COMMUNICATION TO THE EDITOR

Antimicrobial activity of doripenem against bacterial isolates from humans and animals

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β -Lactam antibiotics, such as penicillins, cephalosporins and carbapenems, are the largest family of antimicrobial agents, and have been widely used in this clinical practice.¹ However, the emergence and the increased frequency of antimicrobial resistance has become a serious health problem. For this reason, the development of new antimicrobial drugs becomes a worldwide priority. Doripenem (formerly known as S-4661) is a new synthetic 1- β -methyl carbapenem antibiotic developed by Shionogi (Osaka, Japan). Doripenem is a new synthetic 1- β -methyl carbapenem antibiotic with a broad-spectrum activity against clinically

pathogens including *Enterobacteriaceae*, non-fermenting gram-negative, anaerobes, and many gram-positive both *in vivo* and *in vitro*, including some carbapenem resistant.^{2–5} Recently, doripenem was indicated in the United States and Europe for the treatment of intraabdominal and complicated urinary tract infections including pyelonephritis, and approved in the Europe for patients with nosocomial pneumonia including ventilator-associated pneumonia.⁴

The aim of this study is to evaluate the *in vitro* activity of doripenem against enterococci and *E. coli* isolates from wild animals, pigs, pets, poultry and humans in Portugal.

A total of 938 isolates were tested, including 522 enterococci and 416 *E. coli* (62 of which produced extended-spectrum β -lactamases (ESBLs)) were previously recovered from fecal samples of human and animal origin and characterized by using specific primers to species identification and detection of antibiotic resistant genes.⁶ Doripenem standard powder was provided by Johnson & Johnson Pharmaceutical Research & Development, LLC (Raritan, NJ, USA). Doripenem dilutions were prepared and dissolved as recommended by the manufacturer, from a stock solution. The minimum inhibitory concentration (MIC) of doripenem were

Table 1 *In vitro* activity of doripenem against *Escherichia faecium*, *E. faecalis*, *E. coli* and ESBL-containing *E. coli* isolates from human and animal origin

Species	Source	Number of isolates	Number of isolates at each doripenem MIC (mg l ⁻¹)														MIC ₅₀	MIC ₉₀
			0.031	0.062	0.125	0.25	0.5	1	2	4	8	16	32	64	128	>128		
<i>E. faecalis</i>	Human	40						5	6	10	17	2					4	8
	Poultry	92							6	51	31	4					4	8
	Pets	45						7	11	9	15	3					4	8
	Wild animals	73					11	13	25	17	7						2	4
<i>E. faecium</i>	Human	106										7	10	7	32	50	128	>128
	Poultry	54											4	7	19	24	128	>128
	Pets	67										1	4	33	29		64	128
	Wild animals	45										2	12	13	14	4	64	128
<i>E. coli</i>	Human	92	42	18	12	20											0.062	0.25
	Swine	64	35	8	21												0.031	0.125
	Poultry	72	40	14	16	2											0.031	0.125
	Wild animals	126	118	6	2												0.031	0.031
ESBL-containing <i>E. coli</i>	Human	3	3														NA ^a	NA ^a
	Swine	16	15	1													0.031	0.031
	Poultry	24	14	3	7												0.031	0.125
	Wild animals	19	18	1													0.031	0.031

Abbreviations: ESBL, extended-spectrum β -lactamases; MIC, minimum inhibitory concentration.
^aNA, not applicable. Insufficient strains to calculate MIC₅₀ and MIC₉₀.

determined using the Clinical Laboratory Standards Institute microbroth dilution method.⁷ The reference strains tested included *E. faecalis* ATCC 29212 and *E. coli* ATCC 25922. Interpretation of MIC results was performed in accordance with Clinical Laboratory Standards Institute breakpoints criteria.

The distribution of the doripenem MICs against enterococci and *E. coli* isolates, from different species and origins, is shown in Table 1. All the *E. faecalis* were inhibited by $\leq 16.0 \text{ mg l}^{-1}$ doripenem, whereas *E. faecium* isolates showed higher doripenem MIC values (range from 16.0 to $\geq 128 \text{ mg l}^{-1}$). These results are very similar to those obtained during the surveillance study reports against gram-positive pathogens, wherein the MIC₅₀ and MIC₉₀ values were 4 and 8 mg l^{-1} , respectively. Although doripenem inhibited *E. faecalis* isolates the clinical significance of this surveillance data remains uncertain.³ Moreover, the enterococci isolates from wild animals showed twofold more susceptibility to doripenem in comparison with other enterococcal origin, except in the *E. faecium* pets isolates, in which it showed an identical MIC₅₀ and MIC₉₀.

The *E. coli* isolates were significantly more susceptible than enterococci isolates, with MIC₅₀ and MIC₉₀ values between 0.031 and 0.25 mg l^{-1} , respectively. The doripenem activity against *E. coli* was similar to that demonstrated recently by others for doripenem activity against *Enterobacteriaceae*, in which the overall MIC₉₀ values have ranged from 0.03 to 0.5 mg l^{-1} .⁵ It is interesting to underline the relatively lower susceptibility of the human *E. coli* isolates to the doripenem,

showing a MIC₅₀ and MIC₉₀ twofold greater than animal *E. coli* isolates. This lower susceptibility in human isolates can reflect the different use of antimicrobials in humans, animals, and consequently in the environment. In general, ESBL producers show lower susceptibility to the majority of the beta-lactam antibiotics than the non-producers.⁵ Our study showed that ESBL-containing *E. coli* isolates are susceptible to doripenem with MIC₅₀ and MIC₉₀ values between 0.031 and 0.125 mg l^{-1} , respectively. These present data support the findings of others authors, wherein doripenem, as others carbapenems, meropenem and imipenem, remains active against ESBL-containing *Enterobacteriaceae*.^{5,8}

In summary, although doripenem has not been effective among enterococci, our *in vitro* study has shown that this new antibiotic is a potent agent against *E. coli*, including ESBL-containing *E. coli* isolates, and can be an attractive choice, alone or in combination with others antimicrobial agents, to optimize therapeutic treatment success, including infections caused by multidrug resistant strains.

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