EzeCHiel validation: comparison of gentamicin drug concentration predictions to a reference method (NONMEM®)

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Background

- Bayesian dosage adjustment currently represents the gold-standard for therapeutic drug monitoring (TDM) and is the method of choice implemented in EzeCHiel, a software aiming at assisting clinicians in TDM.
- Gentamicin, an antibiotic frequently administered to neonates in their first days of life, is a classic candidate to TDM due to its considerable interindividual variability in drug levels and its narrow therapeutic index.
- Thus, gentamicin is a good candidate for the validation of EzeCHiel against the current reference approach implementing Bayesian adjustment (NONMEM®).

Methods

- A total of 3039 concentrations collected in 994 preterm and 455 term newborns treated at the University Hospital Center of Lausanne between December 2006 and October 2011 were collected for the analysis.
- Nonlinear mixed effect modeling software (NONMEM®) was used to perform the population pharmacokinetic modeling.
- The final model was implemented in EzeCHiel for Bayesian prediction and dosage adjustment. At this stage, EzeCHiel does not accommodate between-parameters correlation.
- An a priori (prior any measurement) and a posteriori (following concentration measurement) EzeCHiel concentration predictions were compared to those from NONMEM® with a new set of patients. A total of 137 gentamicin concentrations were collected in 71 neonates treated at the University Hospital Center of Lausanne between January 2013 and April 2013.

Results

- A two-compartment model best characterized gentamicin disposition (fig. 1 and fig. 2). Average clearance was 0.444 L/h/kg (CV 25%), central volume of distribution 0.442 L/kg (CV 18%), intercompartmental clearance 0.440 L/h/kg and peripheral volume of distribution 0.122 L/kg. Additive and proportional residual error were 0.89 mg/L and 18% respectively.
- Body weight, gestational age and postnatal age were found to influence gentamicin kinetics in neonates.

Conclusion & Discussion

- EzeCHiel is able to predict a priori and a posteriori concentrations, but yet less precisely in the latter case.
- Bayesian a posteriori calculation have still to be refined to correct overestimation made by EzeCHiel compared to the reference method. In particular, Bayesian method currently implemented in EzeCHiel does not include the correlation between clearance and volume, and the management of the mixed residual error needs to be solved. It will further be added and a new validation will be performed.
- Yet EzeCHiel appears promising to implement a Bayesian adjustment approach in a user-friendly portable tool ready for clinical use.