Physiologically-Based Pharmacokinetic Predictions of Lorazepam Paediatric Clearance

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ABSTRACT

Drug clearance is an important pharmacokinetic parameter as it describes the rate of elimination of a drug from the body. The aim of this project was to develop a physiologically-based pharmacokinetic model, with the simulation program Simcyp, to predict the total plasma clearance for lorazepam for the entire paediatric age-range. The mean prediction error for observations in literature were 30% or below for all ages. This model can be used to assess the current dosing recommendations in children of all ages.

Keywords

Physiology-based pharmacokinetics, lorazepam, paediatrics, UGTs, intrinsic clearance

INTRODUCTION

Pharmacokinetics covers the process by which a drug is absorbed, distributed, metabolized and excreted from the body. Drug clearance is an important pharmacokinetic parameter to describe the rate of elimination of a drug,[1] and is described as the volume of blood or plasma from which a drug is completely removed per unit of time.[2,3] In paediatrics, clearance is often expressed per kg of bodyweight. Drugs can be cleared through different mechanisms, including hepatic metabolism and renal clearance of the unchanged drug. Hepatic metabolism utilizes many different enzymes. Drug clearance is an important factor for drug dosing: the quicker a drug is removed from the body, the more of this particular drug needs to be administered.

Physiologically-based pharmacokinetic modelling

Drug research or drug dosing optimization in paediatric population is still challenging.[4] There are many physiological changes in children that influence drug clearance, but this is often not systematically investigated. This is partly due to ethical and practical restrictions, making clinical trials in paediatrics very complex. To optimize drug treatment in paediatrics, there is need for a better understanding of how drugs are cleared through various mechanisms and how this changes with age. This can be achieved by the use of modelling and simulation. There are two basic approaches for studying clearance in paediatrics. The first approach is population pharmacokinetic modelling, which allows to empirically calculate pharmacokinetic parameters, such as clearance.

Models based on this approach can be easily developed as they only require concentration-time data. However, because these models are empirical, they must be developed for one particular drug in one particular population. Thus, these models are not suitable to predict the pharmacokinetic of a different drug or in a different population. The second approach is physiologically-based pharmacokinetic (PBPK) modelling, which is based on physiological and anatomical measurements in combination with physicochemical drug properties. Unlike population models, PBPK models require a large amount of data, which is not always easy to obtain. However, because PBPK models are mechanistic, they can be applied to a wide range of scenarios including different populations or different drugs.[5] In the paediatric population, adult PBPK models are scaled to children using maturation functions which describe the developmental changes from birth to adulthood. For instance, for drugs undergoing hepatic metabolism, changes in liver size and enzyme maturation are used to predict the paediatric clearance based on adult data.[6] Enzyme maturation is implemented as a function describing the changes of enzyme activity or intrinsic clearance per gram of liver. In paediatric PBPK models, several maturation functions, especially those describing maturation of enzyme pathways, are based on very limited experimental data, and further research on these functions is needed to broaden the applicability of paediatric PBPK models.

Glucuronidation

Glucuronidation by uridine 5'-diphospho-glucuronosyl-transferases (UGTs) is a major metabolic pathway[7] and promotes the detoxification of drugs. Glucuronidation serves as a toxicological gatekeeper, as almost 40-70% of clinically used drugs are eliminated by glucuronidation.[8] The mechanism of glucuronidation consists of the transfer of glucuronic acid to the drug molecule to increase its hydrophilicity, so these molecules can be easily excreted by the kidneys. This mechanism is carried out by several types of UGTs. UGTs are glycoproteins which are generally present in the endoplasmic reticulum of hepatic cells. The enzyme activity of UGTs are affected by age, disease state, dietary, environmental chemicals, ethnicity, hormonal factors and genetic polymorphisms. Genetic polymorphisms can lead to different metabolic phenotypes, such as extensive metabolisers or poor metabolisers. Clinically, dose adjustments might be required to correct for differences in metabolic clearance between these phenotypes.

AIM

The primary aim of this research project was to develop a PBPK model to predict the total plasma clearance for lorazepam for the entire paediatric age-range and evaluate the predictive performance of the PBPK model by comparing the predicted plasma clearances to values reported in literature. Lorazepam is a central nervous system active drug and is widely used for the treatment of epileptic seizures, anxiety disorders, and nausea and vomiting induced by chemotherapy.[5,9] Lorazepam was especially selected for this project, because it is mainly metabolized by only two enzymes, namely UGT2B7 and UGT2B15, which allows us to study the enzyme maturation of these particular pathways. This research was part of a larger project, to optimize PBPK models in paediatrics, so that accurate clearance predictions for various drugs in children can be made.

MATERIALS & METHODS

Plasma glucuronidation clearance of lorazepam for adults and children were simulated with Simcyp v.13.0, which is an industry standard software package. In this research, the workflow by Maharaj et al.[5] was adopted, to develop PBPK model. This model includes mathematical equations that describe how important parameters for hepatic clearance (e.g. hepatic blood flow, plasma protein binding) change with age. A simplified overview is displayed in figure 1. In a first step, adult drug clearance is computed using drug-specific (e.g. pH or lipophilicity) and adult system-specific (e.g. liver size, hepatic blood flow, intrinsic clearance) parameters. Adult clearance predictions are compared to literature values to investigate the need of model adjustment. In a second step, a paediatric PBPK model is obtained by scaling the adult system-specific parameters to the paediatric population using maturation functions. Finally, this paediatric PBPK model can be used to simulate clearance throughout the entire paediatric population.
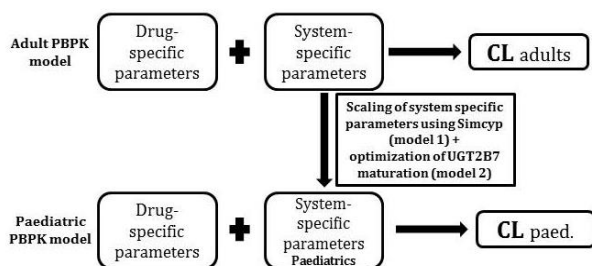

Figure 1: Workflow outline

For the adult PBPK model, adult intrinsic clearance values for UGT2B7 and UGT2B15 were derived from literature.[10,11] The intrinsic clearance describes the metabolic rate in the absence of rate-limiting factors (such as hepatic blood flow or plasma protein binding). The adult intrinsic clearance of 1 mg of hepatic protein for the two UGTs were computed based on the following equation:

$$CLint = \frac{Qh \times CLh}{\left(Qh - \frac{CLh}{B:P}\right) \times fu}$$

Where Qh is the hepatic blood flow (1.73 L/min), CLh is the hepatic plasma clearance due to UGT2B7 or UGT2B15, B:P is the blood to plasma ratio (0.642 for lorazepam) and fu is the unbound fraction (0.11 for lorazepam).[5] Adult values were used for all parameters. The intrinsic clearance for UGT2B15 and UGT2B7 were 5.88 μL/min and 5.22 μL/min, respectively.

Maturation of enzymes in the liver causes changes in intrinsic drug clearance. In paediatric PBPK models, these changes are accounted for by enzyme maturation functions which scale the intrinsic clearance from adults to children. These enzyme maturation functions describe the changes in intrinsic clearance (enzyme activity) with age expressed as percentage of the adult value. Because maturation of enzymes occurs at different rates, different maturation patterns for intrinsic clearances for UGT2B7 and UGT2B15 were implemented in Simcyp to build the paediatric PBPK models. Two different paediatric models were developed and compared. These models have different maturation functions for the intrinsic clearance of UGT2B7 (fig 2):

Model 1: simple linear function as standardly implemented in the Simcyp PBPK software package.

Model 2: non-linear maturation pattern reported in literature by Edginton et al.[12]

Model 2 is based on newly emerging evidence regarding this non-linear maturation function of UGT2B7. The simple linear function in model 1 is derived from limited information and therefore model 2 is developed.[12]

In both models the same non-linear function for UGT2B15 maturation defined in the Simcyp software (fig. 2) was implemented. For the UGT2B15 enzyme, multiple genotypes result in different phenotypes that yield different intrinsic clearances. The 2 main phenotypes are extensive metabolisers and poor metabolisers.[10] The model assumed seventy percent of the individuals in the population to be extensive metabolisers, phenotype for which the drug is quickly eliminated from the body, resulting in a need for a higher dose to maintain a specific therapeutic concentration. Thirty percent of the individuals were assumed to be poor metabolisers, who need a lower dose to maintain a certain therapeutic concentration.[10]
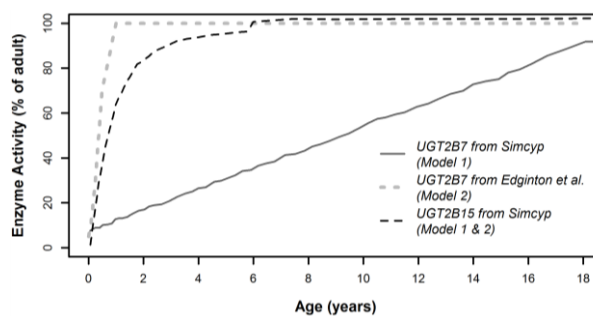

Figure 2: Maturation functions for UGT2B7 and UGT2B15 implemented in Model 1 and Model 2. Enzyme maturation functions describe the changes in intrinsic clearance with age and are expressed as a percentage of adult value.

Model simulations

Using the two developed PBPK models, plasma clearance predictions for lorazepam were made for the entire paediatric age-range, spanning from newborn up to 18-year-old adolescents. Taking inter-individual variability in system-specific parameters and the reported prevalence of UGT2B15 extensive and poor metabolisers into account[10], plasma clearance values were simulated for 100 individuals of each age. In the simulations, the proportion of males and females was equal.

The performance of the paediatric PBPK models in predicting lorazepam plasma clearances was evaluated using reported clearance values from literature.[13] The percentage mean prediction error (%MPE), expressing the accuracy of the prediction, and the root mean square error (RMSE), expressing the precision of the predictions, were calculated by the following equations:

$$\%MPE = \frac{\sum \frac{(predicted - observed) * 100}{observed}}{n}$$

$$RMSE = \sqrt{\frac{\sum(predicted - oserved)^2}{n}}$$

RESULTS AND DISCUSSION

The mean lorazepam clearance predicted by the PBPK model for adults was 0.047 L/h/kg which is in agreement with lorazepam reported literature values.[14–16] Thus, no model adjustment was needed and the adult model was directly used to build the paediatric models.

Model 1 includes the simple linear function for the maturation of UGT2B7 enzyme activity, as implemented in the Simcyp software. Model 2 includes a user-defined non-linear maturation function for UGT2B7 borrowed from Edginton et al.[12] Figure 3 shows the difference in lorazepam plasma clearance predicted by both models across the paediatric age-range.
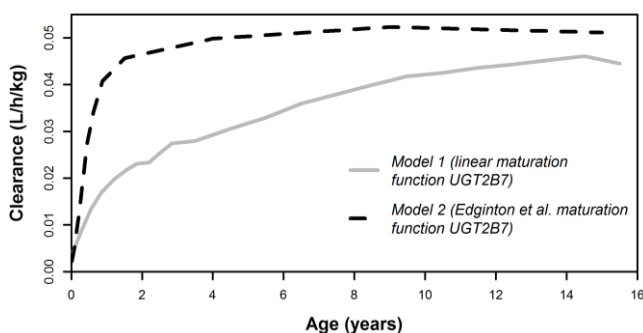

Figure 3: Lorazepam plasma clearance versus age predicted by Model 1 and Model 2.

Table 1 shows the accuracy and precision of the lorazepam clearance predictions by both models. Clearance predictions of Model 2 were more precise (RMSE closer to 0) and more accurate (lower MPE%) than clearance predictions of Model 1 and therefore, Model 2 was in better agreement with the literature values. Both models show the best clearance predictions for lorazepam in children and adolescents between the

age of 12 and 18 years. It is noteworthy that, for both models, the %MPE gets larger towards the lower extreme of the age-range. It is generally more difficult to predict drug clearance at very young ages, because there are many physiological changes taking place early in life. Moreover, there is limited observational data in this age-range to compare the predictions to.[17]

Table 1: MPE% and RMSE for lorazepam clearance values predicted by Model 1 and Model 2.

Age group[13]	% MPE		RMSE	
	Model 1	Model 2	Model 1	Model 2
Study 1: Neonates	-59.76	-24.90	0.012	0.009
Study 2: Children	-51.25	-26.59	0.037	0.019
Study 3: Children	-53.73	-30.32	0.031	0.023
Study 4: Adolescents	-18.92	8.05	0.012	0.005
Study 5: Adolescents	-20.29	-10.61	0.014	0.006
Study 6: Adolescents	-19.58	-11.29	0.011	0.007

The results show a clear improvement of lorazepam plasma clearance predictions for Model 2. In fig. 4 individual PBPK clearance predictions of Model 2 and the geometric mean of these predictions are shown, together with reported clearances from literature.[13] Because clearances from literature were expressed per kg, predicted and literature clearances are presented together versus body weight. Clearance values predicted by Model 2 steeply increase with body weight in new-borns and infants, as can be seen in fig. 4. The clearance predictions remain stable after a bodyweight of approximately 15 kg is attained. The predictions are in reasonable agreement with the observations with %MPE at or below 30% across the entire age-range.
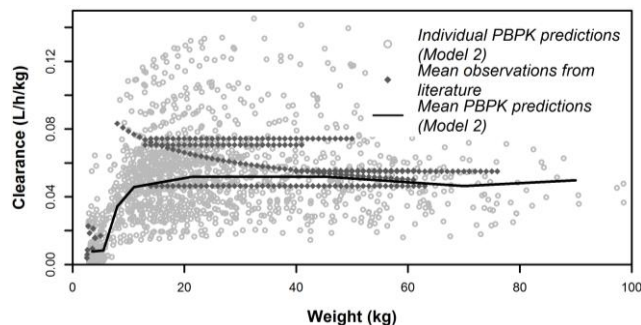

Figure 4: Overview of lorazepam clearance values, including individual PBPK predictions and geometric mean of these predictions by Model 2, and mean observed values reported in literature.[13]

FURTHER RESEARCH

Many maturation functions in paediatric PBPK models are not well characterized and this study shows that discrepancies between enzyme maturation functions do impact the accuracy and precision of clearance predictions in the paediatric population. Therefore optimization and validation of maturation functions is an essential step in the development of paediatric PBPK models.

The optimized PBPK model herein can be used to assess the current dosing recommendations in children of all ages. In this assessment it is important to take the UGT2B15 phenotype into consideration as well. The different phenotypes for UGT2B15 are important and have an impact on the clearance of lorazepam and maybe

other drugs in paediatrics. By taking into account different phenotypes of the UGT2B15 enzyme together with their prevalence in the population, the impact of these phenotypes on drug clearance in children can be further studied. This is necessary to determine whether dose adjustments are required for particular phenotypes. Additionally, an evaluation of the current dosing recommendations could be performed.

CONCLUSION

This study improved the maturation function of the intrinsic clearance of the UGT2B7 enzyme in a PBPK model for children of all ages, thereby improving lorazepam clearance predictions. By using an optimized maturation function for UGT2B7, this PBPK model and the clearance predictions are improved. Due to the generalizability of PBPK models, clearance prediction for other UGT2B7 substrates will likely improve as well.

ROLE OF THE STUDENT

Tamara van Donge was an undergraduate student (bachelor student) working under the supervision of Elisa Calvier when this research was performed. The topic was proposed by the supervisor and extended by the student. The set-up of the methods and processing of the results as well as the writing were done by the student.

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