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Population pharmacokinetics, Monte Carlo simulations and dose adjustment of tazobactam including in the renally impaired

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Background: Tazobactam is a β -lactamase inhibitor that is used in combination with several β -lactams to extend coverage against ESBL producing micro-organisms. It is currently being developed in combination with cefepime with larger doses, up to 2 gr of tazobactam (WCK 4282) to include coverage of KPC producing bacteria. Despite its long use, surprisingly little pharmacokinetic data are available, including renally impaired patients. A series of pharmacokinetic studies were performed to build a population model and to perform Monte Carlo simulations (MCs) to determine target attainment for various potential dosing schedules.

Material/methods: 90 subjects (65 males/25 females) received dosing regimens of 1gr or 2 gr tazobactam (in combination with cefepime) given either bid or tid with infusion times of 0.5-1.5 hour for 6-7 days. Creatinine clearance (CC) ranged from 7.9-191.7 ml/min and weight 52.5-113.8 kg respectively. 2298 concentrations were analysed with nonlinear mixed effect modelling (NONMEM, version 7.2) and the ADVAN5 subroutine. Different one- two-and three compartment disposition models were evaluated and the impact of covariates were determined. Model selection criteria were decrease in objective function, diagnostic plots and Normalised Prediction Distribution errors. MCs using a 5000 subject simulation were performed using Miclab 2.36 (Medimatics, NL) and a protein binding of 20%. Probability of Target Attainments (PTA) were determined for various targets including the inhibition target for KPC of 56% $fT > Ct$ at 0.5 mg/L. The relationship between CC and tazobactam

clearance was used to determine the PTA at high and low CC to provide guidance in dose adjustments.

Results: The data were best described by a two-compartment model. Interindividual variability (IIV) was found on clearance (CL), central volume (V1) and peripheral volume (V2). The IIV on CL and V1 were correlated. Creatinine clearance was a significant covariate on CL (0.0367) and bodyweight as well as age were significant covariates for V2 (0.0077 and 0.0098). The final estimates were 17.3 L/h for CL, 9.09 L for V1, 8.78 L for V2 and 14.1 L/h for intercompartmental clearance (Q). For a 2gr q8h dose and 2h infusion MCs using a CC of 110 ml/min resulted in a PTA of >99% for 60 %fT>Ct above 0.5 mg/L. Dose adjustment to 1gr q8h for CC of <50 ml/min yielded PTA of >99% for both targets, and further dose reduction was required at CC < 30 ml.

Conclusions: Tazobactam pharmacokinetics was well described by a two-compartment population model. Creatinine clearance was a significant covariate for clearance, dose adjustments are required for renally impaired patients. Monte Carlo simulations indicate that for patients with a creatinine clearance of < 110 ml/min the PTA of 60 %fT>Ct above 0.5 mg/L is >99%. These target attainments provide support for high dose tazobactam use against KPC producing bacteria.