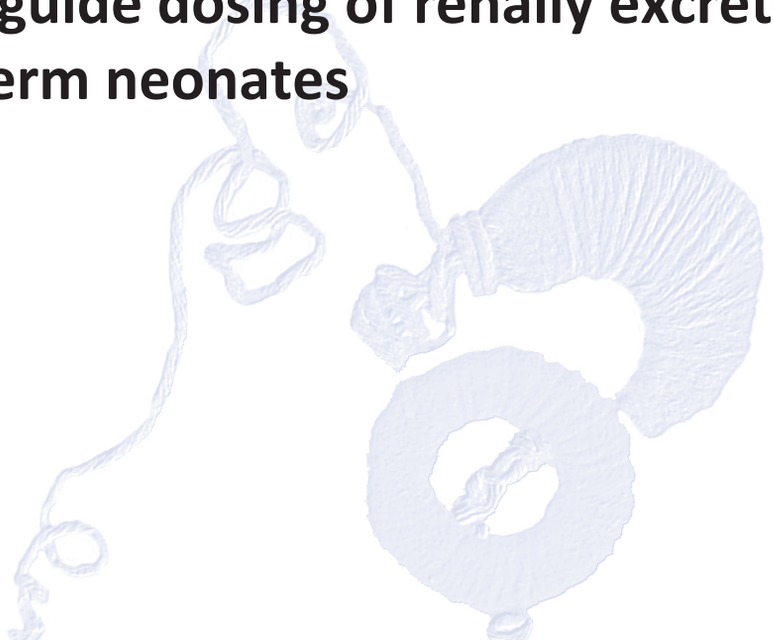
The role of glomerular filtration and active tubular secretion in predicting renal clearance of drugs in children using population pharmacokinetic and physiology-based pharmacokinetic modeling approaches: unspinning the yarn

Cristea, S.

Section II. Population pharmacokinetic modelling to guide dosing of renally excreted drugs in preterm neonates



Chapter 2

Amikacin pharmacokinetics to optimize dosing recommendations in neonates with perinatal asphyxia treated with hypothermia

S Cristea*, A Smits*, A Kulo, CAJ Knibbe,
M van Weissenbruch, EHJ Krekels, K Allegaert

Antimicrob Agents Chemother.
2017 Dec; 61(12): e01282-17

* authors contributed equally

2.1 Abstract

Aminoglycosides pharmacokinetics (PK) is expected to change in neonates with perinatal asphyxia treated with therapeutic hypothermia (PATH). Several amikacin dosing guidelines have been proposed to treat neonates with (suspected) septicemia, however, none provide adjustments in the case of PATH. Therefore, we aimed to quantify the differences in amikacin PK between neonates with and without PATH to propose suitable dosing recommendations.

Based on amikacin therapeutic drug monitoring data collected retrospectively from neonates with PATH, combined with a published dataset, we assessed the impact of PATH on amikacin PK using population modelling. Monte Carlo and stochastic simulations were performed to establish amikacin exposures in neonates with PATH after dosing according to the current guidelines and according to proposed model-derived dosing guidelines.

Amikacin clearance was decreased by 40.6% in neonates with PATH, with no changes in volume of distribution. Simulations showed that, increasing the dosing interval with 12 hours results in a decrease in percentage of neonates reaching toxic trough levels (> 5 mg/L) from 40–76% to 14–25%, while still reaching efficacy targets, compared to current dosing regimens.

Based on this study, a 12-hour increase in amikacin dosing interval in neonates with PATH is proposed to correct for the reduced clearance, yielding safe and effective exposures. As amikacin is renally excreted, further studies into other renally excreted drugs may be required as their clearance may also be impaired.

2.2 Introduction

Aminoglycosides are administered to treat neonates with (suspected) septicemia. Aminoglycosides display a concentration-dependent effect and are almost entirely eliminated by glomerular filtration [1]. Recently, a population pharmacokinetic (PK) model-derived dosing regimen for amikacin [2] was prospectively evaluated in 579 neonates, showing predictive effective and safe amikacin exposure across the entire neonatal population [2, 3]. However, for neonates diagnosed with perinatal asphyxia and treated with therapeutic hypothermia (PATH), prediction of accurate amikacin disposition remains a challenge [2]. This might be due to asphyxia-induced renal impairment with or without the influence of therapeutic hypothermia which is used as standard of care treatment for moderate to severe hypoxic ischemic encephalopathy in (near) term neonates.

Hypothermia reduces the basal and cerebral metabolic rates, decreases the process of excitotoxicity and results in improved neurodevelopmental outcome [1,4,5]. Furthermore, it may alter pharmacologic characteristics of drugs [5,6]. Drug PK profiles do not only depend on drug-specific characteristics (e.g., molecular weight, lipophilicity, etc.), but also on system-specific (physiological) characteristics of the patients (e.g., cardiac output, organ perfusion, glomerular filtration [5], etc.). The system-specific characteristics are known to be affected by the pathophysiological changes that occur during both perinatal asphyxia and hypothermia [7]. This specific combination of patient-related factors impairs the elimination of aminoglycosides, as previously documented for gentamicin [8, 9, 10]. Data on amikacin PK in neonates with PATH are, to our knowledge, not yet available.

The aim of the current study (AMICOOL) was to use population PK modelling and simulation approaches to further characterize amikacin disposition in neonates by quantifying the impact of PATH on amikacin PK. Therefore, PK data collected from neonates with PATH were analyzed together with data from a large and heterogeneous group of neonates without PATH [11]. The findings were used to determine suitable adjustments of the most recent amikacin dosing regimens to improve the exposure in this special population. As amikacin clearance is considered a surrogate for glomerular filtration, the results may provide guidance for other drugs undergoing renal excretion.

2.3 Materials and methods

2.3.1 Data Collection

Amikacin therapeutic drug monitoring (TDM) data from routine clinical care were retrospectively collected from January 2010 to December 2015 from neonates with PATH admitted to the Neonatal Intensive Care Units (NICUs) of UZ Leuven (Belgium) and VUmc Amsterdam (The Netherlands) and receiving amikacin for (suspected) septicaemia. Both centres applied the standard criteria to initiated whole-body hypothermia in term neonates [12]. A total of 83 samples were retrieved, of which 75 were obtained during the hypothermic treatment period, with a median of 1.5 samples per patient (samples range between 1 and 3). Data from neonates participating in other trials (i.e., Pharmacool trial [13]) were excluded.

The study protocols were evaluated and approved by the local institutional review boards: the UZ Leuven ethics committee approved the study protocol, and a waiver for ethical approval was obtained in VUmc according to the Dutch law on research with human participants.

Clinical characteristics at birth and at the time of amikacin TDM were extracted retrospectively from patients' files. Each NICU used separate dosing protocols, summarized in Table 2.1. Effective peak concentrations were considered to be within the 24–35 mg/L interval. To avoid side effects, trough concentrations were preferably below 3 mg/L (target trough level) and strictly under 5 mg/L (toxic trough level).

At UZ Leuven, as part of routine clinical care, amikacin TDM was collected just before administration of the second dose. According to local clinical practice, dosing intervals could be adapted by the treating physician. At VUmc Amsterdam, the first routine amikacin TDM was collected at least 6, but preferably, 12-18 hours after the first amikacin administration. Eventual dosing adaptations were suggested by the VUmc pharmacy, based on the initial amikacin dose and TDM results, according to the maximum a posteriori Bayesian fitting method, using the MW/Pharm version 3.6 (Mediware, Groningen, the Netherlands).

2.3.2 Blood sample analysis

In both centres, amikacin concentrations were initially measured using fluorescence polarization immunoassay (Abbott TDx kit, Abbott Laboratories, Diagnostics Division, Abbott Park, IL, USA) with a lower limit of quantification (LLOQ) of 0.8 mg/L and a coefficient of variation (CV) below 5%. From May 31st 2012, amikacin quantification in UZ Leuven was based on a kinetic interaction of microparticles in solution (KIMS) immunoassay (Roche/Hitachi Cobas c systems, Roche Diagnostics GmbH, Mannheim, Germany) with a LLOQ of 0.8 mg/L and a CV below 4%. From September 2011, amikacin quantification in VUmc Amsterdam was based on a particle-enhanced turbidimetric inhibition immunoassay (PETINIA) (ARCHITECT Systems, Abbott, Abbott Laboratories Inc, Abbott Park, IL, USA) with a LLOQ of 2 mg/L and CV below 4%.

2.3.3 Modeling Dataset

TDM data from neonates with PATH were combined with a previously published dataset of amikacin PK samples taken from preterm and term neonates who were neither diagnosed with perinatal asphyxia nor underwent hypothermic treatment [2,11].

The combined modelling dataset consisted of 930 neonates of which 55 (6%) were treated for PATH. All neonates were younger than 30 days of postnatal age (PNA), and the neonates treated with hypothermia were younger than 4 days. Characteristics of patients in the combined dataset are summarized in Table 2.2. No outliers were identified during the current analysis.

TABLE 2.1 Dosing regimens used for the treatment of neonates with perinatal asphyxia treated with hypothermia (PATH) at the UZ Leuven (Belgium) and VUmc Amsterdam (The Netherlands) neonatal intensive care units (NICU)

NICU	Dosing regimen	Period in use	Regimen summary		
UZ Leuven	Langhendries et al. 1998 [19]	Up to July 2011	Duration of IV infusion: 30 minutes		
			GA (weeks)	Dose (mg/kg)	Dosing int. (h)
			< 28	20	42
			28 to < 31	20	36
			31 to < 34	18.5	30
			34 to < 37	17	24
			37–41	15.5	24
	De Cock et al. 2012 [11]	July 2011–July 2014	Duration of IV infusion: 20–30 min		
			Weight (g)	Dose (mg/kg)	Dosing int. (h)
			0–800	16	48
			800–1200	16	42
			1200–2000	15	36
			2000–2800	15	30
			≥ 2800	15	24
	Smits et al. 2015 [2]	Since July 2014	Duration of IV infusion: 20 minutes		
			Weight (g)	Dose (mg/kg)	Dosing int.(h)
			0–800	16	48
			800–1200	16	42
			1200–2000	15	36
			2000–2800	15	36
			≥ 2800	15	30
VUmc Amsterdam	-	Up to 24 March 2015	Duration of IV infusion: 1 hour		
			Dose (mg/kg)	Dosing interval (h)	
			12	24–36h*	
			* determined by TDM (cfr. methods)		
	-	Since 24 March 2015	Dose (mg/kg)	Dosing interval (h)	
			15	24–36h*	
			* determined by TDM (cfr. methods)		

TABLE 2.2 Combined dataset characteristics: Current TDM dataset with retrospectively collected data from neonates with perinatal asphyxia treated with hypothermia and published dataset [11]

Dataset	TDM**	Published [11]	Combined
Number of neonates	56	874	930
Number of HT Samples (Total)	75 (83)	0 (2174)	75 (2257)
Gestational age (weeks)	38 [35–41]	31 [24–43]	32 [24–41]
Postnatal age (days)	2 [1–4] *	2 [1–30]	2 [1–30]
Birth weight (g)	3184 [1910–4770]	1530 [385–4650]	1795 [385–4770]
Current weight (g)	3184 [1910–4800]	1560 [385–4780]	1800 [385–4800]
Co-admin. of ibuprofen	0	118	118

*one neonate in the TDM dataset did not undergo hypothermia
**cohort consists of n = 13 cases from UZ Leuven and n = 43 cases from VUmc

2.3.4 Pharmacokinetic analysis

The PK analysis and model validation were performed using NONMEM v7.3 and PsN v3.4.2, respectively, both running under Pirana v2.9.0. The results were analyzed using R v3.3.2 running under RStudio v1.0.136.

2.3.5 Model development

For the structural model, a previously published population PK model on amikacin in a large and heterogeneous group of neonates [11] was used as a basis. This model consisted of a two-compartment model with inter-compartmental clearance (Q) estimated as fractions of clearance (CL) and peripheral volume of distribution (V2) equal to the central volume of distribution (V1), respectively and with a combined additive and proportional error model [11]. Birthweight (BW) and PNA were covariates on CL and current weight (CW) was a covariate on V1 [11]. In order to estimate the impact of PATH, we tested a discrete covariate on CL and V1. Statistical considerations were accounted for by the decrease in objective function (-2log likelihood) value with a significance level of $p < 0.05$ (likelihood ratio test) which assumes a $\chi 2$ distribution and the precision of parameter estimates (RSE < 30%). In addition, the model fits were assessed visually using goodness-of-fit (GoF) plots split for the covariate tested.

2.3.6 Model validation

To assess the robustness of the parameter estimates of the final model, a non-parametric bootstrap was performed in which the combined dataset was resampled 1000 times with replacement and with stratification on the origin of the data (TDM or published). The resampled datasets were subsequently fitted with the final model, after which median and 95% confidence intervals of the obtained estimates were calculated.

To assess the predictive properties of the model, a normalized prediction distribution error (NPDE) analysis was performed using the NPDE package in R [14]. Each observed concentration was compared to 1000 simulated values for that observation.
Potential overparameterization was evaluated by calculating the condition number, by taking the eigenvalues from the NONMEM output and dividing the largest one to the smallest one.

2.3.7 Monte Carlo and stochastic simulations

To compare the exposures that would be obtained upon dosing according to three closely related and previously published dosing regimens [2, 11 (Table 2.3), the final model was used to simulate peak (1 hour after start of infusion) and trough (just before the subsequent dose) concentrations. For details regarding the three closely related previously published dosing regimens (Table 2.3) we refer to Smits et al. [2].

The final model was then used to determine, for neonates with PATH, an effective and practical dosing adjustment that would lead to target peak and trough concentrations. For this purpose, different doses and dosing intervals were explored to determine the regimen reaching the predefined peak and trough targets in the highest possible percentage of patients, while keeping in mind its feasibility in clinical practice. For all simulations, target peak and trough concentrations were above 24 mg/L and

TABLE 2.3 Summary of analyzed dosing regimens in model-based simulations

Dosing regimen Reference	**De Cock 2012 (11)**	**Smits 2015a (2)**	**Smits 2015b (2)**	**Proposed dosing regimen**
Description	**Original model based dosing regimen**	**Simplified model based dosing regimen**	**Current dosing regimen**	**Current dosing with 12-hours interval increase**
Current weight (g)				
1200–2000	15 mg/kg, 36h	15 mg/kg, 36h	15 mg/kg, 36h	15 mg/kg, **48h**
2000–2800	13 mg/kg, 30h	15 mg/kg, 30h	15 mg/kg, 36h	15 mg/kg, **48h**
> 2800	12 mg/kg, 24h	15 mg/kg, 24h	15 mg/kg, 30h	15 mg/kg, **42h**

below 5 mg/L, respectively. In all simulations, neonates received two consecutive doses of a dosing regimen, assuming hypothermic treatment throughout the dosing intervals, without intermediate dose adjustments.

For both Monte Carlo (MC) simulations and stochastic simulations (SC), the demographic characteristics (PNA, BW, CW, gestational age) of the neonates with PATH from the TDM dataset were used. For the MC simulations, 2500 individuals were sampled with replacement from this subpopulation, taking time-varying changes and correlations in the demographics into account. For the SC simulations, 4 neonates that are treated with HT were generated. Each had a PNA of 1 day and BW equal to the mean (3093 g), median (3000 g), 5th percentile (1965 g) or 95th percentile (4220 g) of the BW of the neonates with PATH from the TDM dataset. For the SC simulations, for each of the 4 neonates, 2500 individual clearance values were sampled from the frequency distribution of the clearance values obtained in the pharmacometric analysis.

2.4 Results

2.4.1 Population pharmacokinetic model

The CL in neonates with PATH was found to be decreased by 40.6% (9% RSE) as compared to CL in neonates without PATH. The addition of the covariate accounting for PATH on CL led to a reduction in objective function with 73 points ($p < 0.05$) and reduced the unexplained inter-individual variability on CL from 0.116 to 0.104 (10% decrease). PATH was not found to influence any of the other model parameters. The final population PK parameters and bootstrap results are summarized in Table 2.4.

The bootstrap analysis confirmed the precision of parameter estimates of the final model, as the bootstrap medians were very similar to the parameter estimates and within the 95% prediction interval. The GoF

TABLE 2.4 Final population PK parameters and bootstrap results

Parameter estimates	**Units**	**De Cock et al. 2012 (11)**	**Model Estimates (%RSE)**	**Bootstrap Median**	**95% Prediction Interval**
Structural Model					
Clearance	L/h/kg	0.0493 (2.2%)	0.0495 (2%)	0.0497	0.048–0.052
Central Volume of Distribution*	L	0.833 (1.34%)	0.832 (1%)	0.826	0.808–0.845
Intercompartmental Clearance (as a fraction of CL)	L/h	0.415 (12.3%)	0.45 (11%)	0.482	0.402–0.575
Covariates					
Hypothermic treatment	g	-	0.594 (9%)	0.587	0.498–0.673
Birthweight	g	1.34 (2.04%)	1.34 (2%)	1.344	1.294–1.391
Current weight	g	0.919 (2.46%)	0.926 (2%)	0.923	0.884–0.960
Postnatal Age	days	0.213 (9.81%)	0.22 (8%)	0.222	0.198–0.255
Ibuprofen	-	0.838 (3.88%)	0.838 (4%)	0.836	0.779–0.894
Inter-individual Variability				**[Shrinkage %]**	
Clearance	CV%	30% (14.9%)	32% (13%) [17%]	0.105	0.082–0.127
Residual variability					
Additive	mg/L	0.267 (27.2%)	0.305 (24%) [15%]	0.505	0.277–0.758
Proportional	%	0.061 (8.19%)	0.0606 (8%) [15%]	0.057	0.050–0.065

*Central Volume of Distribution = Peripheral Volume of distribution;

plots of the final model did not show any trends or bias which would indicate model misspecifications (Figure 2.1). The NPDEs of the predictions had a mean of 0.025 which was not significantly different from 0 ($p = 0.24$) and a standard deviation of 1.02 which was not significantly different from 1 ($p = 0.49$). Visual inspection of the results did not suggest bias in the model predictions (Figure S2.1). The NPDEs have similar distributions for both populations, with or without PATH (Figure S2.2). The condition number was 39, well below the threshold of 1000, suggesting that the model was not overparameterized and well supported by the data.

As the results of the PK model showed that only CL is influenced by PATH, for neonates with PATH it was proposed to use the most recently published and extensively validated dosing regimen (Smits et al.) with an increased dosing interval of 12 hours, while keeping the same doses (mg/kg). The previously published and the proposed dosing regimens are summarized in Table 2.3.

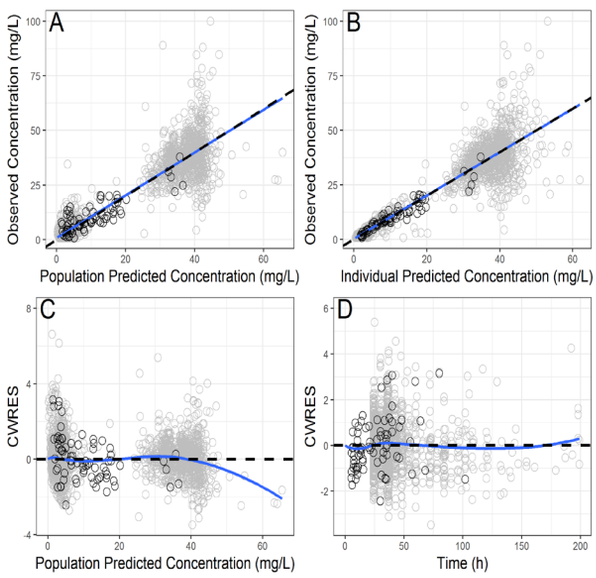


FIGURE 2.1 Population predicted concentration (A) and individual predicted concentration (B) vs. observed concentration; Conditional Weighted Residuals vs. Population predictions (C) and vs. Time after dose (D); Black circles - TDM dataset: asphyxia with hypothermia; Grey circles – Published Dataset

2.4.2 Monte Carlo (MC) and stochastic simulations (SC)

The results of the MC simulations upon dosing according to the three closely related dosing regimens (2, 11) for amikacin and the proposed regimen for PATH are shown in Figure 2.2. In the figure percentages of peak and trough concentrations within predefined target concentration ranges in neonates with PATH, split by the three weight groups used for dosing (Table 2.3), are shown. Results are presented upon the second amikacin dose, as then the target body temperature for hypothermia is mostly achieved.

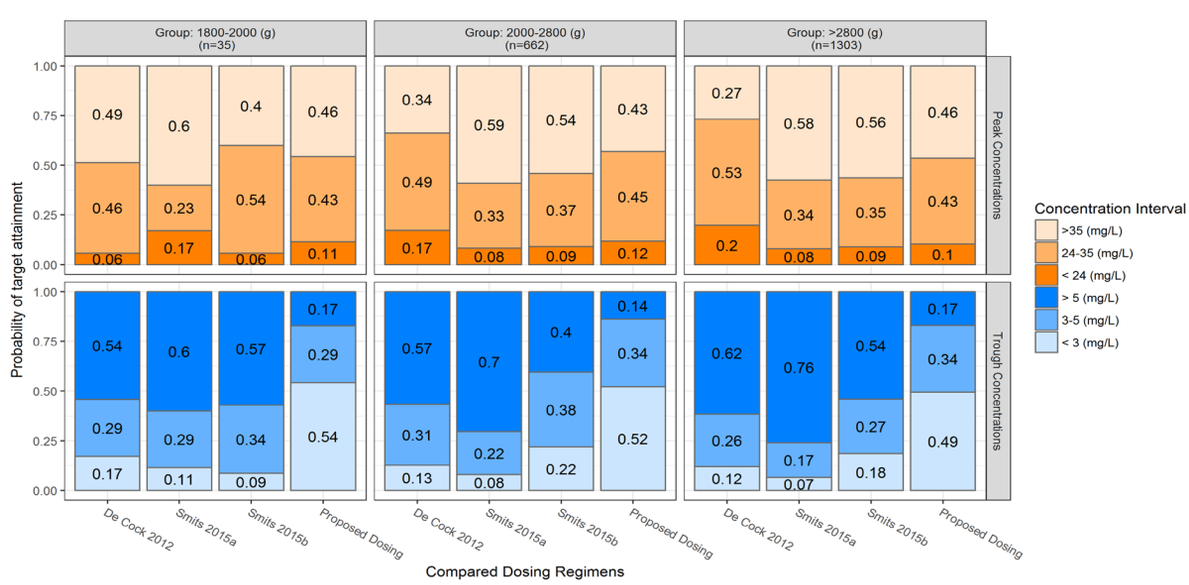


FIGURE 2.2 Stacked bar plots of the Monte Carlo simulations (n = 2500) presenting the results on target peak (upper panels) and trough (bottom panels) concentration attainment after the second amikacin dose. Results are split by three weight groups according to which the doses were calculated (Table 2.3) (left, middle and right panel). In each panel, the three columns on the left show the results obtained with the closely related and previously published dosing regimens [2, 15] whereas the column on the right shows the results of the newly proposed dosing regimen. All simulations were performed for neonates with PATH.

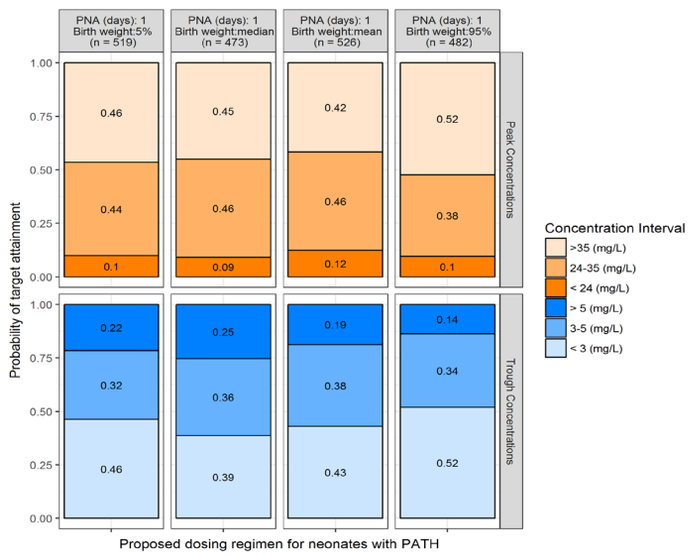


FIGURE 2.3 Stacked Bar of the Stochastic Simulations (n = 2500) presenting the results on target peak (upper panels) and trough (bottom panels) concentration attainment with the model-derived dosing interval. Results are presented after the second amikacin dose with panels for the lower (5%), median, mean and upper (95%) birthweight range of studied neonates with PATH, at the start of the hypothermic treatment

Figure 2.2 illustrates that the regimens currently used in clinical practice reached trough concentrations higher than 5 mg/L in 40% to 76% of neonates, whereas, using the proposed regimen where the dosing interval is increased with 12 hours, this percentage can be reduced to 14–17%. Peak concentrations were below the lower efficacy threshold in 10–12% of the cases only, which is in accordance with the results for the published dosing regimens, where the range was 6–17%.

Figure 2.3 comprises the results of the SC simulations showing how the proposed regimen performed when given to neonates representative of our sample, with specific demographic characteristics and PATH. In this figure, results are presented for the lower (5%), median, mean and upper (95%) birth weights of the population of neonates with PATH. Compared to the published dosing regimens(2), the proposed dosing regimen, where the dosing interval is increased by 12 hours, yielded similar target concentrations for the four tested groups, i.e., 14 to 25% of neonates had trough concentrations above the toxic level and in less than 12% of neonates the effective peak concentrations was not reached (Figure 3).

2.5 Discussion

In this manuscript, we quantified the impact of PATH on amikacin CL in neonates, a potential surrogate for glomerular filtration, and translated this finding in a dosing recommendation tailored for neonates with PATH.

Our model-based approach showed that amikacin CL is decreased with 40.6% in neonates with PATH when compared to neonates without this condition. The model was used for simulations with targeted trough concentrations to determine an effective and practical dosing adjustment for neonates with PATH. The 12-hour increase in the dosing interval of the most recent and extensively validated dosing regimen [2], while keeping the amikacin dose (mg/kg) unchanged, had a minimal impact on the peak concentrations but improved the attained trough concentrations (Figure 2.2).

With unadjusted dosing regimen, the reduced amikacin CL led to trough concentrations above the toxic threshold for a large percentage of the neonates with PATH population (Figure 2.2), increasing the probability of developing adverse reactions such as nephro- and ototoxicity. Achieved peak concentrations were minimally impacted by the reduced CL and increased dosing interval, as these are determined by the dose and the administration rate of the IV infusion.

The MC simulations allowed for a comparison between the performances of the published dosing regimens [2, 11] and the proposed regimen in a group of patients with demographics encountered in this group (Figure 2.2), whereas the SC simulations led to a better understanding of how the proposed dosing regimen would perform in individuals with specific realistic demographic characteristics for neonates with PATH. A PNA of 1 day was considered most relevant for the studied population since

hypothermic treatment is usually started within the first 6 hours after birth and the BW mean, median, 5th and 95th percentiles were calculated for these patients of the TDM dataset (Figure 2.3).

Our results showed that the proposed dosing regimen for neonates with PATH did not impair the attainment of the amikacin treatment efficacy target, with less than 12% of the studied population reaching a suboptimal peak concentration, while the toxic effects were reduced, with less than 17% of the studied population attaining trough concentrations above 5 mg/L (Figure 2.2). This does show, nevertheless, that even with the proposed adjustment, amikacin trough TDM should still be performed as part of routine clinical care, especially in patients with PATH. It should also be noted that the validity of the traditional target concentrations for efficacy and safety of amikacin has not been established for such prolonged dosing intervals, warranting prospective evaluation of the regimen.

Although we provided the first report of amikacin PK in a dual-center cohort of neonates with PATH, other studies were performed for other aminoglycosides (i.e. gentamicin). Frymoyer et al. [8] reported improved attainment of gentamicin target trough levels in neonates with PATH, after increasing the dosing interval from 24 to 36 hours (+ 50%). In addition, peak gentamicin concentrations were minimally impacted by the increase in dosing interval. This is in concordance with our findings for amikacin, and can be explained by the fact that these compounds from the same therapeutic class, eliminated by the same pathway – glomerular filtration – actually reflect the impact of perinatal asphyxia or hypothermia (or both) on the neonatal glomerular filtration rate. De Cock et al. and others previously reported that physiological maturation of amikacin CL can be used to predict ontogeny of other compounds eliminated almost entirely by glomerular filtration [14, 15]. The current findings support this 'semi-physiological' concept, which could be further explored to quantify the impact of perinatal asphyxia and whole-body cooling on the CL of drugs eliminated almost exclusively by glomerular filtration.

Due to the nature of the TDM data (i.e. retrospectively retrieved from patients' files, small number of patients with PATH, sampling during routine care), our analysis has limitations. First, we were unable to disentangle the impact of perinatal asphyxia from the impact of hypothermic treatment on amikacin CL. These are expected to have different extents, as shown in preclinical experiments in newborn pigs by Satas et al. [10] (hypoxia-ischemia) and Koren et al. [17] (hypothermia). They have also shown that, the intensity of the hypothermic treatment could be relevant, as severe hypothermia decreased gentamicin half-life with 36% (10°C temperature drop) [17], whereas, mild hypothermia (4°C temperature drop) did not have an impact on CL [10]. On the other hand, studies in neonates had contradicting results. While Liu et al. reported that 40% of gentamicin trough concentrations in neonates with hypoxic ischemic encephalopathy were above the target 2 mg/L, they could not identify an additional impact of hypothermia on CL [18]. However, Ting et al. [9] showed in neonates with hypoxic-ischemic encephalopathy that hypothermic treatment caused an increase in the half-life of gentamicin, from 7.01 hours in a normothermic group to 9.57 hours (+ 36.5%) in a hypothermic group, which suggests that the hypothermic treatment itself reduces CL as well. With this in mind, we suggest that the results of our study, including the model-derived dosing regimen, should not be extrapolated to populations other than neonates with PATH, or to other drugs, even if eliminated by the same pathway, as the validity of such extrapolations requires further research.

Another limitation is that, both at the initiation of the hypothermic treatment and initiation of the rewarming phase, the body temperature of the neonates is not constant. Since the number of samples collected during these periods was limited, it was not possible to identify a covariate relationship that reflects the dynamic changes in clearance during these periods. As a result, model-based simulations cannot be expected to be accurate for initiation of the cooling process as well as during the rewarming phase. We, therefore, only present simulation-based results for the second amikacin dose, as the body temperature is expected to be stable (33.5°C) throughout this interval.

2.6 Conclusion

To conclude, we identified a significantly decreased (40.6%) amikacin CL in (near) term neonates with PATH. Based on simulations, indicating the achievement of safe trough concentrations (< 5mg/L) while still reaching optimal peak concentrations (> 24 mg/L), we propose a 15 mg/kg dose every 42 hours for children above 2800 g, or 48 hours for children between 1800 g and 2800 g, in this special neonatal population. As a future step, this model-based dosing proposal should undergo prospective validation and eventual clinical implementation.

2.7 Acknowledgements

The authors would like to thank Dr. Swantje Voller for carefully reviewing the code used for the modeling and simulations. The research activities were facilitated by the agency for innovation by Science and Technology in Flanders (IWT) through the SAFEPEDRUG project (IWT/SBO 130033). KA has been supported by FWO Vlaanderen (Senior Clinical Investigatorship, 1800209 N)). CAJK received support from the Innovational Research Incentives Scheme (Vidi grant, June 2013) of the Dutch Organization for Scientific Research (NWO) for the submitted work. All authors declare that they have no conflicts of interest. This work was performed within the framework of Top Institute Pharma project D2-501.

2.8 References

1. Ducher M, Maire P, Cerutti C, Bourhis Y, Foltz F, Sorensen P, Jelliffe R, Fauvel JP. 2001. Renal elimination of amikacin and the aging process. Clin Pharmacokinet 40:947.
2. Smits A, De Cock RFW, Allegaert K, Vanhaesebrouck S, Danhof M, Knibbe CAJ. 2015. Prospective evaluation of a model-based dosing regimen for amikacin in preterm and term neonates in clinical practice. Antimicrob Agents Chemother 59:6344–6351.
3. Smits A, Kulo A, van den Anker J, Allegaert K. 2016. The amikacin research program: a stepwise approach to validate dosing regimens in neonates. Expert Opin Drug Metab Toxicol 0:1–10.
4. Zanelli S, Buck M, Fairchild K. 2011. Physiologic and pharmacologic considerations for hypothermia therapy in neonates. J Perinatol 31:377–86.
5. Van Den Broek MPH, Groenendaal F, Egberts ACG, Rademaker CMA. 2010. Effects of hypothermia on pharmacokinetics and pharmacodynamics: A systematic review of preclinical and clinical studies. Clin Pharmacokinet.49(5):227-294.
6. Pokorna P, Wildschut E, Vobruba V, van den Anker J, Tibboel D. 2015. The Impact of Hypothermia on the Pharmacokinetics of Drugs Used in Neonates and Young Infants. Curr Pharm Des 21(39):5705–5724.
7. Dammann O, Ferriero D, Gressens P. 2011. Neonatal encephalopathy or hypoxic-ischemic encephalopathy? Appropriate terminology matters. Pediatr Res 70:1–2.
8. Frymoyer A, Shirley L, Bonifacio S, Meng L, Lucas S, Guglielmo J, Sun Y, Verotta D. 2013. Every 36-hour Gentamicin Dosing in Neonates with Hypoxic Ischemic Encephalopathy Receiving Hypothermia. J Perinatol. 33:778–782.
9. Ting JY, Kwan E, McDougal A, Osiovich H. 2015. Pharmacokinetics of gentamicin in newborns with moderate-to-severe hypoxic-ischemic encephalopathy undergoing therapeutic hypothermia. Indian J Pediatr 82:119–25.
10. Satas S, Hoem NO, Melby K, Porter H, Lindgren CG, Whitelaw A, et al. 2000. Influence of mild hypothermia after hypoxia-ischemia on the pharmacokinetics of gentamicin in newborn pigs. Biol Neonate 77:50–57.
11. De Cock RFW, Allegaert K, Schreuder MF, Sherwin CMT, De Hoog M, Van Den Anker JN, Danhof M, Knibbe C a J. 2012. Maturation of the glomerular filtration rate in neonates, as reflected by amikacin

clearance. Clin Pharmacokinet 51:105–117.

12. Azzopardi D V, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E, Kapellou O, Levene M, Marlow N, Porter E, Thoresen M, Whitelaw A, Brocklehurst P. 2009. Moderate hypothermia to treat perinatal asphyxial encephalopathy. N Engl J Med 361:1349–1358.
13. Bijleveld YA, de Haan TR, van der Lee HJH, Groenendaal F, Dijk PH, van Heijst A, de Jonge RCJ, Dijkman KP, van Straaten HLM, Rijken M, Zonnenberg IA, Cools F, Zecic A, Nuytemans DHGM, van Kaam AH, Mathot RAA. 2016. Altered gentamicin pharmacokinetics in term neonates undergoing controlled hypothermia. Br J Clin Pharmacol.81(6):1067- 1077.
14. Comets E, Brendel K, Mentré F. 2010. Model evaluation in nonlinear mixed effect models, with applications to pharmacokinetics. J la Société Française Stat 151:106–127.
15. De Cock RFW, Allegaert K, Sherwin CMT, Nielsen EI, De Hoog M, Van Den Anker JN, Danhof M, Knibbe C a J. 2014. A Neonatal amikacin covariate model can be used to predict ontogeny of other drugs eliminated through glomerular filtration in neonates. Pharm Res 31:754–767.
16. Zhao W, Biran V, Jacqz-Aigrain E. 2013. Amikacin maturation model as a marker of renal maturation to predict glomerular filtration rate and vancomycin clearance in neonates. Clin Pharmacokinet 52:1127–1134.
17. Koren G, Barker C, Bohn D, Kent G, Biggar WD,. 1985. Influence of hypothermia on pharmacokinetics of gentamycin and theophylline in piglets. Crit Care Med 13:844–847.
18. Liu X, Borooah M, Stone J, Chakkarapani E, Thoresen M. 2009. Serum gentamicin concentrations in encephalopathic infants are not affected by therapeutic hypothermia. Pediatrics 124:310–315.
19. Langhendries JP, Battisti O, Bertrand JM, Francois A, Kalenga M, Darimont J, Scalais E, Wallemacq P. 1998. Adaptation in Neonatology of the Once-Daily Concept of Aminoglycoside Administration : Evaluation of a Dosing Chart for Amikacin in an Intensive Care Unit. Biol 351–362.

2.9 Supplementary material

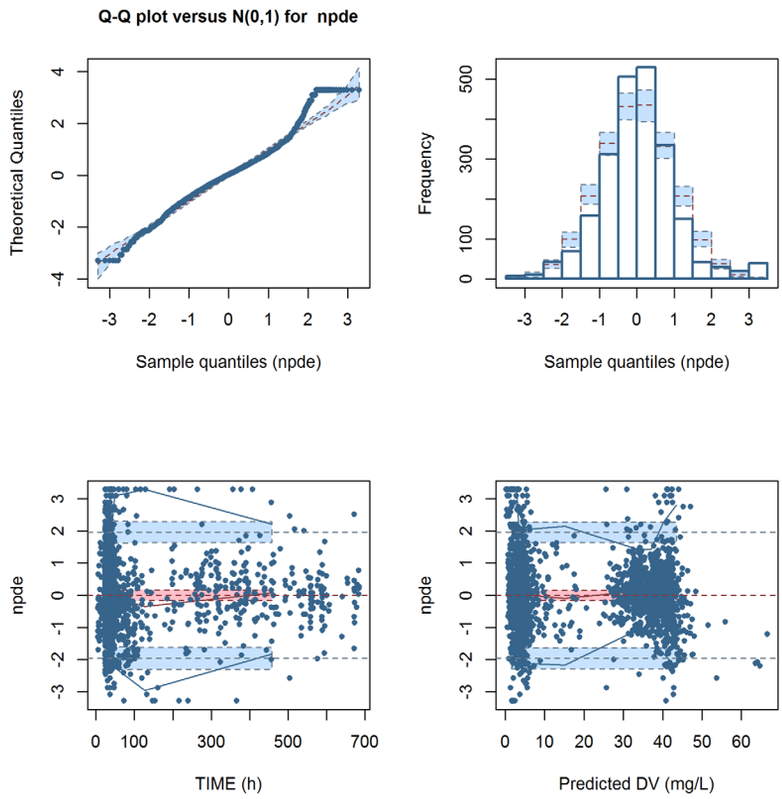


FIGURE S2.1. Normalized prediction distribution errors results of the best model (N = 1000). Both published and TDM datasets are included in the analysis. DV stands for observed amikacin concentrations.

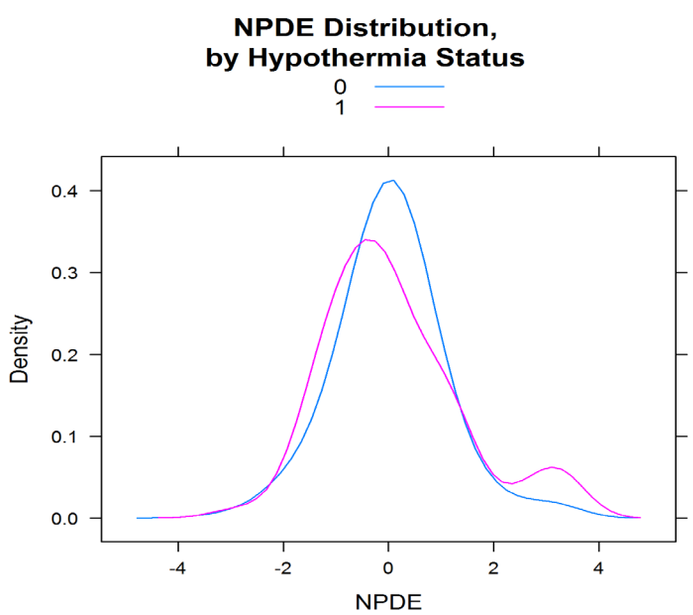


FIGURE S2.2. Normalized prediction distribution errors distribution stratified by hypothermic status: pink line – hypothermia and blue line – normothermia

2.10 Model code

```
; ---------------------------------
;; 1. Based on: De Cock 2012
;; 2. Description:AMICOOL PRJ
$PROB Amikacin PK for PATH patients
$INPUT ID TIME AMT DV MDV RATE GA BW CW PNA IBU COOL
$DATA 20042016-SC-AMICOOL.NM.06.csv IGNORE=@

IGNORE (ID.EQ.182); excluded previously
IGNORE (ID.EQ.521); excluded previously
IGNORE (ID.EQ.523); excluded previously

$SUBROUTINE ADVAN3 TRANS4

$PK
FF=1
FC=1
IF(IBU.EQ.1) FF = THETA(7) ; ibuprofen coadmin as cat cov
IF(COOL.EQ.1) FC = THETA(8) ; hypothermia coadmin as cat cov
TVCL  = THETA(1) * ((BW / 1750) ** THETA(4)) * (1 + (PNA / 2) * THETA(6)) *
      (FF) * (FC)
CL    = TVCL * EXP(ETA(1))
TVV1  = THETA(2) * ((CW / 1760) ** THETA(5))
V1    = TVV1 * EXP(ETA(2))
Q     =     THETA(3) * CL
V2    = V1
S1    = V1

$ERROR

IPRED = F
Y     = F *(1 + ERR(1)) + ERR(2); combined error

$THETA
(0, 0.0493) ;1- CL
(0, 0.833)  ;2- V1
(0, 0.415)  ;3- Q
(0, 1.34)   ;4- BW on CL
(0, 0.919)  ;5- CW on V2
(0, 0.213)  ;6- PNA on CL
(0, 0.838)  ;7- IBU on CL
(0, 0.583)  ;8- COOL on CL

$OMEGA
0.0899      ;CL
0 FIX       ;V

$SIGMA
0.0614
0.267

$EST METHOD=1 INTERACTION NOABORT SIGDIG=3 PRINT=5 MAXEVAL=9999 POSTHOC
$COV COMP PRINT=E
$TABLE ID TIME DV MDV GA BW CW PNA IBU TVCL IPRED CL V1 V2 Q COOL IBU FC FF
ETA1 ETA2 CWRES NOPRINT ONEHEADER FILE=AMICOOL99.tab
```