Novel approach to characterize developmental changes in pharmacokinetics across the human lifespan: application to the prediction of clearance in children

Wang, C.

Chapter 7

Scaling of clearance across the human life span from neonates to adults: conclusions and perspectives

7.1. Introduction

Drug treatment is more difficult in children than in adults. The wide variation in various physiological processes in children leads to a wide variation in treatment response and this warrants an individualized approach to drug treatment in this vulnerable group of patients. Identifying the optimal dose is the key element of a good drug treatment practice for children. At present dose adjustment on the basis of milligram per kilogram of body weight is still widely used. However, dose selection in children should be based on pertinent information with regard to the variation in pharmacokinetics and pharmacodynamics as the key determinants of the drug effect. In that regard also disease and other factors need to be taken into account [1-4].

Interindividual variation in pharmacokinetics and pharmacodynamics in the paediatric population is the result of complex physiological changes during growth and development. Clearance is one of the most important pharmacokinetic parameters of which the value needs to be known for rational dose adjustment. However, collecting blood samples for pharmacokinetic studies in children is not easy and the information available for estimation of drug clearance in children is typically scarce. Therefore, scaling of drug clearance with pharmacokinetic modeling techniques (between adults and children or within paediatric populations) is of great interest for both clinical practice and drug development in pediatrics [4]. In general, there are two modeling approaches to the description of pharmacokinetics: the population pharmacokinetic (POPPK) modeling approach and the physiologically based pharmacokinetic (PBPK) modeling approach. POPPK modeling is a data-driven method aiming at the fitting of pharmacokinetic models to observed drug concentrations, while PBPK modeling is a physiological knowledge based method aiming to predict pharmacokinetics based on pertinent information on the variation in the underlying processes.

To date, for the scaling of drug clearances under the POPPK approach three modeling approaches are used: i) allometric scaling, ii) allometric scaling with a fixed exponent value of 0.75 combined with an age based maturation function, and iii) systematic covariate analysis. As neither allometric scaling nor allometric scaling plus an age-based maturation model can describe the developmental

changes in drug clearance with adequate statistical stability and predictive performance across the entire age-span, we explored, in a systematic covariate analysis, the utility of novel functions to describe developmental changes in clearance across the entire human life span. As bodyweight was found to be the best descriptor for drug clearance across different pediatric age groups in many studies, the research in this thesis focused on the identification of novel functions to describe the changes in drug clearance across the whole life span on the basis of bodyweight without additional covariates.

7.2. The observation of different values for the allometric exponent

The objective of the research described in **Chapter 3** was to explore the variation in the value of the allometric exponent for children in different age groups in a systematic covariate analysis. To this end a large database with pertinent information on the pharmacokinetics of propofol across the human lifespan was established. Data from seven propofol studies were included in the analysis (neonates, infants, toddlers, children, adolescents, adults1, and adults2). In a systematic manner, two out of the six study populations were randomly combined resulting in 15 combined datasets. In addition, the data of the seven studies were regrouped into five age-groups (according to FDA Guidance 1998), from which four combined datasets were prepared consisting of one paediatric age-group and the adult group. In each of these 19 combined datasets, the allometric scaling exponent for clearance was estimated using population pharmacokinetic modelling (NONMEM 7.2).

The results of this study show a large variety in the value of the allometric exponent for clearance with values ranging from 0.2 to 2.01 when analyzing combined datasets of two paediatric populations. While the lowest values of the exponent of 0.2 was identified between infants and toddlers, the highest exponent of 2.01 was found between neonates and infants. These findings show that there is no single unique value of the allometric exponent that can describe the variation in clearance across the human age-span. This implies that especially in the pediatric age range, the widely applied ¾ allometric function is inappropriate to describe and predict drug clearance in preterm

and term neonates, infants and young children. Also in literature, this function was found to systematically over-predict clearance for neonates and under-predict clearances for infants [5-8]. There are indications that the results found for propofol in this chapter, apply to other drugs as well. For example, the value of the exponent of 0.88 for propofol in toddlers and children (model 10), appears to be in good agreement with findings on oxycodone clearance in children aged between 6 months to 7 years, where a value of the allometric exponent of 0.875 has been reported [9]. It is concluded that for the scaling of clearance between two paediatric populations, the allometric exponent needs to be estimated rather than fixed to the value 0.75 in order to account for differences in maturation between different age groups, since the values appear to be highly varyiable. However, as with increasing age the estimated allometric scaling line moved slowly towards 0.75 (**Chapter 3**, **Figure 3-3 B** to **E**), it seems that ¾ allometric scaling function may be of value in older children (>4 years) towards adults.

7.3. Exploring a novel descriptive model for the scaling of the clearance of propofol

In **Chapter 4**, we tested four different models based on different allometric equations, to capture changes in propofol clearance in the complete dataset from chapter 3 comprising almost every stage of human life. The four different models were: model I - 3/4 allometric scaling model; model II- mixture model; model III - bodyweight-cut-point separated model and model IV - bodyweight-dependent exponent model. We found that fixing of the allometric exponent to the value of 0.75 (the ¾ allometric model; model I) resulted in an adequate description of the variation in clearance in adults, adolescents, children and toddlers, but that it yielded a significant under-prediction in infants and an over-prediction in term and preterm neonates. The results of the mixture model (model II) and the bodyweight-cut-point separated model (model III) showed that a value of the allometric exponent different from 0.75 is more suitable for neonates and infants. In fact, both models identified an allometric exponent larger than 1 for the subpopulation that was composed of mainly neonates and infants, resulting in improved description of clearance in these youngest patients with the lowest body weight in comparison to the ¾ allometric model.

This has been reported before for morphine clearance in children younger than 3 years of age, where a value of the allometric exponent of 1.44 was found to best describe the developmental changes in clearance [10]. Similarly, Mahmood reported that the error in the prediction of clearance decreased when the scaling exponent increased from 0.75 towards 1 when studying a range of different drugs in children younger than 1 year of age [11].

Even though the overall performance improved significantly, the use of two different allometric exponents for different human subpopulations as implemented in model II and model III resulted in ambiguous clearance predictions for the individuals on the boundaries of the pediatric subpopulations. Therefore, in this study, a novel approach to the description of the variation in clearance across the entire life span was introduced, which is based on an allometric equation with an exponent that varies in a continuous manner with bodyweight (model IV). This bodyweight-dependent exponent (BDE) model contains a sigmoidal function to describe the change in the value of the allometric exponent with bodyweight. It is shown that this function allows for the best description of maturational changes in propofol clearance across the entire human life span. For propofol clearance, the exponent was found to decrease in a sigmoidal manner with bodyweight from 1.34 to 0.55, with half the decrease in exponent reached at a body weight of 3.78 kg. It was also illustrated that the BDE function is flexible in capturing very different shapes of the relation between clearance and bodyweight (**Figure 7-1**).

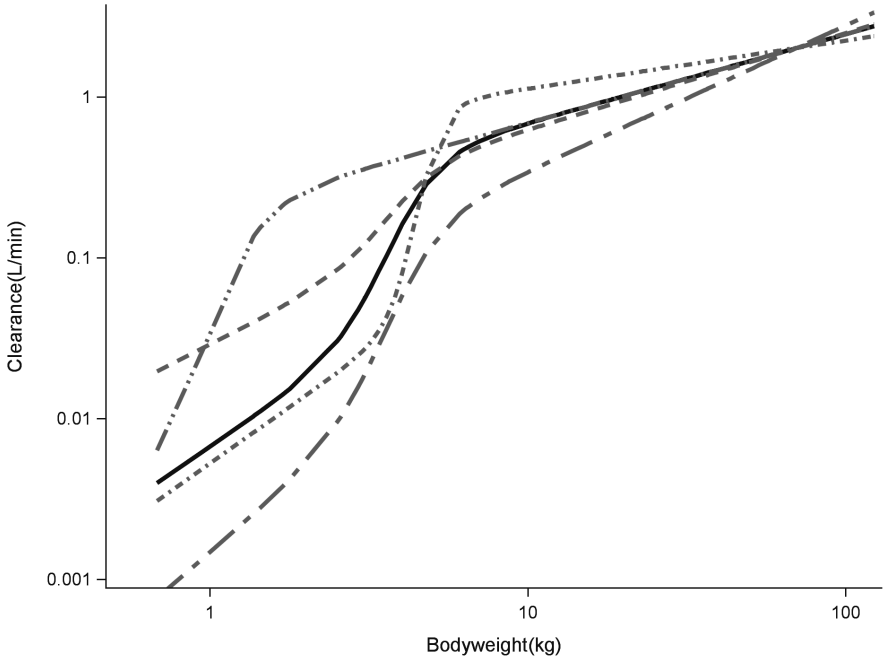

Figure 7-1 Simulations for the bodyweight-dependent exponent (BDE) model for scaling clearance $\left(\mathbf{Cl_i} = \mathbf{Cl_p} \times \left(\frac{\mathbf{BW_i}}{\mathbf{70}}\right)^{\mathbf{k}}\ \mathbf{k} = \mathbf{k_0} - \frac{\mathbf{k_{max}} \times \mathbf{BW_i^{\gamma}}}{\mathbf{k_{50}^{\gamma}} + \mathbf{BW_i^{\gamma}}}\right)$ on the basis of different values for the parameters of the bodyweight-dependent exponent $\left(\mathbf{k} = \mathbf{k_0} - \frac{\mathbf{k_{max}} \times \mathbf{BW_i^{\gamma}}}{\mathbf{k_{50}^{\gamma}} + \mathbf{BW_i^{\gamma}}}\right)$.

Solid black curve: BDE model predicted clearance curve with k_0 = 1.34, k_{max} = 0.79, k_{50} = 3.78, γ= 5.24 (final PK model of Chapter 4); dashed grey curve: BDE model predicted clearance curve with k_0 = 1, k_{max} = 0.4, k_{50} = 3.78, γ= 5; long dash short dash grey curve: BDE model predicted clearance curve with k_0 = 1.7, k_{max} = 0.8, k_{50} = 3.78, γ= 5; short dash dot grey curve : BDE model predicted clearance curve with k_0 =1.4, k_{max} = 1.1, k_{50} = 4.5, γ= 10; medium dash double dot grey curve: BDE model predicted clearance curve with k_0 = 1.34, k_{max} = 0.8, k_{50} = 1, γ= 5.

7.4. Applying the novel BDE model to morphine and morphine-3-glucuronide

In **Chapter 5**, the novel bodyweight-dependent exponent model was applied to characterize the developmental changes in morphine clearance across the entire pediatric age-range. To this end, morphine and morphine-3-glucuronide (M3G) concentration data from 358 (pre)term neonates, infants, children and adults, and morphine concentration data from 117 adolescents were analyzed using NONMEM 7.2. Based on available data, two models were developed: i) a

model using morphine data only (model 1) and ii) using morphine and M3G data (model 2). In model 1, morphine clearance across the pediatric age range was very well described by a bodyweight-based exponential function in which the allometric exponent decreased in a sigmoidal manner with bodyweight (BDE model) from 1.47 to 0.88, with half the decrease in the value of the exponent reached at a body weight of 4.01 kg. In model 2, the exponent for the formation and elimination clearance of M3G was found to decrease from 1.56 to 0.89 and from 1.06 to 0.61, with half the decrease reached at body weights of 3.89 and 4.87 kg, respectively. Using the BDE model, there was no need to use additional covariates to account for size or age. These study results not only confirmed the model results based on children less than 3 years in which an exponent of 1.44 was identified [10], but also provides a basis for extrapolation to older age-ranges by the quantification of the maturation of glucuronidation across the entire pediatric age-range with the estimation of a lower exponent for higher bodyweight ranges. Moreover, it seems that applying an allometric function in which the exponent is allowed to vary with bodyweight itself results in an optimal description of the varying rates of maturation of glucuronidation clearance of morphine across all age ranges without the need for additional age-based covariates (PNA <> 10 days) that were reported when a single allometric exponent is used [10, 12, 13] (**Chapter 5**, **Figure 5-5**).

7.5. Using the novel BDE model for paracetamol

In **Chapter 6**, we further tested the BDE model for describing variation in paracetamol clearance across whole paediatric age-span. A total of 220 subjects from eight previously published studies on paracetamol pharmacokinetics were included in the analysis, including (pre)term neonates, infants, children and adults. Population pharmacokinetic modelling was performed using NONMEM 7.2. In the covariate analysis for clearance, linear functions, power functions and a power function with a bodyweight-dependent exponent were tested. It was clearly shown that the BDE model describes the age-related changes in clearance of paracetamol across the human life span best, and without the need for inclusion of additional age variables as a covariate. For clearance, the exponent was found to decrease in a sigmoidal manner with bodyweight from 1.2 to 0.75, with half the decrease in exponent reached at a

body weight of 12.2 kg. Based on the final model, simulations were performed to derive optimized dosing guidelines across the entire paediatric age range. In this respect, a model based intravenous paracetamol dose calculation table for children was provided aiming for similar paracetamol exposure across the paediatric age range. This is of particular relevance because there is yet no dosing information on paracetamol iv in preterm neonates (Europe) or in children younger than 2 years of age (US).

7.6. Perspectives

7.6.1. The best descriptive predictor for clearance

In this thesis, an important question was how to accurately describe maturation in clearance across the human life span. A complicating factor in the analysis of age-related changes in pharmacokinetics is the correlation between covariates that can be used as the basis for the description of maturation. Specifically the covariates bodyweight and age are correlated during growth and development of a child. Bodyweight is often referred to as measure of size only, whereas age is referred to as a measure of maturation. The relationship between age and bodyweight has been investigated by demographic surveys. Based on these survey results, growth charts have been developed. In **Figure 7-2**, data from the CDC growth chart percentiles table (http://www.cdc.gov/growthcharts/data/zscore/) are plotted in four panels demonstrating the relationship between weight and age for boys and girls younger or older than 2-3 years of age. These graphs show that between birth and adulthood the relation between age and bodyweight is highly non-linear.

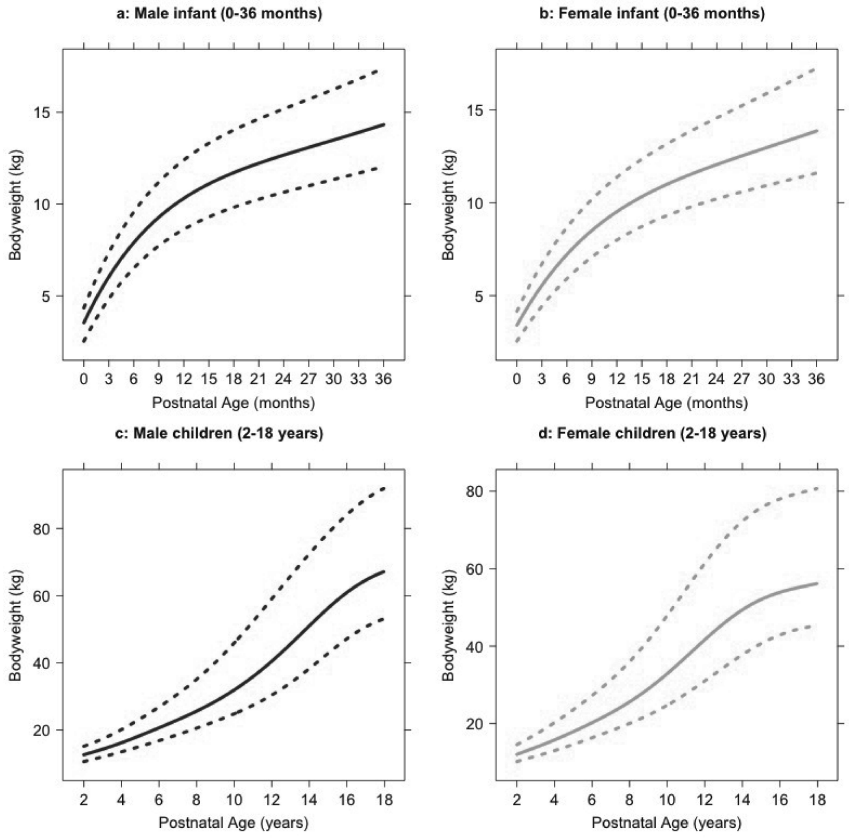

Figure 7-2 CDC growth chart plot (5%, 50% and 95% percentile) for different age-ranges divided by gender based on CDC percentiles table (http://www.cdc.gov/growthcharts/data/zscore/).

However, for neonates, in particular when both prematurely born neonates and term neonates are considered, the correlation between weight and postnatal age may not be that obvious. **Figure 7-3** shows a plot of body weight against postnatal age (PNA), postmenstrual age (PMA), gestational age (GA) with the corresponding Pearson's Correlation Coefficient values in 874 preterm and term neonates from a previous publication of our group [14]. The plot shows that bodyweight is highly correlated with PMA or GA, and that there is less correlation between bodyweight and PNA. In PBPK models, postnatal age instead of bodyweight is typically used as a basis for maturation functions in paediatrics. However, it seems from these results that in neonates, bodyweight, PMA or GA instead of PNA is preferred to describe maturation in clearance across the human age range.

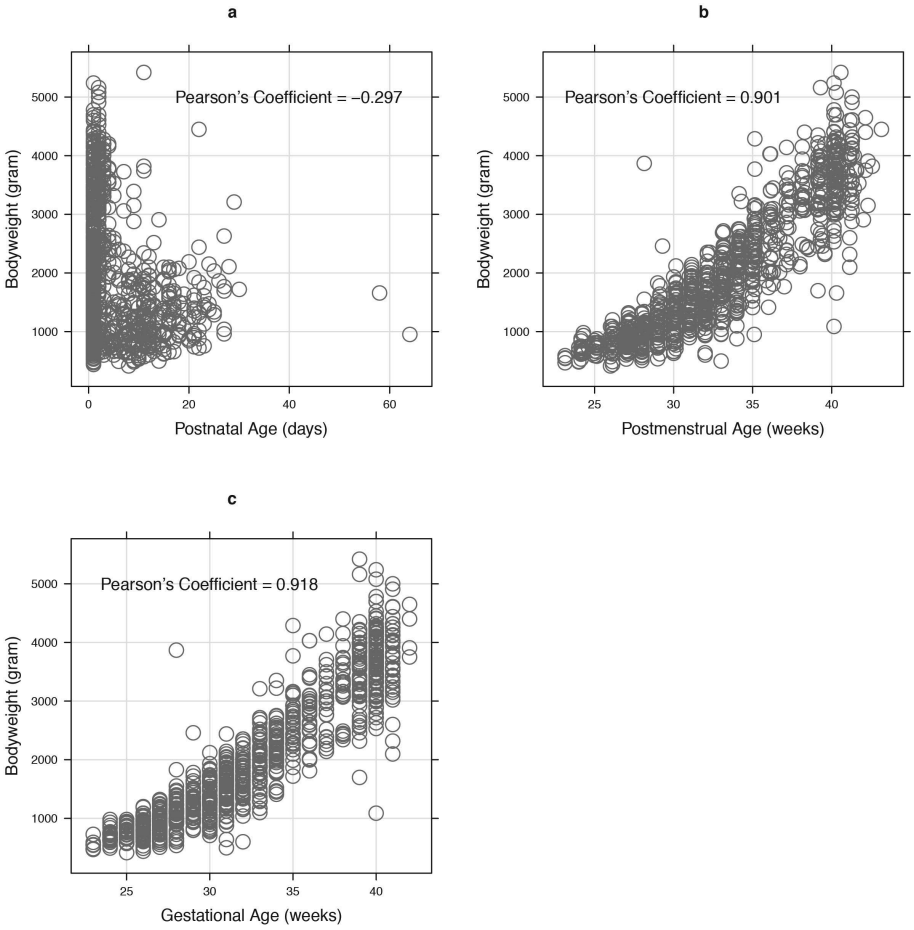

Figure 7-3 Scatter plots of bodyweight against postnatal age (PNA), postmenstrual age (PMA) and gestational age (GA) in 874 preterm and term neonates [14].

For scaling clearance across the pediatric age-range with inclusion of preterm and term neonates, we found in this thesis, that the bodyweight based scaling approach (BDE model) can describe the changes in drug clearance without the need for additional (age-related) covariates. We think that this can be explained by the fact that the BDE model is highly flexible in nature and can capture many different nonlinear relations between bodyweight and clearance (**Figure 7-1**). Describing changes in clearance across the human age range on the basis of one covariate only seems of importance as the implementation of two (correlated) covariates on one parameter may lead to bias in parameter estimates [15]. After

implementation of the BDE function it was found that age variables have no influence on inter-individual variability in clearance of propofol, morphine and paracetamol. In previous studies in which a fixed exponent was used, very often other covariates were needed to obtain an optimal description of the data, as was reported for morphine under the age of 3 years for instance [10, 16]. From these results, it is concluded that body weight may play a role as a surrogate of different age variables (PNA, PMA, or GA) across the whole pediatric age-span. Eventually, the influence from both weight and age on clearance is explained by an advanced BDE equation with bodyweight as the only covariate. Results from this thesis on propofol (**Chapter 3** and **Chapter 4**), morphine (**Chapter 5**), paracetamol (**Chapter 6**), busulfan (**Appendix I**) and midazolam (**Appendix II**) show that the BDE model can result in adequate prediction of clearance across the entire pediatric age-span. From a model diagnostic point of view, the BDE model has adequate goodness-of-fit properties for different age groups and has good empirical Bayes estimates (EBE) diagnostics. Besides, the BDE model also allows for a weight based dose recommendation, as was shown for paracetamol in **Chapter 6**. Therefore, we conclude that bodyweight alone can be used as descriptor for clearance across the human age range, provided advanced functions such as the BDE model are applied, and the results are confirmed by proper validations [17].

7.6.2. Full or simplified BDE function?

In this thesis we present the BDE model to describe maturation of clearance across the human life span for three drugs propofol (**Chapter 4**), morphine (**Chapter 5**), paracetamol (**Chapter 6**). In the meantime the model has also been applied to busulfan (**Appendix I**), midazolam (**Appendix II**) and a number of antibiotics (gentamicin, tobramycin and vancomycin; unpublished observations). The BDE model was developed based on a sigmoidal equation that was initially derived for propofol (**Chapter 4**). Later on, it was simplified to a power equation for busulfan, midazolam and antibiotics. **Table 7-1** shows the BDE equations and the corresponding parameter estimates that were idenfified in those studies. In studies of propofol, morphine and paracetamol, for the exponent BDE or k a sigmoidal equation

$$Cl_i = Cl_p \times \left(\frac{BW_i}{70}\right)^k \;,\; k = k_0 - \frac{k_{max} \times BW_i^\gamma}{k_{50}^\gamma + BW_i^\gamma} \qquad (1)$$

was used in the BDE model, albeit with the identification of different parameter estimates for k (or the bodyweight dependent exponent). **Table 7-1** shows that all estimates of the parameter k_0 were found to be greater than 1 in studies for propofol, morphine and paracetamol (1.35, 1.56 and 1.2 respectively). Besides, k_{max}, which represents the decrease in k from k_0 at the hypothetical body weight of 0 kg, was found to vary between drugs (0.79, 0.67 and 0.45 for propofol, morphine and paracetamol, respectively) even though at adulthood similar values for k were observed (0.56, 0.89, and 0.75 at a weight of 70 kg) (**Table 7-1**, **Figure 7-4 a**). Concerning the parameters k_{50} and γ, for propofol and morphine, we observed an early and steep decrease in *k* with corresponding estimates of k_{50} = 3.71 kg, γ = 5.1 and k_{50} = 3.89 kg, γ = 3.61, respectively (**Figure 7-4 a**), which results in a stair-climbing pattern of increase in clearance over bodyweight from newborn babies to adults on a log-log scale (**Figure 7-4 b**). However, this decrease in *k* appears to be much slower for paracetamol with corresponding estimates for k_{50} = 12.2 kg and γ = 1.2 (**Figure 7-4 a**), resulting in a water-overflowing pattern of increase in clearance over bodyweight from newborn babies to adults in a log-log scale (**Figure 7-4 b**).

In studies on busulfan, midazolam and antibiotics, a power equation

$$Cl_i = Cl_p \times \left(\frac{BW_i}{70}\right)^k, k = L \times BW^M \quad (2)$$

was used in the BDE model (**Table 7-1**, **Figure 7-4 c**). The decrease in *k* over bodyweight for those drugs is rather slow compared to previous three drugs, although the magnitude in decrease varies very much among those five drugs (**Figure 7-4 c**). In contrast to the sigmoidal BDE function, which is highly flexible (**Figure 7-1**), the simplified power BDE equation lacks the flexibility of capturing different shapes with a trade-off of stable model estimates. Obviously, the simplified BDE model is preferred because of the parsimonial rule (estimation of 2 parameters instead of 4 parameters for k, **Table 7-1**). In our analysis, the simplified model was selected for busulphan for which no data from preterm and term neonates were available (**Figure 7-4 c,d**, **Table 7-1**). However, also for midazolam the simplified BDE equation was able to capture changes in clearance, even though the study covered the whole life span including preterm and term neonates. We think that this may be explained by the pathway that is involved, which is CYP3A oxidation in case of midazolam.

As such, beside the age range studied, the pathway involved may determine whether a simplified or a sigmoidal BDE function is needed. The study of three antibiotics is another example of the identification of a simplified or power BDE equation across the whole age-span, in this case for drugs that are all eliminated through Glomerular Filtration Rate (GFR). Although the three curves of *k* and clearance versus bodyweight in the antibiotics study were different from those identified for midazolam and busulfan, no large differences were found between these three antibiotics (**Figure 7-4 c,d**, **Table 7-1**). Given the fact that these three antibiotics are all eliminated through the same pathway (GFR), this finding may provide the basis for the extrapolation of this simplified BDE model to other drugs eliminated through GFR. This is an approach that has been proposed before [3] and was applied for glucuronidation as well [18].

Table 7-1 Summary of all studies in which the bodyweight-dependent exponent (BDE) model $\left(\mathbf{Cl_i = Cl_p \times \left(\frac{BW_i}{70}\right)^k}\right)$ was used for scaling clearance from adults to children with either a sigmoidal or a power equation for k.

Drug	Equation for BDE (*k*)	k_0	k_{max}	k_{50}(kg)	γ	*L*	*M*	Elimination pathway	Age and BW
propofol[1]		1.35	0.79	3.71	5.1			glucuronidation UGT1A9 & sulfation	PNA: Birth – 81 yrs BW: 0.68 – 122.7 kg
morphine[2]	$k = k_0 - \frac{k_{max} \times BW_i^{\gamma}}{k_{50}^{\gamma} + BW_i^{\gamma}}$	1.56	0.67	3.89	3.61			glucuronidation UGT2B7	PNA: Birth – 36 yrs BW: 0.56 – 85 kg
paracetamol[3]		1.2	0.45	12.2	1.2			glucuronidation UGT1A6 & sulfation	PNA: Birth – 34 yrs BW: 0.505 – 94 kg
busulfan[4]						1.56	-0.226	glutathione S-transferase	PNA: 0.1 – 26 yrs BW: 3 – 65 kg
midazolam[5]						0.81	-0.135	CYP3A	PNA: Birth – 31 yrs BW: 0.77 – 89 kg
gentamicin[6]	$k = L \times BW^M$					2.6	-0.093	Glomerular Filtration Rate (GFR)	PNA: Birth – 15 yrs BW: 0.44 – 80 kg
tobramycin[6]						2.67	-0.079	Glomerular Filtration Rate (GFR)	PNA: 2 days – 18 yrs BW: 0.485 – 85 kg
vancomycin[6]						2.12	-0.065	Glomerular Filtration Rate (GFR)	PNA: Birth – 17 yrs BW: 0.415 – 85 kg

[1] Chapter 4 in this thesis
[2] Chapter 5 in this thesis
[3] Chapter 6 in this thesis
[4] Appendix I in this thesis
[5] Appendix II in this thesis
[6] Unpublished results

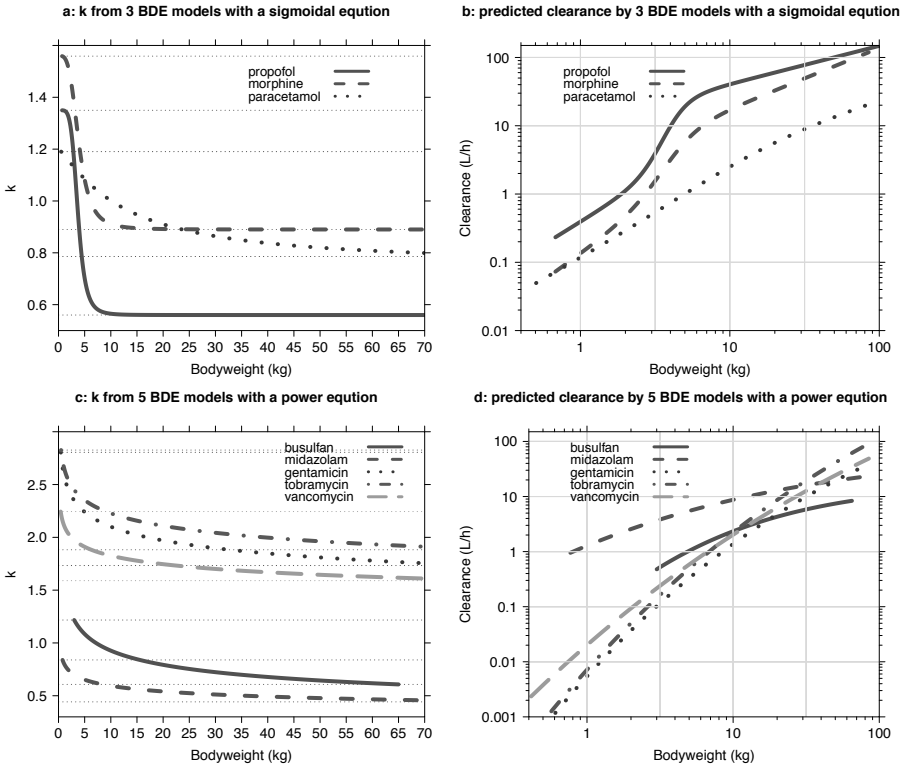

Figure 7-4 Bodyweight-dependent exponent (BDE or k) (panels a and c) and clearance $\left(\mathbf{Cl_i = Cl_p \times \left(\frac{BW_i}{70}\right)^k}\right)$ (panel b and d) versus bodyweight for the models derived for propofol, morphine and paracetamol in which a sigmoidal function $\left(\mathbf{k = k_0 - \frac{k_{max} \times BW_i^\gamma}{k_{50}^\gamma + BW_i^\gamma}}\right)$ for k was used (panel a and b) and for the models derived for busulfan, midazolam, gentamicin, tobramycin and vancomycin in which a simplified (or power) function $\left(\mathbf{k = L \times BW^M}\right)$ for k was used (panel c and d). For specific estimates see Table 7-1.

7.6.3. Physiologically based pharmacokinetic modeling in pediatrics

At present there is an increasing interest in the application of physiologically based pharmacokinetic (PBPK) modeling in paediatric drug development. In PBPK modeling, the human body is considered to be composed of multi-compartments representing actual organs and other physiological spaces. Mass balance equations for each organ describe drug distribution in the organ from arterial blood and its exit into venous blood. The PBPK model is parameterized in relevant drug specific parameters (e.g. LogP and pKa) and biological system

specific parameters (e.g. tissue volumes, the perfusion rates of these tissue compartments, the concentration of binding proteins, the values of the activities of drug metabolizing enzymes, the expression and function of transporters in the excretion). The use of PBPK models for prediction of pharmacokinetics in children from information in adults requires information on the change in the values of the system specific parameters across the paediatric life span. The common approach is to modify a PBPK model that has been validated with adult PK data and then to incorporate the differences in growth and maturation that can affect all system specific parameters. In PBPK modeling, information on the values of the changes in system specific parameters is typically obtained from *in vitro* studies, which is often not available for children of all age ranges including preterm and term neonates. Here we propose to use information from our descriptive BDE models for different metabolic or elimination pathways on the change in for example intrinsic clearance as a measure of developmental changes in system specific parameter in PBPK models. Given the fact that the *in vitro* data are extremely scarce in preterm neonates, the information from BDE model may be specifically helpful for this population. Recently, Krekels *et al*. explored such application of the POPPK model in describing developmental changes of UGT2B7-mediated glucuronidation parameters [19]. In the end, they suggested that the maturation profile for UGT2B7 ontogeny in a PBPK model can be improved based on information obtained from a covariate model of a paediatric population model derived for a specific substrate for UGT2B7 on the basis of a systematic covariate analysis [19]. Further studies on using POPPK (covariate) models in adjusting PBPK models for improving the simulation performance of PBPK models in pediatric drug development are encouraged.

7.7. Conclusion

In this thesis, we propose the body weight dependent exponent (BDE) model as novel approach for describing drug clearance over the entire pediatric age-span. This provides us an alternative approach to the previous "weight plus age" approach with better statistical properties. The model offers the advantage of much improved clearance estimates of drugs in clinical practice enabling the prediction of the individualized dose in children, particularly neonates. Moreover, the model provides a basis for the incorporation of information on

the maturation of clearance from *in vivo* studies into physiologically-based pharmacokinetic models for the prediction of developmental changes in clearance for novel drugs. These predictions constitute the scientific basis for optimized clinical trial designs for studies in pediatrics.

References

1. Cella M, Knibbe C, Danhof M, Della Pasqua O. What is the right dose for children? Br J Clin Pharmacol 2010; 70: 597-603.
2. Knibbe CA, Danhof M. Individualized dosing regimens in children based on population PKPD modelling: are we ready for it? International journal of pharmaceutics 2011; 415: 9-14.
3. Knibbe CA, Krekels EH, Danhof M. Advances in paediatric pharmacokinetics. Expert opinion on drug metabolism & toxicology 2011; 7: 1-8.
4. De Cock RF, Piana C, Krekels EH, Danhof M, Allegaert K, Knibbe CA. The role of population PK-PD modelling in paediatric clinical research. Eur J Clin Pharmacol 2011; 67 Suppl 1: 5-16.
5. Bjorkman S. Prediction of cytochrome p450-mediated hepatic drug clearance in neonates, infants and children : how accurate are available scaling methods? Clin Pharmacokinet 2006; 45: 1-11.
6. Peeters MY, Allegaert K, Blusse van Oud-Alblas HJ, Cella M, Tibboel D, Danhof M, Knibbe CA. Prediction of propofol clearance in children from an allometric model developed in rats, children and adults versus a 0.75 fixed-exponent allometric model. Clin Pharmacokinet 2010; 49: 269-75.
7. Mahmood I. Evaluation of Sigmoidal Maturation and Allometric Models: Prediction of Propofol Clearance in Neonates and Infants. American journal of therapeutics 2011.
8. Edginton AN, Willmann S. Physiology-based versus allometric scaling of clearance in children; an eliminating process based comparison. Paed Perinat Drug Ther 2006; 7: 146–53.
9. El-Tahtawy A, Kokki H, Reidenberg BE. Population pharmacokinetics of oxycodone in children 6 months to 7 years old. J Clin Pharmacol 2006; 46: 433-42.
10. Knibbe CA, Krekels EH, van den Anker JN, DeJongh J, Santen GW, van Dijk M, Simons SH, van Lingen RA, Jacqz-Aigrain EM, Danhof M, Tibboel D. Morphine glucuronidation in preterm neonates, infants and children younger than 3 years. Clin Pharmacokinet 2009; 48: 371-85.
11. Mahmood I. Prediction of drug clearance in children from adults: a comparison of several allometric methods. Br J Clin Pharmacol 2006; 61: 545-57.
12. Bouwmeester NJ, Anderson BJ, Tibboel D, Holford NH. Developmental pharmacokinetics of morphine and its metabolites in neonates, infants and young children. Br J Anaesth 2004; 92: 208-17.
13. Anand KJ, Anderson BJ, Holford NH, Hall RW, Young T, Shephard B, Desai NS, Barton BA. Morphine pharmacokinetics and pharmacodynamics in preterm and term neonates: secondary results from the NEOPAIN trial. Br J Anaesth 2008; 101: 680-9.
14. De Cock RF, Allegaert K, Schreuder MF, Sherwin CM, de Hoog M, van den Anker JN, Danhof M, Knibbe CA. Maturation of the glomerular filtration rate in neonates, as reflected by amikacin clearance. Clin Pharmacokinet 2012; 51: 105-17.
15. Bonate PL. The effect of collinearity on parameter estimates in nonlinear mixed effect models. Pharm Res 1999; 16: 709-17.
16. Krekels EH, DeJongh J, van Lingen RA, van der Marel CD, Choonara I, Lynn AM, Danhof M, Tibboel D, Knibbe CA. Predictive performance of a recently developed population pharmacokinetic model for morphine and its metabolites in new datasets of (preterm) neonates, infants and children. Clin Pharmacokinet 2011; 50: 51-63.
17. Krekels EH, van Hasselt JG, Tibboel D, Danhof M, Knibbe CA. Systematic evaluation of the descriptive and predictive performance of paediatric morphine population models. Pharm Res 2011; 28: 797-811.
18. Krekels EHJ, Neely M, Panoilia E, Tibboel D, Capparelli E, Danhof M, Mirochnick M, Knibbe CAJ. From Pediatric Covariate Model to Semiphysiological Function for Maturation: Part I-Extrapolation of a Covariate Model From Morphine to Zidovudine. CPT: pharmacomet syst pharmacol 2012; 1: e9.
19. Krekels EHJ, Johnson TN, den Hoedt SM, Rostami-Hodjegan A, Danhof M, Tibboel D, Knibbe CAJ. From Pediatric Covariate Model to Semiphysiological Function for Maturation: Part II-Sensitivity to Physiological and Physicochemical Properties. CPT: pharmacomet syst pharmacol 2012; 1: e10.