CERTARA
Implementing Translational Science

SIM CYP
simulator | consultancy | education

Misconceptions on the issue of high vs low hepatic extraction ratio:
the forgotten element of age variation

Khaled Abduljalil

Tripos SIM CYP Pharsight

The Problem

Hepatic clearance is determined by their hepatic extraction ratio (E_H)

$$CL_H = Q_H \times E_H \longrightarrow E_H = CL_H / Q_H$$

E_H generally classified as :

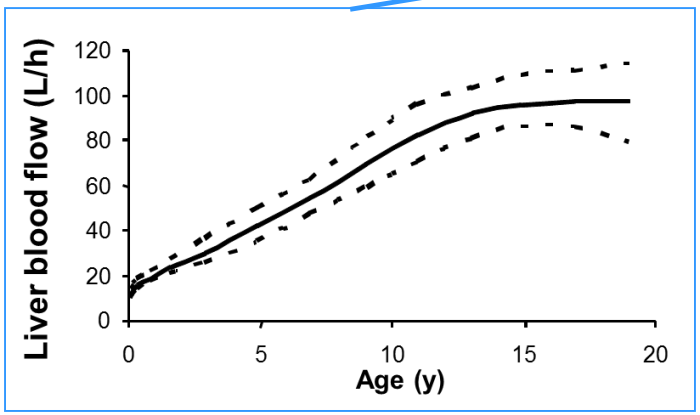
- Low (<0.3) → warfarin, phenytoin, ... etc.
- Intermediate (0.3-0.7) → Quinidine, codeine, nortryptyline, ... etc.
- High (>0.7) → morphine, verapamil, propranolol, ... etc.

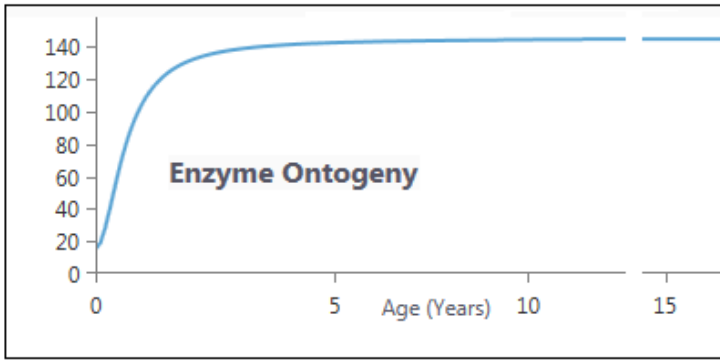
E_H is commonly considered as an inherent attribute of drug with a fixed value.

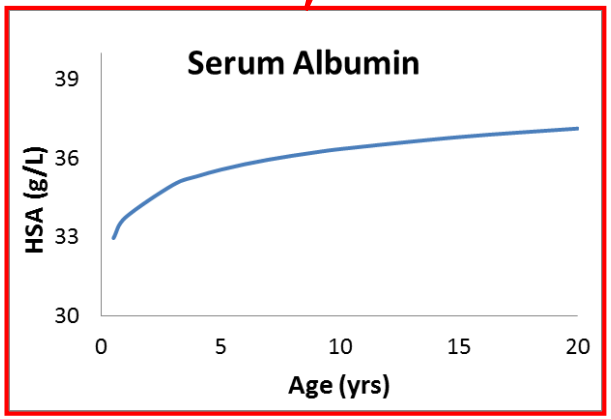
CERTARA

Extraction ratio

$$\text{Extraction Ratio} = \frac{fu_B * CLu_{int,H}}{Q_H + (fu_B * CLu_{int,H})}$$







CERTARA

Objective

To investigate age-related changes in E_H from birth to 17 years for

- Midazolam
- A drug X with 10 x midazolam $CLu_{int,H}$
- A drug Y with 0.1 x midazolam $CLu_{int,H}$

To identify commonly applied covariates in paediatric PopPK studies

CERTARA

Methods

- Data on midazolam CL_{iv} (0 to 17 yrs) were collected from the literature.
- $CL_{H,B}$ was calculated from CL_{iv} considering ontogeny of contributing parameters (renal function, fu, B:P etc.) (Salem et al., 2014).
- Impact of age-related changes to fu_B, $CLu_{int,H}$ and $Q_{H,B}$ were investigated on relative paediatric to adult E_Hs.
- A comprehensive literature survey was carried out to identify commonly applied covariates in paediatric PopPK studies.

CERTARA

Results

❑ **Midazolam**

- fu_B decreased from 0.15 at the age of 3 days to 0.06 in adulthood,

- $CLu_{int,H}$ increased from 0.05 L/h to 2057 L/h.

- E_H is low at birth (0.02) and increases with age and becomes intermediate by about 7 months when it approximates the adult value (~ 0.6).

❑ **Drug with MDZ-$CLu_{int,H}$ x10**

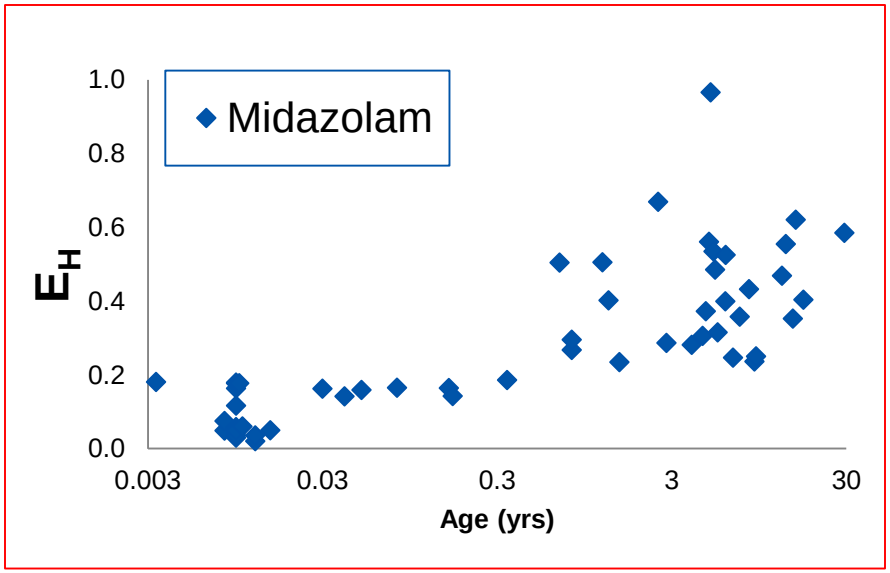
E_H is remain high from birth although E_H reached adult level (0.9) at about 8 months

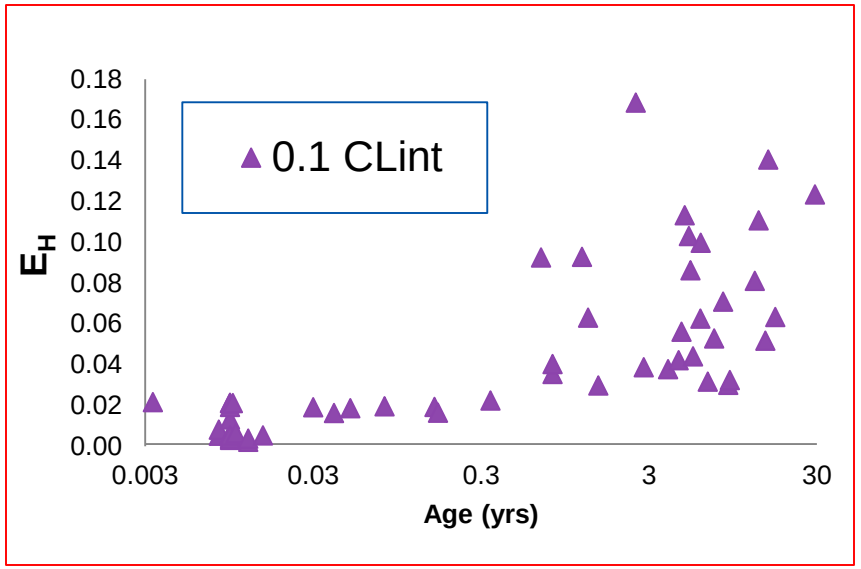
❑ **Drug with MDZ-$CLu_{int,H}$ x 0.1**

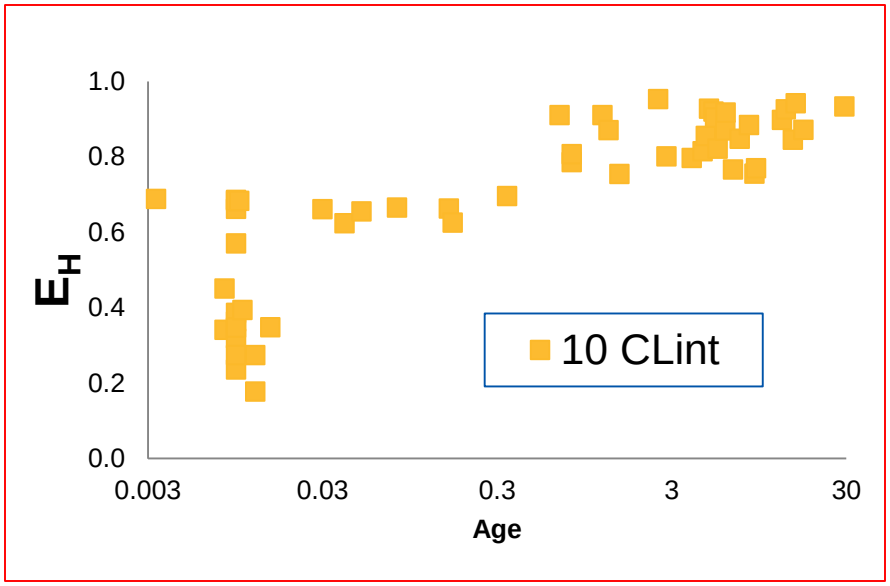
E_H is remain low from birth although only 30% of adult E_H value (0.1) is achieved by the first year

CERTARA

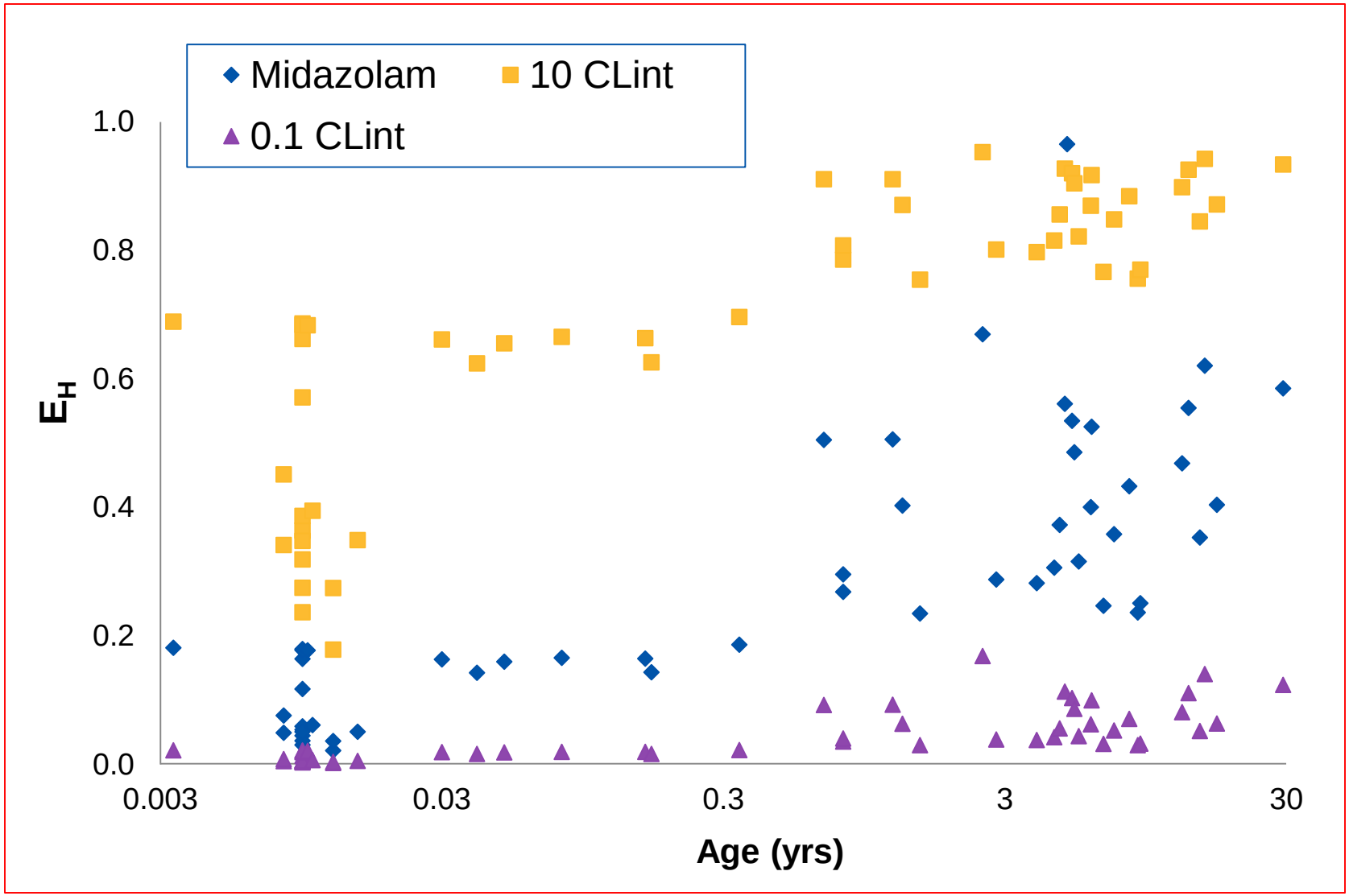
Hepatic Extraction ratio





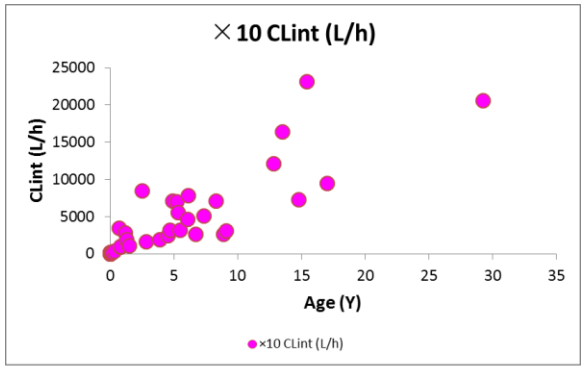


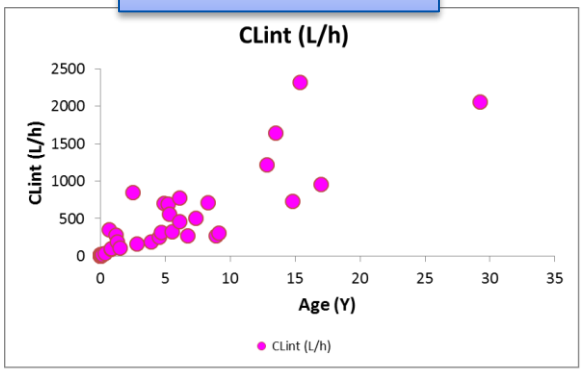
Hepatic Extraction ratio of the studied examples

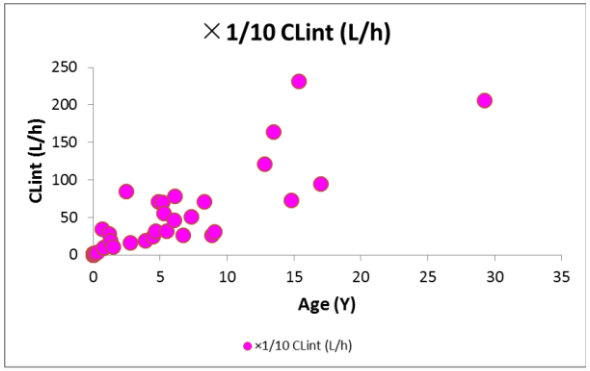


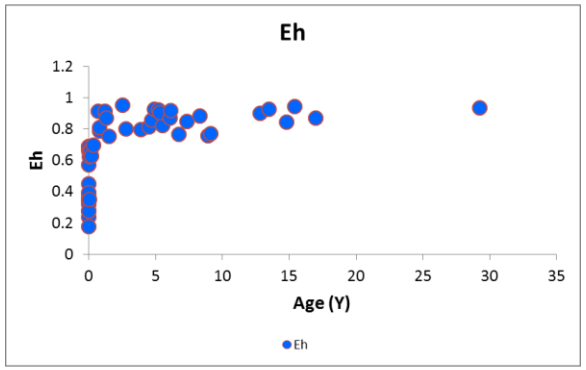
Results

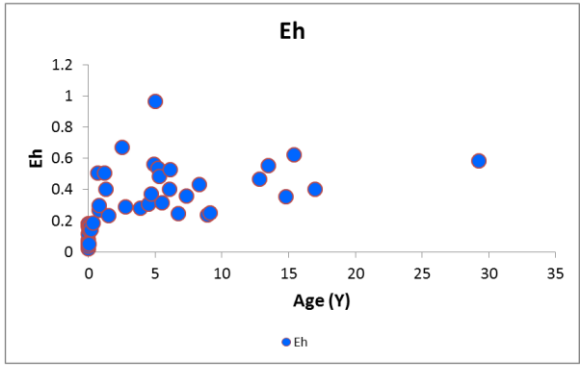
Midazolam

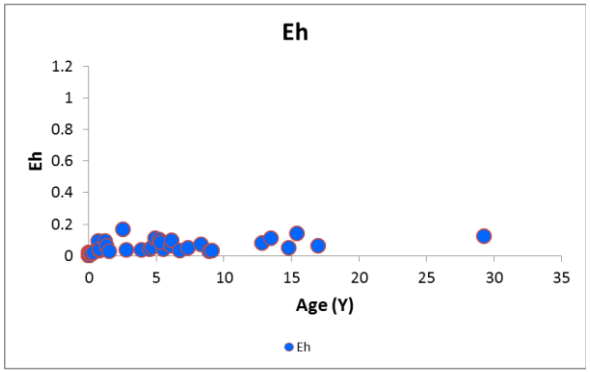


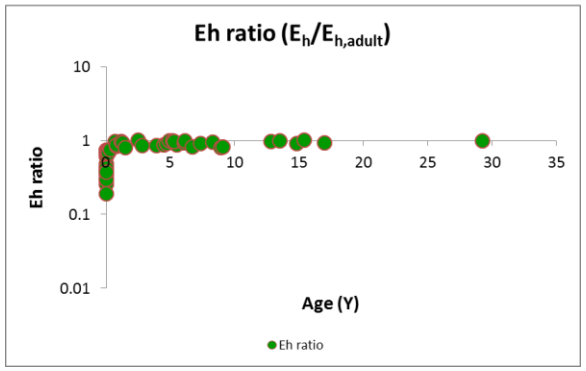


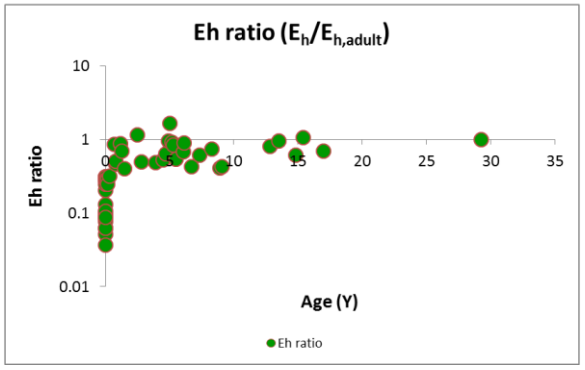


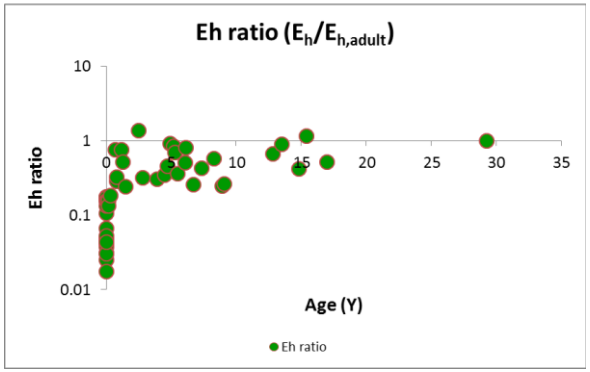












CERTARA

PopPK Survey results

- Total of 121 PopPK studies investigated paediatric patients.
- Half of these studies did not consider interaction between covariates at all.
- Majority includes WT and AGE(GA, PNA, PMA)

Covariates in all studies
Post-menstraul age
Postnatal age
Weight
BMI
BSA
Height, head circumference
Sex
Race
Serum creatinine
Clearance of creatinine
Unconjugated bilirubin
Bilirubin
Aminotransferase
Alkaline phosphatase
Globulin conc
Platelet counts
Glomerular filtration rate
CYP2C19 genotypes
2C9 genotype
CYP2D6 genotypes
OCT1 genotypes

CERTARA

Conclusion

- Coining a drug as ‘high extraction’ cannot be universally applied at lower ages
- Low extraction drugs in adults will be low extraction in paediatrics, too.
- This has implications for selecting covariates to study in populations involving wide age range and include neonates or young children.
- Attention should be paid to interaction terms of covariate during analysis of such data (e.g. age-albumin, genotype-age) as impact of some of the covariates might change with age.

CERTARA

Acknowledgements

Farzaneh Salem

Simcyp Limited, Sheffield, UK

Yoshiteru Kamiyama

Astellas Pharma Inc, Japan

Amin Rostami-Hodjegan

Simcyp Limited, Sheffield, UK & Manchester University, UK

Questions ?

CERTARA

$$\text{Extraction Ratio} = \frac{f_{u,b} \times CLu_{int}}{Q_h + (f_{u,b} \times CLu_{int})}$$

$$fu(paed) = \frac{1}{1 + \frac{(1 - fu(adult) \times [P]_{paed}}{[P]_{adult} \times fu(adult)}}$$

$$Q_{H,B} = \frac{25.5}{100} \times \text{Cardiac output}$$

$$fu_B = \frac{fu(paed)}{B:P}$$

$$CLu_{int} = \frac{Q_{H,B} \times CLH}{fu_B(QH_{,B} - CLH)}$$

CERTARA