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P1954 Population pharmacokinetics of zidebactam (WCK5107), a novel beta-lactam enhancer antibiotic, in individuals with various renal function

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Background: Zidebactam (WCK 5107) is a novel antibiotic belonging to the class of diazabicyclooctane. It possesses both direct antimicrobial activity as well as is active as a beta-lactamase inhibitor. It is currently being developed in combination with cefepime for the treatment of infections caused by multi-drug resistant micro-organisms. To examine its pharmacokinetic properties in individuals including those with impaired renal function, pharmacokinetic studies were performed. We here present a population pharmacokinetic model to be used for the design of clinical dosing regimens including dose adjustments for individuals with impaired renal function.

Materials/methods: 148 volunteers (96 males, 52 females) received zidebactam (+/- Cefepime) including both single dose and multiple dose regimens and individuals with various renal functions. Dosing was from 250-3000mg and infusion times 1h to 3h. Demographic characteristics (mean, range) include: age (40.7y, 18-77), weight (76.5kg, 49.9-104.9), creatinine clearance (CrCL) (124.7mL/min, 12.2-240.4). Pharmacokinetic parameters were estimated by means of Non-Linear Mixed Effect Modeling (NONMEM). The models were implemented in the NONMEM advan5 subroutine using the foce method with interaction. Model validation included Normalized Prediction Distribution Error's and inspection of relevant plots.

Results: A total number of 3788 observations were analysed. The best structural model was a two-compartment model with a combined error, and interindividual variability on clearance (CL), central volume (V1), peripheral volume (V2) and intercompartmental clearance (Q). Correlations between the terms of interindividual variability were included. Covariates could explain part of the interindividual variability. The included covariates are: CrCL on CL and Q, weight on V1, age as well as gender on V2. In the final model, the values for CL and V1 were 5.90L/h and 8.31L, respectively. V2 and Q were 5.69L and 7.03L/h, respectively. Zidebactam clearance ranged from 1.05L/h (CrCL 12.2 mL/min) to 9.60L/h (CrCL 240.4 mL/min).

Conclusions: The pharmacokinetics could be well described by a two-compartment model. Creatinine clearance was a significant covariate for clearance, indicating that dose adjustments are required for renally impaired patients. The model parameter estimates and variability can be used in Monte Carlo Simulations for the development of rational dosing regimens in patients, including those with renal impairment.