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Title Page

Considering Age Variation when Coining Drugs as High vs Low Hepatic Extraction Ratio

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Running Title Page

Running Title: Consequences of Age Variation in Hepatic Extraction Ratios

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Text pages: 13 (Including References)

Tables: 1 (2 in Supplementary Material)

Figures: 3 (1 in Supplementary Material)

References: 17

Abstract: 254

Introduction: 333

Discussion & conclusions: 837

Abbreviations

AAG, alpha-acid glycoprotein; B:P, Blood to plasma ratio; $CLu_{int,H}$, Hepatic intrinsic clearance of unbound drug; $CL_{H,B}$, Hepatic metabolic clearance; E_H, Hepatic extraction ratio; *fu*, Fraction of drug in plasma unbound; fuB, Unbound drug in blood; MPPGL, Microsomal protein per gram of liver; PopPK, Population pharmacokinetics; Q_H, Hepatic blood flow.

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Abstract

Hepatic extraction ratio (E_H) is commonly considered as ‘an inherent attribute’ of drug. It determines the main physiological and biological elements of the system (patient attributes) which are most significant in inter-individual variability of clearance. E_H consists of three age-dependent parameters: fraction of unbound drug in blood (fu_B), hepatic intrinsic clearance of unbound drug ($CLu_{int,H}$) and hepatic blood flow (Q_H). When 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 fu_B, $CLu_{int,H}$ and Q_H, E_H of midazolam and two hypothetical drugs with 10-fold higher and 10-fold lower $CLu_{int,H}$ than midazolam were investigated in paediatrics based on known ontogeny functions. E_H was simulated using Simcyp V14. This was then complemented by a comprehensive literature survey to identify commonly applied covariates in paediatric 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 $CLu_{int,H}$ and fu_B than adults and reducing impact of Q_H on clearance. The drug with 10-fold higher $CLu_{int,H}$ was categorised as high extraction from 4 days old onwards, whilst the drug with 10-fold lower $CLu_{int,H}$ 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 young paediatric patients. E_H cannot be considered as an inherent drug property without considering the effect of age.

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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 the Equation 1:

$$CL_{H,B} = E_H \times Q_H \qquad \textbf{Equation 1}$$

E_H is calculated from fraction of drug unbound in blood (fu_B), hepatic intrinsic clearance of unbound drug ($CLu_{int,H}$) and Q_H according to Equation 2:

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

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 E_H of a drug is considered as an inherent attribute of the drug and presented with a fixed value. However, this classification does not consider that the parameters in Equation 2 are age-dependent and changes in these parameters will affect E_H. For example, a rise in fu_B, for low E_H drugs increases hepatic metabolic clearance, whereas for high extraction drugs this does not affect metabolic clearance. Unless the age-related physiological changes in fu_B, $CLu_{int,H}$ and Q_H occur in parallel, it is expected that 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 analysing population pharmacokinetic (PopPK) studies. However, since applying 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.

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The primary aim of this study is to investigate relative differences in E_H with age using *in vivo* midazolam data and two hypothetical high and low extraction drugs through modelling and simulation techniques. We also use the concept of the age varying E_H to examine whether the interaction between covariate terms in modelling clearance have been considered in the PopPK studies.

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Materials and Methods

Literature Data collection

Data on midazolam systemic clearance in paediatrics from birth to 17 years were collected from the literature. Literature search strategy and methodology for deconvolution of clearance to arrive at $CL_{H,B}$ from midazolam systemic clearance (using blood to plasma ratio (B:P)) 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 $CLu_{int,H}$ than midazolam was designed by multiplying and dividing the deconvoluted midazolam $CLu_{int,H}$ by 10 as proposed by (Salem et al., 2014) to mimic a high and low extraction drug, respectively. Then, using the relevant $CLu_{int,H}$, Q_H and fu_B in Equation 2, E_H was calculated.

A number of simulations in Simcyp Paediatric v14 were carried out for midazolam, a drug with 10-fold higher and 10-fold lower $CLu_{int,H}$ than midazolam to show age related changes in the magnitude of E_H. One hundred subjects were simulated consisting of equal proportion of males and females and combination of age bands (1 day, 1 month, 2 years and 12 years as well as adult). E_H was calculated using Equation 3 from the output data. Mean values of E_H at each age band were plotted against age for each of the simulated drugs.

Calculation of hepatic extraction ratio

Hepatic extraction ratio was calculated from CL_H and Q_H for midazolam and the other two hypothetical drugs assuming well-stirred model using Equation 3;

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

Sensitivity analysis

Sensitivity analysis was carried out with a view to identify which component of the extraction ratio ($CLu_{int,H}$, Q_H and fu_B) plays the most dominant role in variation of E_H from those of adult

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values at any given age. The impact of age dependent Q_H was evaluated by fixing fu_B and $CLu_{int,H}$ (L/h/g of liver) to the adult values for all age ranges. This involved assumptions on lack of any ontogeny for 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 values of $CLu_{int,H}$ (L/h/g of liver) were used to calculated the paediatric $CLu_{int,H}$ values per whole liver by applying age-related liver weight. E_H was plotted against age and patterns were compared. In another set, only fu_B values were fixed to adult values to demonstrate the sensitivity of E_H to age related changes in Q_H and $CLu_{int,H}$ (L/h) without impact of age-related changes in binding. E_H was calculated and plotted against age and compared with the original set of results (where all age-related parameters had been considered).

In order 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 paediatric values of enzyme abundance relative to adults at given age (in this case CYP3A4) alongside relative values for liver volume, hepatic blood flow and MPPGL.

Population Pharmacokinetic studies (PopPK)

A comprehensive literature survey using Pubmed was carried out to identify commonly used covariates in paediatric PopPK studies for drugs after intravenous administration. No year or journal or language restriction applied to the search process. Collated publications were carefully checked for modelling covariates and the form of the covariates-clearance relationship in the reported model. Studies that considered the interaction between covariates and clearance were identified. Interaction between covariate terms was also considered if the presence of a covariate modifies the impact of another covariate in a multiplicative or exponential way. Where there are different clearance models for different paediatric age ranges, interaction with age is also considered. Interaction between covariate terms was not considered if only one covariate was considered in the final clearance model or if the covariates are in linear additive relationship to the clearance. Corresponding authors were contacted where modelling section was not clear.

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Results

Midazolam hepatic extraction ratio

Hepatic extraction ratio of midazolam, after deconvolution of clinical systemic clearance, increased with age. 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 E_H increases with age for midazolam and two other hypothetical compounds. The degree of change in E_H with age depends on magnitude of $CLu_{int,H}$ against the given enzyme. As shown in the figure, 10-fold reduction in $CLu_{int,H}$ results in a drug with low hepatic extraction across the paediatric and adult age range whereas 10-fold increase in $CLu_{int,H}$ shifts the drug from so called intermediate to high extraction status.

Sensitivity analysis

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

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

The rate of change with age for liver volume, hepatic blood flow and MPPGL as a fraction of adult values are shown in Figure 3. This figure shows the changes in underlying parameters of $E_{H.}$ The changes in blood flow and liver volume relative to adults occurs almost in parallel to each other. Therefore, the discrepancy in Q_H and liver size alone cannot account for the observed differences in 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. **Error! Reference source not found.** summarises the contributing parameters to E_H that are

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reported in Figure 3. Needless to say, if 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 E_H.

Analysis of covariates in population pharmacokinetic (PopPK) studies

A total of 120 PopPK studies were retrieved in paediatric 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). Table S1 in supplements summarises the most commonly used covariates in the analysed PopPK studies (Supplemental Table 1). Table S2 in supplements shows all the analysed PopPK studies with interaction between covariates (Supplemental Table 2).

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Discussion and Conclusions

E_H of the drugs in this study increases with age due to rapid physiological changes in parameters determining E_H after birth including the ontogeny of enzyme abundance and to a lesser extent MPPGL. Although not relevant to the cases represented in this study, ontogeny of plasma proteins can play a significant role in age-related changes of E_H for highly bound, low extraction drugs. As shown previously by several authors, concentration of plasma proteins increases with age whereas unbound fraction of drugs in plasma and therefore in blood decreases with age (Sethi et al., 2015, Johnson et al., 2006 and McNamara and Alcorn, 2002). The ontogeny of plasma protein binding and enzyme abundance on any given compound depends on the extent of binding to particular protein and the importance of that enzymatic pathway to the overall elimination of 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 paediatrics. For the particular case studies in this report, where the binding was not a major factor, and CYP3A4 was the main metabolising 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 generalised to other drugs metabolised by other pathways with caution. $CLu_{int,H}$ 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 and hence resulting in similar or different $CLu_{int,H}$ and E_H values from what has been shown in this study. Changes in E_H is not confined to age-varying parameters. Induction or inhibition of drug metabolising enzymes for a capacity limited drug and inhibition of drug metabolising enzyme for a flow limited drug can also change the extraction ratio of drugs. In addition changes to Q_H and fu_B due to hemodynamic changes occurring in clinical conditions and progression of disease may affect the extraction ratio of drugs. This consideration can be more important in preterm neonates due to prematurity of metabolic pathways, special populations such as

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elderly and pregnancy that can affect free fraction of the drug (f_u), enzyme activity and/or Q_H which ultimately can alter E_H.

Since the determinants of CL (covariates) change with age, it is not right to assume no-interaction between age and covariates. In some of the analysed PopPK studies here, the interaction between covariate terms were not identified by their authors. The reason for lack of such interactions can be the wide age range in some of these studies with 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 are likely to be fully mature. These investigations are not likely to find that the addition of age into their clearance models provide a better fit. Another reason for lack of interaction origins from unbalanced blood sampling in the early life after birth compared with older children. Some pharmacokinetic studies retrospectively analysed the available samples of drug concentration in blood or plasma where the relevant covariates are not always available. Also some relevant covariates such as f_u may not have been measured in new-borns. Only one PopPK study on morphine concluded an independent clearance model is required for new-borns (Knibbe et al., 2009).

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

Hepatic extraction also contributes to determination of oral bioavailability of drugs. Currently, there are contradicting evidence as to bioavailability of drugs is different between paediatrics 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). While in clinical practice bioavailability of drugs is assumed to be similar between paediatrics and adults, the current study supports bioavailability also can be an age-dependant parameter and reduce with age since E_H changes with age. Assuming a higher

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hepatic extraction and therefore lower bioavailability in neonates, oral clearance can be overestimated in this population and unnecessarily higher doses given to neonates. However, the clinical significance of this under 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 paediatrics. Unless the age-related changes in factors determining E_H occur at the same rate, extraction ratio will be different between paediatrics and adults. More attention should be given to interaction terms of covariate during analysis of such data as the impact of certain physiological covariates might change with age. Further clarification of underlying mechanisms for metabolism (and bioavailability) of drugs should heavily rely on modelling 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

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Figure Legends

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

Figure 2 Simulated hepatic extraction in Simcyp v14 shows changes with age for midazolam, a drug with 10-fold higher $CLu_{int,H}$ and a drug with 10-fold lower $CLu_{int,H}$. A high or intermediate extraction drug in adults is not necessarily a high or intermediate exteraction drug in paediatric subjects. Dashed lines are the same E_H values with age when fu_B is remained unchanged (fu_B=0.05). Dotted lines show the limits for high (>0.7) and low (0.3>) extraction.

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

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Tables

Table 1. Examples of age-related parameters defining 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	mg of microsomal protein per gram of liver	Barter et al., 2008
CYP3A4 and CYP1A"	pmol of enzyme abundance	Salem et al., 2014
Liver volume	ml of liver	Johnson et al., 2005
Albumin and AAG	Plasma proteins concentration (g/L)	Johnson et al., 2006 and Sethi et al., 2015

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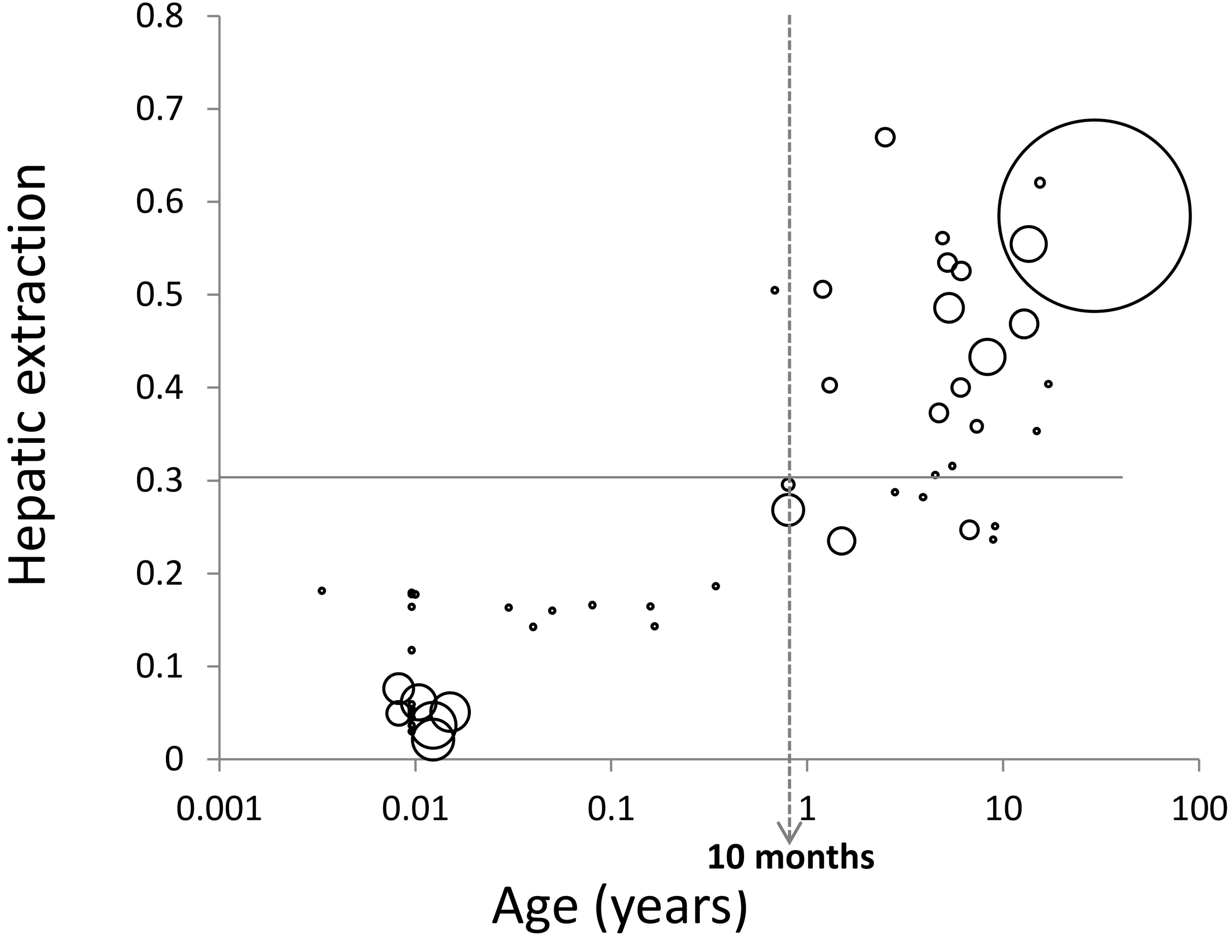
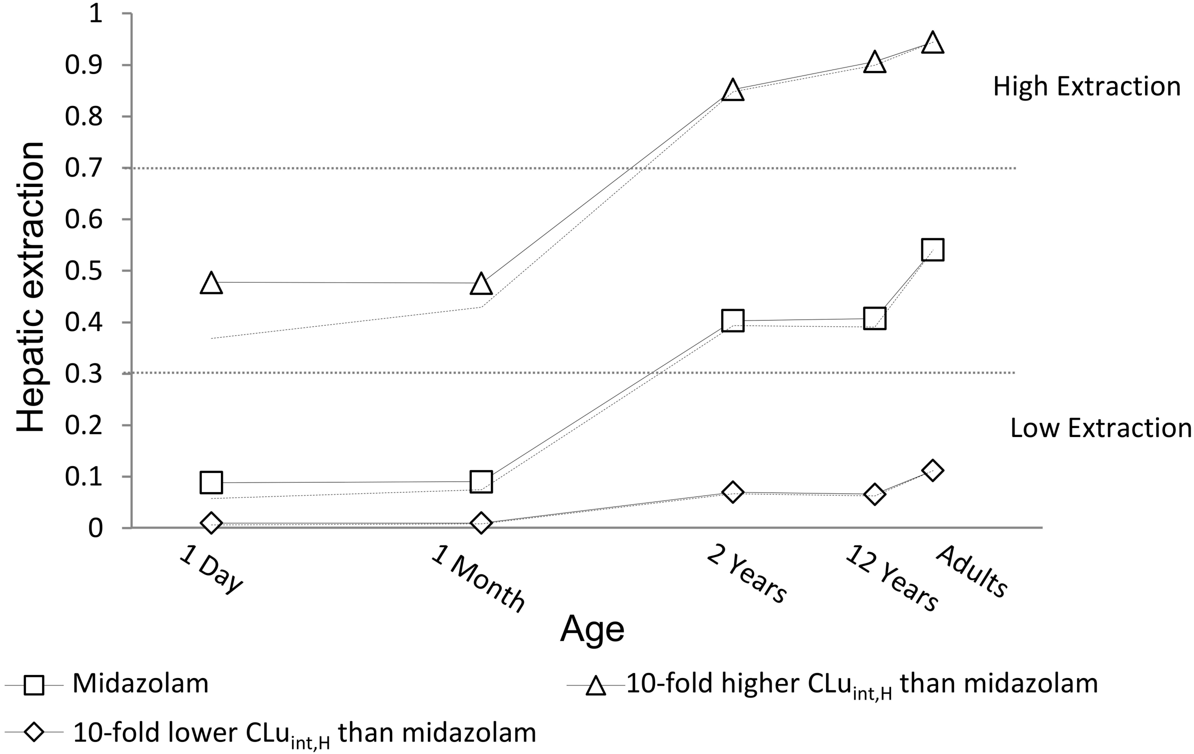
Figure 1



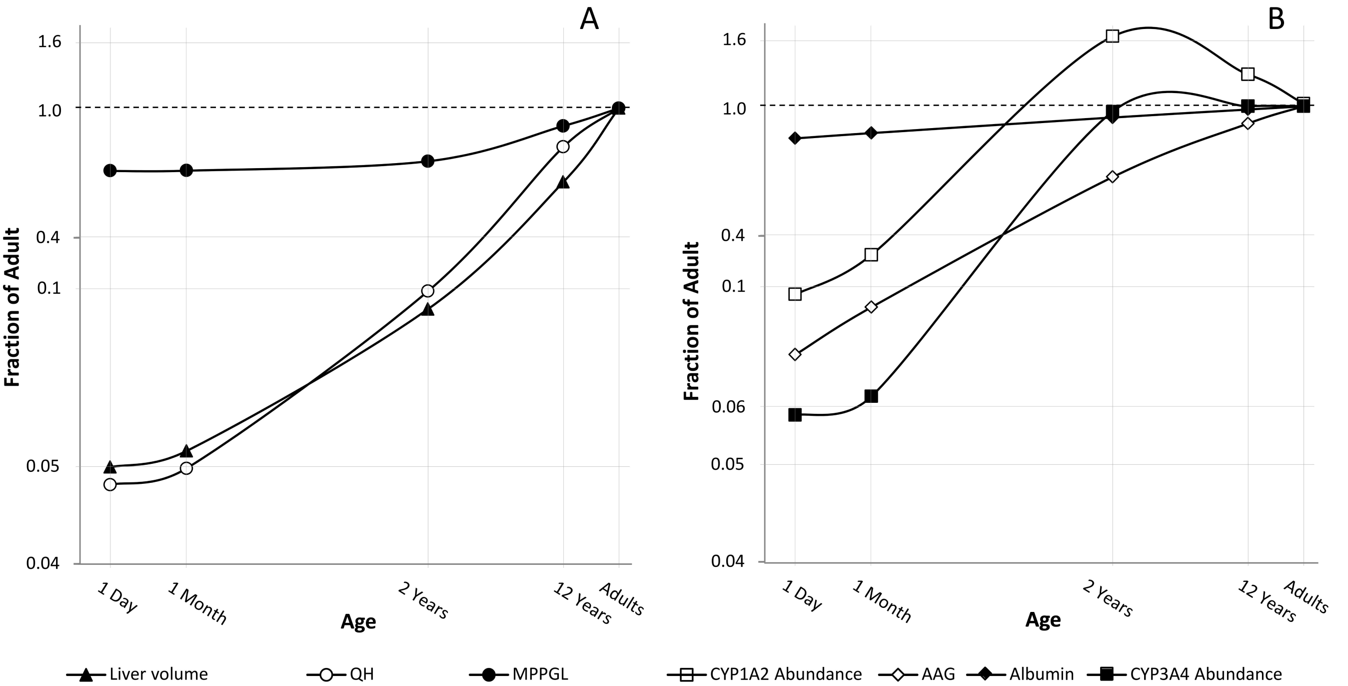
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Hepatic extraction
0.001
0.01
0.1
1
10
100
10 months
Age (years)

Figure 2



1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Hepatic extraction
High Extraction
Low Extraction
1 Day
1 Month
2 Years
12 Years
Adults
Age
Midazolam
10-fold higher CLu$_{int,H}$ than midazolam
10-fold lower CLu$_{int,H}$ than midazolam

Figure 3



A
1.6
1.0
0.4
0.1
0.05
0.04
Fraction of Adult
1 Day
1 Month
2 Years
12 Years
Adults
Age
B
1.6
1.0
0.4
0.1
0.06
0.05
0.04
Fraction of Adult
1 Day
1 Month
2 Years
12 Years
Adults
Age
Liver volume
QH
MPPGL
CYP1A2 Abundance
AAG
Albumin
CYP3A4 Abundance