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P1970 Population pharmacokinetics and dose adjustment of cefepime/tazobactam high dose (WCK4282) in patients with intermittent haemodialysis

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Background: The combination cefepime with tazobactam is being developed as a high-proportion combination to be infused over 90 min (WCK4282) for the treatment of ESBL, Class C β-lactamases, and KPC producing micro-organisms. Whereas dose adjustments for altered renal functions have been suggested based on population pharmacokinetic models, data and dosing recommendations in patients on intermittent haemodialysis (IH) is lacking. A pharmacokinetic study in such patients was undertaken.

Materials/methods: Six patients on IH were included and received a single dose of 1000mg/1000mg cefepime/tazobactam infused over 1.5h after the end of the dialysis. Samples were taken up to 48h after the start of infusion. Pharmacokinetic parameters were estimated using NONMEM. Monte Carlo simulations (MCS) were performed using Miclab 2.36 (Medimatics, NL). Probability of Target Attainments (PTA) were determined for various targets using a 5000 subject MCS. To provide guidance in dose adjustments 50% *f*T>MIC of cefepime at the clinical breakpoint of 16mg/L and 60% *f*T>Ct of tazobactam at 0.25mg/L and 20% *f*T>Ct of tazobactam at 8mg/L (for carbapenemase producers) was used.

Results: In total 90 (cefepime) and 87 (tazobactam) observations were available. A two-compartment model best described the data for both drugs (table). MCS showed that a single dose of 2 gram cefepime and tazobactam after the end of dialysis resulted in a PTA of 99.9% and 67.2% after 72h, respectively. In order to reach the tazobactam target once daily doses of tazobactam 500mg are necessary (PTA 100%). PTA's for the first cefepime doses of 500mg or 1000mg for 24h are 16.3% and 99.3%, respectively. The PTA for the first 3 doses of cefepime 500mg is 98.2%.

PK parameters	cefepime	Tazobactam
Clearance (L/h)	0.597 (0.0261)	2.36 (0.0802)
V1 (L)	12.4 (0.188)	11.8 (0.106)
V2 (L)	6.36 (0.127)	8.41 (-)
Q (L/h)	5.96 (-)	10.2 (0.481)

Parameter estimates (interindividual variability)

Conclusions: The pharmacokinetics of both drugs are well described by two-compartment models. Because of the relatively short half-life of tazobactam once daily dosing is required. Based on the simulations, a loading dose of 1000mg/1000mg on the first day after dialysis and doses of 500mg/500mg cefepime/tazobactam on the second and third day are suggested.