The Pharmacodynamics of Doripenem Against Pseudomonas aeruginosa and Acinetobacter spp.

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Abstract

Background: Doripenem (dori) is a novel parenteral carbapenem with broad in vitro activity against Gram-negative pathogens such as Enterobacteriaceae and Acinetobacter spp. (MIC 0.2-2.5 μg/mL, respectively). The dose-T>MIC relationship to antibacterial effect (ABE) and emergence of resistance (EoR) are well studied for these species. We aim in this vitro pharmacodynamic model (IVPM) to examine the relationship of T>MIC to ABE and EoR.

Methods: A single-compartment IVPM was used to simulate dosing every 8 hours to produce a T>MIC range (100%). Two strains of P. aeruginosa (MC 0.24 and 0.75 μg/mL) and 3 strains of Acinetobacter (MIC 0.45, 0.75, and 3 μg/mL) were used. The initial inoculum was 250 μg/mL, experiments were performed over 48 h, MIC was assumed to be a log change in viable count at 24 h (d24) and growth on MIC x2 plates at day 24 was examined. T>MIC was related to d24 using a sigmoid Emax model.

Results: The T>MIC for P. aeruginosa strain MC 0.24 and 0.75 μg/mL to produce a 2-log drop in viable count was 24 and 25 ± 11%, respectively. For the 3 Acinetobacter strains (MIC 0.45, 0.75, and 3 μg/mL), T>MIC for static effect was 37 ± 12, 30 ± 11, and 50 ± 12 for log changes of 2, 1, and 0 log CFU/mL, respectively. Growth on MIC x2 and x4 plates occurred at T>MIC of ≥32%.

Conclusions: For dori, >10% T>MIC was associated with a 2-log reduction in viable count of P. aeruginosa and Acinetobacter spp. Risk of EoR is minimal if ≥15% T>MIC is maintained.

Introduction

• Doripenem is an important carbapenem. It has a single-6-hydroxy group protecting against β-lactamase and a 1-methyl group preventing metabolism by renal dehydropeptidases.

• A new, specific activity of in vitro killing and in vivo activity, with the benefit of lower minimum inhibitory concentrations (MIC) to Pseudomonas aeruginosa.

Doripenem MICs for P. aeruginosa are in the range of 0.125-6.25 μg/mL, with strains having an 8-log to 10-fold difference in sensitivity of MIC due to differences compared with imipenem and meropenem.

• Doripenem MICs of Acinetobacter spp. are similar to those of imipenem, with less than a 1-log killing difference between strains.

• Pharmacokinetics are linear and a single intravenous (IV) bolus injection of 500 mg gives a peak AUC of 28-32 ng/mL and an AUC of 35-40 ng/mL. The terminal half-life is about 1 hour, with about 10% of the dose appearing unchanged in the urine. Protein binding is ~93%.

• Free dori-T>MIC is the dominant pharmacodynamic index for dori at the murine thigh infection model, exposure of >30% T>MIC was associated with a 24-hour static effect, whereas exposures of ≥90% T>MIC were associated with maximum killing.

• Doripenem is approved in the United States for complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI). In Europe, doripenem is approved for cIAI and cUTI, as well as nosocomial pneumonia and ventilator-associated respiratory infections. Doripenem has not been approved for cUTI in the USA.

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• A single compartment IVPKM was used to simulate dori dosing 8 hrly to produce a T>MIC range (100%). Two strains of P. aeruginosa (MC 0.24 and 0.75 μg/mL) and 3 strains of Acinetobacter (MIC 0.45, 0.75, and 3 μg/mL) were used. The initial inoculum was 250 μg/mL, experiments were performed over 48 h, MIC was assumed to be a log change in viable count at 24 h (d24) and growth on MIC x2 plates at day 24 was examined. T>MIC was related to d24 using a sigmoid Emax model.

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Conclusions: For dori, >10% T>MIC was associated with a 2-log reduction in viable count of P. aeruginosa and Acinetobacter spp. Risk of EoR is minimal if ≥15% T>MIC is maintained.