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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®) .

Objectives

- To provide a pharmacokinetic model of gentamicin in neonates population for Bayesian forecasting into the framework of TDM.
- To validate EzeCHiel by comparing its concentration predictions to a reference method (NONMEM®) using the model previously made.

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 **m**ixed **e**ffect **m**odeling 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 0.044 L/h/kg (CV 25%), central volume of distribution 0.442 L/kg (CV 18%), intercompartmental clearance 0.040 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.

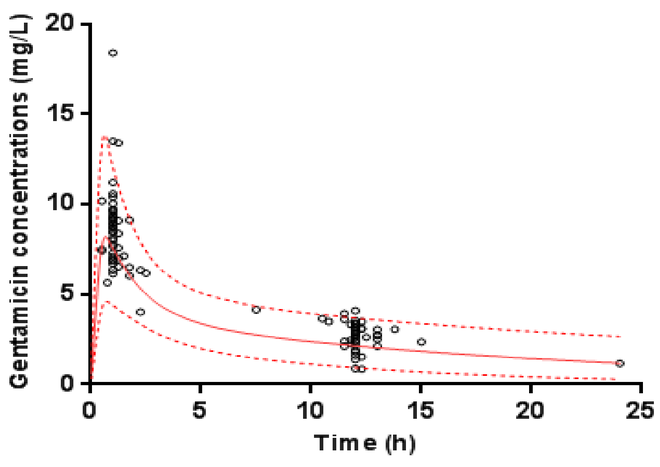

Fig. 1. Gentamicin concentrations versus time plot. Collected from 71 neonates treated between Jan. 2013 and Apr. 2013 with population prediction (solid line) and the 80% prediction interval (dotted lines).

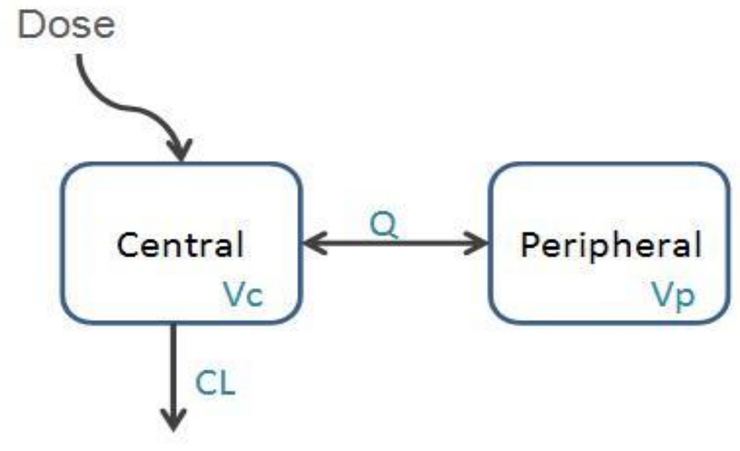

Fig. 2. Two-compartmental model. Described in terms of clearance (CL), central volume of distribution (Vc), intercompartmental clearance (Q) and peripheral volume of distribution (Vp).

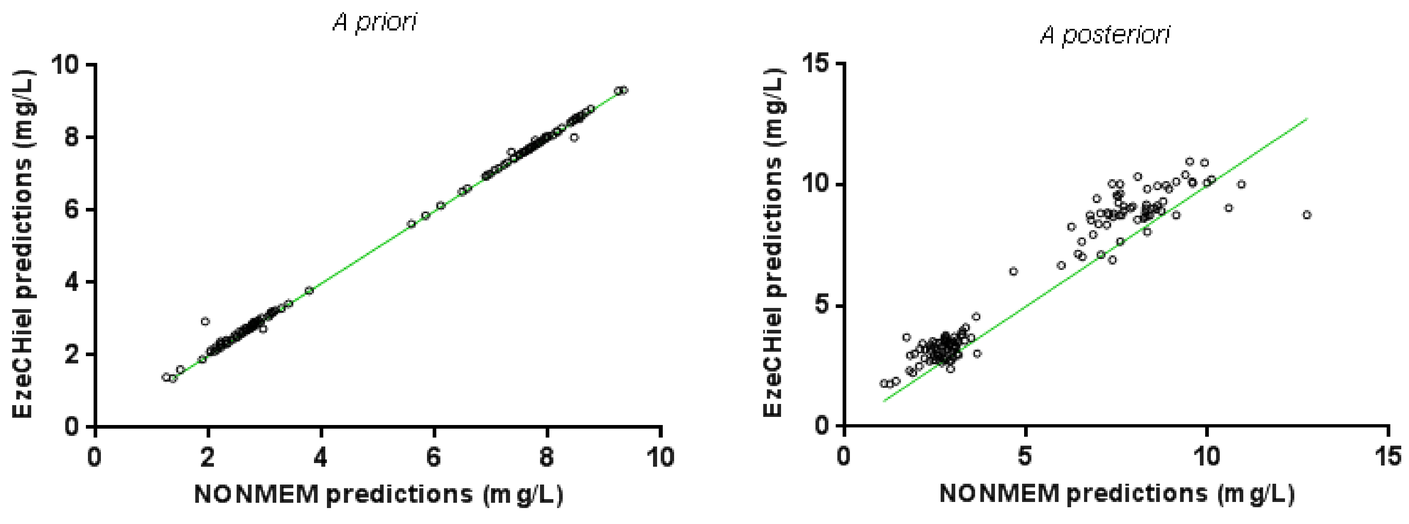

Fig. 3. *A priori* and *a posteriori* NONMEM predictions versus EzeCHiel predictions.

- A correlation of 86% was found between clearance and central volume of distribution.
- *A priori* predictions showed to be properly forecasted by EzeCHiel (fig. 3).
- *A posteriori* predictions appeared overestimated by EzeCHiel in comparison with NONMEM ® (fig. 3).

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.