Background: An improved understanding of how antibiotic exposure affects the risk of antibiotic resistance is essential to any dosing strategy. This is especially important for carbapenems, which are widely used to treat severe sepsis due to Gram-negative rods. We used an in vitro pharmacokinetic model (VTPKM) to establish the drug exposure of doripenem (dor) related to emergence of resistance in P. aeruginosa (Pa).

Methods: A fractional, single compartment VPKPM was used to simulate dor T>MIC values in the range 0-100%. An inoculum of 10^5 CFU/mL was used with a Pa strain MIC 0.5mg/L. Total viable counts and resistant subpopulations were quantified over 48 h. Subpopulations were assessed by culture onto recovery media containing MICSx2, x4, x8, and x16. The pharmacodynamic index was related to antibacterial effect and resistant subpopulations using a sigmoid (E)max model.

Results: The T>MIC for a 24-h static effect, -1 log, and -2 log drop were 29.8%, 32.5%, and 35.6%, respectively. Emergence of resistance (EoR) on MICSx4 plates occurred maximally at 12%-25%. Dose fractionation was performed with a fixed T>MIC of 12.5%, 25% and 37.5%. Dor was administered either 48 hourly, 24 hourly, or 8 hourly over 48 h. Growth on MICSx8 plates at 24 h and 48 h is shown.

INTRODUCTION

• Doripenem is an injectable carbapenem. It has a trans-6-hydroxyethyl group protecting against β-lactamases and a (β-1)-methyl group preventing inactivation by renal dihydropeptidases.
• Doripenem has a similar spectrum to imipenem and meropenem with the benefit of lower MICs than imipenem to Pseudomonas aeruginosa.
• Doripenem MIC50 for P. aeruginosa are in the range 0.125-0.5 mg/L with strains on average a 2 log-3 doubling dilution reduction of MIC compared with imipenem.
• Pharmacokinetics are linear and a single IV 1-hour infusion of doripenem 500 mg gives a Cmax in 25-25 mg/L and an AUC of 35-40 mg•h/L. The terminal half-life is about 1 h and protein binding is 40%.
• T>MIC is the dominant pharmacodynamic index. The T>MIC to produce a 24-h bacteriostatic effect, -1 log drop, and -2 log drop with P. aeruginosa were 25% ± 11%, 30% ± 11%, and 35% ± 13%, respectively. Emergence of resistant subpopulations occurred at T>MIC 12.5%-29%.
• We used an in vitro dilutional pharmacokinetic model of infection to simulate different T>MIC exposures and different dose fractionations to achieve the different T>MIC exposures in order to assess the impact on P. aeruginosa population dynamics.

MATERIALS AND METHODS

In Vivo Pharmacokinetic Model

• A single-compartment dosing model was employed: 90% Medline’s were both passed through the lungs to the bacterial chamber via a peristaltic pump at a flow rate of 0.21 mL/h (basal halff-life 1 h). Doripenem was added every 1 h, 24 h, or 48 h.
• Doripenem MIC50 was used with an MIC close to the MICmax of 0.24 mg/L was used, a strain with an MIC close to the MICmax.

Pharmacokinetics

• A range of pharmacokinetic profiles were simulated initially to produce a T>MIC range of 0-100%, then 8-hourly, 24-hourly, 48-hourly doses of doripenem were simulated to produce T>MIC targets of 12.5%, 25%, and 37.5%

Antibacterial Effect and Emergence of Resistance

• Experiments were performed with an initial inoculum of 10^5 CFU/mL. Simulations were performed over 48 h. Antibacterial effect was determined by log change in viable counts at 24 h and 48 h. The emergence of resistance was assessed by bacterial growth on recovery plates containing x2, x4, x8, x16, and x32 MIC concentrations of doripenem before antibiotic exposure (T0) and after 24 h and 48 h.

RESULTS

• The correlation of free drug T>MIC (fT>MIC) and the antibacterial effect of doripenem to emergence of resistant subpopulations is shown on Figure 1. The T>MIC for a 24-h static effect is 29.8%, -1 log reduction in count is 32.5%, and -2 log reduction in count is 35.6%. Resistant subpopulations were observed at T>MIC values of 12%-25%.

CONCLUSIONS

• T>MIC for doripenem is related to antibacterial effect: T>MIC 20.8% produces a 24 h static effect, T>MIC 35.6% ≤ 2 log drop in counts. Antibiotic-resistant subpopulations are amplified at T>MIC of 12.5% and 25%.
• Multiple dosing produces a defined T>MIC (12.5%, 25%, or 37.5%) has a greater antibacterial effect at T>MIC target of 27.8%, and amplification of resistant subpopulations is reduced when compared with larger infrequent dosing.
• Paradoxically, multiple dosing to produce lower T>MIC values, that is 12.5% and 25%, produced amplification of resistant subpopulations when compared with larger frequent dosing.

Dosing strategies for β-lactams designed to optimise antibacterial effect may paradoxically amplify resistant bacterial subpopulations at low drug exposures.

Reference
