Towards a system-based pharmacology approach to predict developmental changes in renal drug clearance in children

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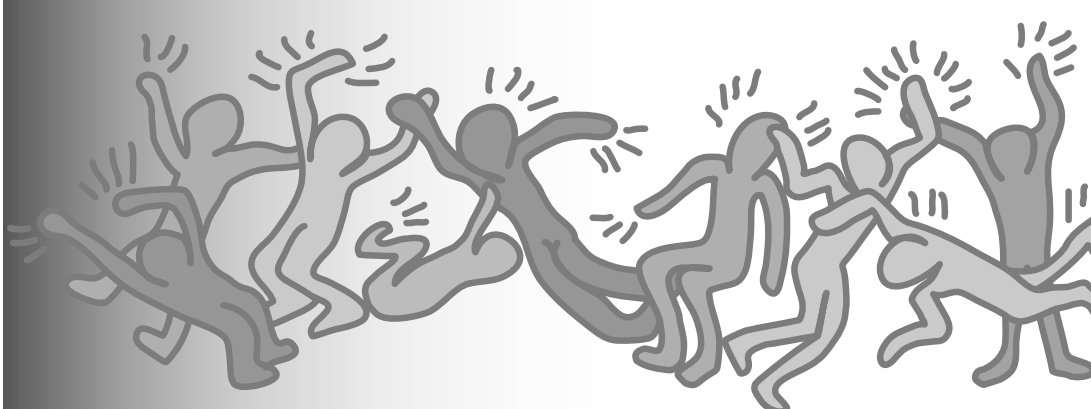
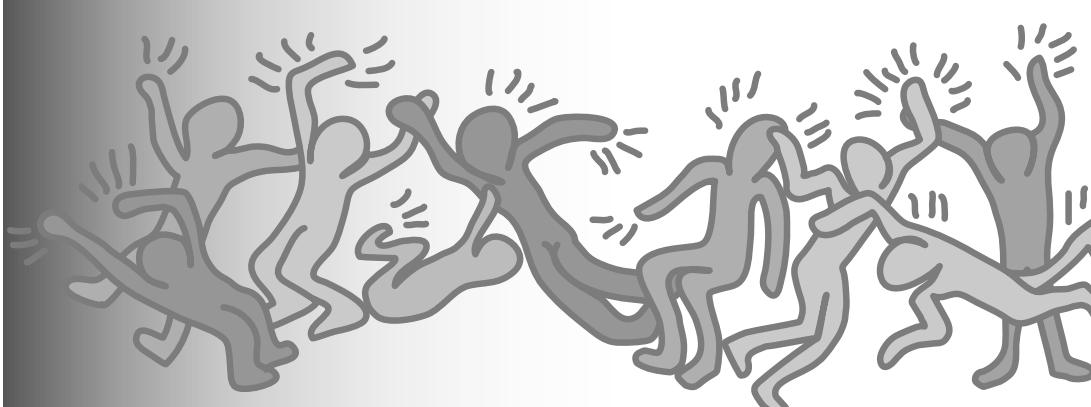
Section VI

Summary, Conclusions and Perspectives



Chapter 10

Conclusions and Perspectives



10.1 Towards a system-based pharmacology approach to predict developmental changes in renal drug clearance

To date, dosing guidelines in children are often empirically derived from dosing guidelines in adults based on linear extrapolations based on bodyweight. However, children can not be considered small adults. During development, changes in body composition, cardiac output and blood flow are seen as well as developmental changes in drug metabolizing enzymes, liver and kidneys. All of these factors may influence the pharmacokinetics of drugs. Furthermore differences in pharmacological response may be seen between children and adults due to differences in expression of receptors or differences in disease status, which influence the pharmacodynamics. The magnitude of these changes may not be solely reflected by differences in bodyweight. Therefore it is of utmost importance to characterize these developmental changes in pharmacokinetics (PK) and pharmacodynamics (PD) to develop evidence-based and individualized dosing regimen [1]. The absence of this information poses otherwise significant risks to over- or underdosing leading to adverse or even toxic effects or therapeutic failure, respectively [2,3].

Renal clearance is responsible for the elimination of a large number of water-soluble drugs and metabolites and is therefore of large importance when characterizing the pharmacokinetics of drugs. Renal clearance includes glomerular filtration, tubular secretion and reabsorption and each of these processes is subject to different developmental changes [4]. To estimate the renal clearance of drugs in children, a thorough understanding of these developmental changes in the different subprocesses contributing to renal function is needed. Therefore the aim of the research described in this thesis was to characterize the developmental changes in renal function over the entire pediatric age range. To this end, a system-based pharmacology approach was applied implicating that within the models for the different subprocesses contributing to renal function a distinction was made between system-specific and drug-specific properties [5].

In **chapter 2** of this thesis we have highlighted the potential value of population pharmacokinetic and pharmacodynamic modeling in pediatrics. Performance of clinical studies in children is associated with several ethical, practical and economical issues. Since it is unethical to perform clinical studies in healthy children, studies are performed in children suffering from a disease. As a consequence only a limited number of patients are available. Moreover the small blood volume should be taken into account limiting the number and volume of blood samples. To overcome these

issues with regard to the analysis of pediatric data, the population approach should be applied. This population approach using non-linear mixed effect modeling allows for the analysis of dense, sparse, balanced or unbalanced data, making the application highly suitable in pediatric clinical practice. Additionally, it permits the exploration of the influence of different covariates such as bodyweight, age and other covariates, to explain the variability in drug response. Finally, using this approach, PK-PD studies can be designed in the most efficient manner in order to obtain the maximum information on the PK-PD parameters with the highest precision. Once a population PK and/or PD model is developed, internal and external validations should be performed [6]. If the model performs well in these validation procedures, model simulations can be used to define a dosing regimen which in turn needs to be tested and challenged in a prospective clinical trial [6]. This methodology will improve the efficacy/safety balance of dosing guidelines, which will be of benefit to the individual child. The population approach using non-linear mixed effect modeling was applied in this thesis to describe the developmental changes in renal clearance for different drugs across the pediatric age range.

10.2. Developmental changes in GFR in preterm and term neonates by describing the pharmacokinetics of renally excreted antibiotics

Previously it has been described that during the first month of life, a rapid rise in glomerular filtration is seen. Therefore in **chapter 3** of this thesis the developmental changes in glomerular filtration were described using data of amikacin in 874 preterm and term neonates (birth bodyweight 385-4650g, postnatal age 1-30 days, gestational age 24-43 weeks). Amikacin was used as a paradigm compound to reflect GFR because it is almost entirely eliminated through GFR, Postmenstrual age proved to be the most significant covariate on clearance based on the systematic covariate analysis. However, birth bodyweight and postnatal age, representing antenatal and postnatal maturation of the kidney, respectively, proved to be superior over postmenstrual age alone. Birth bodyweight was implemented on clearance using a power function with an exponent of 1.34 and postnatal age was implemented using a linear function with a slope of 0.2. Furthermore a decrease (16%) in clearance was seen when ibuprofen was co-administered. Based on the final pharmacokinetic model, which was validated both internally and externally, simulations were performed to illustrate exposure to amikacin in preterm and term neonates following currently used dosing regimens. Based on the simulations it could be concluded that the currently used dosing regimens should be revised as they may possibly increase the risk of toxicities since

target through values between 1.5-3 mg/L were often not reached. Consequently a new model-based dosing regimen was developed for preterm and term neonates aged between 1 and 30 days, and based on current bodyweight, postnatal age and co-administration of ibuprofen.

In **chapter 4**, this new model-based dosing regimen was prospectively evaluated in 579 preterm and term neonates (median birth bodyweight 2285g (range 420-4850g), postnatal age 2 days (range 1-30 days), gestational age 34 (range 24-41 weeks)). The analysis showed that across the entire neonatal age range the 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 24mg/L were reached in almost all patients with different bodyweight, postnatal age and use of ibuprofen. 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.

Based on the prospective study, it can be concluded that the 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.

To develop rational, evidence-based and individualized dosing regimen for specific drugs, pharmacokinetic and/or pharmacodynamic models need to be developed and validated [6,7] as seen in chapter 3. However to facilitate model development for groups of drugs, a more system-based pharmacology approach is needed [5]. This approach was applied in **chapter 5,** in which it was evaluated whether the covariate model for amikacin, describing the developmental changes in GFR in preterm and term neonates (chapter 3), could be extrapolated to other renally excreted drugs. To perform this analysis five different neonatal datasets on netilmicin, tobramycin, vancomycin and gentamicin were used. Using this approach a distinction was made between system-specific and drug-specific information [5]. The covariate model that included birth bodyweight, postnatal age and co-administration of ibuprofen was considered to be system-specific while the population value was considered drug-specific (equation 1).

$$CL_i = CL_p \bullet \underbrace{(\frac{bBW}{bBW_{Median}})^{1.34} \bullet (1+(0.213 \bullet \frac{PNA}{PNA_{Median}})) \bullet 0.838_{ibuprofen}}_{\text{Amikacin covariate model}}$$

Drug specific property

(Equation 1)

Subsequently the descriptive and predictive performance of the models using the amikacin covariate model was compared to the independent reference models, which were developed based on a systematic covariate analysis. Based on the analysis, it was concluded that the descriptive and predictive properties of the models developed using the amikacin covariate model were good and fairly similar to the independent reference models, as expressed by the goodness-of-fit plots and the normalized prediction distribution error method. Finally, the same covariates as in the covariate model of amikacin, i.e. birth bodyweight and postnatal age, were identified as the most important descriptors of clearance in the independent reference models. Consequently it was concluded that pediatric covariate models contain system-specific information describing the developmental changes in the underlying physiological processes. This approach in which information of one drug is extrapolated to another drug eliminated through the same route will lead to optimization of study design, sparse data analysis and will facilitate the development of individualized and evidence-based dosing regimen.

10.3. Developmental changes in renal function (GFR and tubular processes) in preterm and term neonates by describing the pharmacokinetics of cefazolin

Chapter 6 of this thesis focused on describing the pharmacokinetics of cefazolin in preterm and term neonates. In adults it is know that cefazolin is eliminated by both GFR and active tubular secretion [8,9] and that protein binding varies between 70-90% [10,11,12,13]. However in children and certainly in neonates only limited information is available on the pharmacokinetics of cefazolin. Therefore in chapter 6 of this thesis the pharmacokinetic properties of cefazolin were described in 36 preterm and term neonates (birth bodyweight 540-4200g, postnatal age 1-30 days, gestational age 24-40 weeks). Based on total and unbound cefazolin concentrations, a one compartment model was developed in which total and unbound concentrations were linked by estimation of the protein binding (B_{max}) and the dissociation constant (K_D) which

were estimated to be 136 mg/L and 46.5 mg/L, respectively. Birth bodyweight and postnatal age were found as most important covariates on clearance of cefazolin using a power and linear function, respectively. Furthermore, it was found that albumin was linearly correlated with B_{max}. Based on this final model, Monte Carlo simulations were performed to illustrate the exposure to cefazolin following the currently used dosing regimens. According to the results, it was suggested to adjust the dosing regimen proposed by the Dutch Children's Formulary [14] to attain unbound concentrations during 60% of the dosing interval above a concentration of 8 mg/L, which corresponds to the minimal inhibitory concentration according to The Clinical and Laboratory Standards Institute (CLSI) for susceptibility of Staphylococcal species [15] and to guarantee a similar exposure in all patients.

10.4. Renal and hepatic elimination of propylene glycol in preterm and term neonates

Drug formulations often contain excipients to increase solubility and/or stability of drugs. One of the frequently used excipients is propylene glycol (PG). Propylene glycol is normally considered to be safe. However toxic effects have been reported in the adult, pediatric and neonatal population and may include bradycardia, depression of the central nervous system, increase in anion gap, lactic acidosis, hepatic dysfunction and kidney injury [16,17,18,19]. As a consequence both the Food and Drug Administration (FDA) and the European Medicine Agency (EMA) have established guidelines considering the maximum daily dose of propylene glycol. However, a large discrepancy is seen between both guidelines. While the FDA established an acceptable daily intake of 25mg/kg bodyweight, the EMA proposed a maximum daily dose of 400mg/kg in adults and 200mg/kg in children [20]. This discordance in both guidelines indicates the lack of information on the safe use of propylene glycol in adults but also in the pediatric age range. To date, no pharmacokinetic studies in the pediatric age range were available on propylene glycol. Only a limited number of reports was found in literature informing on the toxic effects of propylene glycol [18,21,22,23,24,25]. Therefore in **chapter 7**, the pharmacokinetics of propylene glycol co-administered intravenously with paracetamol (800mg PG/1000mg paracetamol) or phenobarbital (700mg PG/200mg phenobarbital) were described in 62 preterm and term neonates (birth bodyweight 630-3680g, postnatal age 1-30 days, gestational age 24-41 weeks). A one compartment model was developed in which birth bodyweight and postnatal age were found as most important covariates on clearance. Current bodyweight was found as most important covariate on volume of distribution and proved 1.77 times higher when co-administered with phenobarbital compared to

paracetamol. Based on this final pharmacokinetic model, simulations were performed to illustrate propylene glycol exposure when co-administered with paracetamol and phenobarbital. Based on the simulations, it was shown that the population mean propylene glycol peak and trough concentrations ranged between 33-144 and 28-218 mg/L (peak) and 19-109 and 6-112 mg/L (trough) for paracetamol and phenobarbital, respectively, depending on birth bodyweight and age of the neonates.

In **chapter 8** of this thesis, renal and hepatic elimination of propylene glycol was quantified in these preterm and term neonates. In adults, it is known that 45% of propylene glycol is eliminated through the renal route and 55% is metabolized in the liver by alcohol dehydrogenase (ADH) to lactate and pyruvate [26,27]. Due to immaturity of the renal function, renal clearance of propylene glycol may be expected to be lower in neonates compared to adults. Even though the pharmacokinetics of propylene glycol have been characterized in preterm and term neonates in chapter 7, no distinction could be made between renal and hepatic elimination of propylene glycol in that analysis. It is however important to characterize the magnitude of both pathways in neonates because when it appears that one pathway or the other is more dominant in neonates this may play a role in the significance of age-specific drug-drug interactions. Therefore in chapter 8, renal and hepatic elimination of propylene glycol was characterized. The pharmacokinetic analysis was performed based on concentrations of propylene glycol in both plasma and/or urine collected in 69 (pre) term neonates (birth bodyweight 630-3980g, postnatal age 1-30 days gestational age 24-41 weeks). Birth bodyweight and postnatal age were identified as most important covariates on hepatic clearance. Since a time-dependent trend was seen in the renal excretion of propylene glycol, different models were tested based on time after first dose, urine volume and amount of creatinine in urine. Renal clearance was 15% of the total clearance after the first dose but increased over time to 25% at 24hours after the first dose. This increase was best described by a hyperbolic function based on time after the first dose. Although renal clearance increased with time after first dose up to 25%, renal clearance in neonates was substantially lower compared to adults for which renal clearance of propylene glycol was reported to be about 45% of the total clearance. As a consequence, since in neonates hepatic clearance of propylene glycol is determined as the most important elimination route, this may implicate that drug-drug interactions at the alcohol dehydrogenase enzyme are more important in neonates compared to adults. Furthermore, this may potentially also indicate that renal failure is of less importance in neonates compared to adults considering the total elimination of propylene glycol. It is concluded that, to evaluate whether the increase in renal clearance of propylene glycol indicates an auto-induced increase in renal secretion or failure of tubular reabsorption of propylene glycol, further studies are needed.

10.5. Developmental changes in GFR from neonates until adults described using different renally excreted antibiotics

Glomerular filtration is responsible for the elimination of a large number of water-soluble drugs and their metabolites. GFR is well defined in adults and is estimated to be around 120 mL/min [4]. More uncertainty rises in the pediatric age range as GFR is supposed to reach adult levels at about 6 months – 1 year of age [4]. However an exact quantification of GFR throughout the pediatric age range is missing. Therefore, the aim in **chapter 9** was to describe the developmental changes in GFR from (pre) term neonates until adults (N=1760 patients, bodyweight 415g-85kg, age 1 day-18 years) by describing the pharmacokinetics of gentamicin, tobramycin and vancomycin, which are drugs that are almost entirely eliminated through GFR. Since the analysis was based on data of three different drugs combined into one analysis, a system-based pharmacology approach was used. This means that, as explained in chapter 5, a distinction was made between system-specific and drug-specific properties. The covariate model tested on clearance was considered to contain system-specific information reflecting the developmental changes in GFR applicable to all drugs while the population value was considered to be a drug-specific parameter. Across the entire pediatric age range, from premature neonates until adults, bodyweight was found as most significant covariate on clearance and volume of distribution. The effect of bodyweight was best described on clearance using an allometric function in which the exponent changed with bodyweight from 1.4 in neonates to 1 in adults. This indicates that the largest increase in clearance of these different drugs, reflecting GFR, is seen during the first weeks of life. This maturation function, developed in **chapter 9**, may possibly be used to describe evidence-based and individualized dosing regimen for renally excreted drugs over the entire pediatric age range.

10.6. Perspectives

The aim of the research described in this thesis was to describe the developmental changes in renal function. Renal function consists of glomerular filtration, tubular secretion and reabsorption. In this thesis we primarily focused on describing the developmental changes in glomerular filtration on the basis of analyses on drugs that are primarily excreted through GFR. Once the developmental changes in GFR are described, this information can be used to describe the developmental changes in tubular processes by studying drugs that are excreted on the basis of these different subprocesses.

Glomerular filtration is rapidly rising during the first weeks of life. Moreover, also large differences in GFR are seen between preterm and term neonates. Therefore in the first part of this thesis we focused on describing the developmental changes in GFR in neonates. Subsequently the maturation of the renal function was described across the entire pediatric age range. As explained in the introduction of this thesis (chapter 1), several methods can be used to measure GFR. The most practical manner to assess GFR in healthy individuals is by measuring creatinine clearance. Since creatinine is an endogenous compound, the burden to evaluate GFR can be kept to a minimum for each individual. However, a few remarks should be considered when creatinine is used to evaluate GFR. First of all, creatinine is not only filtered by GFR but also in part secreted by tubular secretion [4,28]. In addition, the measurement of creatinine clearance based on plasma samples can be complicated since the formation of creatinine depends on muscle mass, age and gender [4]. Furthermore in the first days of life creatinine values reflect maternal renal function [29,30,31]. Finally, the Schwartz formula which is often used to estimate GFR in children based on serum creatinine and body length, often leads to overprediction of GFR [32]. Consequently, due to the reasons mentioned above, creatinine is not the best marker to assess GFR. Other markers like inulin or radioisotopes [33,34] have amongst other things the disadvantage that these compounds are exogenous implicating that the burden for each individual will be increased when evaluating GFR compared to creatinine. Therefore to perform these analyses the pharmacokinetics were described of amikacin, netilmicin, tobramycin, vancomycin and gentamicin, which are drugs that are almost entirely eliminated through GFR. Since GFR was evaluated by describing data of renally excreted drugs, data could be directly obtained from clinical practice without administering diagnostics or other compounds specific for this analysis. The latter is of course of major importance for children so that the burden for each patient can be kept to a minimum. However, this also implicates that the developmental changes in glomerular filtration were characterized in non-healthy or sick patients.

In chapter 3 the GFR model for neonates was developed based on data of amikacin obtained in 874 preterm and term neonates, covering an extensive range in gestational age, birth bodyweight and postnatal age. This analysis in which a tremendous amount of data of amikacin was used to characterize developmental changes in GFR in preterm and term neonates was never performed before as previous analyses were based on a smaller number of patients and a more narrow age range compared to our analysis. Moreover, the model developed in chapter 3 was both internally and externally validated. Consequently this model, describing the developmental changes in GFR based on amikacin clearance, could then be used to describe clearance of other renally excreted drugs in neonates (chapter 5). This extrapolation to the other renally excreted drugs was performed to populations

with the same clinical characteristics and disease status compared to the amikacin dataset since all patients were admitted to the neonatal intensive care unit and were treated with aminoglycosides or glycopeptides when sepsis was suspected. However, since critical illness (i.e. sepsis) may have an influence on clearance, these models should not be applied in other patient populations until the accuracy of the model has been evaluated in those populations. In a previous study by Ince *et al.* [35] it was reported that critical illness severely reduced the CYP3A4-mediated clearance of midazolam. Therefore, the effects of critical illness on the developmental changes in glomerular filtration should be further analyzed, even though renal excretion can not be compared to CYP3A4 metabolism. Moreover the use of this kind of drugs (aminoglycosides, glycopeptides) may cause renal toxicity after repetitive dosing [36]. Furthermore, the model performance should also be evaluated in patients on extracorporeal membrane oxygenation (ECMO) treatment. Previously it has been shown that the very invasive ECMO treatment influences the pharmacokinetic parameters of various drugs [37,38,39,40,41,42]. In a study of Dodge *et al.* [43], it was concluded that neonates on ECMO receiving gentamicin had a higher volume of distribution and a lower clearance of gentamicin compared to neonates off ECMO. In conclusion, this means that the model developed in chapter 3 should not be applied to other patient populations until the accuracy and predictability of this model is evaluated in this population. The model can however be seen as a primary basis in which a large amount of data was used. Moreover, besides the fact that the model was both internally and externally validated, it was also used to predict other renally excreted drugs.

As explained in the introduction of this thesis, the objective of this thesis was to describe the developmental changes in renal function by the use of a more system-based pharmacology approach. The key feature of this approach is that a distinction was made between system-specific and drug-specific properties. This approach was first applied in chapter 5 of this thesis. The amikacin covariate model for neonates, which was considered to be system-specific, was extrapolated to netilmicin, tobramycin, vancomycin and gentamicin, which are drugs that are almost entirely eliminated through GFR (chapter 5). The applicability of this GFR model, based on amikacin was also illustrated in an analysis performed by Zhao *et al.* [44], in which the model of amikacin was used to predict clearance of vancomycin. Based on that study, it was concluded that the model describing the developmental changes in GFR based on amikacin can be used to predict dosage regimens of other renally excreted drugs by GFR in preterm and term neonates. However, it should be emphasized that the final pharmacokinetic models for amikacin, netilmicin, tobramycin, gentamicin and vancomycin as developed in section II of this thesis are only of significance in a specific age range namely preterm and term neonates. The exponential increase in clearance

with birth bodyweight (exponent of 1.34) seen in preterm and term neonates will not be applicable to older children and adults as the renal function will be gradually flattening. Therefore, in the last section of this thesis (chapter 9) the developmental changes in GFR were quantified over the entire pediatric age range based on three renally excreted drugs using a bodyweight-dependent exponent model, in which the exponent changes depending on bodyweight. This bodyweight-dependent exponent function permits that the exponent gradually changes according to bodyweight and is able to characterize more rapid changes in neonates compared to adults. Previously similar bodyweight-dependent exponential covariate models were developed to scale clearance of propofol [45,46], busulfan [47], midazolam [48] and morphine [49] from neonates until adults. In all these models, a higher exponent was found in neonates and young children (exponent >1) compared to older children and adults as found in the model describing the developmental changes in GFR from neonates (exponent of 1.4) until adults (exponent of 1). In our opinion, the innovative and progressive aspect of the model quantifying the developmental changes in GFR over the pediatric age range, described in this thesis, is that it was based on the combination of three renally excreted drugs, gentamcin, tobramycin and vancomycin allowing for the distinction between drug and system-specific properties [5]. It should however, be highlighted that further research is needed to evaluate the generalizability of the models describing the developmental changes in glomerular filtration in neonates (section II) and from neonates until adults (chapter 9). Since in the current analyses, all drugs have fairly similar physicochemical and pharmacokinetic drug properties, the influence of different physicochemical and pharmacokinetic drug properties to the extrapolation to other drugs should be characterized on the basis of physiologically-based modeling. This was also done in an analysis by Krekels *et al.* [50], in which the influence of differences in physicochemical properties was evaluated on the extrapolation possibilities of the glucuronidation function developed using morphine data. Finally, in a next step, as performed for amikacin in neonates (chapter 3), the final pharmacokinetic models should be used to evaluate the currently used dosing regimens for amikacin, gentamicin, tobramycin, netilmicin and vancomycin in neonates and over the entire pediatric age range. If it appears that the currently used dosing regimen should be revised, new model-based dosing regimens should be developed and tested in a prospective analysis in a similar manner as amikacin (chapter 4).

Although renal function consists of glomerular filtration, active tubular secretion and reabsorption, we primarily focused on describing the maturation in glomerular filtration. Once the developmental changes in GFR were characterized, we hypothesized that this information could be used to describe the developmental changes in tubular processes by studying drugs that are excreted by both GFR and tubular processes. Development of tubular processes starts from 36 weeks of

gestation and continues during childhood [4]. In comparison with glomerular filtration, development of tubular processes is delayed [4,51,52]. For the glomerular filtration rate, it is known that adult levels are reached at approximately 6-12 months of age while for the tubular processes adult levels are not reached until 1-5 years of age [52]. Since large differences are seen in renal function between preterm and term neonates during the first month of life, we decided to initially start with the quantification of the developmental changes in tubular secretion in preterm and term neonates, as performed for GFR using amikacin as a model drug. Since cefazolin is a drug which is both eliminated by GFR and active tubular secretion [8,9], this drug was used as a paradigm compound to quantify the maturational changes in tubular secretion in neonates. To perform this analysis it was supposed that when clearance of cefazolin was higher than the clearance of GFR, it was due to active tubular secretion. Consequently based on these assumptions, the semi-physiological GFR model based on amikacin clearance from chapter 3 was directly incorporated on cefazolin clearance. This implicated that birth weight was implemented on clearance using an allometric function with an exponent of 1.34 as well as postnatal age using a linear function with a slope of 0.213 (chapter 3). Although the population clearance value is considered a drug-specific parameter, it was fixed to the value obtained in the final pharmacokinetic model of amikacin (equation 2). The reason for this approach was that we found in chapter 5, in which the amikacin covariate model reflecting GFR in (pre)term neonates was extrapolated to four other renally excreted drugs, that all initial population values were very similar for all these different drugs. Therefore, in this analysis the initial population clearance value was not estimated but fixed to the value (0.0493 L/h for a neonate with a birth bodyweight of 1750g and a PNA of 2 days) obtained in final pharmacokinetic model of amikacin.

$$CL_i = \underbrace{\{\, CL_{p\ amikacin} \bullet \left(\frac{BWb}{BWb_{Median}}\right)^{1.34} \bullet (1 + (0.213 \bullet \frac{PNA}{PNA_{Median}}))\,\}}_{\text{Developmental changes in GFR based on amikacin clearance}} + \underbrace{\{\, CL_{p\ cefalozin} \bullet \text{Covariates}\,\}}_{\text{Developmental changes in tubular processes}}$$

(Equation 2)

The remaining part was then considered to describe clearance through active tubular secretion. Consequently, to quantify these developmental changes in active tubular secretion, a systematic covariate analysis was performed based on free cefazolin concentrations collected in the 36 preterm and term neonates used for the analysis in chapter 6. Similar to GFR, birth bodyweight and postnatal age were identified as most relevant covariates for active tubular secretion. By fixing the developmental changes of GFR to the results obtained with amikacin, we were able to isolate and quantify the developmental changes in tubular secretion. Table I gives an

Table I: Population pharmacokinetic parameter estimates of the simple model, the final pharmacokinetic model and the bootstrap analysis.

Parameter	Simple model	Final pharmacokinetic model	Bootstrap final pharmacokinetic model
	Value (CV%)	Value (CV%)	Value (CV%)
Fixed effects			
Glomerular filtration			
CL_{GFR} p in $CL_{GFR} = CL_{GFR}$ p x (bBW/median)^{m} x (1+(PNA/median)xn)	0.0493 FIX	0.0493 FIX	0.0493 FIX
m	1.34 FIX	1.34 FIX	1.34 FIX
n	0.213 FIX	0.213 FIX	0.213 FIX
Tubular processes			
CL_{Tub} (L/h) = CL_{Tub} p	0.0848 (31.7)	-	-
CL_{Tub} p in $CL_{Tub} = CL_{Tub}$ p x (bBW/median)^{o} x ((PNA/median)^{p})	-	0.147 (15.0)	0.146 (16.0)
o	-	1.99 (28.8)	2.03 (31.0)
p	-	0.271 (43.5)	0.266 (47.7)
V (L) = Vp	1.86 (8.1)	-	
Vp in V = Vp x (cBW/median)^{q}	-	1.98 (5.5)	1.97 (6.1)
q	-	1.19 (13.1)	1.21 (14.8)
Interindividual variability (ω^2)			
ω^2 CL	0.243 (31.9)	0.12 (37.2)	0.108 (40.1)
ω^2 V	0.253 (31.1)	0.0649 (33.3)	0.06 (36.9)
Residual variability (σ^2)			
σ^2 (proportional)	0.0469 (27.5)	0.0473 (27.3)	0.047 (28.5)

CL_{GFR} = clearance through glomerular filtration, CL_{GFR} p= population value for clearance through GFR, CL_{Tub} = Clearance through tubular processes, CL_{Tub}p= population value for clearance through tubular processes, V = Volume of distribution, Vp = population value for volume of distribution, bBW = bodyweight at birth, cBW = current bodyweight, PNA = postnatal age, median values for the covariate model on GFR are based on the GFR model based on amikacin, median values for the covariate model on tubular processes and volume of distribution are based on the currently used cefazolin dataset

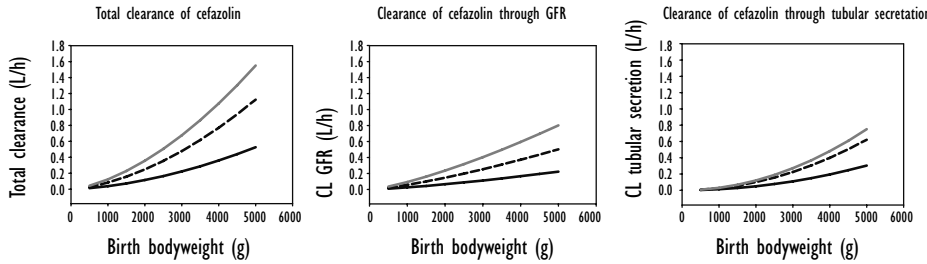


Figure 1: Model-based predicted total clearance (= sum of clearance through GFR and tubular processes) (left), clearance through GFR (based on the developmental changes in GFR seen with amikacin (equation 2) (middle) and clearance through tubular secretion (based on free cefazolin concentrations) (left) of cefazolin *versus* birth bodyweight for postnatal age of 1 (black line), 14 (dotted line) and 28 days (grey line).

overview of the parameter estimates of the simple and final pharmacokinetic model together with the values obtained from the bootstrap analysis. The model-based total clearance (sum of clearance through GFR and tubular processes), clearance through GFR and clearance through tubular processes of cefazolin *versus* birthweight for PNAs of 1, 14 and 28 days is illustrated in figure 1. Figure 1, in which clearance through tubular processes is illustrated *versus* birth bodyweight for PNAs 1, 14 and 28, indicates that the largest increase in tubular secretion is seen during the first 14 days. This may be explained by the upregulation of transporters (organic anion or cation transporters) in the kidney during the perinatal period to compensate the increased concentrations of various compounds after birth. Furthermore, this figure illustrates a lower clearance of cefazolin by tubular processes compared to glomerular filtration in neonates below 3.5 kg during the first 14 days. However, in neonates with a birth bodyweight above 3.5 kg the tubular clearance of cefazolin seem to transcend the glomerular filtration. Nevertheless on day 28, glomerular filtration is the most important elimination route of cefazolin in all neonates, which corresponds well with previously reported results that renal tubular development is delayed compared to GFR. The applicability of this model in which the developmental changes in tubular secretion were characterized in preterm and term neonates should subsequently be tested using other renally excreted drugs, which are undergoing both glomerular filtration as tubular processes. Finally in next step the maturational changes in tubular secretion should be described from neonates until adults. To perform that analysis and to be able to characterize the developmental changes in tubular secretion over the pediatric age range, the model described in chapter 9 can be used as a basis as this model is describing the developmental changes in GFR across the pediatric age range.

In summary we can claim that the developmental changes in glomerular filtration were described from preterm and term neonates to adults using a system-based pharmacology approach [5]. This implicated that a distinction was made between system-specific and drug-specific properties making it possible to extrapolate information of one drug to another drug. Further studies need to be performed to evaluate to what extent this approach is applicable to other drugs with different physicochemical drug properties. The preferred approach to perform this analysis is by the use of physiologically-based pharmacokinetic modeling approaches because this allows for simulations for a variety of drugs and physiological situations. Furthermore, the developmental changes in the other subprocesses that contribute to renal clearance (tubular secretion and reabsorption) should be characterized across the entire pediatric age range. To perform the latter analyses, the models describing the developmental changes in GFR can be used as a basis. The transition to a more system-based pharmacology approach and the combination of different strategies (extrapolation to other drugs, adult data or non-clinical data) will result in an approach focusing on the underlying system instead of focusing on the drugs and may facilitate development of pharmacokinetic models and evidence-based dosing regimens in the pediatric population.

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