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Comparison of Short Versus Prolonged Infusion of Standard Dose of Meropenem Against Carbapenemase-Producing *Klebsiella pneumoniae* Isolates in Different Patient Groups: A Pharmacokinetic–Pharmacodynamic Approach

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ABSTRACT

Dose optimization is required to increase carbapenem's efficacy against carbapenemase-producing isolates. Four clinical *Klebsiella pneumoniae* isolates were used: one susceptible to meropenem with minimum inhibitory concentration (MIC) 0.031 mg/L and 3 verona integron-borne metallo bete-lactamase-1–producing isolates with MICs 8, 16, and 128 mg/L. The human pharmacokinetics of short (0.5-h) and prolonged (3-h) infusion regimens of 1 g meropenem every 8 h were simulated in an *in vitro* pharmacokinetic–pharmacodynamic model. Time-kill curves were constructed for each isolate and dosing regimen, and the %T > MIC associated with maximal bactericidal activity was estimated. The percentage of pharmacodynamic target attainment for isolates with different MICs was calculated for 350 ICU, surgical, and internal medicine patients. The isolates with MIC ≤8 mg/L were killed with both dosing regimens. The %T > MIC corresponding to maximal bactericidal activity was ~40%. The percentages of target attainment were >90%, 61%-83%, 23%-33%, and <3% with the short infusion regimen and >90%, 98%-99%, 55%-79%, and <5% with the prolonged infusion regimen for isolates with MIC ≤2, 4, 8, and ≥16 mg/L, respectively. The lowest target attainment rates were observed for the ICU patients and the highest for internal medicine patients. The prolonged infusion regimen was more effective than the short infusion regimen against isolates with MIC 4-8 mg/L.

Introduction

Klebsiella pneumoniae is a frequent colonizer of the human gastrointestinal tract and nasopharynx but also responsible for serious nosocomial infections, such as bacteremia and ventilator-associated pneumonia.[1] The emergence of carbapenemase-producing *K pneumoniae* (CP-Kp) isolates complicated the management of these infections, which are usually associated with high mortality rates, particularly in immunocompromised patients.[2,3] Carbapenemases confer reduced susceptibility or resistance to a wide range of antibiotics, including penicillins, cephalosporins, and carbapenems.[2] CP-Kp isolates that produce verona integron-borne metallo bete-lactamase (VIM)-type metalloenzymes exhibit wide variation in minimum inhibitory concentrations (MIC) to carbapenems.[4,5] In search for more effective therapeutic approaches, efforts have been made to optimize the dosing regimen of carbapenems.[6,7]

Prolonged infusion regimens have been proposed to increase the effectiveness of treatment with meropenem compared with standard short infusion regimens. Clinical pharmacokinetic studies showed that the 3-h infusion of 1-2 g of meropenem every 8 h is not toxic.[8] However, there are neither comparative pharmacodynamic studies of the 3-h and half-hour infusion regimens for CP-Kp isolates with different MIC values nor comparative pharmacokinetic–pharmacodynamic studies for different patient populations. We, therefore, simulated the human pharmacokinetics of

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meropenem after 0.5- and 3-h infusion regimens of the standard dose of 1 g and studied the pharmacodynamics against VIM-producing *K pneumoniae* (VP-Kp), using an *in vitro* pharmacokinetic–pharmacodynamic model. Furthermore, the target attainment rates in different patient groups treated with these 2 regimens were calculated for isolates with different MICs.

Materials and Methods

Isolates, Drug, and Medium

Four clinical isolates of *K. pneumoniae* were used, one susceptible to meropenem with MIC of 0.031 mg/L (TZAN59) and 3 VIM-1–producing isolates, 6/100, SEC2 and SEC4 with meropenem Clinical and Laboratory Standards Institute MICs of 8, 16, and 128 mg/L, respectively. The bla_{VIM-1} gene, responsible for the production of the VIM-1 enzyme, was detected by polymerase chain reaction, as described previously.[9] The isolates were stored in −70°C and revived after subculturing in McConkey agar plates at 37°C for 18-24 h. Bacterial suspensions were prepared in normal saline from cultures in Muller–Hinton agar plates and adjusted to 0.5 McFarland with a densitometer (Biomereux, Marcy-L'Etoile, France) to obtain a final concentration of 10^7 CFU/mL, which was verified by quantitative cultures. A clinical formulation of meropenem was used (Meronem IV 500 mg; AstraZeneca, Athens, Greece) and cation-adjusted Muller–Hinton broth (CAMHB, Oxoid, Athens, Greece) according to the instructions of the Clinical and Laboratory Standards Institute. All isolates were tested twice.

In Vitro *Pharmacokinetic–Pharmacodynamic Model*

A previously developed closed diffusion/dialysis *in vitro* pharmacokinetic model was applied in the present study to simulate human pharmacokinetics of meropenem and study its antibacterial effect (Fig. 1).[10] This model has been recently validated using *in vivo* data from a thigh infection animal model.[11]

In Vitro *Pharmacokinetics*

Two dosing regimens of meropenem were simulated, the standard short (0.5-h) and the alternative prolonged (3-h) infusion regimen of 1 g every 8 h. In the *in vitro* model, the peak concentrations of mean ± SD 100 ± 30 and 30 ± 10 mg/L with a half-life <2 h were targeted[8] (Fig. 2) as previously found in patients.[6,12,13] For the short infusion regimen, meropenem was added simultaneously in both compartments to reach maximum concentration in the internal compartment within 0.5 h after adding the drug, whereas for the prolonged infusion regimen, meropenem was added only in the external compartment and diffused to the internal compartment reaching the maximum concentration 3 h after the addition of the drug. After the end of infusion, the contents of the external compartments were replaced with drug-free CAMHB twice within 1 h to simulate the biphasic decline of meropenem concentrations after the end of infusion. This procedure was repeated every 8 h for 24 h simulating the daily meropenem pharmacokinetics in humans.

Drug levels were determined at regular intervals by an agar diffusion microbiologic assay using as indicator the susceptible *Escherichia coli* strain ATCC25922 in Mueller–Hinton agar.[14] The method detects concentrations from 0.06 to 120 mg/L with good reproducibility (coefficient of variation <25%) and a linear correlation between concentrations and inhibition zones ($R^2 > 0.95$).

In Vitro *Pharmacodynamic Analysis*

The bacterial load in the internal compartments was evaluated periodically at regular intervals with 20-μl sampling followed by quantitative cultures in Muller–Hinton agar plates, which were incubated for 24 h at 37°C. Preliminary experiments were

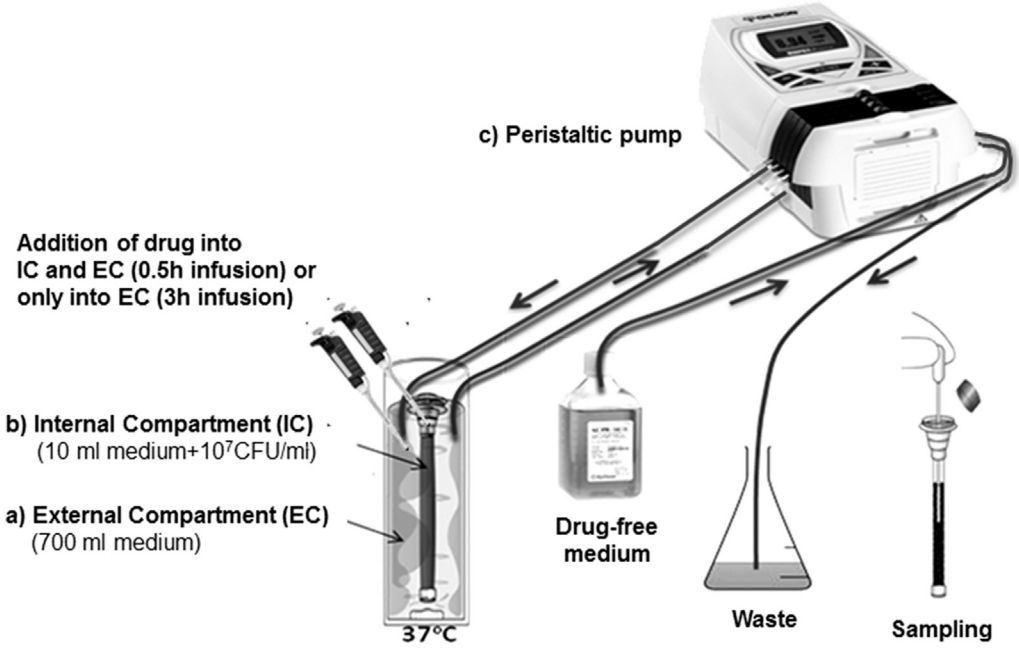

Figure 1. *In vitro* pharmacokinetic–pharmacodynamic model that simulated the pharmacokinetics of meropenem and studied the action of 2 regimens used in clinical practice against *Klebsiella pneumoniae* isolates. It consists of (a) a glass container containing 700 mL of culture medium (external compartment), (b) a 10-mL volume tube of semipermeable cellulose membrane that allows free diffusion of molecules with a molecular weight <1000 kDa, into which the bacterial inocula is injected (internal compartment), and (c) a peristaltic pump that introduces the medium in the container, while removing its contents in accordance with the clearance rate of the test drug (adapted from Meletiadis et al.[10]).