Session: P062 Zidebactam and other new Gram-negative antibiotic potentiators

Category: 5b. Pharmacokinetics/pharmacodynamics of antibacterial drugs & therapeutic drug monitoring

24 April 2017, 12:30 - 13:30
P1299

Population pharmacokinetics of zidebactam (WCK 5107), a novel beta-lactam enhancer antibiotic

Anouk Muller*[1], Johan Mouton[2]

[1]*Medical Centre Haaglanden; Department of Medical Microbiology*

[2]*Erasmus University Medical Center; Department of Medical Microbiology and Infectious Diseases*

Background: Zidebactam (WCK 5107) is a novel antibiotic belonging to the class of diazabicyclooctanases. It possesses both direct antimicrobial activity as well as is active as a beta-lactamase inhibitor. In addition it exerts an enhancer effect with PBP3-targeting beta-lactams. 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, a series of pharmacokinetic studies were performed. We here present a population pharmacokinetic model to be used for the design of clinical dosing regimens.

Material/methods: 106 volunteers (60 males, 46 females) received zidebactam in 13 different cohorts, including both single dose and multiple dose regimens. Dosing was from 250-3000 mg and infusion times 1h to 3h. Important demographic characteristics (mean, range) further include: age (32.7 y, 18-56), weight (74.5 kg, 49.9-102.6), creatinine clearance (132.5 ml/min, 83-218). Pharmacokinetic parameters were estimated by means of Non-Linear Mixed Effect Modeling (NONMEM). The models were implemented in the NONMEM ADVAN5 subroutine and the analysis was performed using the FOCE method with INTERACTION. Model validation included Normalized Prediction Distribution Error's and inspection of relevant plots. A covariate analysis was also performed.

Results: A total number of 3097 observations were available for population pharmacokinetic analysis. The best structural model without covariates was a two-compartment model with a combined error, and interindividual variability on clearance (CL), central volume (V1) and V2. A correlation between the interindividual variability on CL and V1 was also found and included in the model. Covariates could explain part of the interindividual variability. In the final model, the values for CL and V1 were

estimated separately for the different dosing regimens and ranged between 5.0 and 6.4 L/h for CL and 7.1 and 10.9 L for V1. V2 and Q were 4.61L and 5.4L/h, respectively. The omega (block) estimates (interindividual variability) were 0.0136, 0.0201, 0.0275 and 0.0161 for CL, interaction, V1 and V2, respectively. Part of the interindividual variability could be explained by creatinine clearance on CL, body weight on V2 and 'single vs multiple dose' on V1.

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