobramycin,

ciprofloxacin, cefepime, cefotaxime, ceftazidime, piperacillin-tazobactam, imipenem, and meropenem. According to the CLSI [10] criteria, *E. coli and Klebsiella* spp. isolates with increased MIC results (≥2 µg/mL) for cefotaxime and/or ceftazidime were suspected of being ESBL-producing isolates. Phenotypic confirmation of these strains was performed using Etest ESBL strips (cefotaxime/cefotaxime+clavulanic acid, and ceftazidime/ceftazidime+clavulanic acid) (bioMérieux, Marcy l'Etoile, France). Isolates were defined as susceptible or resistant to antibiotics in accordance with the breakpoints approved by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [11]

Results and discussion

Table 1 summarizes the MICs of doripenem and the comparator agents against the bacterial isolates included in the study. The phenotypic confirmatory test confirmed all Enterobacteriaceae isolates to be ESBL-producers. Doripenem showed activity against the ESBL-producing isolates tested. The doripenem MICs at which 50% and 90% of the isolates were inhibited (MIC_{50} and MIC_{90}) were 0.06 µg/mL and 0.12 µg/mL, respectively. Both doripenem and meropenem inhibited 100% of the ESBL-producing Enterobacteriaceae at ≤0.5 mg/L. Most of these organisms (96%) were resistant to ciprofloxacin. The MIC_{90} of doripenem (0.12 µg/mL) was 4-fold lower than that of imipenem (0.5 µg/mL) for the ESBL-producing Enterobacteriaceae.

Against *P. aeruginosa*, the MIC_{90} of doripenem and meropenem were both 2 µg/mL, 4-fold lower than that of imipenem (8 µg/mL). At a concentration of ≤2 µg/mL, doripenem, meropenem, and imipenem inhibited 90.5%, 89.6%, and 82.1% of *P. aeruginosa* isolates, respectively. Other agents with similar

activity to doripenem against *P. aeruginosa* included tobramycin, cefepime, and amikacin (90% to 95% of susceptibility). Doripenem maintained its activity against imipenem-nonsusceptible isolates of *P. aeruginosa*. At a concentration of ≤4 µg/mL, doripenem inhibited 15 of the 25 isolates with MICs for imipenem of >4 µg/mL.

The distribution of doripenem MICs against the organisms tested is indicated in Table 2. According to the doripenem breakpoints approved by the US Food and Drug Administration (FDA) (susceptible, ≤0.5 µg/mL for Enterobacteriaceae, and ≤2 µg/mL for *P. aeruginosa*) [12], all of the ESBL-producing Enterobacteriaceae and 90.5% of the *P. aeruginosa* isolates were susceptible to doripenem.

In this study, doripenem is very active against ESBL-producing Enterobacteriaceae and *P. aeruginosa* isolates. Its activity is similar to that of meropenem and slightly better than that of imipenem. Our results are consistent with those of other investigators [4,7].

Doripenem is well tolerated and less associated with the adverse effects when compared with imipenem or meropenem [13,14]. It also showed less potential to select resistant mutants than meropenem [15, 16]. As has been described in previous studies [4,7,17], we also found some *P. aeruginosa* isolates that were resistant to imipenem and meropenem with low MICs for doripenem. These favourable characteristics, together with the potent in vitro activity observed in this study and by other authors [4-7], suggest that doripenem could be a therapeutic alternative against infections caused by these multidrug-resistant organisms.

Acknowledgments

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Table 1. In vitro activities of doripenem and other antimicrobial agents against extended-spectrum-β-lactamase (ESBL)–producing Enterobacteriaceae and *Pseudomonas aeruginosa* isolates.

Organism (no. of isolates)	Antimicrobial agent	MIC (µg/mL)			% Resistant strains [b]
		Range	50%	90%	
(ESBL)–producing Enterobacteriaceae[a] (201)	Doripenem	0.015 - 0.5	0.06	0.125	0
	Imipenem	≤0.25 - 2	≤0.25	0.5	0
	Meropenem	≤ 0.05	≤0.5	≤0.5	0
	Piperacillin-tazobactam	≤ 8 - >64	≤8	>64	27.4
	Cefotaxime	≤ 1 - >32	32	>32	93.0
	Ceftazidime	≤ 0.25 - >16	8	>16	57.2
	Cefepime	≤ 1 - >16	8	>16	53.2
	Amikacin	≤ 4 - >32	≤4	16	5.0
	Tobramycin	≤ 2 - >8	8	>8	52.5
	Ciprofloxacin	≤0. 25 - >2	>2	>2	96.0.
P. aeruginosa (201)					
	Doripenem	0.06 - >8	0.5	2	5.0
	Imipenem	≤ 0.2 5 - >8	1	8	9.5
	Meropenem	≤ 0.5 - >8	≤ 0.5	2	4.5
	Piperacillin-tazobactam	≤8 - >64	≤ 8	32	11.9
	Ceftazidime	≤0.25 - >16	1	16	11.5

Table 1 (continued)

Organism (no. of isolates)	Antimicrobial agent	MIC (µg/mL)			% Resistant strains [b]
		Range	50%	90%	
	Cefepime	≤1 - >16	≤ 1	8	6.5
	Amikacin	≤4 - >32	≤4	8	2.0
	Tobramycin	≤2 - >8	≤ 2	≤2	9.5
	Ciprofloxacin	≤0.25 - >2	≤ 0.25	>2	23.4

[a] *E. coli*, 153 isolates and *K. pneumoniae*, 48 isolates.

[b] MICs for resistant isolates are those approved by the EUCAST [11].

Table 2. Distribution of doripenem MICs

Organism (no. of isolated tested)	Cumulative % inhibited at MIC (µg/mL)								
	≤ 0.06	0.12	0.25	0.5	1	2	4	8	>8
E. coli (153)	88.9	98.0	99.3	100					
K. pneumoniae (48)	50.0	83.3	100						
P. aeruginosa (201)	3.5	10.9	33.8	59.2	80.6	90.5	95.0	99.0	100