Maturation of GFR in preterm and term neonates reflected by clearance of different antibiotics

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Introduction
The developmental changes in GFR were previously quantified in (pre)term neonates aged up to 1 month on the basis of the clearance of amikacin. In this developmental renal excretion model[1], the maturation of GFR was predicted by birth weight (BWb) and postnatal age (PNA).

The aim of this study is to assess model performance when this developmental renal excretion model[3] is used to describe maturation in clearance of other renally excreted antibiotics in (pre)term neonates.

Using this approach a distinction is being made between system specific and drug specific information in paediatric pharmacokinetic models.

Methods
Datasets:
Two datasets were used containing different antibiotics. The first dataset contained 386 netilmicin concentrations available from 97 preterm and term neonates[2] (Birth weight (BWb) (470-3000 g). Postnatal age (PNA) 1-30 days). The second dataset contained 752 vancomycin concentrations obtained from 273 neonates[3] (BWb 385-2550 g, PNA 1-30 days).

Model building:
Two pharmacokinetic models were developed for both netilmicin and vancomycin respectively, according to standard methods. The difference in the model building process between both models was the implementation of the covariate model. The first model used the developmental renal excretion model[1] for amikacin clearance in neonates as covariate model. In the second model (the comprehensive covariate model[4]), a systematic covariate analysis was performed. The descriptive and predictive performance was compared between the two models for both netilmicin and vancomycin.

Developmental renal excretion model[1][4]
Comprehensive covariate model[4]

Systematic covariate analysis:
• Covariates implemented using a linear or allometric equation
• Objective function used to test significance:
  - Forward inclusion: p < 0.005
  - Backward deletion: p < 0.001

Evaluation of descriptive and predictive performance of the developmental renal excretion model compared to the comprehensive covariate model[4]
1. Objective function
2. Goodness-of-fit plots
3. Normalized Prediction Distribution Error (NPDE) method (1000 simulations)
4. Individual and population parameter estimates vs most predictive covariate
5. Bootstrap analysis
6. Shrinkage

Results: Model Building
For the developmental renal excretion model, BWb and PNA were the most important covariates for CL. Similarly for the comprehensive covariate model the same covariates were identified. The drug specific clearance values (CLD) for netilmicin (0.0507 L/h/kg) and vancomycin (0.0532 L/h/kg) in the model using the developmental renal excretion model were close to the estimated clearance value of amikacin (0.0493 L/h/kg).

Developmental renal excretion model
Comprehensive covariate model

Netilmicin
\[ CL = 0.0632 \times \left( \frac{BWb}{1000} \right) \times PNA \]

Vancomycin
\[ CL = 0.038 \times \left( \frac{BWb}{1440} \right) \times PNA \]

Results: Evaluation
The descriptive performance of the model using the developmental renal excretion model was similar compared to the comprehensive covariate models based on evaluation of the objective function, basic goodness-of-fit plots and the individual and population parameter estimates versus most predictive covariate. The models using the developmental renal excretion model had only a slightly higher objective function (netilmicin p<0.05, vancomycin p<0.001) compared to the comprehensive covariate models.

Developmental renal excretion model
Comprehensive covariate model

Netilmicin
Vancomycin

Figure 2: Observed vs individual and population predicted concentrations for netilmicin (top) and vancomycin (bottom)

Predictive performance[4]
The predictive performance of the model using the developmental renal excretion model was similar compared to the comprehensive covariate models considering the NPDE (figure 3) and bootstrap results.

Developmental renal excretion model
Comprehensive covariate model

Netilmicin
Vancomycin

Figure 3: NPDE of netilmicin and vancomycin vs time and vs predicted concentration.

Conclusions
Use of the developmental renal excretion model quantifying maturation in GFR mediated amikacin clearance for the analysis of netilmicin and vancomycin clearance in neonates, results in similar descriptive and predictive performance compared to the comprehensive covariate model.

We conclude that using system specific information in addition to traditional drug specific modeling may lead to optimization of sparse data analysis in children.