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Section II

Developmental Changes in Glomerular
Filtration in Preterm and Term Neonates by
Describing the Pharmacokinetics of Renally
Excreted Antibiotics

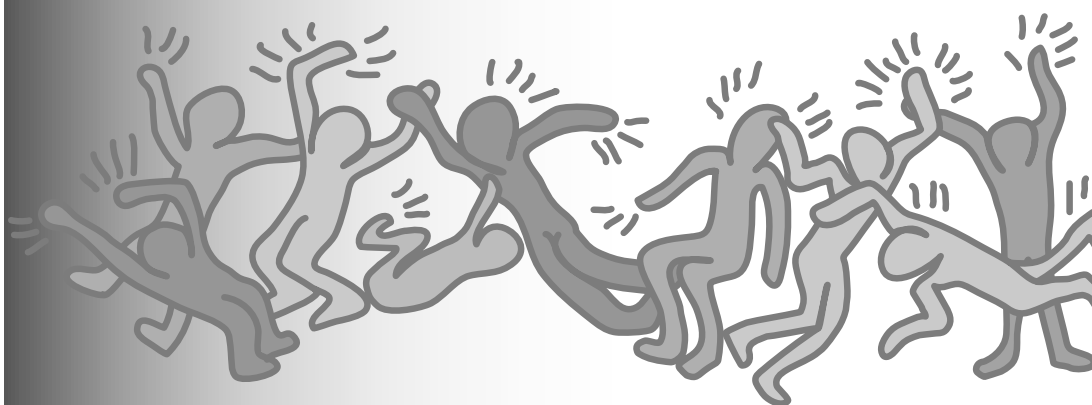


Chapter 3

Maturation of glomerular filtration rate in neonates as reflected by amikacin clearance

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Abstract

Background and Objectives

During the newborn period and early infancy, renal function matures resulting in changes in glomerular filtration rate (GFR). This study was performed to quantify developmental changes in GFR in (pre)term neonates by use of amikacin clearance as proof of concept. The model was used to derive a rational dosing regimen in comparison to currently used dosing regimens for amikacin.

Methods

Population pharmacokinetic modeling was performed in NONMEM 6.2. using data of 874 neonates obtained from two previously published datasets (gestational age 24-43 weeks; postnatal age 1-30 days; birth weight 385-4650 g). The influence of different age and weight related and other covariates was investigated. The model was validated both internally and externally.

Results

Postmenstrual age was identified as the most significant covariate on clearance. However the combination of birth weight and postnatal age proved to be superior over postmenstrual age alone. Birth weight was best described using an allometric function with an exponent of 1.34. Postnatal age was identified using a linear function with a slope of 0.2 while co-administration of ibuprofen proved to be a third covariate. Current weight was the most important covariate for volume of distribution using an allometric function. The external evaluation supported the prediction of the final pharmacokinetic model. This analysis illustrated clearly that the currently used dosing regimens for amikacin in reference handbooks may possibly increase the risk of toxicities and should be revised. Consequently a new model-based dosing regimen based on current bodyweight and postnatal age was derived.

Conclusions

Amikacin clearance, reflecting GFR in neonates, can be predicted by birth weight representing the antenatal state of maturation of the kidney, postnatal age representing postnatal maturation and co-administration of ibuprofen. Finally the model reflects maturation of GFR allowing for adjustments of dosing regimens of other renally excreted drugs in preterm and term neonates.

3.1. Introduction

During the newborn period and early infancy renal function matures, resulting in differences in glomerular filtration rate (GFR) at different stages of development. Although GFR is well defined in adults and many efforts were undertaken in the past to describe the maturation of GFR in the pediatric age range^[1-6], the description of GFR is still limited in pediatrics, particularly in neonates. Nephrogenesis starts in the embryo at week 5-6 of gestation and is completed at week 36^[7-9]. Birth causes hemodynamic changes leading to an increase in renal blood flow and a decrease in renal vascular resistance resulting in rapidly rising GFR during the first weeks of life^[4, 7-9] approaching adult GFR levels at approximately 6-12 months of age. To define safe and effective dosing regimens for renally excreted drugs throughout the pediatric age range GFR, particularly in the first year of life, needs to be quantified.

Different methods have been described to calculate GFR in neonates based on either determination of clearance of endogenous (creatinine^[10, 11]) or exogenous compounds (inulin^[11-14], radio-isotopes^[11]). However several limitations are linked to each of these methods making routine application cumbersome in pediatric and certainly in neonatal clinical practice^[10, 12, 15-17]. The most pragmatic method, which has been proposed before^[18, 19] is to assess GFR in the pediatric age range by determination of the clearance of a drug that is exclusively eliminated by GFR.

Therefore the aim of this study was to describe the pharmacokinetics of amikacin in preterm and term neonates with specific emphasis on clearance, since this parameter reflects GFR. A full covariate analysis was performed in which the influence of all bodyweight and age related, and other covariates on amikacin clearance were tested. The results based on the present amikacin datasets may ultimately serve to predict the maturation of both GFR and clearance of other renally excreted compounds in preterm and term neonates.

3.2. Methods

3.2.1. Patients

Model building was based on data from 874 neonates, obtained after combining two published datasets^[1, 2]. Both studies were conducted at the University Hospital Leuven Belgium. More details on the studies can be found in the original articles^{[1,}

^{2]}. Patients were enrolled in any of the two studies when at least two samples (peak and trough) were available for each patient. In the first study, 205 preterm neonates were considered. Forty-three patients were excluded since they received acetylsalicylic acid while other patients received ibuprofen (n=71), or no nonsteroidal anti-inflammatory drugs (n=91). In the second study, data from 715 patients were collected of which 71 patients received ibuprofen while the other patients (n=668) did not receive any nonsteroidal anti-inflammatory drugs. Three patients were considered as outliers due to administrative errors and were excluded from the second dataset. Data on prenatal use of betamethasone were also collected. More details on patient characteristics are shown in table I.

3.2.2. Drug administration, bloodsampling and assay

Before 2002, an amikacin dose of 20mg/kg/36hours was administered to neonates with a postmenstrual age below 30 weeks and 20mg/kg/24hours to neonates with a postmenstrual age of ≥ 30 weeks. After 2002, dosing was based on Langhendries *et al.*^[20].

Amikacin (Amukin®; Bristol Myers Squibb, Braine-l'Alleud, Belgium) was administered by an intravenous infusion over 20 minutes. Blood samples were collected just before (trough) and 1 hour after initiation of administration (peak) of the second dose. In some of the individuals, more than two samples were available. Amikacin concentrations were measured with fluorescence polarization immunoassay using an Abbott TDx kit (Abbott Laboratories, Diagnostics Division, Abbott Park, IL, USA). The lower limit of quantification was 0.8 mg/L. The coefficient of variation (CV) was <3.5% (assessed at 5, 15 and 30 mg/L).

3.2.3. Pharmacokinetic analysis and model evaluation

The pharmacokinetic analysis was performed using the non-linear mixed effects modeling software NONMEM version 6.2. (Globomax LLC, Hanover, MD, USA). Tools like S-Plus, PsN, XPose and R were used to visualize and evaluate the models. Model building was performed in four different steps: (i) selection of structural model, whereby a one- as well as a two-compartment model was tested, (ii) choice of statistical sub-model, (iii) covariate analysis, (iv) model evaluation. To discriminate between different pediatric (covariate) models the framework proposed by Krekels *et al.*^[21] to systematically evaluate the descriptive and predictive performance of pediatric models was used as a guide. This framework was used because evaluation tools that are routinely used in the adult population may not suffice in the pediatric population due to the scarcity of the data, the increased variability in dosing and

Table I: Clinical characteristics of the patients in both model building datasets and external datasets, presented as median (range).

	Model building dataset 1 (15)	Model building dataset 2 (16)	External dataset 1 (17)	External dataset 2 (18)
Number of patients	162	712	80	159
Gestational age (weeks)	28 (24-30)	33 (24-43)	26 (24-41)	31 (25-42)
Postnatal age (days)	2 (1-3)	2 (1-30)	16 (3-30)	1 (1-3)
Birth weight (g)	1052 (475-1910)	1990 (385-4650)	880 (440-4430)	1740 (526-5420)
Current bodyweight (g)	1052 (475-1910)	1990 (385-4780)	1060 (450-4430)	1665 (526-5420)
Co-administration of ibuprofen	71 (43%)	47 (6%)	0	0

Birth weight = weight at day of birth, current bodyweight = weight at day of blood sampling

sampling schemes or the heterogeneity in the population. Therefore advanced and additional diagnostics next to standard tools may be required in the pediatric population compared to the adult population. This includes the following standard tools: discrimination between models by comparison of the objective function (OFV) and total number of parameters. A decrease in OFV of more than 7.8 points was considered as statistically significant ($p < 0.005$ based on χ^2 distribution). Furthermore, the goodness-of-fit plots (both observed *versus* individual and population predicted concentrations, time as well as population predictions *versus* conditional weighted residuals) were evaluated with specific emphasis on observed *versus* population predicted concentrations^[21]. Moreover improvement of individual plots, confidence intervals of the parameter estimates and correlation matrix were assessed. Over-parameterization (ill-conditioning) was tested by calculating the condition number by dividing the largest eigen value to the smallest eigen value^[22]. Finally in pediatric datasets there is often not enough information to accurately estimate the inter- and intra-individual variability. Therefore shrinkage was considered^[23]. Other pediatric specific evaluation tools are mentioned in the section Covariate analysis and Internal evaluation procedure.

3.2.4. Covariate analysis

Covariates were plotted independently against the individual *post hoc* parameter estimates and the weighted residuals to visualize potential relationships. The following covariates were evaluated for inclusion: gestational age, postnatal age, postmenstrual age (sum of gestational and postnatal age), birth weight (weight at day of birth), current bodyweight (weight at day of blood sampling), co-administration of

ibuprofen, prenatal exposure to betamethasone and creatinine concentrations. Information on co-administration of dopamine, ventilation and positive blood culture was not available for all patients. Consequently they could not be evaluated as possible covariates. However in the past it was shown that the impact of these covariates was not significant [1, 6, 24].

Potential covariates were separately implemented into the model using a linear or allometric equation (equation 1).

$$P_i = P_p \cdot \left(\frac{Cov}{Cov_{Median}} \right)^k \quad (\text{Equation 1})$$

In this equation P_i represents the individual parameter estimate of the i th subject, P_p equals the population parameter estimate, Cov is the covariate and k is the exponent which was fixed to 1 for a linear function or estimated for an allometric function. The significance of a covariate was statistically tested by use of the objective function. A p value <0.005 was applied to evaluate the covariates in the forward inclusion (decrease of OFV of at least 7.8 points) while a more stringent p value of <0.001 was used in the backward deletion (decrease of OFV of at least 10.83 points). When two or more covariates were found to significantly improve the model, the covariate causing the largest reduction in OFV was left in the model. Additional covariates had to reduce this OFV further to be retained in the model. In order to select the final covariate model, as suggested by Krekels *et al.* [21], individual and population parameter estimates were plotted against the most predictive covariate to evaluate whether the individual predicted parameters were equally distributed around the population predicted parameters. The choice of the covariate model was further evaluated as discussed in the previous paragraph whereby the results of the internal evaluation were also considered.

3.2.5. Internal evaluation procedure

The final pharmacokinetic model was validated using two methods [21]: (i) the bootstrap resampling method, and (ii) the normalized prediction distribution error (NPDE) method. The bootstrap analysis to evaluate the stability was performed in S-plus, version 6.2.1 (Insightful software, Seattle, WA) with NM.SP.interface version 05.03.01 (© by LAP&P Consultants BV, Leiden, The Netherlands). The model building datasets were resampled 1000 times to produce a new dataset of the same size containing a different combination of individuals. The parameter estimates were summarized in terms of mean values and standard errors and were compared with the

estimates obtained from the model building datasets.

The accuracy of the model was evaluated with the NPDE method ^[25, 26] in which the observed and simulated concentrations are compared using the NPDE software package in R. In this study each observation was simulated 1000 times after which the software assembled the predictions in a cumulative distribution and determined the value of the cumulative distribution at the observed concentration. The normalized prediction distribution errors were then obtained after applying the inverse function of the normal cumulative density function ^[25, 26]. The NPDE as simulation-based diagnostic is preferred over the visual predictive check (VPC) since it is easier to interpret when data are obtained during routine clinical practice causing a high variability in both dosing and sampling schemes. Consequently a NPDE is often preferred over a VPC in the analysis of pediatric datasets. The results of NPDE method are visualized in different graphs: (1) quantile-quantile plot (2) histogram showing the distribution of the normalized prediction distribution errors which are expected to follow a normal distribution, (3) scatterplot NPDE versus time and (4) scatterplot NPDE versus predicted concentrations.

3.2.6. External evaluation procedure

External evaluation was performed by using two published external datasets ^[6, 27]. In total 517 concentrations were available obtained from 80 neonates in the first ^[6] and 159 neonates in the second external dataset ^[27]. In external dataset 1, peak (taken 60 minutes after start of infusion) and trough concentrations (measured at 24 hours) were available. In external dataset 2, only 1 sample was available, which was collected between the first and second dose. More details on the studies (including information on co-medication and prenatal drug treatment) can be found in the original articles ^[6, 27]. In neither one of these two external datasets, ibuprofen was administered. Patient characteristics of the external datasets are given in table I.

The final pharmacokinetic model (with all parameters fixed to final values with $\text{maxeval}=0$ and without covariance step) was used to simulate concentrations for each data point of the two external datasets. Additionally, the final pharmacokinetic model was used to compute the NPDE ^[25, 26] for each of the external datasets. Each concentration was simulated 1000 times.

Finally parameters of the final model were re-estimated on the basis of the two model building datasets and external dataset 1. In a second step both external datasets combined with both model building datasets were analyzed.

3.2.7. Simulations of currently used dosing regimens

The parameter estimates from the final pharmacokinetic model were used to simulate concentration time profiles upon different dosing regimens currently used or suggested in reference textbooks^[6, 20, 28-30]. Simulations were performed in three patients (gestational age 24, 32, 40 weeks) selected from the two model building datasets. The three patients were selected to cover the entire study population in terms of bodyweight and gestational age. For the first preterm patient (gestational age 24 weeks) the lowest birth weight was chosen. In the second preterm (gestational age 32 weeks) and third term patient (gestational age 40 weeks) a median birth weight of 1730 g and 3520 g, was chosen respectively. In the simulations, five consecutive doses were administered starting from day at birth. The simulations were performed excluding the interindividual and residual variability. Based on the results a new dosing schedule was designed, aiming to achieve C_{max} values in the range of 24-35 mg/L^[6] and trough values below or between 1.5-3 mg/L^[31]. Since the dose was given over 20 minutes in the model building datasets while in most reference textbooks (Neofax®^[28], Red Book®^[29], BNFc^[30], Sherwin et al.^[6]) an infusion time of 30 minutes is applied, both infusion rates were used to simulate the concentration-time profiles of the model-based dosing regimen.

3.3. Results

3.3.1. Patients and data

The pharmacokinetic analysis was based on 2186 observations from 874 neonates obtained from two studies performed by Allegaert et al.^[1, 2]. The external evaluation was executed using two previously published datasets^[6, 27] containing data of 80 and 159 neonates respectively. A summary of all patient characteristics is presented in table I.

3.3.2. Pharmacokinetic model building

A two compartment model parameterized in terms of clearance (CL), inter-compartmental clearance (Q), volume of distribution of central compartment (V₁) and peripheral compartment (V₂) was preferred over a one compartment model since it was able to describe the model building datasets more accurately. The objective function of the final two compartment model (OFV=7738) was significantly lower ($p<0.001$) compared to the corresponding one compartment model (OFV=7946).

Furthermore the goodness-of-fit plots improved. In particular samples taken later than 48 hours after dosing were more accurately described using the two compartment model. However, when estimating Q and V2 independently of CL and VI, no covariance step could be given, probably due to over parameterization of the model. As a result the model was simplified by estimating Q and V2 as fraction of CL and VI, respectively, resulting in no increase in OFV and even better diagnostics plots. Because of failure of the bootstrap, V2 was equalized to VI in the final model which only resulted in an increase in OFV of 7 points and similar diagnostic plots. The residual variability was best described using a combined additive and proportional error model.

Table II: Population parameter estimates of the final pharmacokinetic model based on two model building datasets, the values obtained after bootstrap of the final pharmacokinetic model and the model parameter estimates after combining the model building datasets together with the external datasets.

Parameter	Simple model	Final pharmacokinetic model (Model building datasets)	Bootstrap final pharmacokinetic model	Model building datasets and external dataset 1	Model building datasets, external dataset 1 and external dataset 2
	Value (CV%)	Value (CV%)	Value (CV%)	Value (CV%)	Value (CV%)
Fixed Effects					
CL (L/h)	0.0743 (3.11)				
CL(L/h/kg BWb)		0.0493 (2.21)	0.0495 (2.68)	0.0496 (2.3)	0.0485 (2.06)
Q (fraction of CL)	0.681 (6.3)	0.415 (12.3)	0.446 (13.94)	0.422 (12.3)	0.36 (10.9)
CL* $((\text{BWb}/\text{median})^\theta)$	-	1.34 (2.04)	1.34 (2.22)	1.34 (2.02)	1.33 (1.84)
CL*(1+ θ *(PNA/median))	-	0.213 (9.81)	0.217 (10.33)	0.211 (9.1)	0.202 (10.6)
CL* θ (IBU)	-	0.838 (3.88)	0.836 (4.13)	0.838 (3.96)	0.851 (3.43)
VI=V2 (L/kg cBW)	0.716 (2.19)	0.833 (1.34)	0.827 (1.47)	0.836 (1.34)	0.845 (1.18)
VI* $((\text{cBW}/\text{median})^\theta)$	-	0.919 (2.46)	0.915 (2.52)	0.909 (2.22)	0.91 (2.14)
Interindividual variability					
ω^2 (CL)	0.677 (6.51)	0.0899 (14.9)	0.0917 (15.36)	0.097 (13.9)	0.0822 (13.3)
Residual Error					
σ^2 (proportional)	0.184 (6.25)	0.0614 (8.19)	0.0580 (8.47)	0.0614 (8.26)	0.0592 (8.07)
σ^2 (additive)	1.15 (13.6)	0.267 (27.2)	0.489 (36.73)	0.3 (25.9)	0.297 (23.7)

CL = Clearance, Q = Intercompartmental clearance, VI = volume of distribution of central compartment, V2 = Volume of distribution of peripheral compartment, BWb = bodyweight at birth, cBW = current bodyweight, PNA = postnatal age, θ (IBU)=1 : no co-administration of ibuprofen, θ (IBU)=0.838 : co-administration of ibuprofen

3.3.3. Systematic covariate analysis

The systematic covariate analysis identified current bodyweight as most important covariate implemented on volume of distribution using an allometric function (table II) causing a drop in the OFV of 1488 points. For clearance postmenstrual age was identified as most important covariate causing a drop in OFV of 1160 points. However, birth weight and postnatal age together proved to be superior (Δ OFV 1598 points) to postmenstrual age alone. The model using postmenstrual age as covariate on clearance was not able to describe the data as well as the final model with birth

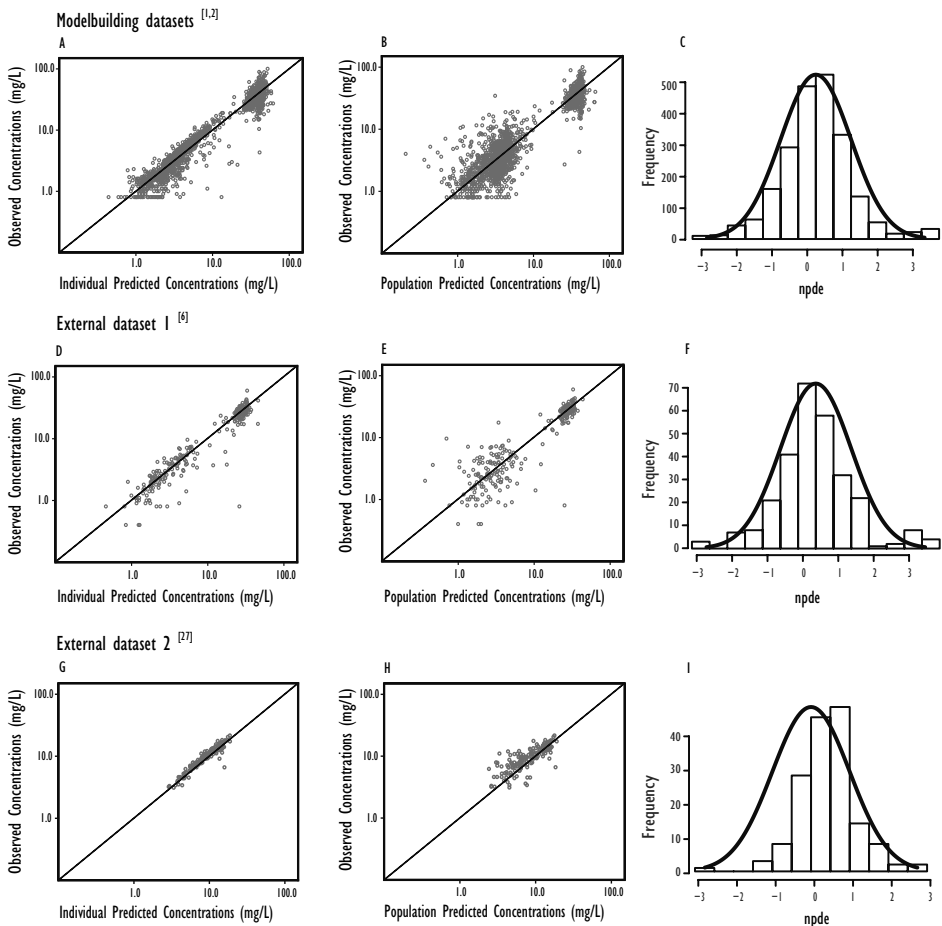


Figure 1: Observed versus individual predicted concentrations and observed versus population predicted concentrations of (a-b) the model building datasets ^[1,2], (d-e) external dataset I ^[6] and (g-h) external dataset 2 ^[27]. The histograms show the distribution of the NPDE method of (c) the model building datasets, (f) external dataset I and (i) external dataset 2. The solid line represents a normal distribution.

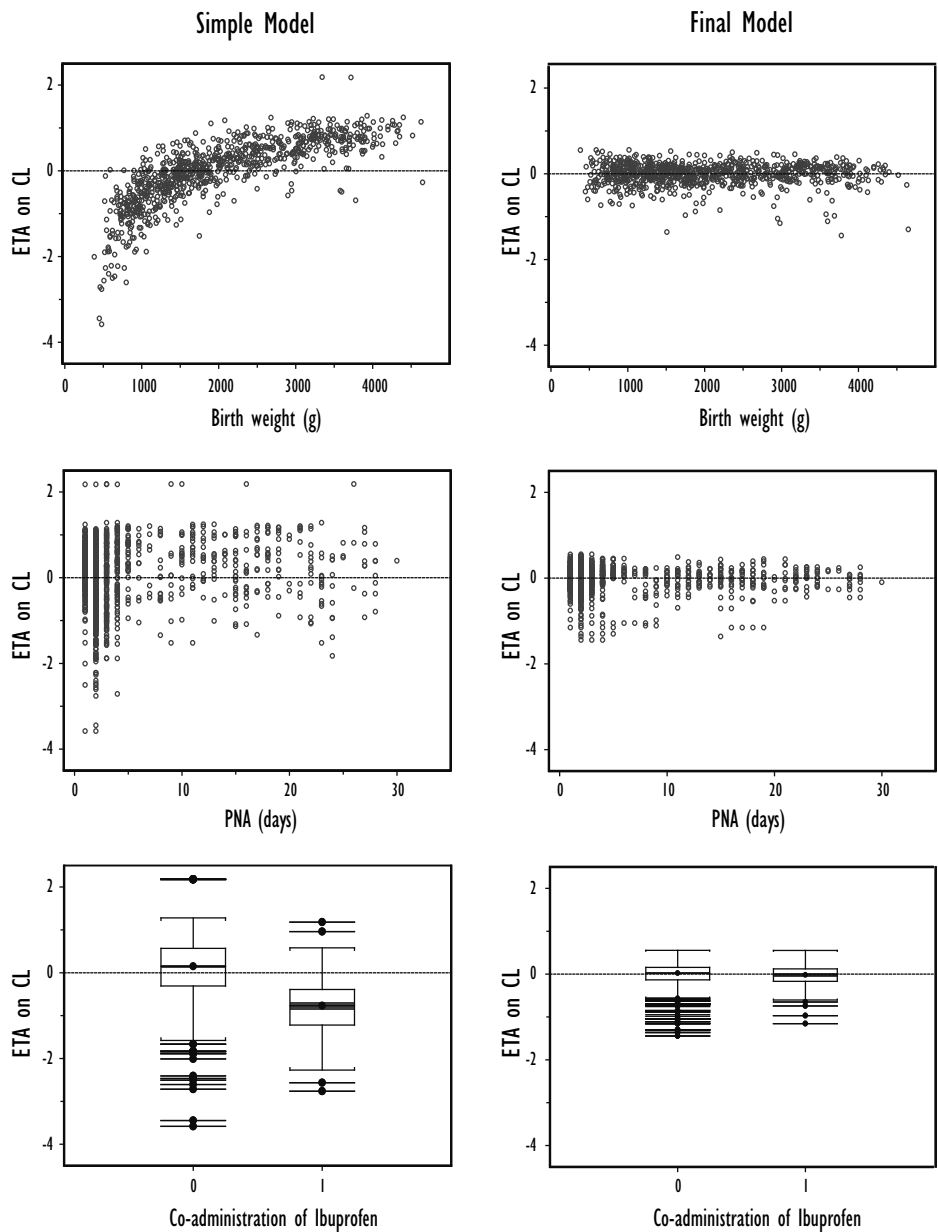


Figure 2: Interindividual variability for clearance (Eta on CL) versus birth weight, postnatal age (PNA) and co-administration of ibuprofen for the simple (left) and the final model (right).

weight and postnatal age unless additionally the covariates birth weight and/or postnatal age also were introduced. Consequently birth weight was implemented as first covariate on clearance using an allometric function with an estimated exponent of 1.34 (ΔOFV 940 points). A further decrease in OFV of 659 points was achieved by implementing postnatal age linearly on clearance. The model further improved by introducing co-administration of ibuprofen (ΔOFV 26 points) as third covariate on clearance. A correlation between creatinine concentrations and clearance, as seen in adults, was not identified in this population.

3.3.4. Final pharmacokinetic model and internal evaluation

Table II gives an overview of the parameter estimates of the simple and final pharmacokinetic model together with the values obtained from the bootstrap analysis. In figure 1a-b, observed versus individual and population predicted concentrations are given for the final pharmacokinetic model, while in figure 1c the histogram of the NPDE is shown. The histogram follows the normal distribution expected by the solid line indicating the accuracy of the final pharmacokinetic model. No trend was seen in the NPDE versus time or versus predicted concentrations (data not shown). In figure 2 interindividual variability in clearance is plotted against birth weight, postnatal age and co-administration of ibuprofen for the simple and the final pharmacokinetic model to illustrate that by introducing these three covariates into the model, a significant part of the interindividual variability (68%) is explained. This is also reflected by the estimate of interindividual variability in clearance which was reduced from 0.677 to 0.0899 when the three covariates were introduced (table II). Plotting the population and individual predicted values for clearance versus birth weight (data not shown) as proposed by Krekels *et al.* [21] illustrated that the individual predicted values are equally scattered around the population predicted values. No ill-conditioning was detected since the condition number (value of 43) for the final pharmacokinetic model was far below the critical value of 1000.

The model-based predicted clearance values of the final pharmacokinetic model versus birth weight for PNA 0, 14, 28, with and without co-administration of ibuprofen are illustrated in figure 3. The figure shows horizontally the influence of birth weight representing the antenatal maturation and vertically postnatal age representing postnatal maturation.

3.3.5. External evaluation of the final model

The predictive performance of the final pharmacokinetic model was evaluated using two previously published external datasets [6, 27] (table I). In figure 1 observed

Table III: Amikacin dosing recommendations in preterm and term neonates according to 5 dosing regimens currently used or suggested in reference text books.

Guideline	Currently used dosing guidelines					Interval (hours)
	Gestational age (weeks)	Postnatal age (days)	Current body-weight (g)	Duration IV infusion (minutes)	Dose (mg/kg)	
Langhendries <i>et al.</i> ^{[21]*}	< 28	-	-	20	20	42
	28-30	-	-		20	36
	31-33	-	-		18.5	30
	34-37	-	-		17	30
	> 37	-	-		15.5	24
Sherwin <i>et al.</i> ^[17]	< 29	-	-	30	15	36
	29-36	-	-		14	24
	> 36	-	-		15	24
		0-7	-		18	48
Neofax [®] (2009) ^[32]	< 30 or **	8-28	-	30	15	36
		> 28	-		15	24
	30-34	0-7	-		18	36
		> 7	-		15	24
	> 34	-	-		15	24
RedBook [®] (2009) ^[38]	-	1-30	< 1200	30	7.5	18-24
			1200-2000		7.5	12
		0-7	> 2000		7.5-10	12
		>7	1200-2000		7.5-10	8-12
BNFc (2009) ^[39]	-		> 2000	30	10	8
		-	-		15	24

* 6 hour prolongation of dosing interval when ibuprofen is co-administered

** Neonates suffering from asphyxia, having a patent ductus arteriosus or co-administration of indomethacin

versus individual (d,g) and population predicted concentrations (f,i) are given for both the external datasets. Additionally, the histograms of the NPDE are shown in figure If and Ii respectively. While the final pharmacokinetic model is able to predict the data of external dataset 1 with adequate precision and without bias, a slight bias is seen for external dataset 2 in which sampling was not performed at peak and trough timepoints but in between these two moments. This small bias is observed in figure Ih showing observed versus predicted concentrations as well as in figure Ii in which the normal distribution is shifted from the solid line. Furthermore a trend was seen in the NPDE versus time and the npde versus predicted concentrations (data not shown).

However combined analysis of the two model building datasets and the external dataset I as well as the model building datasets and both external datasets, revealed that fairly similar parameter values were obtained (table II), indicating the stability of the final pharmacokinetic model.

3.3.6. Simulations of currently used dosing regimens

Concentration-time profiles for amikacin for three different individuals (gestational age 24, 32 and 40 weeks and birth weight 480, 1730 and 3520g, respectively) following five different dosing regimens currently used or proposed in reference textbooks (table III) were predicted on the basis of the final pharmacokinetic model (figure 4). Peak concentrations below the target range of 24-35 mg/L^[6] and concentrations above the aimed trough concentration range of 1.5-3 mg/L^[31] are represented by a black dot while predicted peak and trough concentrations within the target range are indicated by open circles. The dosing guidelines suggested by the Red Book® and the British National Formulary for children (BNFc) are potentially inducing toxicity in preterm and even term neonates since target trough values are not reached which may be associated with a higher risk for nefro- or ototoxicity^[32, 33] due to aminoglycoside accumulation. Although the dosing guidelines according to Langhendries *et al.*^[20], Sherwin *et al.*^[6] and Neofax® approach the target trough concentrations more closely, adjustments are needed for all of them since target

Table IV: A model-based dosing regimen for preterm and term neonates based on target C_{max} concentrations of 24-35 mg/L and trough concentrations below 2-5 mg/L.

Model-based dosing regimen						
Guideline	Gestational age (weeks)	Postnatal age (days)	Current bodyweight (g)	Duration IV infusion (minutes)	Dose (mg/kg)	Interval (hours)
	-		0-800		16	48
	-		800-1200		16	42
	-	< 14	1200 - 2000		15	36
	-		2000 - 2800		13	30
Model-based dosing regimen *	-		≥ 2800	20/30	12	24
	-		0-800		20	42
	-		800 - 1200		20	36
	-	≥ 14	1200 - 2000		19	30
	-		2000 - 2800		18	24
	-		≥ 2800		17	20

*10 hours prolongation of dosing interval when ibuprofen is co-administered

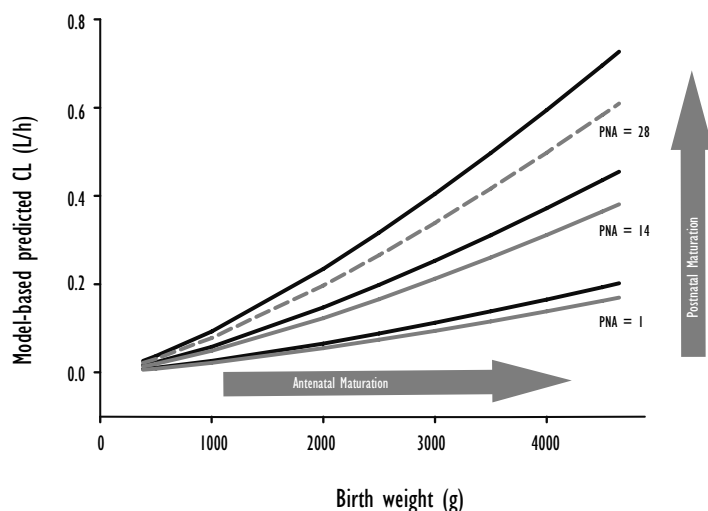


Figure 3: Model-based predicted amikacin clearance values versus birth weight for postnatal age (PNA) of 0, 14 or 28 days with (black line) and without (grey line) co-administration of ibuprofen.

trough concentrations below 1.5-3 mg/L are only reached in patient 2 by Neofax®. Target peak and trough values are only reached in all three patients using the model-based new dosing regimen (table IV) which is based on current bodyweight (covariate for volume of distribution, determining the peak concentration), postnatal age and co-administration of ibuprofen (covariates for clearance determining the dosing interval).

3.4. Discussion

During infancy renal function matures resulting in changes in GFR, which is most pronounced in neonates. Since amikacin is almost entirely eliminated by GFR, we aimed to quantify developmental changes in GFR in (pre)term neonates by describing the maturation of amikacin clearance.

The pharmacokinetic model developed in this study was based on 2186 trough and peak concentrations from 874 (pre)term neonates obtained from two datasets^[1, 2] covering an extensive variation in gestational age, postnatal age and birth weight. An internal and external evaluation was performed to demonstrate descriptive and predictive properties. Birth weight, representing maturation of GFR until birth^[34], proved to be the most important covariate for clearance. Birth weight, which

ranged between 385g and 4650g, was found to influence clearance on the basis of an allometric function as shown in figure 3. Maturation after birth was quantified using postnatal age (range 1-30 days) as covariate for clearance (figure 3). In previous studies ^[1, 2, 4, 6, 35-38], which were often based on a more restricted number and range in patients and data, these two processes were merged together into one covariate, postmenstrual age, which is a combination of gestational and postnatal age. The model with postmenstrual age was inferior compared to the final pharmacokinetic model with both birth weight and postnatal age unless birth weight and postnatal age were added as second and third covariate to postmenstrual age. We consider our approach using birth weight and postnatal age superior because the combination of postmenstrual age, birth weight and postnatal age repeatedly uses the same information. More specifically, birth weight and postnatal age as morphometric surrogates for organ function are distinctly different and independent covariates since birth weight reflects the antenatal maturation and postnatal age is representing postnatal maturation. The limited predictive value of postmenstrual age in this analysis may be explained by the large variation in gestational and postnatal age, as postmenstrual age does not distinguish between pre- and postnatal maturation. Meanwhile birth weight also proved to be a superior covariate compared to gestational age. For the same gestational age, a large range in birth weight was observed in our datasets, showing that birth weight represents more accurately the antenatal maturation thereby reflecting (dys)maturation or (dys)function of the neonate. The specific influence of birth weight, postnatal age and co-administration of ibuprofen is given in figure 3. This figure illustrates clearly how clearance of amikacin increases with birth weight (antenatal maturation) and postnatal age (postnatal maturation). Large differences in clearance values (4.4 fold) are observed when comparing an individual with a birth weight of 1 kg (0.026 L/h) and 3 kg (0.112 L/h) at day 1. This difference in clearance is still present at day 28 between an individual of 1 kg (0.092 L/h) and 3 kg (0.404 L/h) indicating that catch-up growth of prematurely born neonates (e.g. normalizing in height, weight and clearance values) does not appear in the first month. Furthermore it also illustrates the reduction in GFR following administration of ibuprofen ^[1, 39-42] causing a decrease in amikacin clearance of 16.2%. This decrease in clearance by ibuprofen was seen before and is caused by inhibition of the cyclo-oxygenase cascade inducing a downregulation in the formation of prostaglandins. This results in a reduction of the vasodilative effects which normally help to support the glomerular filtration rate and glomerular perfusion leading to a decrease in clearance.

In some previous trials, GFR was determined by measuring the clearance of inulin, which is considered as the gold standard^[13]. In most of these publications gestational age was found as most important covariate for clearance in (pre)term neonates ^[43-45], followed by an increase in GFR due to postnatal age ^[44, 45]. However these findings are

based on a smaller number of patients and more narrow age range compared to our analysis in which birth weight and postnatal age were identified as most important covariates. Although the use of amikacin as a marker for GFR may also have some restrictions - amikacin itself may influence the renal function after repetitive dosing as well as the fact that amikacin is often given to treat neonatal sepsis, a disease state that also may influence renal function - our findings are based on a very large dataset of preterm as well as term neonates with a postnatal age up to 30 days. Furthermore as discussed previously birth weight was found to represent more accurately the antenatal maturation of the kidney in our analysis compared to gestational age. Moreover practical and ethical constraints make a prospective evaluation of maturation of GFR by measuring clearance of inulin not possible in this age group.

Model-based concentration-time profiles were simulated for three different patients using 5 different dosing guidelines (table III, table IV) (figure 4). According to our simulations the dosing guidelines suggested by Langhendries *et al.* ^[20], Sherwin *et al.* ^[6] and Neofax® approach the target values closely even though target trough values between 1.5-3 mg/L ^[31] are not reached, except in patient 2 by Neofax® (figure 4). A possible explanation might be that target trough values between 2-5 mg/L ^[20, 28] instead of 1.5-3 mg/L ^[31] were aimed for in the past. Regarding the dosing guidelines suggested by Langhendries *et al.* ^[20] target trough values may also not be reached since this dosing regimen was only validated for neonates directly after birth, implying that postnatal age was not taken into account. However, all dosing regimens for amikacin currently used or suggested in reference handbooks in both preterm and term neonates up to 30 days possibly increase the risk of toxicities and therefore need to be updated. Especially the dosing regimens proposed in the Red Book® and BNFc may potentially induce nefro- and ototoxicity in preterm and even term neonates since target trough values are not reached ^[32, 33]. Moreover potential risk of oto- and nephrotoxicity is not only related to higher trough concentrations but is also linked to treatment duration. Therefore future studies should be considered on treatment duration to even further reduce amikacin toxicity. Finally, exposure to aminoglycosides in neonates with mutations in the MT-RNRI gene that are associated with aminoglycoside-induced hearing loss ^[46] should be avoided. A prenatal screening in which mothers are tested for these variants would prevent the exposure of aminoglycosides to babies at risk.

Based on the final pharmacokinetic model a new dosing regimen was developed by adjusting the dose to current bodyweight (covariate for volume of distribution, determining the peak concentration), postnatal age and co-administration of ibuprofen (covariates of clearance, determining the dosing interval). When ibuprofen is co-administered it is suggested to extend the dosing interval to 10 hours since

trough concentrations between 1.5-3 mg/L are not yet reached upon a prolongation by 6 hours. For the model-based dosing regimen concentration-time profiles were simulated using an infusion time of 20 and 30 minutes. Both infusion times resulted in the same trough concentrations and only slightly higher peak concentrations when the dose was administered over 20 minutes which are of no clinical relevance. This limited influence of infusion rate was expected since the final pharmacokinetic model based on data using an infusion time of 20 minutes was able to describe accurately the data of external dataset 1 in which an infusion time of 30 min was applied.

Even though the final model described the data of all age and weight ranges most adequately a slight bias was observed in the plot 1b. When re-evaluating retrospectively the medical records it seemed that these individuals were suspect for perinatal asphyxia. Although Langhendries *et al.* ^[20] proposed before that the time interval for amikacin dosing needs to be adapted following perinatal asphyxia, we were not able to identify in our datasets which patients were suffering from asphyxia since no robust indicators have been identified in practice. Therefore we could not study asphyxia as a covariate. In order to better determine the impact of perinatal asphyxia in future models, we suggest to prospectively report potential indicators (Apgar score, lactate, Thompson score) ^[47].

Although the stability of the final pharmacokinetic model was indicated by the bootstrap and the NPDE as well as the ability to predict external dataset 1 accurately, the predictive performance was slightly biased for external dataset 2. This could not be explained by differences in age or bodyweight or any other covariate between external dataset 2 and the other datasets. The only observed discrepancy was the time at which samples were taken. Unlike the model building datasets and external dataset 1, no peak and trough but only midterm samples, taken between 3.5 - 33 hours, were available in external dataset 2. While this result indicates that the final pharmacokinetic model is not entirely able to describe the midterm samples which are concentrations measured in a different phase of the distribution, the results of external dataset 1 show that the model very well predicts peak and trough concentrations which are used as surrogate markers for respectively efficacy and safety of amikacin. In this respect it can be emphasized that in clinical practice only trough samples are of interest in terms of aminoglycoside accumulation monitoring meaning that midterm samples should be avoided.

The clinical response was not investigated in the new dosing regimen and may be considered as one of the limitations of this study. However amikacin was given in this population when an infection was suspected. Another remark can be made on the adequate use of antibiotics given in association with the aminoglycosides. Aminogly-

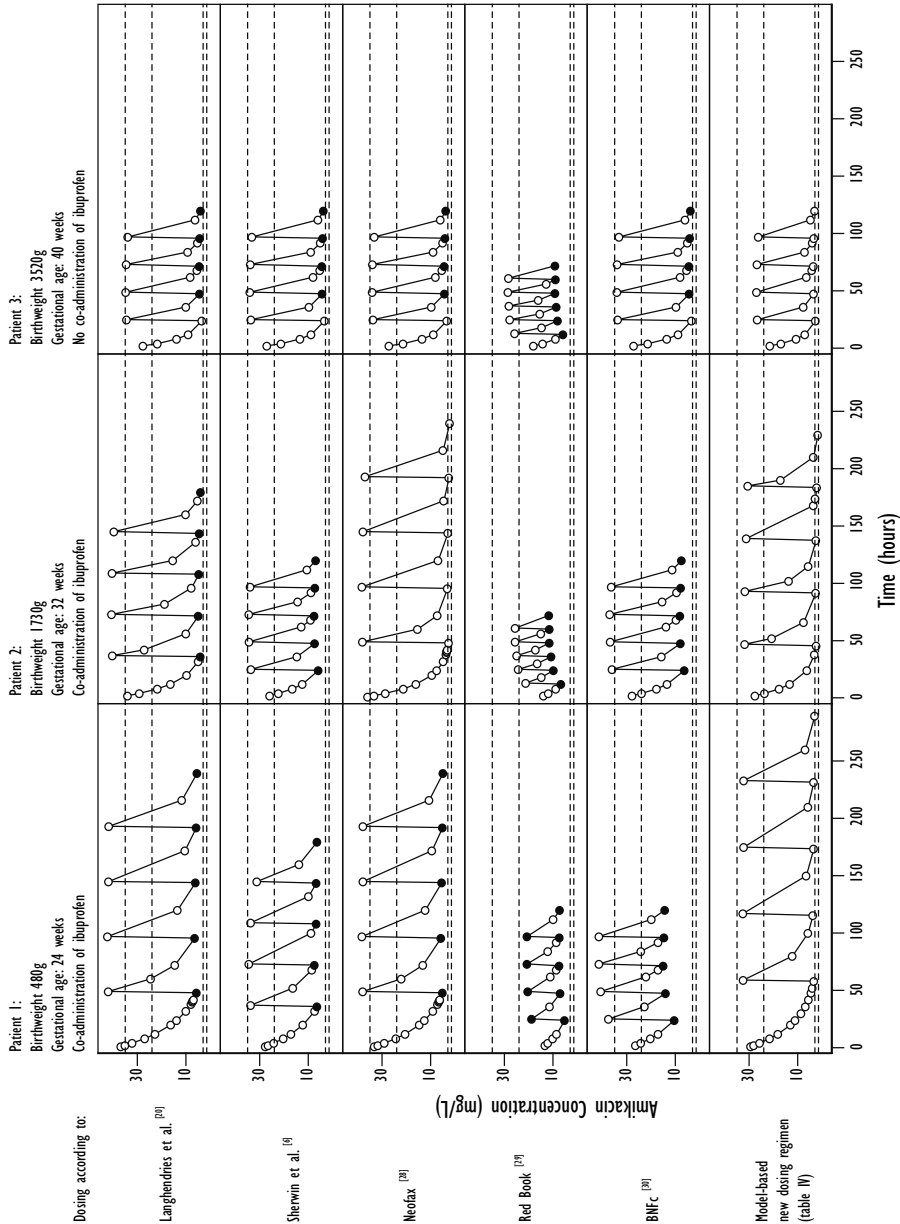


Figure 4: Model-based predicted concentration-time profiles for three individuals using five different dosing guidelines (Langhendries et al. [20], Sherwin et al. [6], Neofax® [28], Red Book® [29] and British National Formulary for children (BNFc) [30] (table III) and according to the model-based new dosing regimen (table IV). GA = gestational age, BWb = birth weight. The dotted lines indicate the target peak (24-35 mg/L) and trough (1.5-3 mg/L) amikacin concentrations aimed for. Peak concentrations below and trough concentration above the target range are indicated by a black dot.

cosides are often administered in association with beta-lactam antibiotics. Although it is well known that aminoglycosides exhibit a postantibiotic effect, the acceptable duration between two administrations in terms of this postantibiotic effect remains still unclear. Future studies are needed to develop rational dosing schemes for the antibiotics given in association with amikacin based on the new dosing regimen.

Finally creatinine concentrations could not be identified as a significant covariate in this study. To a certain extent, this was anticipated since creatinemia in the first 3 days of postnatal life reflects maternal renal function. In addition, creatinemia trends throughout neonatal life display an initial progressive increase with peak concentration in the second part of the first week of life due to passive back leaking of creatinine through the renal tubular cells, with a subsequent decrease throughout neonatal life ^[15, 16].

3.5. Conclusions

Amikacin clearance in neonates can be predicted by combination of the morphometric surrogates for organ function: birth weight representing the antenatal state of maturation of the kidney, postnatal age representing postnatal maturation and co-administration of ibuprofen. Postmenstrual age proved to be less predictive compared to the contribution of birth weight and postnatal age together. This study shows notably that the dosing regimens for amikacin suggested in reference handbooks for both preterm and term neonates up to 30 days need to be updated. Finally the model reflects maturation of GFR allowing for adjustments of dosing regimens of other renally cleared drugs.

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