Population Pharmacokinetics of Gentamicin in Preterm and Term Newborn Infants

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Background and Objectives

Gentamicin is an aminoglycoside antibiotic commonly used in the prophylaxis and treatment of gram-negative infections in the neonatal population. Gentamicin is eliminated almost exclusively by glomerular filtration, and changes in gentamicin clearance (CL) in the neonate are likely to correlate with the functional maturation of the glomerular filtration rate.

The aim of the present study was to describe the population pharmacokinetics (PK) of gentamicin in preterm and term newborn infants and to identify predictive covariates relevant for new improved dosing regimens. A second aim was to evaluate cystatin C (cysC) as a marker for renal function in the neonatal population.

Patients and Methods

Patients

42 neonates were enrolled in a prospective clinical trial at the neonatal intensive care unit, University Children's Hospital, Uppsala, Sweden. 592 samples were analyzed for gentamicin concentration (TDx, Abbott Laboratories). Besides routine drug monitoring samples there were on average four extra study-samples taken per individual. Covariates collected included: body weight (BW), gestational age (GA), postnatal age (PNA), gender, Screatinine, ScysC and CLcysC calculated according to the formula of Larsson et al. developed from pediatric and adult patients.

Table 1. *Summary of patient characteristics*

		Median (n=42)	Range
Demographics	WT (kg)	1.42	0.495 – 4.58
	GA (weeks)	29	23 - 41
	PNA (days)	1	0 - 45
	Screa (µmol/L)	77	19 - 154
	ScycC (mg/L)	1.62	1.09 – 2.39
	CLcycC (ml/min)	48	24 - 77
Pharmacokinetics	Number of samples per ind.	13	4 - 33
	Treatment duration (days)	5	1 - 11
	Number of treatments per ind.	1	1 - 5

Basic model

Data was analyzed using NONMEM (version VI beta) with log-transformed data. One-, two- and three-compartment models were tried as well as additive, proportional and combined additive and proportional residual error models. Log-normal distribution was assumed for inter individual variability (IIV).

Covariate model

Body weight was included as primary covariate according to an allometric power model. The power exponent used was 1 for volume of distribution and ¾ for clearance. The standardized covariate model building method within the PsN toolkit was used to explore covariate relationships.

Results

The basic model was a two compartment model with IIV on CL and V1 with a combined additive and proportional residual error model. GA and PNA were identified as significant covariates for CL and inclusion resulted in a reduction in OFV as well as in unexplained IIV (Table 2). In the final model, GA was included in a linear fashion and PNA in a piecewise linear fashion with estimation of the breakpoint (Fig. 1-2, Table 3). CystatinC or creatinine was not found to be correlated to CL (Fig. 3). No significant covariates besides BW were found for V1 or for the other parameters.

Table 2. *Model development*

No	Model	OFV	IIV CL	IIV V1
1	Basic model	-527.46	72 (14)	68 (15)
2	Allometric model	-749.47	34 (16)	12 (85)
3	2 + PNA-CL (linear)	-943.13	37 (17)	14 (56)
4	2 + PNA-CL (linear) + GA-CL (linear)	-1001.76	17 (31)	13 (56)
5	2 + PNA-CL (piecewise linear) + GA-CL (linear)	-1048.58	16 (36)	13 (52)

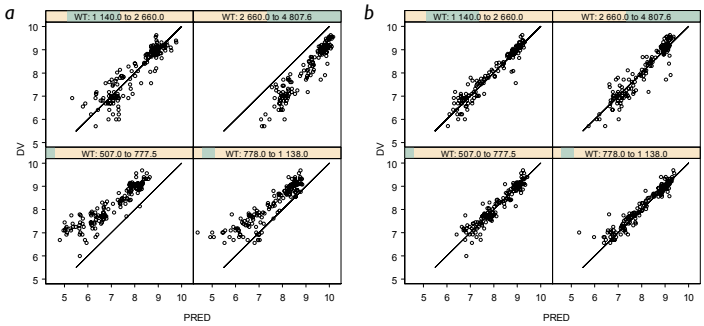

Figure 1. *Goodness of fit plots. Observed versus predicted gentamicin concentrations based on basic model (a) and final model (b) separated on WT classes.*

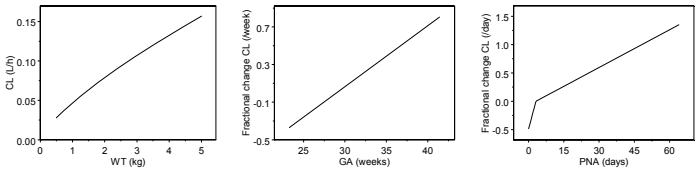

Figure 2. *Model predicted changes in CL with covariates WT, GA and PNA.*

Table 3. *Population parameter estimates with relative standard error, RSE (%)*

Parameter	Estimate (RSE (%))	
CL (L/h)	0.0469 (4.2)	$CL = \theta1 \times WT^{¾} \times (1+CLGA) \times (1+CLPNA)$
GA (/week)	0.0647 (10)	$CLGA = \theta2 \times (GA-GA_{Median})$
PNA-BP (days)	3.15 (12)	$BP = PNA^{20} / (PNA^{20} + \theta5^{20})$
PNA-slope1 (/day)	0.154 (23)	IF PNA≤BP: CLPNA = θ3 x (PNA - BP)
PNA-slope2(/day)	0.0222 (16)	IF PNA>BP: CLPNA = θ4 x (PNA - BP)
Q (L/h)	0.0763 (17)	$Q = \theta6 \times WT^{¾}$
V1 (L)	0.432 (4.1)	$V1 = \theta7 \times WT^{1}$
V2 (L)	0.405 (7.9)	$V2 = \theta8 \times WT^{1}$
IIV CL (%)	16 (36)	
IIV V1 (%)	13 (52)	
Add error (mg/L)	0.121 (33)	
Prop error (%)	21.3 (11)	

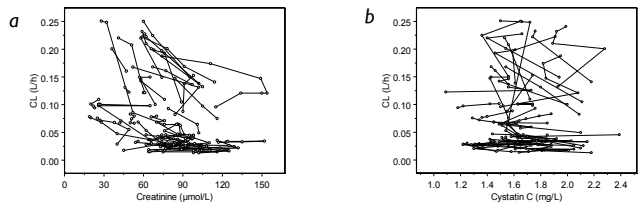

Figure 3. *Empirical Bayes estimates of CL versus Screa (a) and ScysC (b).*

Conclusions

- ✓ A PK model including the covariates BW, GA and PNA was developed describing the developmental PK of gentamicin in preterm and term neonates.
- ✓ Based on these data, CysC was not found to be correlated with gentamicin clearance. Therefore CysC is not likely to be a predictive marker of renal function in this patient population.

References

Larsson A, et al. Scand J Clin Lab Invest 2004; 64: 25-30