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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 1mg/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 Center of Lausanne between December 2006 and October 2011.
- **Non**linear **m**ixed **e**ffect **m**odeling (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 indometacin (INDO), presence of patent ductus arteriosous (PDA) and concomitant ventilation (invasive (IV) and non-invasive (NIV)).

RESULTS

Data

- Concentrations measured at peak and at about 12 hours after the last dose represent 42% and 40% of the measurements, respectively. Most measurements (86%) were performed after the first administration and only 3% of concentrations were available beyond 72 hours of treatment.

Characteristics	Value
Dose (mg/kg)	2.9 (1.0-20.2) [a]
BW (g)	2170 (440-5510)[a]
GA (wk)	34.0 (24.2-42.1)[a]
PNA (d)	1 (0-94) [a]
PMA (wk)	34.4 (24.2-42.4) [a]
Male	834 (57.5) [b]
IV	301 (20.8) [b]
NIV	861 (59.4) [b]
PDA	153 (10.6) [b]
Furosemide	5 (0.3) [b]
Dopamine	136 (9.4) [b]
Indometacin	27 (1.9) [b]

a median (range)
b count (%)

Characteristics of the patients

Structural and error model

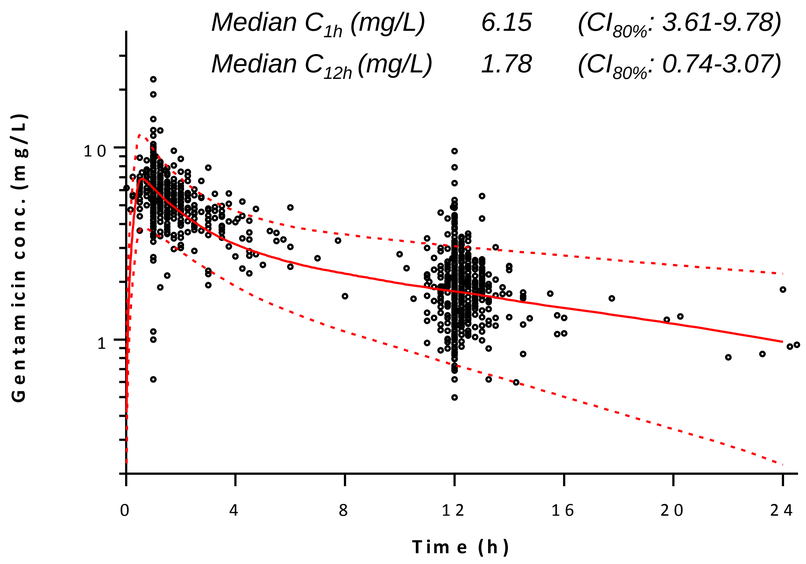
- A two-compartment model best characterized gentamicin pharmacokinetics. Average clearance (CL) was 0.095 L/h (CV 25%), central volume of distribution (V_c) 0.960 L (CV 18%), intercompartmental clearance (Q) 0.086 L/h and peripheral volume of distribution (V_p) 0.261 L.
- A mixed error model was used to describe intra-patient variability, where additive and proportional residual error were 0.199 mg/L and 17% respectively.
- A correlation of 87% was found between clearance and central volume of distribution.

Parameters	Population means			
	Estimate	*SE(%)*	*IIV(%)*	*SE(%)*
θ_{CL} (L/h)	0.095	1	25	10
θ_{BWCL}	0.75	-		
θ_{GACL}	2.034	4		
θ_{PNACL}	0.036	20		
θ_{DOPACL}	-0.096	37		
θ_{FUROCL}	-0.318	43		
θ_{Vc} (L)	0.960	3	18	44
θ_{BWVc}	1	-		
θ_{GAVc}	-0.519	15		
θ_{DOPAVc}	0.098	29		
θ_{Q} (L/h)	0.086	32		
θ_{Vp} (L)	0.261	16		
Correlation CL-V_c (%)	87	21		
Additive residual error (mg/L)	0.199	17		
Proportional residual error (%)	17	5		

Final population pharmacokinetic parameter estimates of gentamicin in neonates

Covariate model

- BW on CL and V_c (following allometric equations with a power of 0.75 and 1 respectively) was the covariate that markedly improved the description of the data. This factor explained 57% of the variability in CL and 76% in V_c.
- Further covariates were GA and PNA on CL (increasing CL by 6% per week and 3.5% per day respectively) and GA on V_c (decreasing V_c by 1.5% per week).
- Co-administration of dopamine reduced CL by 10% and increased V_c by 10%.
- CL was reduced by 32% in presence of furosemide. Although not significant, indometacin reduced CL by 12%.



Gentamicin concentrations versus time plots with population prediction (solid line) and the 80% prediction interval (dotted lines) for a first dose.

Model equations

$$TVCL = \theta_{CL} \times \left(\frac{BW}{2170}\right)^{0.75} \times \left[1 + \theta_{GACL} \times \left(\frac{GA - 34}{34}\right)\right] \times \left[1 + \theta_{PNACL} \times \left(\frac{PNA - 1}{1}\right)\right] \times (1 + \theta_{DOPACL}) \times (1 + \theta_{FUROCL})$$

$$TVV_C = \theta_{V_c} \times \left(\frac{BW}{2170}\right) \times \left[1 + \theta_{GAV_c} \times \left(\frac{GA - 34}{34}\right)\right] \times (1 + \theta_{DOPAV_c})$$

Simulation

- Model based simulation confirms that preterm infants need higher dose, superior to 4 mg/kg, and extended interval dosage regimen to achieve adequate concentration.

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/).

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