Poster

[P25-1] P25-1: Anti-infective drugs (1): Aminoglycosides and beta-lactams

Chair: Andrew McLachlan, Australia

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[P25-1-1] Population pharmacokinetic modeling approach to compare different amikacin dose rates in children with cystic fibrosis: Are we efficient enough?

Jean-Baptiste Woillard[1], Stephane Bouchet[2], Amazigh Lakdhari[3], Stephanie Bui[4], Fanck Saint-Marcoux[5], Pierre Marquet[6], Christian Woloch[7] (1.CHU Limoges, Univ Limoges, 2.CHU Limoges, 3.CHU Limoges, 4.CHU Limoges, 5.CHU Limoges, Univ Limoges, 6.CHU Limoges, Univ Limoges, 7.CHU Limoges)

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Background

Amikacine is a large spectrum, concentration dependent aminoglycoside used for the treatment of Gram negative organisms severe infections. However, one of its main adverse effects is renal tubular toxicity. For pediatric patients with cystic fibrosis, the recommended dosing is between 30 and 35 mg/kg/d once daily. The objective of this work was to develop a non-parametric pharmacokinetic population model (POPPK) for amikacin in children with cystic fibrosis (CF) and to investigate with Monte-Carlo simulations, efficacy and toxicity at different dose rates for different MIC clinical breakpoints.

Methods

Data from 60 CF children hospitalized in the CRCM of the CHU Bordeaux were used. The model was implemented in Pmetrics. After determination of the population pharmacokinetics parameters (POPPK) and the associated influent covariates, 1000 time-concentration profiles were simulated for 7 different dose rates between 15 and 60 mg/kg/d to predict the probability of having a peak of serum amikacin 10 fold the MIC &trough level (C_0) lower than 2.5 mg/L (following ANSM recommendations) for different MIC values between 0.5 and 32 mg/L.

Results

110 serum amikacin concentrations were used to develop the POPPK. The mean±SD amikacin dose, weight and serum creatinine were 29±10mg/kg/j, 36±18kg and 39±15mol/L, respectively.

The final structural model was a 1-compartment model with linear elimination. Body weight and serum creatinine significantly influenced amikacin apparent distribution volume and clearance respectively. The mean bias=-0.0716 [CI 95%], imprecision=0.329 [CI 95%] and the r^2=0.994 between individual predicted concentration and observed concentrations.

Monte-Carlo simulations showed that for sensitive bacteria with MIC less than 8, a dose of at least 30 mg/kg/d has to be used to attain a 100% success rate whereas for bacteria with MIC over 8 (ex. *Pseudomonas aeruginosa* ($MIC_{50amikacine}$=8)), a dose of at least 50 mg/kg/d allows a high probability of success [90 %] with C_0 lower than 2.5 mg/L.

Conclusions

The amikacin dose currently used in children with CF (30 mg/kg once daily) is efficient for sensitive Gram-negative pathogens. However for resistant pathogens (MIC>8 mg/L), a dose of at least 50 mg/kg/d should

lead to efficacy with an absence of nephrotoxicity.