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Evaluation of doripenem in an experimental model of resistant *Pseudomonas aeruginosa* pneumonia

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Sir,

In a previous study we demonstrated that doripenem, the most recently approved carbapenem, exhibited antimicrobial activity similar to that of imipenem or meropenem in an experimental rabbit model of susceptible *Pseudomonas aeruginosa* pneumonia.[1] Mutational inactivation of *oprD* is known to be the main mechanism of imipenem resistance in the absence of acquired carbapenemase. Although *oprD* inactivation also increases the MICs of meropenem and doripenem, clinical resistance to these drugs is thought to require additional mechanisms.[2] In this work we compared the efficacy of doripenem versus imipenem or meropenem against a resistant *oprD*-inactive strain of *P. aeruginosa* in an experimental model.

The experimental rabbit model of pneumonia has been described previously.[3] The bacterial strain was a Δ*oprD* PAO1, which is resistant to carbapenems after inactivation of OprD porin, a carbapenem-specific transport porin.[4] This strain was provided by courtesy of Professor P. Plésiat, Besançon, France. MICs of meropenem, doripenem and imipenem were 8, 1 and 16 mg/L, respectively. Antibiotics were delivered through a venous catheter, with changing infusion rates determined by computer-controlled electric pumps, in order to simulate the pharmacokinetics observed in human serum.[5]

Animals were randomly assigned to four groups: (i) controls (no treatment); (ii) meropenem group [computer-controlled syringe-pump infusion to simulate a human equivalent (HE) dosage of meropenem of 1 g three times daily]; (iii) doripenem group (simulating an HE dosage of doripenem of 0.5 g three times daily); and (iv) imipenem group (simulating an HE dosage of imipenem of 1 g three times daily). Evaluation of infection was performed at the end of treatment (2 days). The spleen and both lungs from each animal were weighed and homogenized in 1 mL of saline buffer and used for quantitative cultures on agar for 24 h at 37°C. Viable counts after 24 h of incubation were expressed as the mean ± SD $\log_{10}$ cfu/g of lung. Spleen culture results were expressed quantitatively (positive or negative).

From each animal, plasma antibiotic concentrations were determined by a microbioassay to obtain a pharmacokinetic analysis. Selection of variants resistant *in vivo* to doripenem, meropenem or imipenem was evaluated by spreading undiluted homogenates on agar plates that contained the appropriate antibiotic at a concentration of 4-fold the MIC. Bacterial counts were determined after 48 h of incubation at 37°C.

Quantitative variables were compared using one-way analysis of variance. This analysis was completed with a *post hoc* Bonferroni test. Proportions (percentages) were compared using Fisher's exact test. $P<0.05$ was considered statistically significant. Animals were treated in accordance with institutional policies and the guidelines stipulated by the animal welfare committee. The Committee of Animal Ethics of the University of Nantes approved all animal experimentation in this study.

Mean pulmonary bacterial loads were 3.1 ± 1.3, 2.6 ± 0.4 and 2.8 ± 0.7 $\log_{10}$ cfu/g for meropenem, doripenem and imipenem, respectively, compared with 5.9 ± 0.8 $\log_{10}$ cfu/g for control animals. The results of these pulmonary bacterial counts are shown in Figure 1; they were significantly lower in the treated animals compared with the controls ($P<0.05$), but were similar between the different antibiotic regimens. The proportions of positive versus negative spleen cultures for controls, meropenem, doripenem and imipenem were 4/3, 3/4, 1/6 and 2/7, respectively; they were not statistically different. No resistant mutants were isolated from any of the post-treatment biological samples.

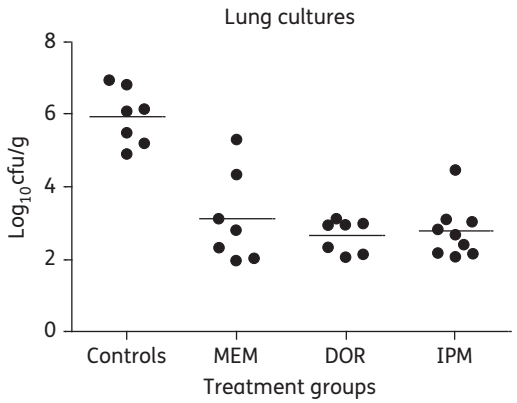

Figure 1. Pulmonary bacterial counts after 2 days of treatment (lung). MEM, meropenem; DOR, doripenem; IPM, imipenem.

Table 1. Pharmacokinetic/pharmacodynamic parameters for the different treatment groups (meropenem, doripenem and imipenem)

	Meropenem 1 g×3	Doripenem 0.5 g×3	Imipenem 1 g×3
C_{max} (mg/L), mean ± SD	42 ± 12	45 ± 8	75 ± 16
$t_{1/2}$ (h:min)	01:23	01:36	01:10
Percentage of time above MIC	57	100	44
Estimated AUC (mg·h/L)	53	33	76

Despite higher MICs, humanized imipenem and meropenem were as efficient as doripenem in this experimental model of resistant *P. aeruginosa* pneumonia; the three regimens achieved significant bactericidal activity within the lungs, despite MICs of 8 mg/L of meropenem and 16 mg/L of imipenem. Such an efficacy is surprising for the imipenem-resistant strain, though pharmacokinetic data could offer an explanation.[6] Pharmacokinetic/pharmacodynamic parameters are summarized in Table 1. The periods of time above MIC were 4 h 35 min (57%), 8 h (100%) and 3 h 29 min (44%) for meropenem, doripenem and imipenem, respectively. These time periods could explain imipenem's clinical efficacy, even for the *in vitro* resistant strain. This is also a possible explanation for the observed difference in the three treated groups. Even though differences between bactericidal activity did not reach significance, we observed less spread within the results for animals treated with doripenem compared with the other two groups; this also resulted in a smaller standard deviation in the doripenem group. This may confer an advantage to this drug when treating resistant organisms.

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Transparency declarations

None to declare.

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