Population pharmacokinetic study of gentamicin in newborn infants: a retrospective analysis in a large cohort

OBJECTIVES
- To investigate clinical and demographic factors influencing gentamicin pharmacokinetics in a large cohort of unselected newborns.
- To derive optimal regimen to achieve optimal therapeutic targets of 8 mg/L for peak and under 1 mg/L for trough concentrations.

METHODS
- A total of 3039 gentamicin serum concentrations were collected in 994 preterm and 455 term newborns treated at the University Hospital of Lausanne between December 2006 and October 2011.
- Nonlinear mixed effect modeling (NONMEM®) was used to develop a population pharmacokinetic model describing gentamicin disposition in this population.
- Continuous covariates were body weight (BW), gestational age (GA), postnatal age (PNA), postmenstrual age (PMA) defined as the sum of PNA and GA.
- Categorical covariates were sex, cotreatment with furosemide (FURO), dopamine (DOPA) and indomethacin (INDO), presence of patent ductus arteriosus (PDA) and concomitant ventilation (invasive IV) and non-invasive (NIIV).

RESULTS

Model equations
- **TCL = \(\theta_C \times \left(\frac{BW}{2170}\right)^{0.75} \times \left[1 + \theta_{GACL} \times \left(\frac{GA - 34}{34}\right)\right] \times \left[1 + \theta_{PNAACL} \times \left(\frac{PNA - 1}{1}\right)\right] \times \left[1 + \theta_{DOPACL} \times (1 + \theta_{FUROACL})\right] \times \left[1 + \theta_{DOPAWL}\right] \times \left[1 + \theta_{FUROWL}\right] \times \theta_{WL}\) mg/L
- **T.V = \(\theta_C \times \left(\frac{BW}{2170}\right) \times \left[1 + \theta_{GACL} \times \left(\frac{GA - 34}{34}\right)\right] \times \left[1 + \theta_{PNAACL} \times \left(\frac{PNA - 1}{1}\right)\right] \times \left[1 + \theta_{DOPACL} \times (1 + \theta_{FUROACL})\right] \times \left[1 + \theta_{DOPAWL}\right] \times \left[1 + \theta_{FUROWL}\right] \times \theta_{WL}\) mg/L

DISCUSSION-CONCLUSION
- To our knowledge, this study is the largest population pharmacokinetic analysis of gentamicin in a cohort of unselected neonates.
- Gentamicin shows a two-compartment kinetics in the newborns where size (represented by BW as a surrogate) and maturation (represented by GA and PNA) are the most important covariates influencing individual pharmacokinetic parameters.
- Dopamine and furosemide were also found to have a relevant effect. Probably, dopamine is an indicator of bad general state associated with diminished clearance (cardiovascular instability, a diminished renal blood flow and increase of the vascular resistance).
- Even if PMA predicts gentamicin clearance, separating the two distinct covariates GA and PNA better fits the data than PMA alone.
- The model will serve to elaborate a Bayesian tool for gentamicin dosage individualization in newborns (http://www.ezechiel.ch/).