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

Roosmarijn F.W. De Cock, Karel Allegaert, Catherine M.T. Sherwin, Matthijs de Hoog, Johannes N. van den Anker, Meindert Danhof, Catherijne A.J. Knibbe

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** [1] 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.

[1] De Cock *et al.* PAGE 19 (2010); abstract 1900

Methods

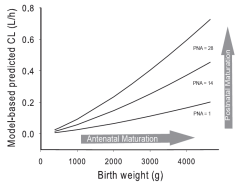
Datasets:

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] **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

Figure 1: Developmental renal excretion model: Clearance (CL) *vs* birth weight (BWb)

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

[2] Sherwin *et al. Eur J Clin Pharmacol* **64**, 1201-8 (2008)
[3] Allegaert *et al. Ther Drug Monit* **29**, 284-91 (2007)
[4] Krekels *et al. Pharm. Res.* 28 (4), 797-811 (2011)

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 (CL_p) 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

$$CL_i = CL_p * \left\{ \left(\left(\frac{BWb}{BWb_{median}} \right)^{1.34} \right) * (1 + 0.213 * \left(\frac{PNA}{PNA_{median}} \right)) \right\}$$

System specific information

Drug specific property

Comprehensive covariate model

Netilmicin

$$CL_i = 0.0632 * \left\{ \left(\frac{BWb}{1000} \right)^{1.34} * \left(\left(\frac{PNA}{15} \right)^{0.481} \right) \right\}$$

Vancomycin

$$CL_i = 0.038 * \left\{ \left(\left(\frac{BWb}{1140} \right)^{1.1} \right) * (1 + 0.955 * \left(\frac{PNA}{14} \right)) \right\}$$

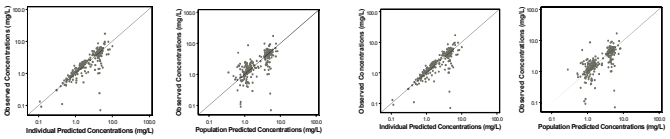
Results: Evaluation

Descriptive performance[4]

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

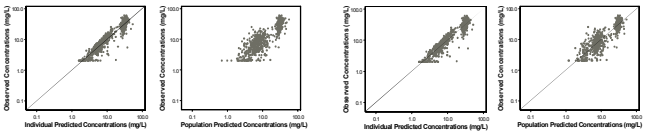


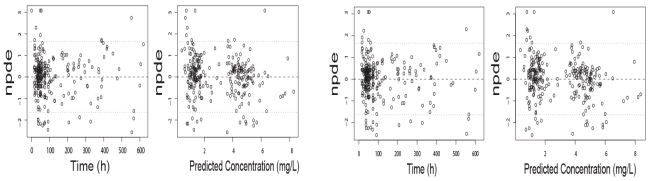
Figure 2: Observed *vs* individual and population predicted concentrations for netilmicin (top) and vancomycin (bottom)

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

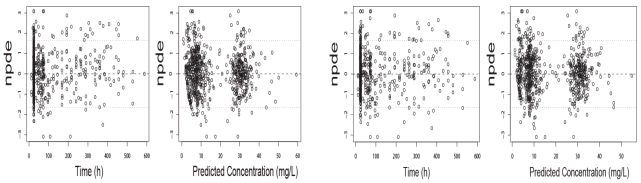


Figure 3: NPDE of netilmicin and vancomycin *vs* time and *vs* predicted concentration.

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.**

Leiden /Amsterdam Center for Drug Research
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