

Predicting glomerular filtration rate using clearance of amikacin in neonates – Model Evaluation

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Introduction

Throughout childhood, many physiological changes occur. These changes result in differences in glomerular filtration (GFR) and tubular secretion/absorption processes at different stages of development.

The aim of this study is to describe the PK of amikacin, a drug which is almost entirely eliminated by the kidney, to quantify age-related developmental changes in GFR in neonates.

Methods



Model building

A population PK model was developed in NONMEM VI. The following covariates were tested for significance: birthweight (BWb), current body weight (cBW), postmenstrual age (PMA), postnatal age (PNA), gestational age (GA), creatinaemia, co-administration of ibuprofen and dopamine, growth restriction, positive blood culture, mechanical ventilation and prenatal exposure to betamethasone.

Data Model building

- 165 preterm neonates, GA 24-30 weeks and PNA 1-2 days¹
- 715 preterm and term neonates, GA 24-43 weeks and PNA 1-30 days²

Data External validation:

- 80 (pre)term neonates, GA 24-41 weeks and PNA 3-30 days³

Validation methods:

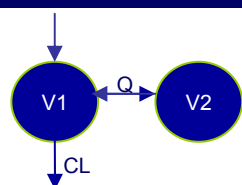
- Diagnostics
- Bootstrap validation method (1,000 replicates)
- Mirror plots
- Normalized Prediction Discrepancy Error (NPDE) method.

1) Allegaert et al. Br. J. Clin. Pharmacol. 2006

2) Allegaert et al. Drug. Metab. Lett. 2008

3) Sherwin et al. Eur. J. Clin. Pharmacol. 2009

Model building



$CL = TH1 \cdot BWb^k \cdot (1 + (PNA^n)) \cdot FF \cdot TH4$
 $V1 = TH2 \cdot cBW^m$
 $V2 = V1$
 $Q = CL \cdot TH3$
 $(FF=1 \text{ IF } IBU=1 \text{ FF}=TH4)$

- **Birthweight (BWb)** most predictive covariate for CL
- **Postnatal age (PNA)** second covariate and co-administration of **ibuprofen** third covariate for CL
- **Current body weigh (cBW)** most predictive covariate for V

Table 1: Parameter estimates

Parameter	Value (CV%)	Bootstrap Value (CV%)
Fixed Effects		
TH1 (L/h/kg BWb)	0.0493 (2.21)	0.0495 (2.68)
TH2 (L/kg cBW)	0.833 (1.34)	0.827 (1.47)
TH3	0.415 (12.3)	0.446 (13.94)
k	1.34 (2.04)	1.34 (2.22)
m	0.919 (2.46)	0.915 (2.52)
n	0.213 (9.81)	0.217 (10.33)
TH4	0.838 (3.88)	0.836 (4.13)
Inter-individual Variability		
ω^2 (CL)	0.0899 (14.9)	0.0917 (15.36)
Residual Error		
σ^2 (proportional)	0.0614 (8.19)	0.0580 (8.47)
σ^2 (additive)	0.267 (27.2)	0.489 (36.73)

ω^2 =variance, σ^2 =intra-individual variance, CV=coefficient of variation

Validation

Internal validation

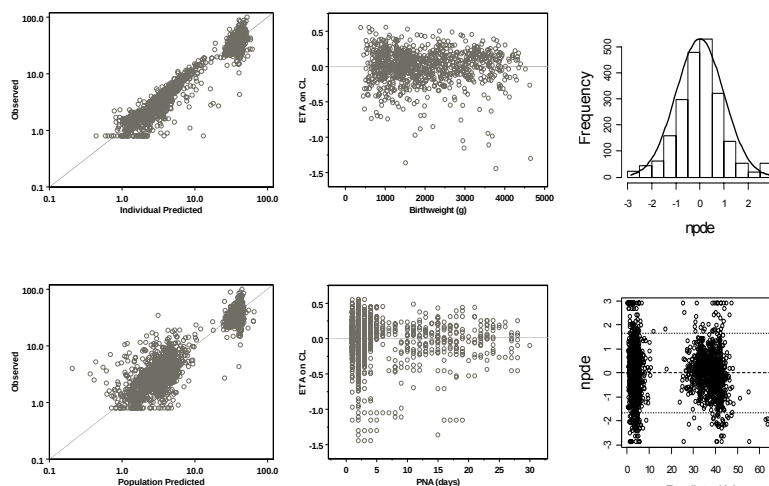


Fig. 1. Diagnostic plots.

A. Observed vs Individual Predicted.
B. Observed vs Population Predicted

Fig.2. Eta on CL vs Birthweight and PNA

Fig.3. NPDE Validation results

External validation

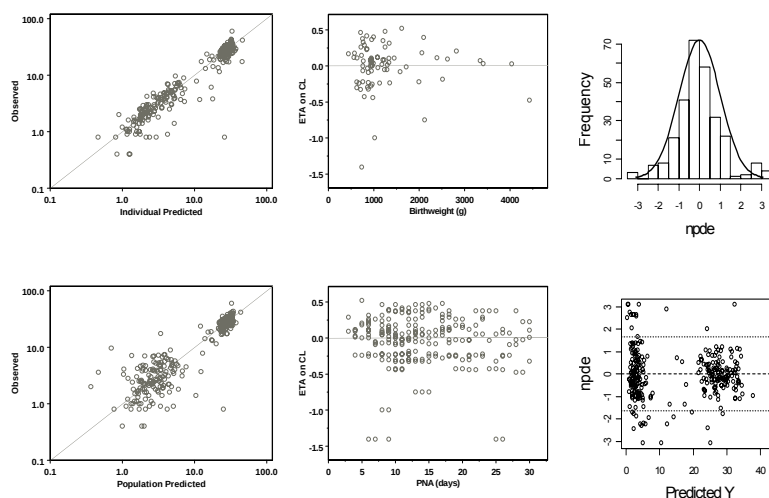


Fig.4. Diagnostic plots.

A. Observed vs Individual Predicted.
B. Observed vs Population Predicted

Fig.5. Eta on CL vs Birthweight and PNA

Fig.6. NPDE Validation results

Conclusions & Perspectives

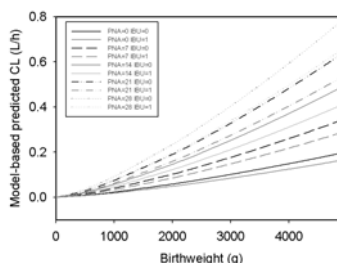


Fig.7. Model-based predicted clearance values vs birthweight for PNA 0,7,14,21,28 and coadministration of ibuprofen.

- The model is able to adequately predict amikacin concentrations in all datasets, including the external dataset.

- Variability in clearance in neonates is partly explained by birthweight, PNA and co-administration of ibuprofen.

- While birthweight represents the antenatal state of maturation of the kidney, PNA represents postnatal maturation of renal clearance.