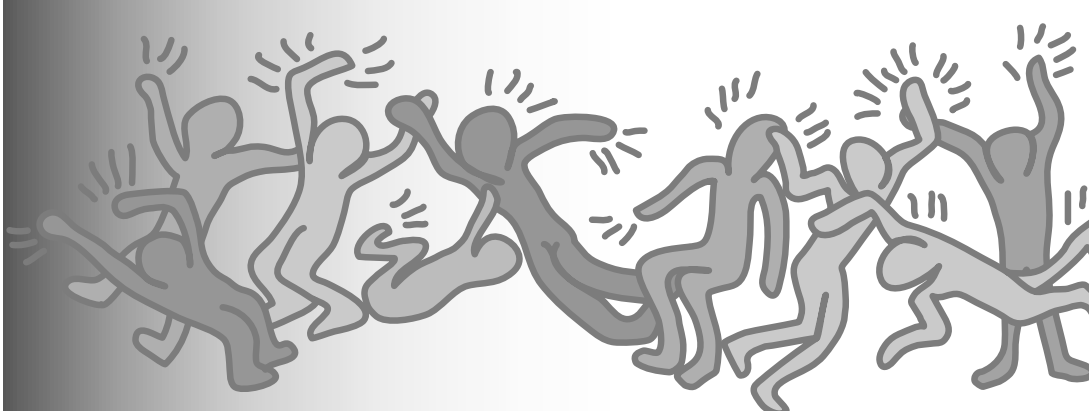
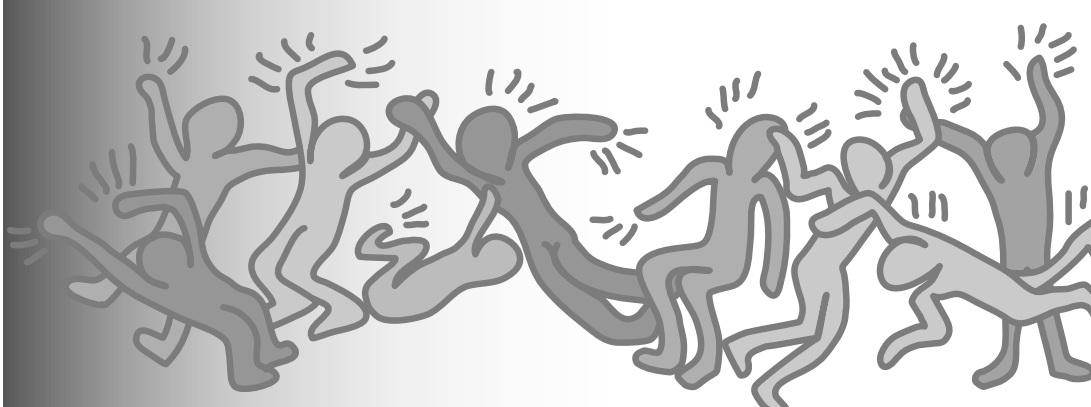
Section I

Background and Introduction



Chapter 1

Scope and Outline



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

The response to drugs may be different in children compared to adults. Notwithstanding these differences, to date, evidence-based drug dosing algorithms are often lacking in the pediatric age range [1-4]. This can be explained by ethical, practical and economical issues which may seriously impede the design and implementation of pediatric clinical trials [2, 4, 5]. Consequently, drug doses for children are often empirically derived from adult dosing guidelines based on bodyweight or age, irrespective the physiological differences due to developmental changes [1, 3, 6-8]. Despite the shortcomings of empirically scaling from adult dosing regimen to children, it is still the most commonly used approach which may result in therapeutic failure [9] or occurrence of toxic effects [10-13].

These differences in drug response between children and adults may be caused by differences in pharmacokinetics (PK), pharmacodynamics (PD) or both. While a child grows, differences are seen in body composition, maturation of drug metabolizing enzymes, cardiac output, blood flow and functionality of the drug eliminating organs liver and kidneys. All these differences are seen as potential sources influencing the pharmacokinetics of drugs [14]. Furthermore, developmental changes in the functionality and expression of receptors and differences in disease status may alter the pharmacodynamics and therefore the pharmacological response to drugs [14, 15]. In order to develop rational evidence-based dosing schemes in children, these developmental changes in pharmacokinetics and pharmacodynamics need to be characterized.

To counterbalance the lack of information on PK and PD of drugs in children, the Pediatric Regulation (EMA) came into force in Europe [16]. The main aim of this regulation was to facilitate the development and availability of drugs for children. Furthermore, funding by the European Union became available to promote research of off-patent drugs in children. As a result a large increase was seen in the number of PK and/or PD studies in children, potentially leading to evidence-based and individualized dosing schemes in children. However, despite the efforts of the industry and academia to perform research in children, most of the drugs in pediatrics are still used in off-label or unlicensed manner [1, 3, 4].

Performing PK/PD studies in the pediatric age range is very challenging. Besides

the fact that only a limited number of children is available, since studies are only performed in children suffering from a particular disease, also ethical, practical and economical issues occur (e.g. limited number and volume of blood samples). In addition to the use of very sensitive analysis techniques which require only a very small blood volume, advanced statistical tools are needed so that the burden for each child is kept to a minimum while still addressing the study objective: the development of rational, evidence-based and individualized dosing regimens in children. Consequently, the population approach using non-linear mixed effect modeling is the preferred approach since all data of all patients are simultaneously analyzed while still taking into account that different observations originate from different patients. An important advantage of this approach is that it allows the analysis of dense but also sparse and unbalanced data, which is often encountered in clinical practice. Furthermore by using this approach both the inter- and intra-individual variability can be estimated separately [17, 18]. Finally specific predictors of variability also called covariates, in PK or PD can be identified which subsequently can be used to determine new evidence-based and individualized dosing regimens [19-22].

However, if for each drug, models needs to be developed and validated over the entire pediatric age range to obtain rational, evidence-based and individualized dosing guidelines, a tremendous amount of time and costs will be involved. Therefore the objective of the research described in this thesis was to describe the developmental changes in renal function by using a more system-based pharmacology approach [23]. This means that the developmental changes of the various subprocesses that contribute to renal clearance (glomerular filtration, tubular secretion and tubular reabsorption) need to be characterized.

Renal clearance is responsible for the elimination of a large number of water-soluble drugs and their metabolites. Various mechanisms contribute to the renal clearance: glomerular filtration, tubular secretion and tubular reabsorption. Each of these processes exhibit different rates of maturation in an independent way [24]. Although renal clearance is well defined in adults, limited information is available on the developmental changes in renal function in the pediatric age range. It is known that nephrogenesis starts at week 5-6 of gestation and continues until 36 weeks of gestation [14, 25, 26]. Development of tubular processes starts from 36 weeks of gestation and continues during childhood. During the first weeks of life, a rapid increase is seen in glomerular filtration and tubular functions due to haemodynamic changes [24]. Moreover, development in tubular processes seems to be delayed in comparison with glomerular filtration. For the glomerular filtration rate, it is known that adult levels are reached at approximately 6-12 months of age when corrected for body surface area. Meanwhile the development of tubular processes is more gradual since adult

levels are not reached until 1-5 years of age [24]. Since the renal elimination of most of the drugs is covered by glomerular filtration and only a limited number of drugs is undergoing tubular secretion or reabsorption, the primary focus in this thesis was to describe the developmental changes in glomerular filtration. Moreover, once the developmental changes in GFR are characterized, this can be used to describe the maturation of tubular processes.

To estimate GFR, different methods can be used. First, GFR can be measured by determination of the inulin clearance which is considered to be the gold standard because inulin is an exogenous substance that is completely filtered by the glomerulus and not secreted or reabsorbed by the renal tubules [27]. Although simplified methods have been proposed to determine GFR from the decrease of the inulin concentration in plasma rather than from 24 hour urine collection, still some limitations are linked to this technique. These can make the routine application cumbersome in paediatric and certainly in neonatal clinical practice. Some of the constraints are the limited commercial availability of inulin, the burden caused by collection of additional blood samples and the advanced assay methodology that is required to measure inulin concentration in blood [28-30]. A second method to assess GFR is by measuring creatinine clearance. There is however a number of factors that must be taken into account when using creatinine clearance as a substitute for glomerular filtration. First of all creatinine is not only filtered by the glomerular filtration but also in part secreted by the tubular secretion [24, 31]. Moreover, the formation of creatinine is determined by age, muscle mass and gender and this complicates the estimation of creatinine clearance in children on the basis of plasma concentrations. In addition, in the first days of life, serum creatinine concentrations reflect maternal creatinine concentrations [25, 32, 33]. Furthermore, serum creatinine concentrations are known to increase with a peak in the second part of the first week of life with a subsequent progressive decrease throughout neonatal life making it difficult to interpret the renal function based on creatinine in the first week of life. The peak creatinine concentration is most pronounced in the most immature neonates and is due to passive back leak of creatinine through renal tubular leaky cells [33]. Although the Schwartz formula based on creatinine concentrations and body length is often used to estimate GFR, it often leads to overprediction of GFR [34]. Due to the reasons mentioned above, it is preferred not to use creatinine as a marker to measure GFR in children and certainly not in neonates. A third method to measure GFR is by injection of radioisotopes [28, 29]. This method is also not recommended in children for the same reasons mentioned as with inulin.

Therefore, the most pragmatic method, which has been proposed before, is to assess GFR in the pediatric age range by determining the clearance of a drug which

is exclusively eliminated by GFR [35-37]. Moreover, when evaluating GFR by describing the clearance of renally excreted drugs, information can directly be obtained during clinical practice. Finally, in the context of the system-based pharmacology approach, it will also be evaluated whether information on the developmental changes in the clearance of one drug can be used to describe clearance of other drugs eliminated by the same route. This implicates that a distinction is made between system-specific and drug-specific properties to evaluate whether the system-specific properties derived from one drug describing the underlying physiological changes, can be extrapolated to other drugs, eliminated through the same route.

1.2. Developmental changes in glomerular filtration in preterm and term neonates by describing the pharmacokinetics of renally excreted antibiotics

In *Section II* of this thesis a system-based pharmacology approach is used to describe the developmental changes in GFR in preterm and term neonates. Using this approach, the pharmacokinetics of one specific aminoglycoside, i.c. amikacin, a drug which is almost entirely eliminated by GFR, are first described in preterm and term neonates. To characterize these developmental changes, a systematic covariate analysis is performed in which all potential covariates are tested for significance and included in the model when they are sufficiently predictive of the variability in amikacin clearance. Based on the model, including the model covariates, a new model-based dosing algorithm can be developed for amikacin in neonates. Secondly, to extrapolate information from one drug to another drug, a distinction is made between system-specific and drug-specific information in the derived model. In this respect, the pediatric covariate model can be considered to contain system-specific information on the developmental changes in GFR and therefore the covariate model can be extrapolated to the other renally excreted drugs [23, 38, 39].

In **chapter 3**, the developmental changes in GFR were quantified in 874 preterm and term neonates aged between 1-30 days by describing maturation in clearance of amikacin. In a systematic covariate analysis the influence of birth bodyweight, current bodyweight, postmenstrual age, gestational age, postnatal age, co-administration of ibuprofen and creatinine was studied. To ascertain that the model was able to describe the data without bias, the model was both internally and externally validated [40, 41]. The internal validation was based on two different methods: a bootstrap analysis and a normalized prediction distribution error (NPDE) analysis. For the external validation two different datasets were used. Finally simulations were performed to obtain a

new optimized and individualized dosing algorithm for amikacin in preterm and term neonates which would result in achieving target peak and trough concentrations in each individual neonate.

In **chapter 4** the new-model based dosing regimen for amikacin in neonates was tested in a prospective clinical trial including 579 preterm and term neonates. In this study it is assessed whether the proposed dosing regimen for amikacin resulted in the expected concentrations and whether further dose adjustments need to me made.

In **chapter 5** the system-based pharmacology approach is applied for between drug extrapolations. In this chapter it is illustrated how information of one drug is extrapolated to other drugs eliminated through the same route. Using this approach, it is hypothesized that covariate models contain quantitative information on the developmental changes in the underlying physiological pathways [23]. To test this hypothesis, the covariate model of amikacin, describing the developmental changes in GFR in preterm and term neonates, was directly extrapolated to four other renally excreted drugs: netilmicin, tobramycin, vancomycin and gentamicin. Meanwhile, the population values describing the absolute values of parameters like clearance and volume of distribution are still estimated in the population analysis as they are considered to be drug-specific. The descriptive and predictive performance of the models using the amikacin covariate model was compared to the independent reference models which were developed for each dataset based on a systematic covariate analysis. This approach in which information of one drug is extrapolated to another drug can be considered a semi-physiological approach which may lead to optimization of sparse data analysis in children. Furthermore another not unimportant advantage is the large reduction in both time and costs when models can be developed using information of one drug to another drug.

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

Renal function consists of glomerular filtration, active and passive tubular secretion and reabsorption. Cefazolin is a drug which is eliminated by both GFR and active tubular secretion [42, 43]. In **chapter 6**, the pharmacokinetics of cefazolin are described in preterm and term neonates. On the basis of both total and free cefazolin concentrations in 36 neonates, a one compartment pharmacokinetic model

was developed in which non-linear protein binding was taken into account. In a systematic covariate analysis, all potential covariates (age and weight related covariates, albumin, creatinine, free fatty acids, bilirubin, gender) were tested for significance. In addition, based on the final model, Monte Carlo simulations were performed to illustrate the exposure to cefazolin following currently used dosing regimens and to derive an optimal dosing regimen in preterm and term neonates.

To be able to quantify the developmental changes in tubular secretion in neonates, it was hypothesized that when clearance of cefazolin was higher than the clearance through GFR, it is due to clearance by tubular processes. In the previous section, the developmental changes in GFR were quantified by describing the pharmacokinetics of amikacin in neonates. Consequently, this semi-physiological GFR model based on amikacin clearance was directly incorporated on cefazolin clearance. The remaining part was then considered as describing the clearance by active tubular secretion. To quantify these developmental changes in active tubular secretion, a systematic covariate analysis was performed. These results are discussed in the section "Summary, conclusions and perspectives" of this thesis.

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

Besides the active substance(s), drug formulations often contain excipients. One of the frequently used excipients to increase the solubility and/or stability is propylene glycol. In general, excipients are considered to be safe, however toxic effects were reported in adults, children and neonates due to the administration of propylene glycol [44-48]. This may be explained by the limited knowledge on the pharmacokinetics of propylene glycol. 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 to lactate and pyruvate [49, 50]. However, renal clearance of propylene glycol is expected to be lower in neonates compared to adults, due to immaturity of the renal function. Therefore, the aim of this section was to characterize renal and hepatic elimination of propylene glycol in preterm and term neonates.

In a first analysis (**chapter 7**) the pharmacokinetics of propylene glycol were quantified based on 372 plasma samples of propylene glycol co-administered with intravenous paracetamol or phenobarbital, available in 62 preterm and term neonates. Based on a systematic covariate analysis different covariates were tested. The final model was subsequently used to simulate exposure to propylene glycol upon ad-

ministration of paracetamol or phenobarbital in neonates using the dosing regimens applied in the study.

In **chapter 8** renal and hepatic clearance of propylene glycol was characterized based on both plasma and urine samples of propylene glycol in 69 preterm and term neonates using a one compartment model parameterized in renal clearance, hepatic clearance and volume of distribution. Based on this model, the percentage of propylene glycol eliminated through the renal route and hepatic route was quantified in preterm and term neonates.

1.5. Developmental changes in GFR from neonates until adults

Glomerular filtration is supposed to reach adult levels between 6 months – 1 year of age when expressed per m^2 body surface area. However an exact quantification of the maturation of GFR throughout the pediatric age range is missing. Therefore, the aim in this section (*Section V* – **chapter 9**) was to describe the developmental changes in GFR across the entire pediatric age range from preterm neonates to adults. To perform this analysis, a system-based pharmacology approach was used since the developmental changes in GFR from neonates until adults were characterized by describing the pharmacokinetics of three renally excreted drugs: gentamicin, tobramycin and vancomycin in one analysis whereby again the distinction was made between system-specific and drug-specific properties (see *Section II*). Using this approach the covariate model on clearance for the three drugs is not tested separately but the same covariate model on clearance was implemented for the three drugs as this part of the model is considered to contain system-specific information. Finally the model describing the developmental changes in GFR across the pediatric range was validated by performance of an NPDE analysis [41].

1.6. Conclusion and Perspectives

Section VI of this thesis provides a summary of the results and conclusions of the different chapters of this investigation. Furthermore the results are discussed as well as the applicability of the different covariate models to other drugs. Finally, an overview is given on future perspectives.

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