



In-Vitro Interactions of Doripenem With Other Antibacterial Agents

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ABSTRACT

Introduction: Doripenem is a novel 1-β-methyl carbapenem, slightly more active than meropenem. As with any potent antibiotic it is likely to be used in combination with other agents in empiric settings, either seeking synergy, or where β-lactam-resistant gram-positive cocci are among the likely pathogens. We therefore tested doripenem's activity in combination.

Methods and Materials: Interactions between doripenem and daptomycin, levofloxacin, linezolid, and vancomycin were assessed by agar chequerboards vs 28 staphylococci, enterococci, and pneumococci; interaction with amikacin, levofloxacin, and co-trimoxazole were assessed similarly vs 17 Enterobacteriaceae and 19 nonfermenters.

Results: Doripenem combinations mostly gave addition or, against a minority of isolates, weak synergy, such that geometric mean ΣFIC values were between 0.7 and 1.0, with values for individual isolates mostly between 0.5 and 1.3. Exceptions were (i) doripenem with co-trimoxazole vs gram-negative bacteria, with a geometric mean ΣFIC, 1.07, reflecting frequent indifference or weak antagonism (ΣFIC up to 3.0) of the co-trimoxazole component by doripenem vs *Pseudomonas aeruginosa* only and (ii) doripenem with daptomycin or levofloxacin, with geometric mean ΣFICs of 0.63 and 0.66, respectively, reflecting weak synergy (typically ΣFIC 0.375 to 0.53) vs many *Enterococcus faecalis* and methicillin-resistant *Staphylococcus aureus*, though not other groups. Only in the case of daptomycin and *E. faecalis* did this synergy occur at clinically relevant antibiotic concentrations.

Conclusions: The in-vitro data suggest that doripenem could be safely combined with a range of other antimicrobial agents without risk of antagonism, though with little potential for synergy, except perhaps with daptomycin vs enterococci.

INTRODUCTION

Doripenem is a new 1 β-methyl carbapenem with similar or one-dilution better activity than meropenem.

Doripenem is presently in phase III clinical trials, including for ventilator-associated pneumonia.

Doripenem, like other carbapenems, will mostly be used as monotherapy but it may be used in combination, for example:

- In empirical settings, if methicillin-resistant *Staphylococcus aureus* (MRSA) or enterococci may be present as well as carbapenem-susceptible organisms

- In severe *Pseudomonas aeruginosa* infections, seeking synergy

We therefore investigated the in-vitro interactions of doripenem with other antimicrobial agents.

METHODS AND MATERIALS

Bacteria were selected to represent:

- "Normal" levels of susceptibility, typical for the species

- Doripenem-resistant strains (with resistance definition as for meropenem)

- A wide range of species

Combination agents vs gram-positive bacteria were:

- Daptomycin, levofloxacin, linezolid, and vancomycin

Combination agents vs gram-negative bacteria were:

- Amikacin, co-trimoxazole, and levofloxacin

Chequerboard titration tests were done between doripenem and combination agents on Oxoid Mueller-Hinton agar or, for daptomycin combinations only, on Mast Isotonic Agar with 50 mg/L added Ca⁺⁺. For gram-positive cocci, tests were repeated with 5% sheep blood added, so that pneumococci could be included.

RESULTS

Tables 1 and 2 show geometric mean ΣFIC values for different species groups tested with each combination, whilst **Figures 1 and 2** show ΣFIC distributions.

Most combinations showed addition or weak synergy, with ΣFIC 0.5-1 (some authorities consider synergy to be ΣFIC ≤0.625 but most now base it on values of ≤0.5).

Exceptions to these generalisations were:

- **Doripenem plus co-trimoxazole** – ΣFIC values often indifferent (ΣFIC 1-2) or weakly antagonistic (ΣFIC >2) for *P. aeruginosa*. This is of questionable significance since antagonism entailed a rise in the MIC of co-trimoxazole, a drug to which *P. aeruginosa* is resistant: doripenem MICs were not increased by co-trimoxazole.

- **Doripenem plus daptomycin** – ΣFIC values often ≤0.5 for *E. faecalis* and MRSA, but higher for methicillin-susceptible *S. aureus* (MSSA) or pneumococci. Since *E. faecalis* is only marginally resistant to doripenem and daptomycin MICs are little below breakpoint, this may be of some value.

- **Doripenem plus levofloxacin** – ΣFIC values often ≤0.5 for *E. faecalis* and MRSA but higher for MSSA and pneumococci. Unlikely to be of much value, as susceptibility to the combination remained marginal, and better agents are available against these pathogens.

No consistent synergy between doripenem and other agents vs *P. aeruginosa* with metallo-carbapenemases nor vs the 3 carbapenem-resistant *Acinetobacter baumannii* strains now prevalent in London and SE England (**Table 3** and **Figure 3**).

Table 1. Geometric mean ΣFIC values for doripenem combinations vs gram-negative bacteria

	Amikacin	Co-trimoxazole	Levofloxacin
Enterobacteriaceae (17)	0.87	0.99	0.96
<i>Acinetobacter</i> spp. (5)	0.79	0.81	0.97
<i>P. aeruginosa</i> (14)	0.65	1.29	0.85
All	0.76	1.07	0.92

Table 2. Geometric mean ΣFIC values for doripenem combinations vs gram-positive bacteria

Without blood	Daptomycin	Levofloxacin	Linezolid	Vancomycin
<i>E. faecalis</i> (6)	0.59	0.54	0.71	0.62
MRSA (5)	0.48	0.57	0.60	0.86
MSSA (6)	0.86	0.86	0.96	0.96
All (17)	0.63	0.66	0.75	0.78

With 5% sheep blood	Daptomycin	Levofloxacin	Linezolid	Vancomycin
<i>E. faecalis</i> (6)	0.59	0.54	0.71	0.62
MRSA (6)	0.48	0.57	0.60	0.86
MSSA (5)	0.86	0.86	0.96	0.96
<i>S. pneumoniae</i> (6)	0.93	0.83	0.90	0.79
All	0.75	0.71	0.85	0.84

MRSA = methicillin-resistant *S. aureus*, MSSA = methicillin-susceptible *S. aureus*

FIGURE 1. ΣFIC distributions, gram-negative bacteria

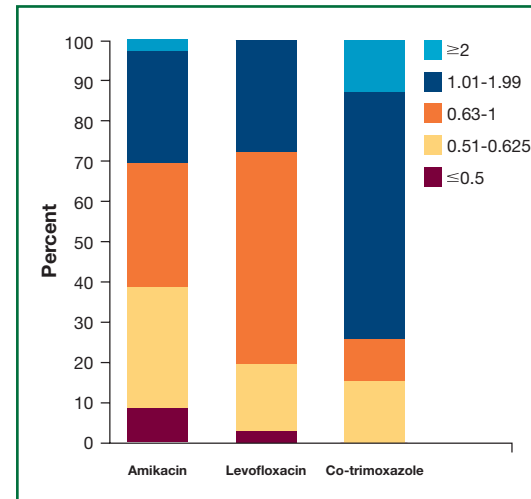


FIGURE 2A. ΣFIC distributions, gram-positive bacteria, tested without blood

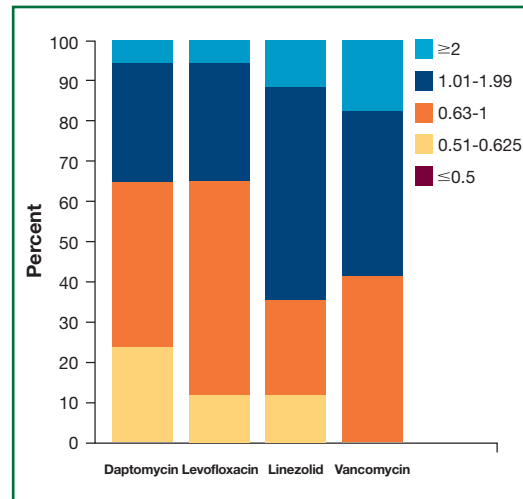


FIGURE 2B. ΣFIC distributions, gram-positive bacteria, tested with 5% blood

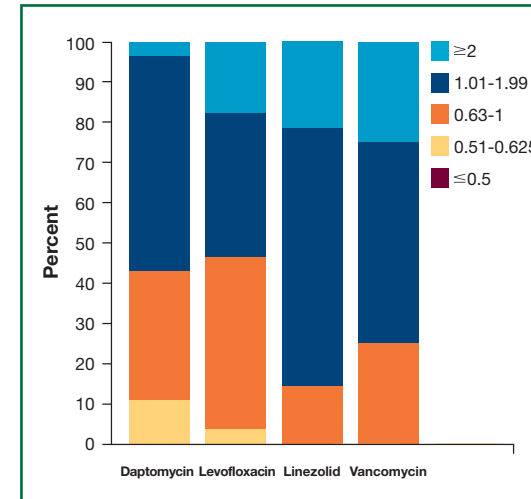
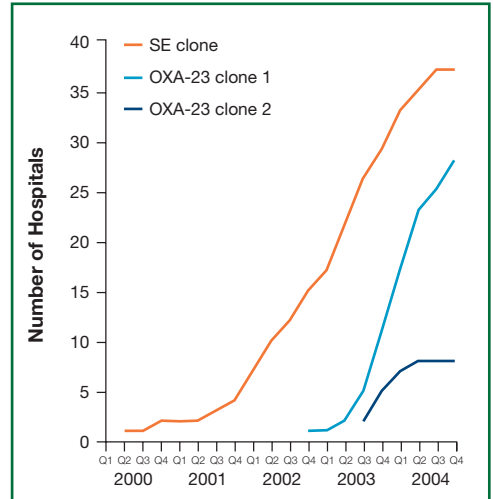


FIGURE 3. Cumulative number of UK hospitals affected by major carbapenem-resistant A. baumannii clones



CONCLUSIONS

Doripenem has a very broad spectrum, resembling that of meropenem. This will normally allow use as monotherapy but doripenem can be used in combination vs difficult strains or when empirical therapy seeks coverage including enterococci and MRSA.

Most doripenem interactions were additive or weakly synergetic, as is anticipated for carbapenems, but indifference and weak antagonism occurred with co-trimoxazole vs *P. aeruginosa*. Synergy was most apparent with daptomycin and levofloxacin vs *E. faecalis* and MRSA. The daptomycin interactions vs enterococci may deserve further study.

Antagonism was uncommon except with co-trimoxazole vs *P. aeruginosa*, where it involved a rise only in the co-trimoxazole MIC.

No useful synergy was seen with amikacin, co-trimoxazole, and levofloxacin vs doripenem-resistant *P. aeruginosa* that produced metallo-β-lactamases, nor against epidemic *Acinetobacter* clones with OXA carbapenemases.