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# Evaluation of 3h vs 6h continuous infusion regimens against carbapenemase-producing *K. pneumoniae* isolates using an *in vitro* pharmacokinetic-pharmacodynamic model

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**Objectives.** *Klebsiella pneumoniae* is associated with a wide range of hospital-aquired infections. The management of these infections is complicated by the multidrug resistant phenotype of many *K. pneumoniae* nosocomial isolates, including resistance to carbapenems. Although it seems that carbapenems retain some level of activity against carbapenemase-producing *K. pneumoniae* (CP-Kp) with low MICs (≤4 mg/L) , their efficacy against CP-Kp isolates with higher MICs remains doubtful. Various dosing regimens have been proposed to treat infections by isolates with high carbapenem MICs. We therefore simulated meropenem pharmacokinetics of 3h and 6h continuous infusion regimens in an in vitro pharmacokinetic-pharmacodynamic model and determined its antbacterial activity against *Klebsiella pneumoniae*.

**Methods.** Four clinical isolates of *K. pneumoniae* were used; one susceptible with MIC of 0.031 mg/l and 3 carbapenemase producing *K. pneumoniae* with MICs 2, 16 and 256 mg/l, respectively. Meropenem pharmacokinetics were simulated in an in vitro pharmacokinetic model with maximal concentrations of 30 mg/L and 15 mg/L previously observed in patients with standard dosing regimens (Binder et al Ther Drug Monitor 2013). The model consists of two compartments; the external compartment, a flask containing 650ml cation-adjusted Muller-Hinton broth (medium), and the internal compartment, a dialysis tube containing 10ml medium with $10^7$ CFU/ml. The internal compartment was made of a of semi-permeable cellulose membrane allowing free diffusion of small molecules (drugs and nutrients) preventing the escape of bacteria (Float-A-Lyzer, SprectumLabs). Meropenem was added to both compartments at concentrations of 30 mg/L and 15 mg/L as 3h and 6h continuous infusion every 24h for 3 days. Drug levels were determined by a microbiological diffusion assay and bacterial growth by quantitative cultures estimating the CFU/ml at regular time points. Pharmacodynamic effects were assessed based on CFU reduction at 72h compared to the drug-free control for each dosing regimens and isolate.

**Results.** Meropenem pharmacokinetics were simulated well in the model with ±15% deviation from target values. The 3h infusion regimen was effective against the susceptible isolate and the CP-Kp isolate with MIC=2 but not against the other two CP-Kp isolates (<2 $\log_{10}$ CFU reduction). The 6h infusion regimen was effective against the susceptible and two CP-Kp isolates with MICs 2 and 16 mg/l (8$\log_{10}$ CFU reduction) but not against the CP-Kp isolate with MIC 256 mg/l.
**Conclusions.** The in vitro PK-PD model indicates that the 3h continuous infusion regimen was effective against CP-Kp isolates with MIC=2 mg/l whereas the 6h continuous infusion regimen was required to treat effectively CP-Kp isolates with MIC=16 mg/l.