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Considering Age Variation When Coining Drugs as High versus Low Hepatic Extraction Ratio

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ABSTRACT

The hepatic extraction ratio (E_H) is commonly considered an "inherent attribute" of drug. It determines the main physiological and biological elements of the system (patient attributes) that are most significant in interindividual variability of clearance. The E_H consists of three age-dependent parameters: fraction of unbound drug in blood ($f_{u,B}$), hepatic intrinsic clearance of unbound drug ($CL_{u.int,H}$), and hepatic blood flow (Q_H). When the age-effects on these elements are not proportional, a given drug may shift from so-called high extraction status to low extraction. To demonstrate the impact of age-related changes on $f_{u,B}$, $CL_{u\cdot int,H}$, and Q_H, the E_H of midazolam and two hypothetical drugs with 10-fold higher and 10-fold lower $CL_{u.int,H}$ than midazolam were investigated in pediatrics based on known ontogeny functions. The E_H was simulated using Simcyp software, version 14. This was then complemented by a comprehensive literature survey to identify the commonly applied covariates in pediatric population pharmacokinetic (PopPK) studies. Midazolam E_H decreased from 0.6 in adults to 0.02 at birth, making its clearance much more susceptible to changes in $CL_{u.int,H}$ and $f_{u.B}$ than in adults and reducing the impact of Q_H on clearance. The drug with 10-fold higher $CL_{u.int,H}$ was categorized as high extraction from 4 days old onward whereas the drug with 10-fold lower $CL_{u.int,H}$ remained low extraction from birth to adulthood. Approximately 50% of collected PopPK studies (n = 120) did not consider interaction between age and other covariates. Interaction between covariates and age should be considered as part of studies involving younger pediatric patients. The E_H cannot be considered an inherent drug property without considering the effect of age.

Introduction

Hepatic metabolic clearance ($CL_{H,B}$) of intravenously administered drugs is determined by hepatic blood flow (Q_H) and their hepatic extraction ratio (E_H), according to eq. 1:

$$CL_{H,B} = E_H \times Q_H \quad (1)$$

The E_H is calculated from the fraction of drug unbound in blood ($f_{u,B}$), the hepatic intrinsic clearance of unbound drug ($CL_{u.int,H}$), and Q_H, according to eq. 2:

$$E_H = \frac{fu_B \times CLu_{int,H}}{Q_H + (fu_B \times CLu_{int,H})} \quad (2)$$

The extraction ratio of the drug is generally classified as high (>0.7), intermediate (0.3–0.7), or low (<0.3) according to the fraction of drug removed during one pass through the liver.

Commonly, the E_H of a drug is considered an inherent attribute of the drug and is presented with a fixed value. However, this classification does not consider that the parameters in eq. 2 are age dependent or that changes in these parameters will affect the E_H. For example, a rise in $f_{u,B}$ for low-E_H drugs increases the hepatic metabolic clearance, whereas for high-extraction drugs this does not affect metabolic clearance. Unless the age-related physiologic changes in $f_{u,B}$, $CL_{u\cdot int,H}$, and Q_H occur in parallel, it is expected that the E_H of drugs varies with age. Therefore, a high-extraction drug in adults will not necessarily remain a high-extraction drug in neonates.

Age-varying E_H can potentially be used as a covariate in clearance models when analyzing population pharmacokinetic (PopPK) studies. However, because applying the extraction ratio directly in the model might not be straightforward, this concept is considered in PopPK models through the interaction between covariate terms in the model. For example, age and body weight are commonly used as covariates in PopPK clearance models where body weight is also affected by age. The interaction between these two covariates should be considered in the model.

We investigated the relative differences in E_H with age by using in vivo midazolam data and two hypothetical high- and low-extraction drugs through modeling and simulation techniques. We also use the concept of the age varying the E_H to examine whether the interaction between covariate terms in modeling clearance has been considered in the PopPK studies.

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ABBREVIATIONS: $CL_{u.int,H}$, hepatic intrinsic clearance of unbound drug; $CL_{H,B}$, hepatic metabolic clearance; CYP3A4, cytochrome P450 3A4 enzyme; E_H, hepatic extraction ratio; f_u, fraction of drug in plasma unbound; $f_{u,B}$, unbound drug in blood; MPPGL, microsomal protein per gram of liver; PopPK, population pharmacokinetics; Q_H, hepatic blood flow.

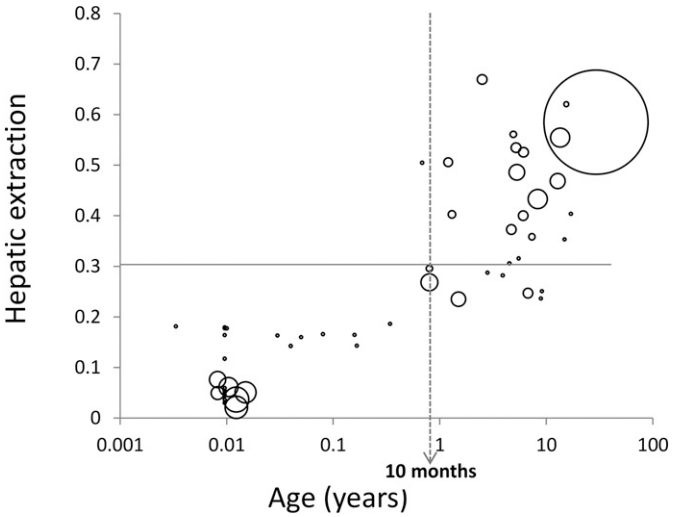

Fig. 1. Hepatic extraction for intravenous midazolam calculated from reports of clinical studies in the literature using ontogeny functions in pediatric subjects and healthy adult volunteers (n = 523).

Materials and Methods

Literature Data Collection. Data on midazolam systemic clearance in pediatrics from birth to 17 years were collected from the literature. The literature search strategy and methodology for deconvolution of clearance to arrive at the $CL_{H,B}$ from midazolam systemic clearance (using the blood-to-plasma ratio) and Q_H based on cardiac output were explained previously (Salem et al., 2014).

Simulations. A drug with 10-fold higher and 10-fold lower $CL_{u\text{-}int,H}$ than midazolam was designed by multiplying and dividing the deconvoluted midazolam $CL_{u.int,H}$ by 10 as proposed by Salem et al. (2014) to mimic a high- and low-extraction drug, respectively. Then, using the relevant $CL_{u.int,H}$, Q_H, and $f_{u.B}$ in eq. 2, E_H was calculated.

A number of simulations in Simcyp Pediatric version 14 (Certara, Princeton, NJ) were performed for midazolam, a drug with 10-fold higher and 10-fold lower $CL_{u.int,H}$ than midazolam, to show the age-related changes in the magnitude of E_H. We simulated 100 subjects, consisting of an equal proportion of males and females and a combination of age bands (1 day, 1 month, 2 years, and 12 years as well as adult). The E_H was calculated using eq. 3 from the output data. The mean values of E_H at each age band were plotted against age for each of the simulated drugs.

Calculation of the Hepatic Extraction Ratio. The hepatic extraction ratio was calculated from CL_H and Q_H for midazolam and the other two hypothetical drugs assuming the well-stirred model, as seen in eq. 3:

$$\text{Hepatic Extraction Ratio} = \frac{CL_{H,B}}{Q_H} \quad (3)$$

Sensitivity Analysis. Sensitivity analysis was performed with a view to identify which component of the extraction ratio ($CL_{u.int,H}$, Q_H, or $f_{u.B}$) plays the most dominant role in the variation of E_H from adult values at any given age. The impact of age-dependent Q_H was evaluated by fixing $f_{u.B}$ and $CL_{u.int,H}$ (l/h/g of liver) to the adult values for all age ranges. This involved assumptions about the lack of any ontogeny for the abundance of the enzymes (pmol per mg of microsomal protein) and no age-related changes in the level of microsomal protein per gram of liver (MPPGL). The value of $CL_{u.int,H}$ (l/h/g of liver) was used to calculated the pediatric $CL_{u.int,H}$ values per whole liver by applying age-related liver weight. The E_H was plotted against age, and the patterns were compared.

In another set, only $f_{u.B}$ values were fixed to adult values to demonstrate the sensitivity of the E_H to age-related changes in Q_H and $CL_{u.int,H}$ (l/h) without the impact of age-related changes in binding. The E_H was calculated and plotted against age and compared with the original set of results (where all age-related parameters had been considered).

To separate the size-related effects (i.e., liver mass and hepatic blood flow) from ontogeny-related factors on E_H, a graphical representation was devised to demonstrate the pediatric values of enzyme abundance relative to adults at a given age (in this case, the cytochrome P450 enzyme 3A4 [CYP3A4]) alongside relative values for liver volume, hepatic blood flow, and MPPGL.

Population Pharmacokinetic Studies (PopPK). A comprehensive literature survey using PubMed was performed to identify commonly used covariates in pediatric PopPK studies for drugs after intravenous administration. No year, journal, or language restriction applied to the search process. Collated publications were carefully checked for modeling covariates and the form of the covariates–clearance relationship in the reported model. We identified the studies that considered the interaction between covariates and clearance. Interaction between covariate terms was also considered if the presence of a covariate modified the impact of another covariate in a multiplicative or exponential way. Where there were different clearance models for different pediatric age ranges, the interaction with age was also considered. Interaction between covariate terms was not considered if only one covariate was considered in the final clearance model or if the covariates were in linear additive relationship to the clearance. When the modeling section was not clear, we contacted the corresponding authors.

Results

Midazolam Hepatic Extraction Ratio. The hepatic extraction ratio of midazolam, after deconvolution of clinical systemic clearance, increased with age. Available data in Figure 1 illustrates that midazolam is a low-extraction drug until about the age of 10 months. However, in some individuals it remained low at the age of 9 years.

Figure 2 shows that the E_H increases with age for midazolam and two other hypothetical compounds. The degree of change in the E_H with age depends on magnitude of $CL_{u.int,H}$ against a given enzyme. As shown in the figure, a 10-fold reduction in $CL_{u.int,H}$ results in a drug with low hepatic extraction across the pediatric and adult age ranges whereas a 10-fold increase in $CL_{u.int,H}$ shifts the drug from so-called intermediate to high-extraction status.

Sensitivity Analysis. Figure 2 compares the E_H when all age-related components ($CL_{u.int,H}$, Q_H, and $f_{u.B}$) are considered (solid lines) with a scenario involving no age-related changes in $f_{u.B}$ (dashed lines). As shown in Fig. 2, the E_H is marginally lower in younger groups if age-related $f_{u.B}$ is not considered. However, this might be different for drugs with higher protein binding.

When the $CL_{u.int,H}$ (l/h/g of liver) and $f_{u.B}$ are fixed to adult values, the changes in the E_H will be driven by age-related changes in Q_H and liver weight (Supplemental Fig. 1). In this scenario, there are no significant differences between the E_H values across pediatric age groups for the three drugs because the low activity of CYP3A4 in younger age groups is not considered.

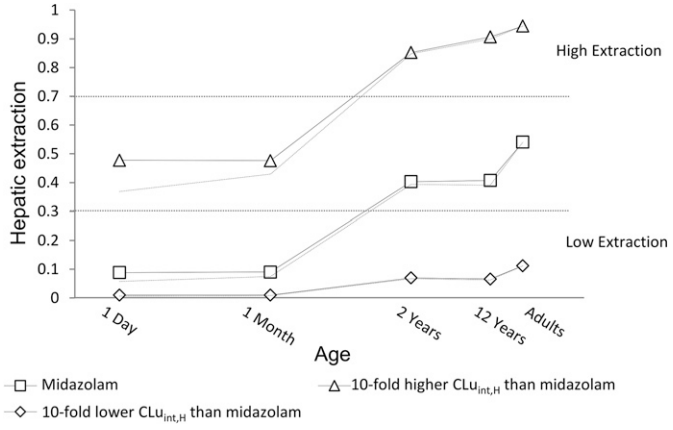

Fig. 2. Simulated hepatic extraction in Simcyp version 14 shows changes with age for midazolam, a drug with a 10-fold higher $CL_{u.int,H}$, and a drug with 10-fold lower $CL_{u.int,H}$. A high- or intermediate-extraction drug in adults is not necessarily a high- or intermediate-extraction drug in pediatric subjects. Dashed profiles are the same E_H values with age when $f_{u.B}$ remains unchanged ($f_{u.B}$ = 0.05). Dotted horizontal lines show the limits for high (>0.7) and low (0.3>) extraction.

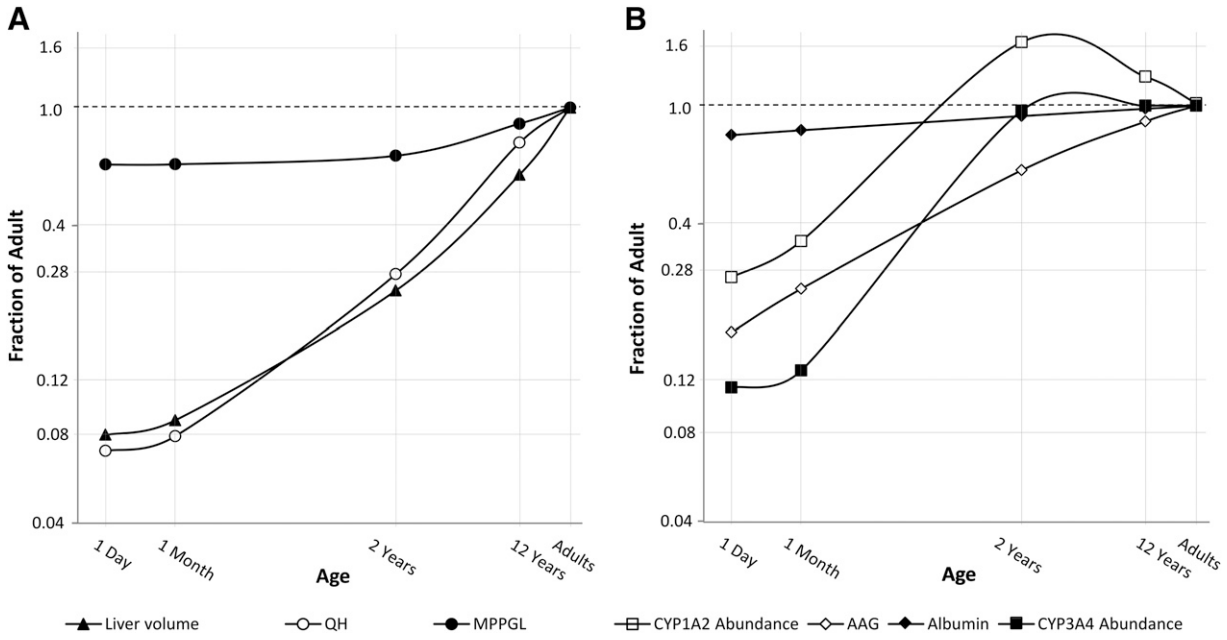

Fig. 3. Age-related variations in parameters defining the E_H are shown as relative values to the corresponding adult level of each parameter. (A) Changes in liver size (Johnson et al., 2005), hepatic blood flow (Guyton, 1991), and MPPGL (Barter et al., 2008) that apply to all drugs. (B) Relative values of serum albumin (Johnson et al., 2003, 2006; Sethi et al., 2015), CYP3A4 abundance (of relevance to our study) (Salem et al., 2014) alongside age variation in serum alpha-acid glycoprotein (AAG) (Johnson et al., 2003, 2006), and abundance of CYP1A2 (Salem et al., 2014). The impact of the parameters shown in *B* will depend on the relative importance of the protein binding to each protein and the role of the specific enzyme to overall elimination.

The rate of change with age for liver volume, hepatic blood flow, and MPPGL as a fraction of adult values are shown in Fig. 3. This figure shows the changes in the underlying parameters of the E_H. The changes in blood flow and liver volume relative to adults occur almost in parallel to each other. Therefore, the discrepancy in Q_H and liver size alone cannot account for the observed differences in the E_H; instead, changes in intrinsic activity to the level of enzyme abundance and to a lesser extent MPPGL are determinants of age-varying E_H. Table 1 summarizes the contributing parameters to E_H that are reported in Fig. 3. Needless to say, if the relative values to adult for all these elements had a similar rate of change with age, no age-related differences would have been anticipated in the E_H.

Analysis of Covariates in Population Pharmacokinetic Studies. A total of 120 PopPK studies were retrieved in the pediatric age range (birth to 18 years) for intravenously administered drugs. The interaction between covariate terms was not considered in 50% of the studies (n = 60). Supplemental Table 1 summarizes the most commonly used covariates in the analyzed PopPK studies. Supplemental Table 2 shows all the analyzed PopPK studies with interaction between covariates.

Discussion and Conclusions

The E_H of the drugs in this study increases with age due to the rapid physiologic changes in the parameters determining the E_H after birth, including the ontogeny of enzyme abundance and to a lesser extent MPPGL. Although it is not relevant to the cases represented in this study, the ontogeny of plasma proteins can play a significant role in age-related changes of the E_H for highly bound, low-extraction drugs. As shown previously by several investigators, the concentration of plasma proteins increases with age whereas the unbound fraction of drugs in plasma and thus in blood decreases with age (McNamara and Alcorn, 2002; Johnson et al., 2006; Sethi et al., 2015).

The ontogeny of plasma protein binding and enzyme abundance on any given compound depends on the extent of binding to a particular protein and the importance of that enzymatic pathway to the overall elimination of a drug. As a consequence, a drug that is coined a high, low, or intermediate hepatic extraction compound in adults is not necessarily going to carry the same extraction category in pediatrics. For the particular case studies in this report, where the binding was not a major factor and CYP3A4 was the main metabolizing enzyme, we demonstrated the switch from high extraction or intermediate extraction to low extraction in neonates and younger children. However, the results from this study should be generalized to other drugs metabolized by other pathways with caution. The $CL_{u.int,H}$ value is an interplay between the enzyme abundance and kinetic parameters (V_{max} and K_m).

The difference in enzyme abundance, depending on the pathway and age, can be masked or stressed by enzyme kinetic parameters, resulting in similar or different $CL_{u.int,H}$ and E_H values from those we

TABLE 1

Examples of age-related parameters defining the E_H and prior knowledge on their age dependency

Parameter	Definition	Age-Dependency Model
Q_H	Hepatic blood flow as a function of cardiac index	Guyton, 1991
MPPGL	Micrograms of microsomal protein per gram of liver	Barter et al., 2008
CYP3A4 and CYP1A2	Picomoles of enzyme abundance	Salem et al., 2014
Liver volume	Milliliters of liver	Johnson et al., 2005
Albumin and AAG	Plasma proteins concentration (g/l)	Johnson et al., 2006; Sethi et al., 2015

AAG, alpha-acid glycoprotein.

have shown in our study. Changes in E_H is not confined to age-varying parameters. Induction or inhibition of drug-metabolizing enzymes for a flow-limited drug can also change the extraction ratio of drugs.

In addition, changes to Q_H and $f_{u.B}$ resulting from hemodynamic changes occurring in clinical conditions or during the progression of disease may affect the extraction ratio of drugs. This consideration can be more important in preterm neonates because of the prematurity of metabolic pathways, in special populations such as elderly, and in pregnancy, which can affect the free fraction of the drug (f_u), enzyme activity, and/or Q_H, which ultimately can alter the E_H.

Because the determinants of CL (covariates) change with age, it is incorrect to assume no interaction between age and covariates. In some of the PopPK studies we have collected, the interaction between covariate terms was not identified by the investigators. The reason for the lack of such interactions can be the wide age range in some of these studies with a limited number of subjects at lower end of spectrum. In addition, several investigations only examined older subsets of children, where the ontogeny of enzymes responsible for metabolism is likely to be fully mature. These investigations are not likely to find that the addition of age into their clearance models provides a better fit.

Another reason for the lack of interaction originates from unbalanced blood sampling in early life after birth compared with older children. Some pharmacokinetic studies retrospectively analyzed the available samples of drug concentration in blood or plasma where the relevant covariates were not always available. Also some relevant covariates such as f_u may not have been measured in newborns. Only one PopPK study on morphine concluded that an independent clearance model is required for newborns (Knibbe et al., 2009).

The results in this study suggest that $CL_{u.int,H}$ is the most important parameter that affects the E_H of drugs. Due to rapid physiologic changes after birth and especially in the neonatal period, the E_H of drugs can be significantly affected by changes in the $CL_{u.int,H}$.

Hepatic extraction also contributes to the determination of the oral bioavailability of drugs. Currently, there is contradicting evidence as to whether the bioavailability of drugs is different between pediatrics and adults (Harper et al., 1988; Stratchunsky et al., 1991; Pinkerton et al., 1993; Hassan et al., 1994; Fujiwara et al., 1996; Anderson et al., 2002; Crill et al., 2006; Zane and Thakker, 2014). In clinical practice the bioavailability of drugs is assumed to be similar between pediatrics and adults, but our study supports that bioavailability also can be an age-dependant parameter and can change with age because the E_H changes with age. Assuming a higher hepatic extraction and thus a lower bioavailability in neonates, oral clearance can be overestimated in this population, and unnecessarily higher doses can be given to neonates. However, the clinical significance of these underestimations and overestimations is not clear and requires further investigation.

In conclusion, a high-extraction drug in adults is not necessarily a high-extraction drug in pediatrics. Unless the age-related changes in factors determining the E_H occur at the same rate, the extraction ratio will be different between pediatrics and adults. More attention should be given to the interaction terms of covariates during analysis of such data as the impact of certain physiologic covariates might change with age. Further clarification of the underlying mechanisms for the metabolism (and bioavailability) of drugs should heavily rely on modeling and simulation techniques.

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Authorship Contributions

Participated in research design: Salem, Abduljalil, Kamiyama, Rostami-Hodjegan.

Performed data analysis: Salem, Abduljalil, Kamiyama.

Wrote or contributed to the writing of the manuscript: Salem, Abduljalil, Rostami-Hodjegan.

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Drug Metabolism & Disposition

Supplementary Material

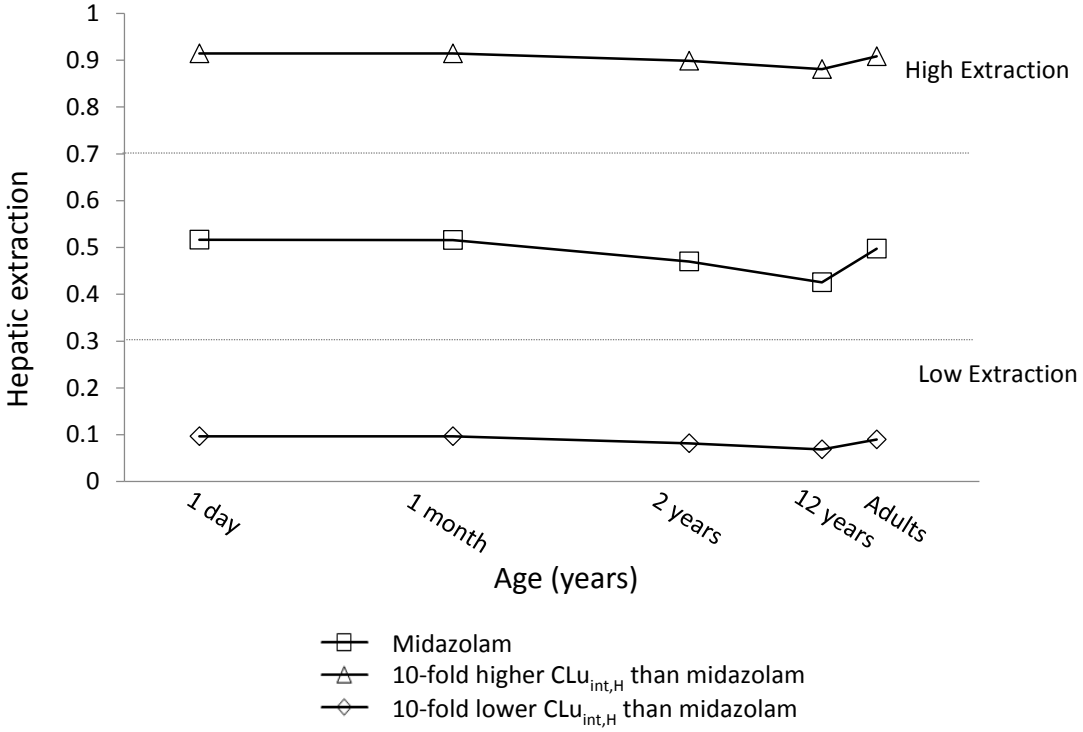

Figure S1 E_H changes with age for midazolam, a drug with 10-fold higher and lower CLu_{int}, are minimal when the enzyme abundance (pmol per MPPGL), MPPGL and fu_B are fixed to the adult values. The slight variation around 12 years relates to higher cardiac index (cardiac output to body surface area). Cardiac index values for 1 day, 1 month, 2 years, 12 years and 25 years are 2.33, 2.35, 2.50, 2.67, 3.80 and 2.5 L/min/m^2 (Johnson et al., 2006; Guyton., 1991).

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Drug Metabolism & Disposition

Table S1 Summary of covariates considered in analysing PopPK studies. However, not all of these covariates resulted in significant reduction of objective function and were included in the final model.

Covariate	Category
Post-menstrual age	Age
Postnatal age	
Post-conception age	
Starting age on breast milk	
Day of treatment	Time
Period of intubation before study entry	
Post-transplant days	
Weight (birth weight or current weight)	Size
Weight (allometric scaling, linear and exponential model)	
Body mass index	
Body surface area	
Fat free mass (Allometric scaling)	
Body length	
Head circumference	
Male and Female	Sex
Race	Ethnicity
Cratinine (Serum or clearance)	Biomarker
Billirubin (unconjugated)	
Aminotransferase	
Alkaline phosphatase	
Globulin concentration	

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Drug Metabolism & Disposition

Platelet counts	
Glomerular filtration rate	
Oxygen concentration	
Nephrectomy	Clinical Condition
Systemic inflammatory response syndrome	
Critical illness	
Hepatic dysfunction	
Health status	
Apgar score at 1 minute and 5 minutes	
Birth asphyxia	
Feed intolerance	
Presence of respiratory distress syndrome	
Patent ductus arteriosus	
Respiratory support and form of support	
Infection	
Co-medication (phenobarbital, parental nutrition, diuretic, enzyme inducer, dexamethasone, nephrotoxic drug)	Therapy
Carboplatin therapy	
Surfactant therapy	
CYP2C19 inhibitors	
Route of delivery	Maternal
Prenatal smoking history,	
Current multiple pregnancy	
Antepartum haemorrhage	
Chorioamnionitis	
Preeclampsia	

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Premature rupture of the membranes	
Genotypes (CYP2C19, 2C9, CYP2D6, OCT1)	Genotype
Study centre	Other
Inter-occasion variability	

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Table S2 Summary of the analyses PopPK studies with significant covariates. Where interaction between covariates was considered, the relevant covariates are identified.

ID	Compound	Population	Covariates	Covariate Interaction	Reference
1	Acetaminophen	PN=1–144 days	Weight, PMA, unconjugated bilirubin	Weight & PMA & unconjugated bilirubin	(Palmer et al., 2008)
2		27-42 weeks PCA	PCA, Weight	PCA & Weight	(Allegaert et al., 2004)
3		neonates (27-45 weeks PMA)	Weight, PCA	PCA & Weight	(Allegaert et al., 2011)
4		premature - 14 years	Weight (allometric),PCA	PCA & Weight	(Anderson et al., 2005)
5		6 months-2 years	Weight	No	(Prins et al., 2008)
6		Neonates to adolescents	PNA, Weight (allometric)	PNA and Weight	(Zuppa et al., 2011)
7		neonates	Weight, PMA	description of covariates interaction in the final model was not clear	(van Ganzewinkel et al., 2014)
8		1 day -34 years	Weight -dependent exponent model	No	(Wang et al., 2014)
9		4 days to 3 months.	age, Weight	age & Weight	(Anderson et al., 2000)

10		1 day to 6 months.	Weight & PCA	Weight & PCA	(Anderson et al., 2002)
11		< 18 years children	Weight	No	(Mohammed et al., 2012)
12	Actinomycin-D	children (1.6 to 20.3 years)	Weight	No	(Mondick et al., 2008)
13		< 21 years	Weight	No	(Hill et al., 2014)
14	Acyclovir	preterm and term infants	Weight, PMA	Weight & PMA	(Sampson et al., 2014)
15		0.8–19.9 children	Weight, CrCL	Weight & CrCL	(Zeng et al., 2009)
16		0.25-17yr children	Weight, BSA, GFR, PCA, Scr	Weight & BSA & GFR & PCA & Scr	(Tod et al., 2001)
17	Amikacin	gestational ages from 24 to 41 weeks	Weight, PMA	Weight & PMA	(Sherwin et al., 2009b)
18		gestational age 24–43 weeks; postnatal age 1–30 days	Weight -dependent exponent & PNA	Weight & PNA	(De Cock et al., 2012)
19	Aminophylline	PNA=0-26 weeks	Weight, PNA	No	(Moore et al., 1989)
20	Bevacizumab	children	BMI	Weight & BMI	(Turner et al., 2014)

21	Busulfan	children	Weight	No	(Diestelhorst et al., 2014)
22		0.45-16.7 years	Weight	No	(Nguyen et al., 2004)
23		10 days to 15 years	Weight (allometric)	No	(Paci et al., 2012)
24		94 children (0.4 - 18.8 years)	BSA, Weight	No	(Trame et al., 2011)
25		0.7-13.1 years children	Allometric Weight	No	(Veal et al., 2012)
26		0.2 to 23 years	Weight	No	(Zwaveling et al., 2008)
27		age 0.1-3.3 years old	Allometric Weight, Age	Weight and age	(Savic et al., 2013)
28		0.1 to 26 years	age, WT, BSA	No	(Bartelink et al., 2012)
29	Caffeine	premature neonates 27.6 weeks GSA	Weight, PNA	Weight & PNA	(Charles et al., 2008)
30		premature neonates	Weight, LGA, PNA and parental nutrition	GA & Weight &PNA	(Falcao et al., 1997)
31		premature neonates <32 GW	Weight, PNA	No	(Lee et al., 1997)

32		premature neonates < 34 GW	Weight	No	(Lee et al., 2002)
33	Canrenoate	2 days-0.85 years	Weight, PMA	Weight & PMA	(Suyagh et al., 2013)
34		2 days to 10 years children	Weight	No	(Suyagh et al., 2012)
35	carboplatin	2 m to 18 years	Weight, SeCr, nephrectomy	Weight & SeCr & nephrectomy	(Chatelut et al., 1996)
36	cefepime	Premature & infants <4 mon.	Weight, SeCr	Weight & SeCr	(Capparelli et al., 2005)
37	cefozopran	children	Weight	No	(Ikawa et al., 2009)
38	ceftazidime	10–45 years	Allometric scaling by FFM	No	(Bulitta et al., 2010)
39	ciprofloxacin	0.27-16.9 years	Weight, Age	Weight & Age	(Rajagopalan and Gastonguay, 2003)
40		6 - 16 years	Weight	No	(Schaefer et al., 1996)
41	Clindamycin	Premature Infants to Adolescents	Weight, PMA	Weight & PMA	(Gonzalez et al., 2014)
42	Clonidine	0-15 years	Weight	need full paper	(Potts et al., 2007)

43	cyclophosphamide	age range 1.30 – 9.37 years	GFR, gender	No	(McCune et al., 2009)
44	cyclosporine	children	BSA, posttransplant Days	BSA & posttransplant Days	(Zhou et al., 2013)
45		0.36 - 17.5 years	Weight, Cholesterol, Hct, Scr	Weight & Cholesterol & Hct & Scr	(Fanta et al., 2007)
46		0.9 -20 years	Weight, age, co-med (itraconazole & tobramycine)	description of covariates interaction in the final model was not clear	(Schrauder et al., 2009)
47	cytosine arabinoside	52 paediatric patients	AGE, BSA	AGE & BSA	(Periclou and Avramis, 1996)
48	daunorubicin	children	Weight	No	(Hempel et al., 2003)
49	dexmedetomidine	children	Weight, study centre	No	(Petroz et al., 2006)
50	Diclofenac	aged 1-14 years	Weight	No	(Standing et al., 2011)
51	digoxin	0.33 to 15 years children	SeCr	No	(el-Desoky et al., 2005)
52	doxorubicin	children older than 3 years	BSA, inter-occasion varaibility	No	(Kontny et al., 2013)

53	esomeprazole	0-17 years	Weight, age	description of covariates interaction in the final model was not clear	(Sandstrom et al., 2012)
54	Etomidate	0.53-13.21 years	Allometric WT, Age	Weight & Age	(Lin et al., 2012)
55		14 weeks to 16.7 years	Weight (alometry)	No	(Urien et al., 2011)
56	fluconazole	PNA=0.14 to 12.6 weeks	Weight, postnatal age, gestational age at birth, SeCr	Weight & GA & PNA & Scr	(Wade et al., 2008)
57	flurbiprofen	3 mon. - 13 years children	Weight	No	(Kumpulainen et al., 2010)
58	Ganciclovir	PNA= 8-34 days	WT	No	(Acosta et al., 2007)
59	Gentamicin	14 - 81 years cancer patient	creatinine clearance	No	(Rosario et al., 1998)
			WT, PNA	WT & PNA	(De Cock et al., 2014)
60		neonates	WT , PNA	WT & PNA	(Sherwin et al., 2009a)

61		premature & term neonates(PMA=24.2-42.4wks)	WT, PNA, gestational age	WT, PNA & GA	(Fuchs et al., 2014)
62	hydrocortisone	critically ill neonates	WT, PMA	WT & PMA	(Vezina et al., 2014)
63	indomethacin	premature neonates	WT	No	(Al Za'abi et al., 2007)
64		PNA=1-77 days	WT, PNA	WT & APNA	(Smyth et al., 2004)
65	Irinotecan	children	WT, Age and bilirubin	WT & Age & bilirubin	(Thompson et al., 2008)
66	Ketamin	1.5-14 years children (and adult)	WT	No	(Herd et al., 2007)
67	Lamivudine	2 days to 18 years	WT (alometry), PMA (maturation)	WT & PMA	(Bouazza et al., 2011)
68	Levofloxacin	paediatric & adult	WT, Age	WT & Age	(Li et al., 2010)
69	levetiracetam	PNA=1 - 5 days	WT, PNA	WT & PNA	(Sharpe et al., 2012)
70	lorazepam	3 mon - <18 years	WT	No	(Chamberlain et al., 2012)

71	Melphalan	children	WT, GFR, carboplatin therapy	No	(Nath et al., 2007)
72	Meropenem	GA=29 - 42 weeks	CrCL, WT	No	(van den Anker et al., 2009)
73	Methotrexate	children	WT, Age	No	(Colom et al., 2009)
74	Metronidazole	32 pre-term	WT, PMA	WT & PMA	(Suyagh et al., 2011)
75	Micafungin	children and adult	WT, platelet counts	No	(Tabata et al., 2006)
76	Midazolam	paediatric intensive care unit	WT	No	(Bienert et al., 2013)
77		neonates	WT, GA	WT & GA	(Burtin et al., 1994)
78		1 month to 17 years children	critical illness, WT	critical illness & WT	(Ince et al., 2012)
79		Premature Infants to Adolescents	WT, WT-dependent exponent of allometric exponent function	No	(Ince et al., 2013)
80		6 months to < 16 years	Age	No	(Reed et al., 2001)

81		2 month to 17 years children	WT-dependent exponent function	No	(Ince et al., 2012)
82		paediatric intensive care unit	WT (albumin was added, but removed from the final model not significant)	No	(Bienert et al., 2013)
83	Montelukast	6 - 86 years	WT	No	(Ramakrishnan et al., 2005)
84	Morphine	children	WT, OCT1 genotypes	WT & OCT1 genotypes	(Fukuda et al., 2013)
85		preterm - < 3 years	WT, PNA	PNA (stratified)	(Knibbe et al., 2009)
86		0 - 3 year children	WT, PNA, creatinine, bilirubin,	WT & PNA	(Bouwmeester et al., 2004)
87	Mycophenolic	children and young people	WT, ciclosporin	WT & ciclosporin	(Zeng et al., 2010)
88	Myo-inositol	Infants born in 23-29 weeks of gestation	WT (allometric), CrCL, gestational age	No	(Phelps et al., 2013)
89	Netilmicin	2 to 28 days	cWT, PMA	cWT & PMA	(Sherwin et al., 2008)

90	Omeprazole	critically ill children	WT (allometry)	No	(Solana et al., 2014)
91	Ondansetron	2–38 years	Wt, Age, Sex,	sex & age + wt	(de Alwis et al., 1998)
92	Palivizumab	Preterm infants to adult	age,WT, lung disease, race, antidrug antibody titer	WT, Age, race, lung disease and antidrug antibody titer	(Robbie et al., 2012)
93	Pantoprazole	0.025-16 years	WT, GA, Age, race, gender, 2C9 polymorphisms	WT, GA, Age, race, gender, 2C9 polymorphisms	(Knebel et al., 2011)
94		10 days to 16.4 years	WT, Age, hepatic dysfunction, CYP2C19 inhibitors , systemic inflammatory response syndrome	WT, Age, DDI , SIRS, Hepatic dysfunction	(Pettersen et al., 2009)
95	Phenobarbital	PNA= 0.0–206 days	WT (allometric)	No	(Marsot et al., 2014)
96	Phenytoin	neonates and infants	WT, PNA	WT & PNA	(Al Za'abi et al., 2006)
97		include children	WT	No	(Tanaka et al., 2013)

98	Propofol	obese children and adolescents	WT	No	(Diepstraten et al., 2012)
99		0.25-88 years	WT, age, sex, health status	WT & Age	(Eleveld et al., 2014)
100		3 - 11 years	WT	No	(Kataria et al., 1994)
101		children	WT	No	(Knibbe et al., 2002)
102		pre-term to adults	WT	No	(Wang et al., 2012)
103		from 2.0 to 88 year	WT	No	(Schuttler and Ihmsen, 2000)
104		1 week to 12 year	WT, Cardiac surgery	No (or yes WT & Cardiac Surgery)	(Rigby-Jones et al., 2002)
105	Ranitidine	critically ill children (age: 0.042 - 15.51 years)	WT (allometry)	WT & Cardiac failure/surgery	(Hawwa et al., 2013)
106	Sildenafil	new-born (11-71 hr)	PNA	No	(Mukherjee et al., 2009)
107	Tacrolimus	1-14 years children	Age	No	(Sam et al., 2000)
108		children	WT, serum creatinine;	WT & SeCr	(Wallin et al., 2009)

109	Theophylline	premature neonates	WT, PNA	No	(Lee et al., 1996)
110	Tobramycin	children	WT	No	(Hennig et al., 2008)
111		0.1-18.8 years	WT	No	(Sherwin et al., 2014)
			WT, PNA	WT & PNA	(De Cock et al., 2014)
112	Tramadol	children (0–3 months) and adult (23-57 year)	WT, PCA	WT & PCA	(Allegaert et al., 2005)
113	Tranexamic acid	1.0 - 12 years	WT (alometry)	No	(Grassin-Delyle et al., 2013)
114	Valproic acid	1 to 17 years	Weight	No	(Williams et al., 2012)
115	Vancomycin	neonates	current Weight, birth Weight, SeCr, PNA	current weight, birth weight, SeCr & PNA	(Zhao et al., 2013)
116			Weight, PNA	Weight & PNA	(De Cock et al., 2014)
117	Voriconazole	2 to <12 years	Weight, age, CYP2C19 phenotypes, ALT	Weight, age, 2C19 phenotype, ALT	(Karlsson et al., 2009)
118		2 years to adult	Weight, age, CYP2C19 phenotypes	Weight, age, CYP2C19 phenotypes	(Friberg et al., 2012)
119		2 to 11 years	Weight, 2C19 phenotype	Weight & 2C19 phenotype	(Walsh et al., 2004)

120	2–11 years children	Weight, 2C19 phenotypes, aminotransferase, alkaline phosphatase	Weight & 2C9 phenotype, alanine amino transferase, alkaline phosphatase	(Wahlby et al., 2004)

SeCr: serum creatinine

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