

Session: EP191 Recent advances in PK/PD: efficacy and toxicity

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

25 April 2017, 12:30 - 12:35
EP0943

Population pharmacokinetics, Monte Carlo simulations and dosing recommendations of cefepime using 2h infusion, including renal impairment

Anouk Muller¹, Sachin Bhagwat², Mahesh Patel³, Johan Mouton⁴

¹*Medical Centre Haaglanden; Department of Medical Microbiology*

²*Wockhardt Limited; Drug Discovery Research*

³*Wockhardt Research Centre; New Drug Discovery*

⁴*Erasmus University Medical Center; Department of Medical Microbiology and Infectious Diseases*

Background: Cefepime is a cephalosporin with broad spectrum activity including Amp-C producing Gram-negatives. Cefepime is being developed as a high -proportion combination with tazobactam as an extended infusion (WCK 4282), to extend its coverage against ESBL, Class C β -lactamases, and KPC producing micro-organisms. Given the relatively poor availability of pharmacokinetic data and population models to perform Monte Carlo simulations and determine target attainment for various potential dosing schedules, pharmacokinetic studies were performed over one week of exposure.

Material/methods: 90 (65 males/25 females) subjects received dosing regimens of cefepime (in combination with tazobactam) of 1gr or 2gr given either bid or tid with infusion times of 0.5-1.5 hour for up to 6 days. Creatinine clearance ranged from 7.9-191.7 ml/min and weight 52.5-113.8 kg. Pharmacokinetic parameters were estimated by means of Non-Linear Mixed Effect Modeling (NONMEM 7.2). Models were implemented in the 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. Monte Carlo simulations were performed using Miclab 2.36 (Medimatics, NL) and a protein binding of 20%. Probability of Target Attainments (PTA) was determined for various targets using a 5000 subject Monte Carlo simulation. The relationship between creatinine clearance (CC) and cefepime clearance was used to determine the PTA at high and low clearances for a stasis target of 50% and 1logkill

target of 60% $fT > MIC$ for a clinical breakpoint of 16 mg/L and a 2h infusion to provide guidance in dose adjustments.

Results: A total number of 2951 observations were available for population pharmacokinetic analysis. Data were best described by a two-compartment model and interindividual variability on clearance (CL), central volume (V1) and peripheral volume (V2). The final estimates were 5.22 L/h, 8.05 L, 7.77 L and 10.9 L/h for CL, V1, V2 and Q respectively with interindividual variability of 0.0234, 0.0889 and 0.0727 for CL, V1 and V2 respectively. CC and age were significant covariates for CL and bodyweight for V2. Monte Carlo simulations using a CC of 110 ml/min resulted in a PTA of >99% and 95% for the stasis and 1logkill target respectively. 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. Likewise, for patients with significantly increased CC or augmented clearance, doses need to be increased.

Conclusions: The pharmacokinetics could be best described by a two-compartment 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, micro-organisms with 16 mg/L are covered.