IV-44 *Katarina Vucicevic* Population Pharmacokinetic Modelling of Amikacin in Neonates

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Objectives: The aim of this study was to explore the influence of demographic and clinical covariates, and hence to develop population pharmacokinetic (PK) model of amikacin in neonates with suspected or proven sepsis.

Methods: In total 39 neonates born at term (≥37 weeks gestational age, GA) were included in the study. Amikacin was administered over 1 h infusion, using multiple or once-daily dosing schedule, with daily dose of 15 mg/kg (if postnatal age, AGE ≤7 days) or 20 mg/kg (if AGE >7 days). Two samples were taken per patient, corresponding to the peak and trough serum concentration. The population PK analysis was performed using NONMEM® software (ver.6.2). Internal validation was performed.

Results: Linear one-compartment model with a proportional interindividual error and combined residual error model were used to describe PK of amikacin. The final population model for clearance is: $CL(l/h)=0.12 \cdot (TM/4) \cdot 0.75 \cdot 1.31 \cdot GA \cdot 1.33 \cdot AGE$, where GA=0 for 37-38 gestational weeks, GA= 1 for 39-42 gestational weeks; AGE=0 for postnatal age ≤7 days, AGE=1 for postnatal age >7 days; whereas volume of distribution was weight normalized, and interindividual error was not modeled. The results show that clearance is increased in average by 31 % in neonates of 39-42 gestational weeks compared to neonates of 37-38 gestational weeks, and it was increased in average by 33 % with postnatal age >7 days. The estimate of clearance for a typical patient was 0.12 (0.106 - 0.134) l/h, while interindividual variability of clearance in the studied population was 24.72 (11.79 – 32.91) %, the residual variability estimated the proportional error at 54.41 % and additive error 61.07 µg/mL.

Conclusions: The results suggest that amikacin elimination increases with gestational and postnatal age presumably owing to the process of maturation that is extensively carried out in the first weeks of life. Final population pharmacokinetic model for amikacin can be used to predict the individual concentration of amikacin in neonates, and individualization of therapy.

References:
[1] Bleyzac N, Varnier V, Labaune JM, et al. Population pharmacokinetics of amikacin at birth and interindividual variability in renal maturation. Eur J Clin Pharmacol 2001;57:499-504.