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

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Section I. Background and introduction to modeling renal clearance of drugs in children

Chapter 1

General introduction and scope

1.1 General introduction

Pharmacokinetic (PK) modeling describes drug absorption, distribution, metabolism and excretion by mathematical equations [1]. The parameters of these equations can be used to compare and evaluate different models and their performance as well as to predict drug exposure through PK profiles [2]. Drug exposure needs to be accurately captured as it is relates to the pharmacologic effects of a drug [1].

Differences in size and physiological development between adults and children influence drug disposition as well as pharmacological effects. When differences in drug exposure between children and adults can be attributed entirely to differences in PK, necessary pediatric dose adjustments are generally driven by drug clearance as drug exposure is inversely proportional with clearance at steady-state [3]. PK modeling approaches have been used to estimate and describe the impact of developmental changes on PK parameters, often together with other patient and treatment related factors.

In population PK models, developmental changes that affect clearance are captured using descriptive covariate models. Covariate models capture the correlations between individual deviations from typical model parameters and patient or treatment related variables (i.e. covariates) to describe and predict some of the random variability between individual patients [4]. Covariate analyses are used to identify covariates that are clinically relevant and can be used as a basis for dose adjustments. In pediatric research, patient demographics (e.g. bodyweight, postnatal age, etc.) are the most commonly used covariates to describe changes with development whereas other covariates can be related to patient and treatment related factors (e.g. organ failure, intubation period, drug-drug interactions). In part due to ethical constraints, the number of clinical studies in children is typically limited. The majority of pediatric data comes from prospective or retrospective studies in small pediatric age-groups conducted in clinical practice where covariates such as disease, organ failure, inflammation markers or co-therapy are routinely included in covariate models and used for dose adjustments.

When pediatric PK data is scarce with a limited number of patients per age group and limited sparse sampling for a specific drug that does not support the development of a covariate model, clearance can be scaled from adults to children using empirical approaches. To do so, linear and exponential relationships based on bodyweight are regularly used. These methods are applied to 13-30% of drugs used in pediatric primary care and to 49-87% of drugs used to treat children in hospitals [5]. However, particularly in younger age groups, differences in bodyweight can capture the developmental differences in clearance between adults and children only partially which could lead to biased predictions. Physiologically-based PK models offer a better alternative, as they use system-specific parameters with physiological meaning which are separated from drug-specific parameters. With the inclusion of maturation functions, these system-specific parameters can be scaled from adults to children by describing the changes in developing physiology throughout the pediatric age-range. Based on this information together with drug-specific information (e.g. molecular weight, pH, logP, etc.), pediatric PBPK models can predict clearance values and PK profiles for any drug and any child.

This thesis focuses on drugs cleared by renal excretion for which pediatric doses are scaled based on changes in renal clearance (CL_R). Glomerular filtration (GF), active tubular secretion (ATS), reabsorption, and renal metabolism are processes that contribute to CL_R. Of the top 200 drugs prescribed in the US in 2010, 30% were renally eliminated of which 92% relied, at least partially, on ATS [6]. However, the expression and activity of renal transporters, and their contribution to ATS and CL_R remain understudied in adults as well as in children. Therefore, ATS and its contribution to CL_R in children needs to be better understood before being able to accurately predict CL_R of renally excreted drugs subject to active secretion. Once the age-dependent changes in CL_R are accurately captured throughout the pediatric age-range, it can be used to guide dose selection in children for renally excreted drugs, including those subject to active secretion.

1.2 The role of population PK approaches in predicting pediatric CL_R and guiding pediatric dosing

For pediatric patients for which off-label dosing is common practice [5], covariate models can be used to develop dose regimen that reach an effective and safe exposure from the start of therapy. Vulnerable subpopulations such as preterm neonates, especially those undergoing concomitant treatments (e.g. co-medication, hypothermic treatment, etc.) may require additional dose adjustments on top of the ones correcting for maturational changes. In this thesis, antibiotic agents used for (suspected) neonatal sepsis that are cleared renally by GF will be used to exemplify how to predict CL_R in such special populations using covariate models (Chapters 1 and 2). For these patients, co-therapy is expected to have an influence on CL_R, and therefore the impact of treatment related factors is quantified in addition to the maturation of CL_R. The identified covariate model can then be used to personalize drug dosing for each patient.

In the absence of the data required to build and validate a new covariate model, existing models can be used for extrapolations. For example, covariate models can be extrapolated to younger or older children than the age-range they were developed and validated on to obtain initial CL_R estimates for the drug of interest. When only adult CL_R values are known for the drug of interest, empirical methods based on changes in bodyweight (i.e. allometric and linear scaling) can be used for extrapolation to children. However, these methods have been proven to be inaccurate in some cases, including when used to extrapolate CLR for drugs cleared by GF to certain pediatric age-groups [7,8]. This behavior indicates that weight-related changes are not sufficient for CL_R scaling, and that more information about developmental changes is required for accurate scaling (e.g. maturation functions) [9].

1.3 The role of physiologically-based PK approaches in predicting pediatric CL_R and guiding pediatric dosing

PBPK modelling approaches use system-specific parameters that reflect the human physiological system and are informed by diverse and abundant literature data, usually following an extensive meta-analysis. System-specific parameters are calculated using anthropometric measures that capture differences between individuals using equations that are dependent on patient demographics, and are drug independent. Drug-specific parameters are integrated in PBPK models based on physicochemical properties. Some drug-specific parameters are sensitive to variations in physiology, e.g. the fraction unbound is dependent on concentrations of plasma proteins, blood to plasma ratio is dependent on hematocrit levels, and clearance by active secretion is dependent on transporters abundance and the number of proximal tubule cells per g kidney. Pediatric PBPK models are obtained by accounting for developmental changes in physiology by applying maturation functions to the system-specific parameters. In addition, drug-specific parameters that are sensitive to changes in physiology are expected to change with age.

Recently, physiologically-based PK (PBPK) modelling approaches were acclaimed for accurately predicting CL_R throughout the pediatric age-range for a few example drugs [10]. However, the exact contribution of different processes involved in pediatric CL_R is not yet entirely understood. By using a pediatric PBPK model for predicting CL_R, the contribution of the underlying system- and drug-specific parameters to CL_R can be separated and investigated. The PBPK model for CL_R [11] (equation 1) can be studied in isolation from the full PBPK model. In this thesis, CL_R resulting only from the contribution of GF and ATS [11] will be considered, assuming no contribution of tubular reabsorption, passive diffusion or renal metabolism.

$$CL_R = CL_{GF} + CL_{ATS} = GFR \times f_u + \frac{(Q_R - GFR) \times f_u \times CL_{sec}}{Q_R + f_u \times \frac{CL_{sec}}{BP}} \quad [1]$$

As shown in equation 1, CL_R through GF and ATS is dependent on GF rate (GFR), fraction unbound (f_u), renal blood flow (Q_R), secretion clearance (CL_{sec}), and blood-to-plasma ratio (BP).

Table 1.1. The level of characterization (well, partially, poorly) for system-specific parameters and drug-specific parameters sensitive to changes in system-specific parameters included in the PBPK-based model for CL_R through GFR and ATS (equation 1). Demographic characteristics used as input for the maturation functions of these parameters are included as well.

Characterization of maturation	**Parameters of the PBPK model for CL_R through GFR and ATS**	**Demographic characteristics for maturation functions of system-specific parameters**
	Glomerular filtration rate	$GFR_{maturation} = f(WT, PMA)$
	Fraction unbound	$fu = f(P), with$ $[P]_{maturation} = f(AGE)$
	Renal blood flow:	$Q_R = f(CO, fr), with$ $CO_{maturation} = f(BSA, AGE)$ $fr_{maturation} = f(AGE, GENDER)$
	Blood-to-plasma partitioning:	$BP = f(HEMAT, fu, Kp), with$ $HEMAT_{maturation} = f(AGE, GENDER)$
	Secretion clearance:	$CL_{sec} = f(KW, PTCPGK, CL_{intT}, ont_T), with$
	Kidney weight:	$KW_{maturation} = f(\rho_{kidney}, WT)$
	Proximal tubule cells per gram kidney (PTCPGK)	Unknown maturation
	Transporter-mediated intrinsic clearance	$CL_{int,T}$ = f(transporters activity + expores-sion, ont_T)
	Ontogeny of transporters	$ont_T = f(AGE)$

green - well characterized; orange - partially characterized; red - poorly characterized;
WT – body weight; **PMA** – postmenstrual age; **P** – plasma protein; **CO** – cardiac output; **HEMAT** – hematocrit; **fr**- fraction of cardiac output; **Kp** – blood to plasma partition coefficient; **ρ_{kidney}** - kidney density; **PTCPGK** – proximal tubule cells per gram kidney.

1.4 Towards pediatric dosing for drugs cleared exclusively by glomerular filtration

Urine formation begins with GF, the main passive route involved in renal excretion of small molecules, including drugs. CL_R through GF is dependent on GFR and on protein binding, as only the free fraction of a drug is available to be cleared through this process [12] (see CL_{GF} in equation 1).

GFR has been extensively investigated in adults as well as in children. Various methods have been published for quantifying GFR *in vivo*. GFR can be derived based on endogenous markers (e.g. serum creatinine [13], cystatin C [14,15]), exogenous markers (i.e. inulin, mannitol, etc.) [16–20] or clearance of drugs mainly eliminated by GF (e.g. antibiotics [21]). As such, data on different markers for GFR have been collected throughout the pediatric age-range and used to develop mathematical functions to characterize the maturation of this process. Dependent on the marker used for quantifying GFR, but also on the quality and quantity of data used for development, different maturation functions for GFR have been published. However, it has not been established yet what the best published GFR maturation function is.

In adults, CL_R through GF is proportional to changes in the unbound fraction of the drug in plasma (see CL_{GF} in equation 1). Developmental changes in plasma protein concentrations are known to influence protein binding in children, especially in newborns and infants [22]. In older children human serum albumin and α-acid glycoprotein levels approach adult levels. However, the influence of maturation in the concentration of plasma proteins on drug binding and, implicitly, on pediatric CL_R has not been systematically investigated yet.

1.5 Towards pediatric dosing for drugs cleared by glomerular filtration and active tubular secretion together

In addition to GF, ATS contributes to CL_R by extracting a drug from blood into urine through membrane bound transporters [12]. Transporters involved in tubular secretion (e.g. OAT1/3, OCT2, OCTNs, MATE1, etc.) are located on the apical and basal sides of proximal tubule cells with secretion capacity changing alongside the proximal tubules. Hydrophilic and ionizable drugs are most likely to be substrates for active transporters. Such drugs can have a broad spectrum for transporter affinity, meaning that they can be transported by one or more renal transporters [23]. Hence, ATS of a drug is dependent on physicochemical properties such as lipophilicity, ionization, but also on plasma protein binding and on affinities to one or more renal transporters [23].

There is limited published information about the contribution of active secretion transporters and their ontogeny to ATS and, subsequently, to total CL_R in adults or in children. By performing global sensitivity analyses on PBPK models for CL_R, the contribution of the different transporters and their ontogeny to predicting CL_R for various drugs can be systematically investigated. Such an approach could determine essential system- and drug-specific parameters to accurately predicting CL_R when active secretion processes are involved.

Equation 1 shows a PBPK-based model for CL_R where GF and ATS are included in series, with ATS as a process following GF. All the (system-specific) parameters included in this PBPK-based model together with the demographic characteristics required to derive the maturation functions for each of these parameters are included in Table 1.1. Drug-specific parameters that are influenced by maturation in system-specific parameters (e.g. the concentration of plasma proteins available for drug binding thereby influencing fraction unbound changes with age) are also included in Table 1.1.

The color-coding in Table 1.1 indicates how well the maturation of the system-specific parameters included in the PBPK-based model for CL_R is characterized at the moment, with green being well characterized, orange – partially characterized and red – poorly characterized. Maturation of GFR, plasma proteins, renal blood flow, hematocrit levels, and kidney weight are well characterized. However, pediatric CL_R predictions for drugs that are actively secreted are currently still based on adult values for the number of proximal cells per gram kidney, as there is limited information on (potential) maturation of this parameter. Furthermore, the transporter-mediated intrinsic clearance ($CL_{int,T}$) reflects both the activity and expression of the transporters. *In vivo* ontogeny functions for ATS have previously been based on the quantification of *in vivo* net secretion as the aggregated functionality of one or more secretion and/or reabsorption pathways [19,24]. However, different transporters can have different ontogeny profiles throughout the pediatric age-range that cannot be identified using this method. Furthermore, net secretion implies the quantification of the resultant between active secretion and reabsorption, both of which may involve one or more active transporters. Therefore, separating between different transporters and between the different processes allows for a better understanding of the underlying physiological processes and of their contribution to CL_R. Fortunately, the protein expression of a few renal transporters (i.e. OAT1/3, OCT2, Pgp) was measured in post-mortem kidney samples to characterize their ontogeny throughout the pediatric age-range [25]. However, there is no information yet on how well the ontogeny of protein expression reflects the ontogeny of transporter activity *in vivo* and whether it remains constant with age.

Drug-specific parameters that characterize the drug kinetics for renal transporters (i.e. transporter-mediated intrinsic clearance) are commonly obtained from *in vitro* experiments. The *in vitro* value needs to be extrapolated to its corresponding *in vivo* value to obtain the correct parameter required for the calculation of secretion clearance (CL_{sec}), a key parameter in obtaining clearance through ATS. Even if the methodology for i*n vitro – in vivo* extrapolation is continuously being refined, *in vitro* measurements are

not available for all drugs that undergo active secretion, and can be biased or reported with incomplete information that could eventually lead to a biased *in vitro-in vivo* extrapolation [26].

1.6 A combined population and physiologically-based PK modeling approach to derive key parameters and *in vivo* ontogeny functions for renal transporters

The contribution of model parameters in equation 1 to CL_R predictions can be established by performing sensitivity analyses. As shown in Table 1.1, the ontogeny of two system-specific parameters is partially or poorly characterized (orange or red color), i.e. ontogeny of renal transporters and PTCPGK (the number of proximal tubule cells per gram kidney), respectively. If the results of a sensitivity analysis show that (one of) these parameters have impact on CL_R predictions at certain pediatric ages and/or for particular drugs, then quantifying the maturation of these parameters becomes essential to obtain accurate pediatric CL_R predictions of those drugs.

Poorly and partially characterized ontogeny profiles for certain parameters can be derived in vivo by using a combined approach between population PK and PBPK modelling thereby maximizing the use of available data in children. The information included in a PBPK model that relies on well-established system-specific parameters and their corresponding maturation functions, can be leveraged when combined with the information captured by individual PK parameters to derive those parameters that rely on limited prior information or that are difficult to measure throughout the whole pediatric age-range.

1.7 Conclusion

Population PK methods, such as covariate analyses, are currently used to characterize the maturation of CL_R (such as glomerular filtration) and propose dose adjustments in vulnerable pediatric sub-populations for which sufficient PK data is available. When PK data is scarce or unavailable pediatric CL_R can be obtained using PBPK methods. Such methods allow the study of physiological processes in isolation to find parameters that play a key role in predicting pediatric CL_R. By combining the two methodologies - population PK and PBPK - poorly characterized ontogeny functions can be derived from data collected *in vivo*. By making use of the available data and the current methodologies individual dosing of renally cleared drugs is facilitated and can be further improved.

1.8 Scope of this thesis

The primary scope of this thesis is to apply population pharmacokinetic (popPK) and physiologically-based pharmacokinetic (PBPK) approaches to investigate the influence of glomerular filtration (GF) and active tubular secretion (ATS) on renal clearance (CL_R) in children including assessing the importance of developing accurate maturational functions for various pharmacokinetic processes used in predictions of CL_R in children. For this investigation, the contributions of passive (i.e. GF) and active (i.e. ATS) processes to CL_R are considered. Both processes contribute to pediatric CL_R and are expected to be influenced by developmental changes. Hence, the extent to which these developmental changes impact CL_R is explored in pediatric populations using clinical data of existing drugs, and using a PBPK-based framework for hypothetical drugs with an array of different properties excreted by either GF or both GF and ATS. The projects were performed to meet the following research objectives:

1. Extend existing popPK models by characterizing the development in CL_R for drugs excreted by GF in (pre)term neonates and quantify the influence of disease and co-therapy on CL_R. These covariate models are to be used to propose dosing recommendations (**section II**).
2. Establish a general scaling method for CL_R from adults to children for drugs eliminated by GF and systematically investigate how maturation of plasma protein concentration influences the unbound fraction of drugs, and subsequently, scaling of pediatric CL_R and drug doses (**section III**).
3. Use a pediatric PBPK-based model for CL_R to systematically investigate the influence of transporter ontogeny on the contribution of ATS to CL_R and illustrate how a combined population PBPK approach could be used to derive ontogeny functions for renal transporters involved in ATS (**section IV**).

To meet the stated research objectives, first, dose adjustments will be proposed for preterm neonates treated with antibiotics mainly eliminated by GF, using covariate functions from popPK models that describe the changes in CL_R with development. Secondly, based on a PBPK model the best method for scaling CL_R through GF from adults to children will be identified and this method will be used further for dose scaling. By using PBPK modelling approaches to predict pediatric CL_R throughout the pediatric age-range for hypothetical drugs excreted exclusively by GF that differ in fraction unbound, the influence of maturation on plasma protein expression and the accuracy of the scaling methods will be investigated. Lastly, a PBPK model for CL_R including GF and ATS, will be used to predict pediatric CL_R for an array of hypothetical drugs, to investigate the influence of renal transporter ontogeny on CL_R. More information on renal transporter ontogeny is required, as the only data available is based on a limited sample of post-mortem kidneys [1]. By using a combined PBPK and popPK approach, the information that is included in the PBPK model can be levearaged to estimate parameters that are poorly or partially characterized. The PBPK model for CL_R through GF and ATS has the potential to be used for scaling CL_R from adults to children and for extrapolations between different substrates for the same transporter.
The current section (**Section I**) places our analysis in the context of the current reseach, highlighting the research questions that will be addressed in our studies.

Section II focuses on extending existing popPK models for optimizing dosing regimens of antibiotics cleared mainly by GF. These antibiotics are administrated to (pre)term neonates with (suspected) septicemia who are co-treated for complications such as perinatal asphyxia or patent ductus arteriosus, with therapeutic hypothermia or non-steroidal anti-inflamatory drugs (NSAIDs; ibuprofen or indomethacin), respectively. Previously published models that characterize the PK of the same antibiotics in (pre)term neonates treated only with the antibiotic are extended to include (pre)term neonates with these complications for which they receive co-treatments. Either the complications or the co-treatment or both are expected to affect CL_R. The quantified changes in CL_R of the antibiotic between (pre)term neonates with and without co-therapy (i.e. hypothermia or NSAIDs) serve as basis for drug dosing adjustments for this special population. Dosing adjustments are proposed based on the results

obtained from performing simulations with the popPK models that describe the antibiotic data the best. The efficacy of the treatment is assessed from the trough concentration levels that are correlated to the drug exposure. In **Chapter 2**, the influence of perinatal asphyxia treated with hypothermia is quantified on amikacin CL_R and used for developing dose recommendations in (pre)term neonates. In **Chapter 3**, the influence of co-administrating either of two different NSAIDs to induce closure of patent ductus arteriosus is quantified on vancymcin CL_R and used for dosing recommendations in this neonatal population.

While **section II** focused on using popPK approaches to characterize the development of CL_R and to optimise dosing, the following sections (**sections III** and **IV**) present general methods to scale CL_R and dosing from adults to children in the absence of PK data. In this situation, researchers often use empirical scaling methods based on bodyweight. Recently PBPK approaches became available to serve this purpose as well. PBPK methods are gaining momentum as they have been successfully used to predict pediatric PK parameters [2].

Section III is directed to establish a scaling method for CL_R of drugs eliminated by GF that is accurate throughout the pediatric age-range. CL_R through GF is dependent on GFR and the unbound fraction of the drug. By generating hypothetical drugs cleared exclusively by GF that differ in unbound fraction and type of binding plasma protein (i.e. human serum albumin, α-acid glycoprotein), a systematic investigation was performed to establish how the maturation of plasma proteins impacts scaling CL_R throughout the pediatric age-range. To do so, in **chapter 4**, first, published maturation functions for GFR were compared to observed inulin or mannitol CL_R data reported in literature throughout the whole pediatric age-range to establish the best available function for GFR maturation. Then, this function was used to describe GFR maturation in a PBPK-based model and to scale CL_R from adults to children for all hypothetical drugs. The PBPK-based model for CL_R considered changes in both GFR and protein binding throughout the pediatric age-range. By systematically comparing PBPK predicted CL_R to GFR-based scaled CL_R the impact of maturation of plasma proteins on CL_R predictions was studied in isolation from other contributing factors. In addition to GFR-based scaling, the performance of scaling CL_R with empirical scaling methods (i.e. linear scaling and 0.75 allometric scaling based on bodyweight) was investigated throughout the entire pediatric age-range.

As PBPK models are also useful to increase our understanding of the underlying physiology, in **section IV** we explore a PBPK-based model for CL_R that includes ATS in addition to GF. In **chapter 5**, the influence of the ontogeny of secretion transporters on the contribution of GF and ATS to CL_R was systematically investigated for an array of drugs with various properties, as information about renal transporters ontogeny is limited. While GF is a passive excretion pathway, ATS relies on several transporters for drug excretion. So far, ontogeny functions for renal secretion have been obtained either from *in vivo* clearance, in which case they reflect net secretion clearance by all active renal excretion and reabsorption processes, or from protein expression profiles for individual transporters, in which case it is unknown how protein expression relates to *in vivo* activity. Ontogeny of transporters remains less explored and could influence the predictions of pediatric CL_R with PBPK models of drugs that are actively secreted, making them less reliable. To understand more about the influence of ontogeny, a pediatric PBPK model for GF and ATS is used to predict CL_R for hypothetical drugs with an array of realistic properties. The influence of ontogeny of secretion transporters on CL_R is explored by assuming different extents of transporter ontogeny at various pediatric ages. To quantify the impact of transporter ontogeny we compared the CL_R predictions with or without ontogeny of secretion transporters. Drugs with properties that lead to inaccurate pediatric CL_R predictions in the absence of transporters ontogeny are highly influenced by transporters and their ontogeny. These drugs are expected to be suitable probes to investigate transporters ontogeny further.

In **chapter 6**, ontogeny of *in vivo* renal secretion transporter activity was derived using a combined

popPK and PBPK approach. This method allows the leverage of the physiology-related data integrated in the PBPK model and inform unknown parameters, in this case the ontogeny of OAT3, based on clinically observed drug clearance values. To do so, PK data on clavulanic acid –a drug mainly eliminated by GF – and amoxicillin – a drug mainly eliminated by GF and ATS by OAT3 – that were administrated simultaneously to pediatric patients with ages between 1 month and 15 years was used. The individual post-hoc CL_R values obtained with the population PK models for each of the two drugs were fitted with a PBPK-based model for CL_R. All established maturation functions in the PBPK-based model were fixed to literature values so that the maturation of active CL through the transporters could be estimated. This allowed the estimation of OAT3-mediated intrinsic clearance and its ontogeny profile. Once the ontogeny of OAT3 is identified, it could be used in a PBPK model to predict CL_R for other substrates of the same transporter. Hence, CL_R for piperacillin and cefazolin was scaled to different pediatric ages. Accuracy of these predictions was assessed against typical CL_R predictions obtained from reported population PK models for each drug. Once the ontogeny of individual transporters is well characterized, for instance with the methodology developed here, the used of PBPK models can be extended to predict CL_R of drugs that are actively secreted in children.

Lastly, **section V** summarizes the main findings and concludes the investigations of this thesis. Perspectives and future applications of popPK methods to determine how the relationship between trough concentrations and drug exposure changes with age and dosing frequency are also addressed. In addition, the accuracy with which empirical relationships based on bodyweight can predict PBPK CL_R of actively secreted drugs will be systematically explored to propose general guidelines for pediatric CL_R scaling. Such tools can be further extended by including additional elimination pathways (i.e. reabsorption and metabolism) to understand more about the influence of the development of renal functionality on CL_R throughout the pediatric age-range.

1.9 References

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