Abstract:

Pharmacokinetic changes are often seen in patients with severe infections. Administration by continuous infusion has been suggested to optimize antibiotic exposure and pharmacokinetic/pharmacodynamic (PK/PD) target attainment for β-lactams. In an observational study, unbound piperacillin concentrations (n=196) were assessed in 78 critically ill patients following continuous infusion of piperacillin/tazobactam (ratio 8:1). The initial dose of 8, 12 or 16 g (piperacillin component) was determined by individual creatinine clearance (CRCL). Piperacillin concentrations were compared to the EUCAST clinical breakpoint MIC for Pseudomonas aeruginosa (16 mg/L), and the following PK/PD targets were evaluated: 100% fT>1xMIC and 100% fT>4xMIC. A population pharmacokinetic model was developed using NONMEM 7.4.3 consisting of a one-compartment disposition model with linear elimination separated into non-renal and renal (linearly increasing with patient CRCL) clearances. Target attainment was predicted and visualized for all individuals based on the utilized CRCL dosing algorithm. The target of 100% fT>1xMIC was achieved for all patients based on the administered dose, but few patients achieved the target of 100% fT>4xMIC. Probability of target attainment for a simulated cohort of patients showed, that increasing the daily dose by 4 g increments (piperacillin component) did not result in substantially improved target attainment for the 100% fT>4xMIC target. To conclude, in patients with high CRCL combined with high-MIC bacterial infections, even a CI regimen with a daily dose of 24 g may be insufficient to achieve therapeutic concentrations.

Reference: