Size does matter : drug glucuronidation in children

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Section I

Background and Introduction

Chapter 1

Scope and Intent of Investigation

1.1 Background and Introduction.

There are many sources of variability in drug response that are unique to the paediatric population. Firstly, there are marked increases in body size as well as significant changes in the expression and function of drug metabolizing enzymes and transporters. Additionally, differences in cardiac output and blood flow influence the perfusion of drug eliminating organs, and differences in the acid-base balance, the concentration and composition of drug-binding plasma proteins and other blood components potentially influence plasma protein binding. Moreover, the relative size of organs vary, as well as body composition, with the amount of total body water and extracellular water decreasing with age. All these factors can alter drug exposure in paediatric patients [1]. Furthermore, developmental changes in drug pharmacodynamics influence the variability in paediatric drug response. Changes in the function and expression of receptors and target proteins can alter the pharmacological response to drug exposure, while disease states may also affect the physiological system and physiological feedback mechanisms, making diseases that are unique to the paediatric population or diseases with a different progression in children compared to adults, unique contributors to the variability in paediatric drug response [2].

Unfortunately, the sources of variability in drug exposure and response in children have not been studied in as much detail as they have been in adults. As a result, evidence-based drug dosing algorithms that account for functional differences between children and adults, as well as for functional differences between children of different ages are often lacking. Between 1995 and 2005, off-label and unlicensed paediatric drug prescription was high around the world with the number of paediatric patients receiving at least one off-label or unlicensed drug ranging between 80% to 93% in the neonatal intensive care units, between 36% to 100% in paediatric wards, and between 3.3% to 56% in non-hospital settings [3], without any apparent difference between university hospitals and general hospitals in hospital setting [4,5]. At the same time, out of all the new drugs licensed by the European Medicines Evaluation Agency (EMEA) only 33% was licensed for use in children, 23% for infants and 9% for neonates and while attention to drug licensing for the paediatric population was increased, an increasing trend in drug licensing for the full paediatric population could not be observed during this period [6,7].

When evidence-based dosing information is missing, paediatric drug doses are often empirically extrapolated from adult doses. Consensus-based paediatric drug dosing guidelines are sometimes formalized in paediatric formularies after years of clinical experience [8,9]. To improve paediatric drug dosing, it is essential to study the influence of developmental changes on drug pharmacokinetics and pharmacodynamics

in an integrated manner and to determine the relevance to and interaction with other factors like for instance diseases status, (concomitant) therapy, and genetics. Laws in the US and Europe like the Pediatric Rule (FDA – 1998), the Best Pharmaceuticals for Children Act (FDA – 2002), and the Paediatric Regulation (EMEA – 2007) have been introduced to encourage or compel pharmaceutical companies to perform paediatric studies for new chemical entities. However, to date laws that apply to marketed off-patent drugs are lacking.

The objective of the research described in this thesis was to develop a novel model-based approach to derive drug dosing algorithms for the paediatric population, which account for developmental changes in drug response in this population. Naturally, this approach should take into account changes in drug pharmacokinetics, including absorption, distribution, metabolism and elimination (ADME), as well as drug pharmacodynamics, including effect site distribution, target activation, and signal transduction. However, as a first step in the research on paediatric pharmacology, the studies in this thesis are limited to the developmental changes in drug pharmacokinetics. For many drugs, the developmental differences in drug clearance are thought to be the major cause of age-dependent differences in dose requirements [10]. Specific focus is on uridine 5′-diphosphate glucuronosyltransferase (UGT) 2B7-mediated drug glucuronidation in neonates and young children. The UGT enzyme family is responsible for the glucuronidation of various endogenous en exogenous compounds in humans, but has been studied less extensively than the cytochrome P450 enzyme family, which is involved in the oxidation of the majority of the currently marketed drugs [11]. Inappropriate dose adjustments of UGT substrates in the paediatric population may lead to therapeutic failure or to overdosing, which may cause serious side-effects and even fatalities [12]. In this chapter an outline is presented of the various investigations that are described in this thesis.

Chapter 2 provides an overview of the various *in vitro* and *in vivo* methodologies to study the onset and development, the so-called ontogeny, of hepatic enzyme systems. Special emphasis is on the results obtained with these methods for UGTs. Different endpoints representing different parts of the physiological system that can be studied to determine enzyme ontogeny were identified. Since the number of components interacting with each part of the physiological system increases in going from mRNA transcription, to enzyme expression, *in vitro* enzyme activity, and *in vivo* glucuronidation clearance, conclusions on hepatic enzyme ontogeny may differ when different endpoints are used to characterize the changes in the physiological system. Additionally, different techniques to obtain and/or analyze data from each part of the physiological system may further diversify the results. Based on literature results it could however be concluded that even

though the ontogeny profiles of the different UGT isoenzymes may vary significantly, the onset and development of UGT enzyme expression and activity generally occur after 20 weeks of gestation with a boost in expression and activity occurring in the first weeks of life. Since many other physiological changes also occur within this timeframe and since children are encountered most frequently in hospital settings during the first weeks to months of life, detailed information on clinical changes in drug pharmacokinetic is particularly relevant for the youngest patients. Therefore the focus of the research in the current thesis was on preterm and term neonates to children up to three years of age.

1.2 Paediatric Morphine Glucuronidation Model for Individualized Dosing

An *in vivo* approach was used to study clinically relevant differences in drug disposition and exposure in early childhood. Traditional compartmental and non-compartmental *in vivo* approaches either require dense concentration-time information from each individual, obtained according to a stringent study design to ensure similar drug dosing and blood sampling in each individual, or they rely on imprecise measurements of steady state concentrations. A further drawback of traditional approaches is that they do not allow for the identification of the sources of variability within a population. Therefore 'population modeling', also known as non-linear mixed effect modelling, was the preferred tool for the studies in the current thesis. Population modeling not only allows for the analysis of dense, sparse, and/or unbalanced data, and for the identification and quantification of the sources of variability in a population, it also allows for the identification of significant predictors of this variability, known as covariates [13]. The information obtained on these covariates can subsequently be used as the basis for evidence-based dosing algorithms. A population modeling approach was applied in **Section II** to describe and quantify developmental changes in the glucuronidation of the selective UGT2B7 probe morphine [14,15] in preterm and term neonates, and children up to three years of age. The resulting model, including the model covariates, was used to develop a dosing algorithm for this population.

In **Chapter 3**, sparse and unbalanced concentration-time data on morphine and its two major metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), that were obtained during routine clinical practice from 248 term and preterm neonates to children younger than three years, were analyzed. In a comprehensive covariate analysis, all potential covariates were tested for significance and included in the model when they were sufficiently predictive of variability in morphine disposition to significantly improve the model fit according to predefined criteria. This yielded a

population model that described the developmental changes in morphine clearance and distribution in this young population with a bodyweight-based function. To ascertain that the model indeed described the data without bias, the final model was validated internally using advanced methods like a normalized prediction distribution error (NPDE) analysis, after which simulations were performed to obtain an optimized, individualized morphine dosing algorithm that yields similar steady state concentrations for morphine, M3G and M6G throughout the population of preterm and term neonates to three-year-old children.

Before applying the model-derived morphine dosing algorithm obtained in Chapter 3 in clinical practice, the predictive performance of the paediatric population pharmacokinetic model for morphine and its metabolites was corroborated using six external datasets in **Chapter 4**. This ascertained that the model could not only accurately predict morphine and metabolite concentrations in independent datasets of postoperative and ventilated patients with similar characteristics as the patients in the internal dataset used for model building in Chapter 3, but also in datasets of patients on very invasive extracorporeal membrane oxygenation (ECMO) treatment. The results from this study justified the next step in developing an evidence-based paediatric dosing algorithm for morphine, namely the prospective evaluation of the algorithm in a clinical trial [16].

Chapter 5 describes the results obtained with the prospective validation of the novel paediatric dosing algorithm of morphine. In a randomized controlled trial that compared postoperative analgesic efficacy of morphine and paracetamol in patients under the age of 1 year, the patients in the morphine arm were dosed according to the optimized and individualized paediatric dosing algorithm obtained with the population pharmacokinetic model developed and validated in Chapter 3 and Chapter 4. According to this highly non-linear dosing regimen, neonates younger than ten days received morphine maintenance doses that were between 25% and 50% of the traditional, linear, and consensus-based morphine regimen, whereas older children received up to about 150% of this traditional dose. In this proof-of-principle study, it was assessed whether the proposed morphine doses based on the pharmacokinetic differences quantified in the population model, sufficed to obtain a satisfactory clinical response throughout the population, or whether further dose adjustments based on age-related differences in pharmacodynamics were necessary. The clinical response to morphine was assessed by analyzing the nurse-controlled morphine rescue medication that was administered based on a standardized pain-protocol using validated, age-appropriate COMFORT-behaviour [17] and VAS [18] scores to assess pain. Morphine and metabolite plasma concentrations were measured to ascertain that the concentration predictions by the population model were still accurate in patients dosed according to the novel algorithm, thereby confirming that the model-derived dosing algorithm indeed corrected for age-related differences in morphine pharmacokinetics.

1.3 Semi-Physiological Covariate Model for Paediatric Glucuronidation

It would require a tremendous amount of resources to develop and thoroughly validate paediatric population models for each individual drug in every population in a manner similar to what was described for morphine in Section II. Hence a novel approach is proposed in **Section III**, to limit the amount of resources and expedite the development of population pharmacokinetic models for the paediatric population. This approach is based on the hypothesis that paediatric covariate models for drug elimination describe system-specific properties rather than drug-specific properties [19] and can therefore be directly extrapolated from one drug to another drug that shares a common elimination pathway. The drug-specific parameter values in the population model of the new drug are on the other hand still estimated in a population analysis based on concentration-time data of this drug. As such, this approach can be considered a semi-physiological hybrid between population pharmacokinetic modeling, called top-down modeling, and physiologically-based pharmacokinetic modeling, called bottom-up modeling.

The new semi-physiological approach for the development of paediatric population models is introduced in **Chapter 6**. In this proof-of-concept study, the paediatric covariate model for morphine glucuronidation that was developed and validated in Section II, was directly extrapolated to the glucuronidation of zidovudine, a drug which is also predominantly eliminated through UGT2B7-mediated glucuronidation [15,20]. The descriptive and predictive performance of this semi-physiological model was found to be similar to the descriptive and predictive performance of a reference model that was developed using a comprehensive covariate analysis of the zidovudine data to provide the best description of these data based on statistical criteria.

In **Chapter 7** the physiological and physicochemical basis of the developed semi-physiological paediatric covariate model that quantifies the developmental changes in UGT2B7-mediated glucuronidation clearance for morphine and zidovudine in neonates and young children was investigated. The physiology-based modeling software Simcyp (Simcyp Ltd, Sheffield, UK) allowed for the determination, in strictly quantitative manner, of the influence of distinct system-specific and drug-specific parameters on the ontogeny pattern of the clearance of existing and hypothetical drugs in various populations, including the paediatric population. Using Simcyp the underlying maturational changes in liver volume, milligram microsomal protein per gram of liver, hepatic blood flow, plasma protein concentration, and ontogeny of UGT2B7 expression and function were disentangled and the main drivers of the net observed changes in UGT2B7-mediated glucuronidation in early childhood were identified. Additionally,

it was uncovered how physicochemical drug properties like the molecular mass, the octanol/water partition coefficient (logP), the acid dissociation constant (pKa), influence the magnitude and the ontogeny pattern of UGT2B7-mediated clearance in order to define specific drug properties that would preclude the direct application of the semi-physiological developmental model for paediatric drug glucuronidation.

1.4 Paediatric Model Evaluation

Population modeling allows for the analysis of sparse data, but when data are limited there are risks of drawing erroneous conclusions. This could have far-reaching consequences, especially when population models are used for simulation purposes, for instance to optimize clinical trials in drug development, to derive dosing algorithms for application in clinical practice as was illustrated in Section II, or to extrapolate paediatric covariate models between drugs as was illustrated in Section III of this thesis. Under these circumstances proper assessment of both the descriptive and predictive properties of a model is imperative. This is however often neglected both in the adult and the paediatric population [21,22]. **Section IV** of this thesis therefore focuses on the evaluation of paediatric population models.

Numerous tools for the evaluation of population models currently exist. However, these tools may not always directly suffice for the evaluation of paediatric population models, due to distinctive patient and study characteristics in this special population. The paediatric population is for instance relatively small and can be regarded as a population consisting of multiple subpopulations due to the heterogeneity in maturational status. Additionally, since data in this population are usually obtained during routine clinical practice the variability in dosing and sampling schemes is high, while limitations in sampling size and frequency may cause data to be sparse. A new framework was therefore developed in **Chapter 8** for the systematic assessment of the descriptive and predictive properties of paediatric covariate models. In this framework, existing numerical diagnostics, prediction-based diagnostics, and simulation-based diagnostics are placed into context and adjusted for application to paediatric population models where necessary. Additionally, a new tool to specifically evaluate paediatric covariate models is presented. As an illustration, this new framework was applied to two peer-reviewed, published, paediatric population models for morphine and its two major glucuronides that were based on an identical dataset, but developed with fundamentally different covariate analysis approaches.

In recent years, several studies on the maturation of morphine clearance, using a wide array of different data analysis approaches leading to different pharmacokinetic models, have been published. This raises important questions with regard to the model that best predicts morphine concentrations in the pediatric population. In **Chapter 9** advantages and disadvantages of different data analysis techniques to describe and quantify the *in vivo* maturation of morphine clearance in the paediatric population, like traditional methods, population pharmacokinetic modeling and physiologically-based pharmacokinetic modeling, are discussed. Subsequently, the accuracy of morphine clearance predictions by multiple published paediatric pharmacokinetic models that were based on a variety of datasets and modeling approaches were reviewed. This is important because the value of paediatric pharmacokinetic models mostly depends on clearance predictions and population concentration predictions. Special attention was paid to the accuracy of morphine concentration predictions across different age-groups and the level of evidence supporting each model either in the original publication or in succeeding publications.

1.5 Summary, Conclusion and Perspectives

Finally, in **Chapter 10** of **Section V**, the results of the studies presented in this thesis are discussed in conjunction with each other and perspectives of future research are presented.

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