Chapter 4

Prospective Validation of a Model-based Dosing Regimen for Amikacin in Preterm and Term Neonates

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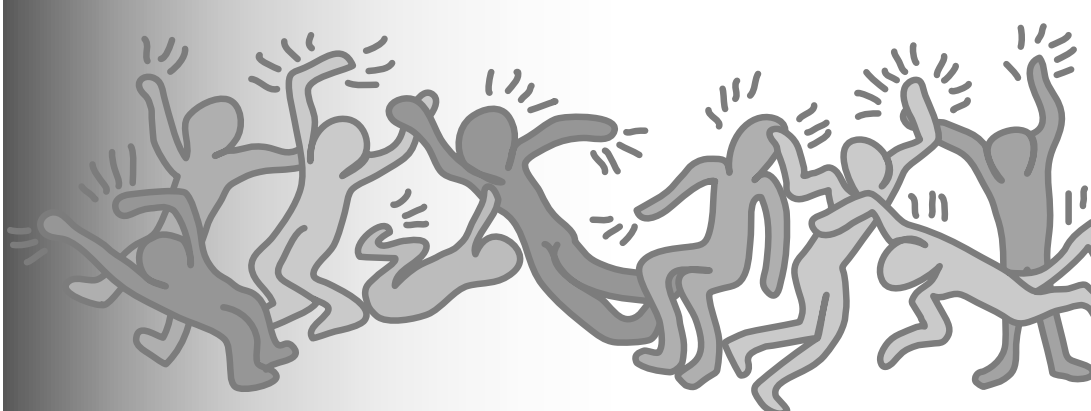

Abstract

Introduction

The dosing regimens for amikacin in neonates in reference handbooks may potentially lead to lack of efficacy and/or toxic effects. Therefore, a novel dosing regimen with bodyweight, postnatal age and co-administration of ibuprofen as covariates was proposed based on a recently derived population pharmacokinetic model. The aim of the current study was to prospectively evaluate the accuracy and precision of this novel model-based dosing regimen for amikacin in preterm and term neonates aged between 1-30 days.

Methods

The model-based dosing algorithm for amikacin was prospectively evaluated in 579 (pre)term neonates (median birth bodyweight 2285g (range 420-4850g), postnatal age 2 days (range 1-30 days), gestational age 34 (range 24-41 weeks)). Observed peak and trough concentrations (n=1195), obtained upon application of the novel dosing algorithm in these 579 individuals, were compared with the concentrations predicted by the model. Additionally, a NPDE (normalized prediction distribution error) was performed for all observed concentrations of the prospective dataset. Finally, Monte Carlo simulations were performed to evaluate amikacin exposure in (pre)term neonates of different bodyweight and age.

Results

Across the entire neonatal population, observed amikacin concentrations were accurately predicted by the final pharmacokinetic model without bias. Moreover the accuracy of the model was confirmed by the NPDE. Based on the Monte Carlo simulations, it was shown that peak concentrations above 24 mg/L were reached in almost all patients with different bodyweight, postnatal age and use of ibuprofen. Depending on bodyweight and age, trough concentrations below 3 mg/L were found for 78-100% of the individuals when ibuprofen was co-administered and for 45-96% of the individuals when ibuprofen was not co-administered.

Conclusion

A novel model-based dosing algorithm for amikacin leads to optimized peak and trough concentrations in preterm and term neonates with varying birth bodyweight,

current bodyweight, postnatal age and ibuprofen co-administration. The model-based approach for dosing drugs in the highly variable population of neonates, as applied here for amikacin, substantially contributes to the individualization of dosing drugs in neonates.

4.1. Introduction

Even to date, drugs in children are often used in an off-label or unlicensed manner [1, 2]. Moreover, despite profound differences between children and adults, most dosing regimens are derived from adult dosing regimens using linear extrapolations based on bodyweight, which may lead to under- or overdosing [3, 4]. This, in turn, may result in therapeutic failure or occurrence of adverse or even toxic effects. In order to establish rational and evidence-based dosing regimens, detailed information is needed on the variation in pharmacokinetics (PK) and pharmacodynamics (PD) of drugs in children [5]. However, the execution of PK-PD studies in children faces significant challenges resulting from ethical considerations and practical issues such as the limited number and volume of blood samples. These limitations can be partly overcome by the application of population PK and/or PD analysis techniques using non-linear mixed effect modeling [3, 4, 6]. The advantage of the population approach is that pharmacokinetic and pharmacodynamic parameters can be derived from dense data but also from sparse and unbalanced data, which is often the case when analyzing data from routine pediatric or neonatal clinical practice. Furthermore, by using this approach both the inter- and intra-individual variability can be estimated separately. Finally, specific predictors of variability also called covariates, can be identified which subsequently can be used as the basis to develop new evidence-based and individualized dosing regimens [4]. When applying this approach it is crucial to establish in a prospective clinical trial whether the proposed dosing regimen indeed leads to the expected concentrations and/or effects [5].

Although amikacin is commonly used in pediatric clinical practice, it has been shown (figure 1) that the currently used dosing regimens for amikacin in reference handbooks may potentially lead to lack of efficacy and/or toxic effects and need to be updated [7]. Therefore on the basis of a population pharmacokinetic model for amikacin which was recently developed, a novel model-based dosing regimen was developed in which the dose is individualized on the basis of current bodyweight (a covariate found for volume of distribution), birth bodyweight, postnatal age and co-administration of ibuprofen (covariates for clearance) [7]. As model-based dosing regimens in which identified covariates are used as a basis for dosing may result

in more effective and safe use of drugs in the pediatric population, the aim of the current study was to prospectively evaluate this novel model-based dosing regimen for amikacin in preterm and term neonates aged between 1-30 days, on the basis of a comparison of the observed *versus* the model-based predicted concentrations, an NPDE analysis and Monte Carlo simulations.

4.2. Methods

4.2.1. Patients

All neonates admitted to the Neonatal Intensive care unit of the University Hospitals Leuven from whom routine amikacin therapeutic drug monitoring (TDM) samples were available between July 2011 and December 2012 were considered for inclusion in this study. During this period a simplified version of the model-based dosing regimen [7], was applied (Table I). Patients were excluded from this analysis if initiation of amikacin treatment was based on a previously used dosing regimen, when data were missing or if patients had a postnatal age above 30 days.

4.2.2. Drug administration and TDM sampling

Amikacin (Amukin, Bristol Myers Squibb, Braine-L'Alleud, Belgium) was administered as an intravenous infusion over 20 minutes. As part of routine clinical care, blood samples for amikacin TDM were collected just before (trough sample) and 1 hour after administration of the second dose (peak sample).

4.2.3. Amikacin assay

Up to May 31th 2012, amikacin concentrations were measured with a fluorescence polarization immunoassay using an Abbott TDx kit (Abbott Laboratories, Diagnostics Division, Abbott Park, IL 60064 USA). The lower limit of quantification (LLOQ) was 0.8 mg/L. According to the insert, the coefficient of variation was < 5% (assessed at 5, 15 and 30 mg/L). From May 31th 2012, amikacin quantification occurred with an immunoassay based on a kinetic interaction of microparticles in solution (KIMS) on Roche/Hitachi Cobas c systems (Roche Diagnostics GmbH, Mannheim, Germany). Also in this assay, the LLOQ was 0.8 mg/L. According to the insert, the coefficient of variation was < 4%. To avoid censoring of data below the LLOQ, these concentrations were replaced by LLOQ/2 (i.e. 0.4 mg/L) as suggested in literature [8].

Table I: Simplified model-based dosing regimen used in the current study and original model-based dosing regimen [7] of amikacin for preterm and term neonates. The differences between both dosing regimens are highlighted in a grey field.

	Simplified model-based dosing regimen		Original model-based dosing regimen [7]	
Current bodyweight (g)	PNA <14 days	PNA ≥ 14 days	PNA <14 days	PNA ≥ 14 days
0-800	16 mg/kg/48h (Gr. 1)	20 mg/kg/42h (Gr. 2)	16 mg/kg/48h	20 mg/kg/42h
800-1200	16 mg/kg/42h (Gr. 3)	20 mg/kg/36h (Gr. 4)	16 mg/kg/42h	20 mg/kg/36h
1200-2000	15 mg/kg/36h (Gr. 5)	18 mg/kg/30h (Gr. 6)	15 mg/kg/36h	19 mg/kg/30h
2000-2800	15 mg/kg/30h (Gr. 7)	18 mg/kg/24h (Gr. 8)	13 mg/kg/30h	18 mg/kg/24h
≥ 2800	15 mg/kg/24h (Gr. 9)	18 mg/kg/20h (Gr. 10)	12 mg/kg/24h	17 mg/kg/20h

The dosing interval was prolonged 10 hours, when ibuprofen was co-administered or when asphyxia was diagnosed/ considered by the treating physician. Duration of the intravenous infusion was 20 minutes. PNA = postnatal age. Gr = dosing group.

4.2.4. Pharmacokinetic analysis

To evaluate the predictive performance of the recently developed pharmacokinetic model [7], a pharmacokinetic analysis was performed using NONMEM VI in which model-based individual and population predicted concentrations were simulated for each observation in the prospective dataset. These simulated individual and population predicted concentrations were obtained by use of the recently developed pharmacokinetic model [7] in which all parameters were fixed to the final values with MAXEVAL = 0 and without covariance step. Subsequently the individual and population predicted concentrations predicted by the population pharmacokinetic model were visually compared to the observed, measured concentrations. Additionally, to evaluate the accuracy, the recently developed pharmacokinetic model [7] was used to compute an NPDE (normalized prediction distribution error method) [9, 10] for each of the observations of the prospective dataset. A histogram of the NPDE distribution and scatterplots showing the NPDE *versus* time and *versus* predicted concentration were used as evaluation tools [9, 10]. Finally the parameters of the recently developed pharmacokinetic model [7] were re-estimated on the basis of the data of the prospective dataset.

4.2.5. Monte Carlo simulations

Monte Carlo simulations were performed to evaluate whether target peak (above 24 mg/L) [11] and trough concentrations (below 3.0 mg/L) [12] of amikacin in preterm and term neonates were attained following the simplified model-based dosing regimen (Table I), the original model-based dosing regimen (Table I) [7], the dosing regimen

proposed by Neofax® [13] and the dosing regimen proposed by the British National Formulary for Children (BNFc) [14]. For the peak concentrations, concentrations below 24 mg/L, between 24 – 35 mg/L [11] and above 35 mg/L were evaluated. For the trough concentrations, concentrations between 1.5 - 3.0 mg/L were evaluated because this was the primary target of the model based dosing regimen [7]. In addition, the percentage of trough concentrations below 1.5, between 3.0 – 5.0 and above 5.0 mg/L was evaluated, the latter because this concentration is associated with toxicity. The results of the Monte Carlo simulations were compared among the different neonatal dosing groups as defined in Table I.

For the Monte Carlo simulations, the covariates identified in this recently developed final pharmacokinetic model [7] - birth bodyweight and PNA (covariates found on clearance) and current bodyweight (covariate found on volume of distribution) - were sampled from the prospective dataset taking into account their correlation. The Monte Carlo simulations were performed twice in 5000 individuals following the model-based dosing regimen, one in which ibuprofen was not co-administered and one in which ibuprofen was co-administered because co-administration of ibuprofen was found to result in a 16% reduction in neonatal clearance [7]. For the simulations, 5 consecutive doses of amikacin were administered over 20 or 30 minutes depending on the dosing regimen (Table I).

4.3. Results

4.3.1. Patients

During July 2011 and December 2012 a total of 701 preterm and term neonates were evaluable for the pharmacokinetic analysis of this prospective evaluation of the model-based dosing regimen. In total a 122 patients were excluded from this analysis: 32 because the dosing regimen was based on a previous dosing regimen, 76 neonates because there were missing data and 14 patients because of a postnatal age above 30 days. A summary of the patient characteristics (N=579) evaluated in this study are presented in Table II together with the patient characteristics of the recently developed model for amikacin [7].

4.3.2. Pharmacokinetic analysis

Figure 2 shows the individual and population predicted concentrations *versus* concentrations observed in this prospective study for the different dosing groups based on current bodyweight and postnatal age as described in Table I. Both panels indicate

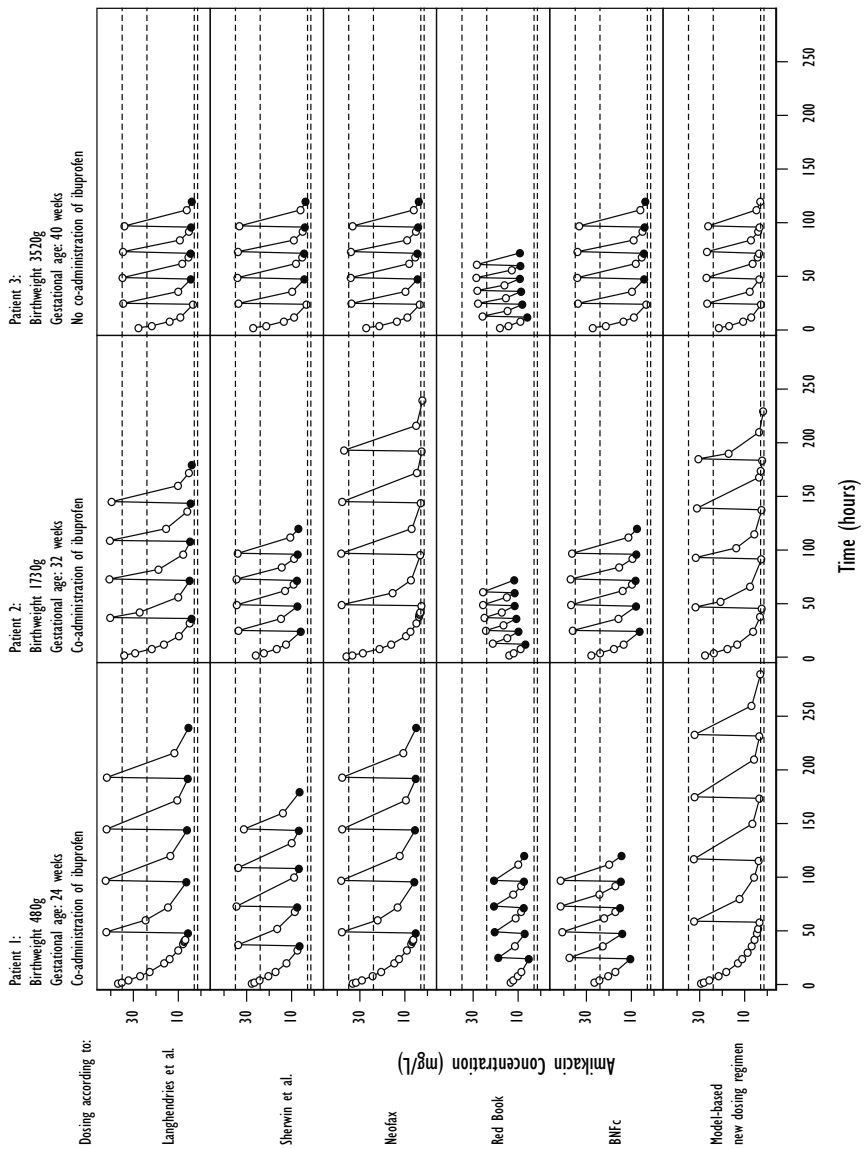

Figure 1: Model-based predicted concentration-time profiles for three typical neonates (480g, 1730g and 3520g) at postnatal age of 1 day on the basis of five different dosing guidelines (Langhendries *et al.*, Sherwin *et al.*, Neofax®, Red Book® and the British National Formulary for Children (BNFc)) and according to the new model-based dosing regimen.

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.

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a lack of bias and an adequate prediction of the observed concentrations across the different bodyweight and age groups. Moreover, the distribution of the data points around the line of unity of the observed *versus* predicted plot indicates that the interindividual variability is both acceptable and similar across the entire neonatal population. This is also reflected in figure 3 in which the interindividual variability on clearance is plotted against birth bodyweight, postnatal age and co-administration of ibuprofen. Figure 3 illustrates that the final pharmacokinetic model of amikacin is able to describe the prospective dataset accurately across the different covariates as no trend is seen in the interindividual variability on clearance *versus* these covariates. This result was obtained such despite the fact that there were small differences between the dataset that was used to build the model [7] compared to the current prospective dataset (Table II). Table III gives an overview of the parameter estimates of the recently published final pharmacokinetic model [7] together with the parameter estimates obtained on the basis of the current prospective dataset in 579 individuals. Based on the values in Table III, it can be seen that fairly similar parameter values are obtained when evaluating the prospective dataset compared to the previously obtained parameters, which indicates the stability of the model. The population value for clearance and volume of distribution was slightly higher in the current prospective dataset (0.066 L/H and 1.03 L) compared to the values of the recently developed amikacin model (0.049 L/H and 0.833 L). This can be explained by the fact that in the current prospective dataset, slightly more mature neonates are included as reflected by the small differences seen in gestational age, postmenstrual age, birth bodyweight and current bodyweight (Table II). Figure 4 shows the results of the NPDE analysis. The histogram follows the normal distribution indicated by the black solid line. Additionally, no trend is seen in the NPDE *versus* time and the NPDE *versus* predicted concentrations indicating the accuracy of the model.

Table II: Clinical characteristics of the patients included in the recently published analysis on amikacin [7] and in the current prospective analysis (median, range, or absolute number and incidence).

Characteristics	Recently developed amikacin model [7] N= 874	Current prospective amikacin analysis N=579
Gestational age (weeks)	32 (24-43)	34 (24-41)
Postmenstrual age (weeks)	33 (24-43)	34 (24-45)
Postnatal age (days)	2 (1-30)	2 (1-30)
Birth bodyweight (g)	1750 (385-4650)	2285 (420-4850)
Current bodyweight (g)	1760 (385-4760)	2100 (420-5040)
Co-administration of ibuprofen (n (%))	118 (13.5)	29 (5)

Table III: Final parameter estimates and coefficients of variation (CV%) of the pharmacokinetic model that was recently developed on the basis of the original dataset (n=874) [7] and on the basis of the current prospective dataset (n=579)

Parameter	Recently developed amikacin model [7] n=879 patients	Current prospective amikacin analysis n=579 patients
Fixed effects		
CLp in CL = CLp x (bBW/median)^m x (1+ n x (PNA/median)) x o (ibuprofen)	0.049 (2.21)	0.066 (3.2)
m	1.34 (2.04)	1.30 (2.95)
n	0.213 (9.81)	0.302 (9.34)
o	0.838 (3.88)	0.846 (6.55)
Vp in V1 = Vp x (cBW/median)^p	0.833 (1.34)	1.03 (1.47)
p	0.919 (2.46)	0.863 (4.03)
Q = r x CL	0.415 (12.3)	0.480 (13.5)
V2=V1	V2=V1	V2=V1
Interindividual Variability		
ω^2 (CL)	0.0899 (14.9)	0.0921 (19.3)
Residual Variability		
σ^2 (proportional)	0.0614 (8.2)	0.0448 (22.3)
σ^2 (additive)	0.267 (27.2)	0.315 (16.3)

CLp = population value for clearance (L/h), Vp = population value for volume of distribution of the central compartment (L), bBW = bodyweight at birth (g), cBW = current bodyweight (g), PNA = postnatal age (days), Q = intercompartmental clearance (L/h), V2 = Volume of distribution of the peripheral compartment (L), median values for the recently developed model for amikacin: bBW = 1750g, PNA = 2 days, cBW=1760g; median values for the current prospective study: bBW = 2285g, PNA = 2 days, cBW = 2100g

4.3.3. Monte Carlo simulations

Monte Carlo simulations were performed to illustrate the exposure to amikacin in two times 5000 preterm and term neonates (with and without ibuprofen administration) following the simplified model-based dosing regimen, the original model-based dosing regimen [7], the dosing regimen proposed by Neofax®[13] and the British National Formulary for Children [14]. In Table IV the percentages of the individuals with trough concentrations after 5 doses below 1.5 mg/L, between 1.5-3.0 mg/L, between 3.0-5.0 mg/L and above 5.0 mg/L and peak concentrations after 5 doses below 24 mg/L, between 24-35 mg/L and above 35 mg/L following the Monte Carlo simulations in 5000 individuals according to the different dosing regimens

are given when ibuprofen is not co-administered. In Table V, these percentages are shown when ibuprofen is co-administered. Both tables are graphically presented in figure 5 and figure 6 in which ibuprofen is not co-administered and co-administered, respectively. In both figures the upper panels (A) represent the trough concentrations while the lower panels (B) represent the peak concentrations. Based on these tables and figures, it can be seen that for the model based dosing regimens (with and without ibuprofen) the percentages for trough concentrations between 1.5 and 3.0 mg/L are relatively constant across the ten different age and weight groups. This confirms the predictions that were performed in the previous analysis [7] as the model based dosing guideline was designed to aim for trough concentrations between 1.5 and 3.0 mg/L across the entire neonatal age range. Overall, the figures and tables show that trough concentrations below 3.0 mg/L [12] are reached in most individuals of the different dosing groups upon the simplified model-based (78-100% and 45-96%) and original model-based dosing regimen (86-100% and 62-92%) whereas these percentages were much lower upon Neofax® (25-96% and 40-100%) and BNFc (2-100% and 3-100%), when ibuprofen is co-administered or not, respectively. From these results, it seems that particularly the dosing guidelines suggested by BNFc may potentially induce toxicity since target trough values below 5 mg/L are not reached in many individuals and specifically in neonates with a postnatal age < 14 days. More specifically, trough concentrations above 5 mg/L which are associated with oto- and nephrotoxicity, were observed in 0-20%, 0-9%, 0-43% and 0-93% of the individuals of the different dosing groups as defined in Table I, for the simplified dosing regimen, original dosing regimen [7], Neofax and BNFc, respectively (Table IV and V). Considering the peak concentrations, it can be seen that for the simplified model-based dosing regimen peak concentrations above 24mg/L are reached in almost all individuals while for the original model-based dosing regimen [7], Neofax® and BNFc target peak concentrations are not reached in all individuals of one or more dosing subgroups. Finally, it can be seen that higher peak concentrations are reached in the different dosing groups upon the dosing regimens of Neofax® or the BNFc compared to the model-based dosing regimens [7].

4.4. Discussion

Recently a population pharmacokinetic model was developed for amikacin in 874 preterm and term neonates [7]. Based on the final model which was both internally and externally validated, a model-based dosing regimen was developed for amikacin in preterm and term neonates aged between 1-30 days [7]. The main aim of this dosing regimen was to obtain trough concentrations of 1.5-3.0 mg/L and peak

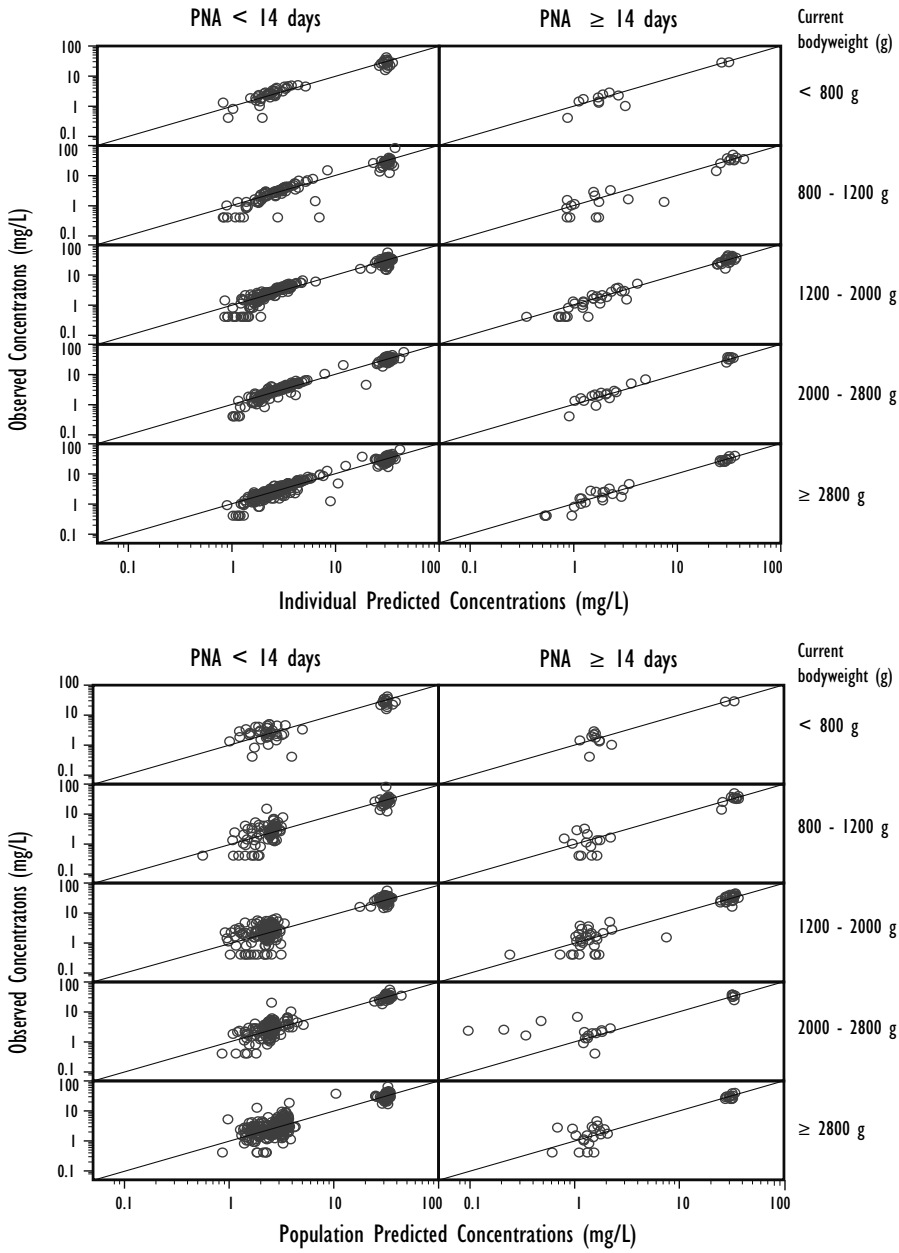

Figure 2: Observed *versus* model-based individual and population predicted concentrations for the different dosing groups based on current bodyweight and postnatal age (Table I) for the current prospective dataset.

concentrations above 24 mg/L across the entire neonatal population for which ten dosing groups were defined [7] (Table I). To reach this aim, the model-based dosing regimen is based on current bodyweight, a covariate found on volume of distribution which determines the peak concentrations, postnatal age and co-administration of ibuprofen, covariates found on clearance which determine the maintenance dose and the dosing interval, respectively (Table I). In order to evaluate whether the model-based dosing guideline for amikacin indeed leads to the expected concentrations, a prospective clinical trial is imperative [4, 5]. In the current prospective clinical study we first evaluated the predictive value of the previously derived model [7] for observed concentrations in a newly collected dataset consisting of 579 preterm and term neonates (Table II) in which neonates were dosed on previously derived covariates (Table I). Furthermore, we evaluated the target attainment of the trough concentrations between 1.5 and 3.0 mg/L [12] and peak concentrations between 24 and 35 mg/L [11] across the entire preterm and term neonatal age range as targets of the model-based dosing algorithm in the original study [7]. For this purpose, Monte Carlo simulations were performed to simulate peak and through concentrations following the model-based dosing guideline and currently used guidelines to evaluate their performance across the different age groups that can be identified in neonates.

Based on the results presented in this analysis, it can be concluded that the final pharmacokinetic model is able to predict the observed concentrations in the current study without bias across the entire neonatal range (Figure 2). Moreover, in figure 3, it is shown that the covariates birth bodyweight, postnatal age and co-administration of ibuprofen are correctly implemented on clearance as no trend is seen when plotting the interindividual variability on clearance *versus* the different covariates. This means that the conclusion that 10 different neonatal dosing groups (Table I) are needed to cover the large differences seen in clearance values between preterm and term neonates is justified. Finally when evaluating figure 2 and figure 3, it can be concluded that only random variability is remained in the model while variability allocated to covariates is explained. This latter is of course of major importance when developing and evaluating new model-based dosing regimens on the basis of these covariates, which we have done in the current analysis.

Another important aim of the current prospective analysis was to evaluate whether the aimed target peak (24-35 mg/L) [11] and trough concentrations (1.5-3 mg/L) [12], as defined in the recently published study [7], were reached in preterm and term neonates. When evaluating the results of the Monte Carlo simulations (Table IV and V and Figure 5 and 6), peak and trough concentrations were found in the target range in most individuals of the different dosing groups in case of the model-based dosing regimens. Moreover, the number of individuals with trough con-

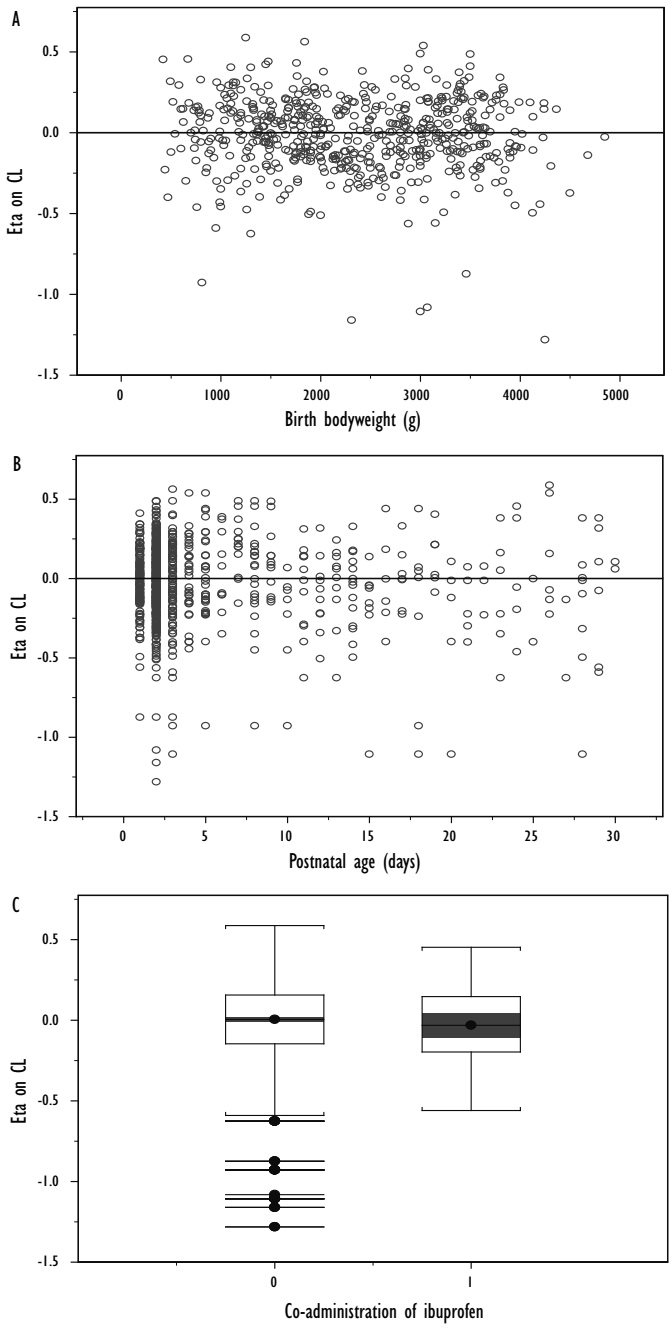

Figure 3: Interindividual variability (eta) on clearance (CL) *versus* birth bodyweight (a), postnatal age (b) en co-administration of ibuprofen (c) for the current prospective dataset using the recently developed pharmacokinetic model [7].

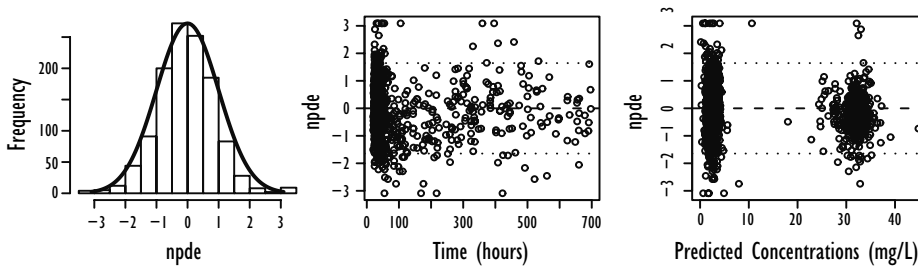

Figure 4: Results of the NPDE analysis performed for the prospective dataset using the recently developed pharmacokinetic model [7]. Left panel: Histograms of the NPDE distribution with the solid line representing a normal distribution as a reference, Middle panel: NPDE *versus* time (hours); Right panel: NPDE *versus* observed concentrations (mg/L).

centrations above 5 mg/L, which are generally related to occurence of oto- and/or nephrotoxicity, are notably lower in the model-based dosing regimens compared to the dosing regimen proposed by Neofax® and BNFc, in particular when ibuprofen is given (Table IV and V). However, 11% and 20% of the individuals of group 7 (current weight 2000-2800g, PNA<14 days) and group 9 (current weight >2800g, PNA<14 days) of the simplified model-based dosing regimen, respectively, had trough concentrations above 5 mg/L when ibuprofen was not co-administered. In addition, as shown in tables IV and V, a higher percentage of individuals with trough concentrations above 3 mg/L (38% and 55%) compared to the original model-based dosing regimen (28% and 38%) can be expected upon this simplification of the model-based algorithm. Although less neonates in group 7 and group 9 are observed with trough concentrations above 3 mg/L upon the original model-based dosing regimen [7], the original model-based dosing regimen does not offer an alternative since a notable number of patients (between 8-33%) does not reach peak concentrations above >24 mg/l needed for efficacy. This deviation may be partly explained by the fact that in the original study, less data of neonates were available in group 7 and 9 compared to the current prospective study. Consequently this indicates the importance of a prospective validation as more information can be obtained in certain age and weight groups. As a result, new Monte Carlo simulations need to be performed in both these groups to evaluate whether lower trough concentrations are obtained when the dosing interval is prolonged.

The Monte Carlo simulations emphasize that the dosing regimen proposed by Neofax® and BNFc for amikacin in preterm and term neonates may potentially lead to toxicity. This applies in particular to the dosing regimen of BNFc, which does not make any distinction between weight or age groups, but proposes a similar dose and

Table IV: The percentage of the individuals of the subgroups 1-10 as defined in Table I with trough concentrations after 5 amikacin doses below 1.5 mg/L, between 1.5-3 mg/L, between 3-5 mg/L and above 5 mg/L and peak concentrations (grey background) after 5 doses below 24 mg/L, between 24-35 mg/L and above 35 mg/L following the Monte Carlo simulations in 5000 individuals according to the different dosing regimens (simplified model-based dosing regimen, original model-based dosing regimen[7], Neofax® [13] and BNFc [14]) when ibuprofen was not co-administered.

Concentration (mg/L)	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7	Group 8	Group 9	Group10
Simplified model-based dosing regimen										
< 1.5	34%	55%	30%	65%	27%	58%	17%	53%	8%	58%
1.5-3	45%	30%	45%	30%	45%	38%	45%	36%	37%	36%
3-5	16%	15%	21%	5%	23%	4%	27%	11%	35%	6%
> 5	5%	0%	4%	0%	5%	0%	11%	0%	20%	0%
< 24	0%	0%	0%	0%	0%	0%	0%	3%	0%	0%
24-35	95%	50%	94%	71%	97%	83%	90%	97%	81%	94%
>35	5%	50%	6%	29%	3%	17%	10%	0%	19%	6%
Original model-based dosing regimen [7]										
< 1.5	33%	55%	29%	43%	25%	56%	25%	60%	16%	61%
1.5-3	41%	30%	48%	36%	47%	36%	47%	32%	46%	25%
3-5	21%	15%	18%	14%	22%	8%	23%	5%	29%	11%
> 5	5%	0%	5%	7%	6%	0%	5%	3%	9%	3%
< 24	0%	0%	0%	0%	0%	0%	9%	3%	24%	9%
24-35	96%	50%	93%	64%	97%	70%	91%	89%	76%	84%
>35	4%	50%	7%	36%	3%	30%	0%	8%	0%	7%
Neofax® [13]										
< 1.5	12%	50%	14%	71%	19%	64%	14%	56%	20%	84%
1.5-3	28%	35%	34%	19%	41%	33%	37%	33%	41%	16%
3-5	36%	15%	25%	10%	24%	3%	30%	11%	24%	0%
> 5	24%	0%	27%	0%	16%	0%	19%	0%	15%	0%
< 24	0%	0%	0%	10%	0%	0%	0%	14%	0%	30%
24-35	31%	100%	44%	90%	50%	100%	49%	86%	52%	70%
>35	69%	0%	56%	0%	50%	0%	51%	0%	48%	0%
BNFc [14]										
< 1.5	0%	0%	0%	31%	1%	50%	3%	79%	9%	76%
1.5-3	3%	50%	5%	38%	12%	40%	24%	18%	34%	24%
3-5	13%	25%	19%	31%	32%	10%	39%	3%	37%	0%
>5	84%	25%	76%	0%	55%	0%	34%	0%	20%	0%
< 24	0%	0%	0%	0%	0%	0%	0%	28%	0%	26%
24-35	43%	100%	48%	100%	63%	100%	73%	72%	78%	74%
>35	57%	0%	52%	0%	37%	0%	27%	0%	22%	0%

Table V: The percentage of the individuals of the subgroups 1-10 as defined in Table I with trough concentrations after 5 amikacin doses below 1.5 mg/L, between 1.5-3 mg/L, between 3-5 mg/L and above 5 mg/L and peak concentrations (grey background) after 5 doses below 24 mg/L, between 24-35 mg/L and above 35 mg/L following the Monte Carlo simulations in 5000 individuals according to the different dosing regimens (simplified model-based dosing regimen, original model-based dosing regimen[7], Neofax® [13] and BNFc [14]) when ibuprofen was co-administered.

Concentration (mg/L)	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7	Group 8	Group 9	Group 10
Simplified model-based dosing regimen										
< 1.5	45%	60%	46%	72%	50%	72%	42%	81%	33%	82%
1.5-3	39%	40%	43%	21%	40%	28%	43%	14%	45%	14%
3-5	13%	0%	8%	7%	9%	0%	12%	5%	18%	4%
> 5	3%	0%	3%	0%	1%	0%	3%	0%	4%	0%
< 24	0%	0%	0%	0%	0%	0%	0%	0%	0%	2%
24-35	97%	50%	95%	50%	99%	85%	96%	92%	93%	80%
>35	3%	50%	5%	50%	1%	15%	4%	8%	7%	18%
Original model-based dosing regimen [7]										
< 1.5	48%	55%	50%	88%	47%	48%	48%	84%	49%	81%
1.5-3	38%	45%	38%	12%	42%	40%	42%	14%	41%	19%
3-5	11%	0%	11%	0%	9%	12%	9%	2%	9%	0%
> 5	3%	0%	1%	0%	2%	0%	1%	0%	1%	0%
< 24	0%	0%	0%	0%	0%	0%	8%	0%	33%	8%
24-35	99%	50%	97%	52%	98%	44%	92%	89%	67%	90%
>35	1%	50%	3%	48%	2%	56%	0%	11%	0%	2%
Neofax® [13]										
< 1.5	7%	35%	7%	52%	13%	37%	7%	44%	10%	63%
1.5-3	18%	40%	22%	38%	30%	48%	26%	33%	40%	33%
3-5	35%	25%	28%	5%	28%	15%	34%	20%	23%	4%
> 5	40%	0%	43%	5%	29%	0%	33%	3%	27%	0%
< 24	0%	0%	0%	10%	0%	0%	0%	5%	0%	12%
24-35	16%	100%	26%	90%	32%	100%	32%	95%	37%	88%
>35	84%	0%	74%	0%	68%	0%	68%	0%	63%	0%
BNFc [14]]										
< 1.5	0%	0%	0%	0%	0%	23%	1%	62%	4%	69%
1.5-3	0%	15%	2%	54%	4%	50%	11%	31%	21%	31%
3-5	7%	40%	9%	38%	20%	23%	32%	7%	37%	0%
>5	93%	45%	89%	8%	76%	4%	56%	0%	38%	0%
< 24	0%	0%	0%	0%	0%	0%	0%	10%	0%	7%
24-35	28%	85%	28%	100%	40%	100%	51%	90%	58%	93.%
>35	72%	15%	72%	0%	60%	0%	49%	0%	42%	0%

dosing interval for all neonates, independent of age or weight. As a result, neonates with a PNA<14 days are particularly at risk for toxic effects as the concentrations remain above the target trough concentrations, when ibuprofen is not given. When ibuprofen is given, even more individuals are at risk. Therefore on the basis of the results of this study, it can be concluded that the currently used dosing regimens in reference handbooks need to be updated, certainly when ibuprofen is co-administered. Moreover it should also be considered to lower the dose in neonates with a PNA<14 days, certainly in the lower weight groups (800-2000g). Considering the administration of ibuprofen, it should however be noted that in the Monte Carlo simulations ibuprofen is given to all weight groups, while in the recently developed amikacin model [7], ibuprofen was only given to preterm neonates in case of open ductus. Since ibuprofen can also be given to these neonates as anti-inflammatory drug, we chose to perform the Monte Carlo simulations also in term neonates when ibuprofen is co-administered to illustrate amikacin exposure. However this means that caution is needed when interpreting the results.

In this analysis we show that amikacin dosing in neonates can be optimized on the basis of a previously developed model resulting in a dosing algorithm that is evaluated in a prospective clinical study. However, when for each drug such an approach should be followed much time and resources would be needed. Therefore, advanced approaches to use information from one drug for another drug are needed [17]. Recently, it was shown by two different groups that the pharmacokinetic covariate model of amikacin contains system-specific information on the developmental changes in glomerular filtration in preterm and term neonates [15]. Consequently the covariate model on amikacin clearance with birth bodyweight, postnatal age and co-administration of ibuprofen as most important covariates could be used to predict the dosage regimens of other renally excreted drugs (netilmicin, tobramycin, gentamicin and vancomycin) in neonates [15, 16]. This semi-physiological approach may be used to optimize sparse data analysis and may facilitate development of pharmacokinetic models and evidence-based dosing regimens in the pediatric population [17]. As a result, in future analyses it should be evaluated whether the different dosing groups used in this prospective analysis, which are based on the recently developed model for amikacin [7], can be applied to the other renally excreted drugs. In this context, it should also be noted that the dosing regimen for amikacin in neonates according to BNFc [14], as illustrated in this analysis, is rather simple while the dosing regimen according to BNFc for gentamicin is much more complicated. Based on the fact that covariate models are considered to contain system-specific information, this is rather remarkable. Therefore, as stated above, the dosing regimens of other renally excreted drugs such as gentamicin, tobramycin, vancomycin and netilmicin in neonates may need to be revised accordingly.

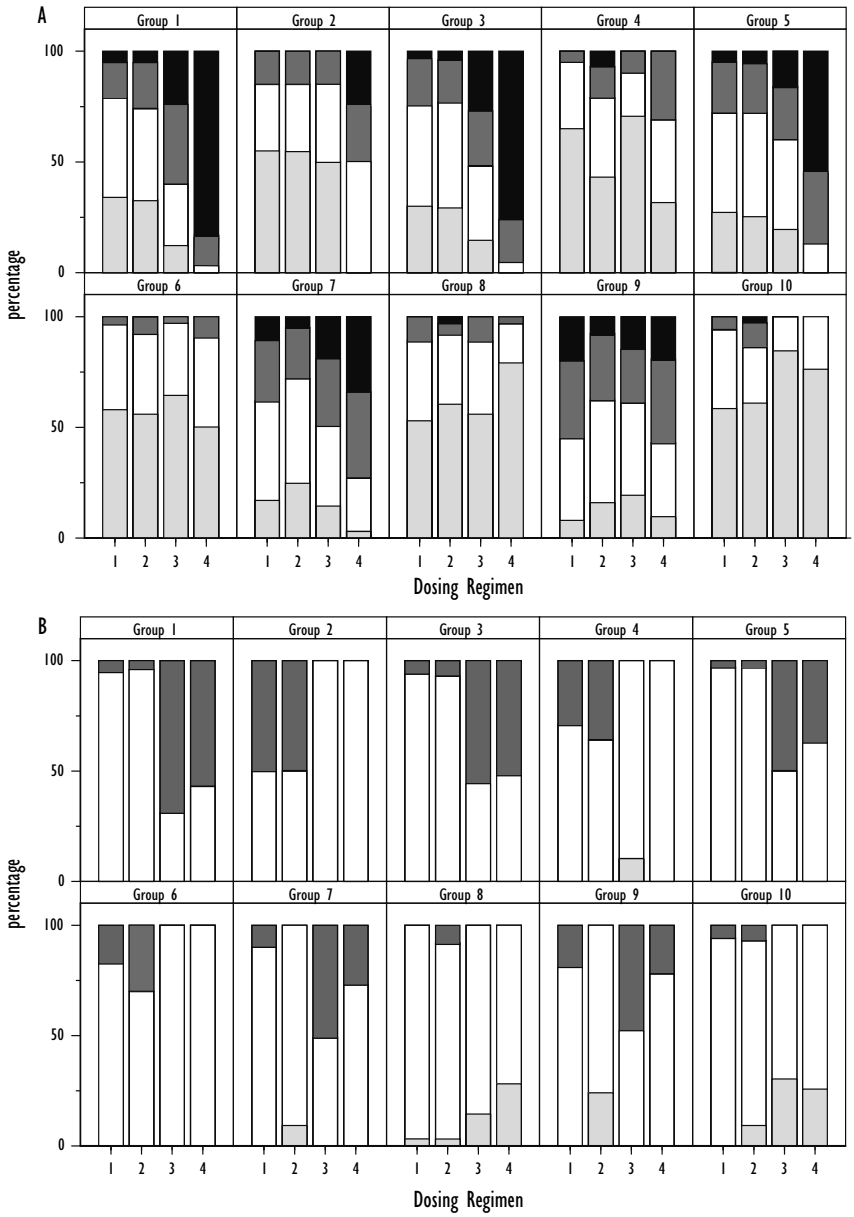

Figure 5: Bar graphs to illustrate the percentages of individuals of the different dosing groups as defined in Table I with A/ trough concentrations after 5 doses below 1.5 mg/L (light grey), between 1.5-3 mg/L (white), between 3-5 mg/L (dark grey) and above 5 mg/L (black) and B/ peak concentrations after 4 doses below 24 mg/L (light grey), between 24-35 mg/L (white) and above 35 mg/L (dark grey) following the Monte Carlo simulations in 5000 individuals according to the different dosing regimen (1= simplified model-based dosing regimen, 2 = original model-based dosing regimen [7], 3 = Neofax® [13], 4 = BNFc [14]) when ibuprofen was not co-administered.

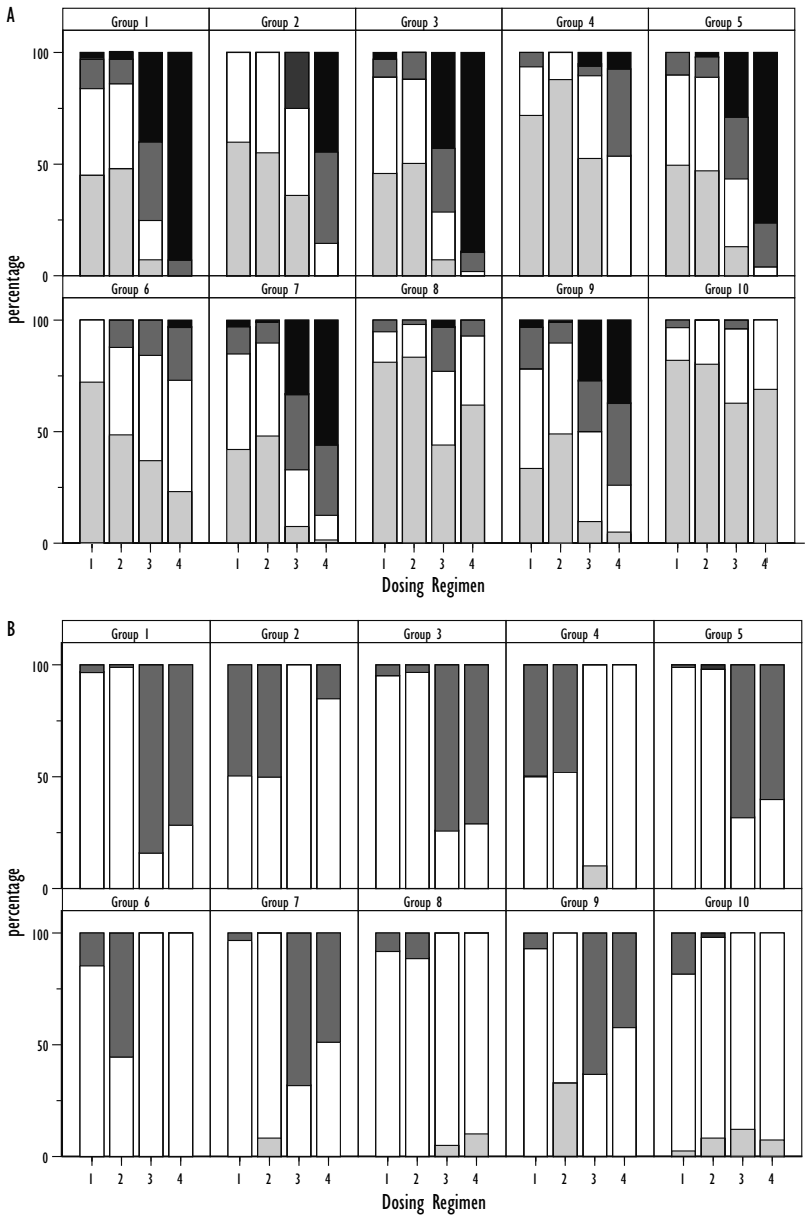

Figure 6: Bar graphs to illustrate the percentages of individuals of the different dosing groups as defined in Table I with A/ trough concentrations after 5 doses below 1.5 mg/L (light grey), between 1.5-3 mg/L (white), between 3-5 mg/L (dark grey) and above 5 mg/L (black) and B/ peak concentrations after 4 doses below 24 mg/L (light grey), between 24-35 mg/L (white) and above 35 mg/L (dark grey) following the Monte Carlo simulations in 5000 individuals according to the different dosing regimen (1= simplified model-based dosing regimen, 2 = original model-based dosing regimen [7], 3 = Neofax® [13], 4 = BNFc [14]) when ibuprofen was co-administered.

Finally it can be concluded that evidence-based dosing regimens are often lacking in the pediatric population due to practical and ethical constraints. Based on the analysis in this study, it can be determined that population pharmacokinetic modeling facilitates the development of drug dosing regimens in children. First of all, the use of this methodology makes it possible to derive pharmacokinetic and/or pharmacodynamic parameters from sparse and unbalanced data. Secondly covariates which explain the interindividual variability can be identified and serve as a guide for individualized dosing. Moreover the pharmacokinetic model used in this study was extensively validated before testing it in a prospective study. Based on this prospective study, it can be concluded that the model-based dosing regimen for amikacin with current bodyweight, postnatal age and co-administration of ibuprofen as covariates, results in target peak and trough concentrations in a very high percentage of individuals. Particularly the consistency of the predictions across the different weight categories are emphasized (figure 5 and 6) as across the different subgroups similar percentages in the target trough concentration range were found (Table IV and V). These predictions are in large contrast with predictions that were obtained upon currently used guidelines such as from Neofax® or BNFc for which the dosing regimens need to be reevaluated, particularly in neonates <14 days and the lower weight groups (800-2000g) or when ibuprofen is given. Consequently model-based dosing regimens in which developmental changes are taken into account may result in more effective and safe use of drugs in the pediatric population.

4.5. Conclusions

A novel model-based dosing algorithm for amikacin yields plasma concentrations that are close to the targeted concentrations in preterm and term neonates with varying birth bodyweight, current bodyweight, postnatal age and ibuprofen co-administration. The model-based approach for dosing drugs in the highly variable population of neonates, as applied here for amikacin, substantially contributes to the individualization of dosing drugs in neonates.

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