Dose Individualization of CYP3A Substrates in Children: Characterization of Intestinal and Hepatic CYP3A Activity in Children to Predict First-pass and Systemic CYP3A-mediated Metabolism

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Cluster Systems Pharmacology

BACKGROUND

Characterization of CYP3A activity in the gut wall and liver is essential for dose individualization of CYP3A substrates in the pediatric population.

AIM: To characterize intestinal and hepatic metabolism of midazolam (surrogate marker for CYP3A activity) in children in order to predict CYP3A-mediated first-pass and systemic metabolism.

METHODS

- Pharmacokinetic (PK) data of midazolam and 1-OH-midazolam in 264 post-operative children aged 1-18 years receiving orally administered midazolam [1]
- Physiological population PK modelling approach [2], based on accepted PBPK principles and physiological parameter values from literature and/or scaled from adults (**Figure 1**)
- Estimation of whole-organ intrinsic clearance in gut wall and liver ($CL_{G,int}$ and $CL_{H,int}$)
- Derived plasma clearance:

$$CL_{plasma} = \frac{Qh \times CL_{H,int} \times f_u}{Qh + (f_u \times CL_{H,int})/(B:P\ ratio)}$$

- Bioavailability is derived using $F_{total} = F_A \times F_G \times F_H$, with $F_A = 1$, $F_G = 1 - E_G$, and $F_H = 1 - E_H$
- Assumptions:
  - Well-stirred model for hepatic extraction: $E_H = \frac{CL_{H,int} \times f_{u,B}}{Q_h + (CL_{H,int} \times f_{u,B})}$
  - 'Qgut' model for midazolam extraction in gut wall: $E_G = \frac{CL_{G,int} \times f_{u,G}}{Q_{gut} + (CL_{G,int} \times f_{u,G})}$ with $Q_{gut} = \frac{Q_{villi} \times CL_{perm}}{Q_{villi} + CL_{perm}}$ in which CL_{perm} depends on effective intestinal permeability per unit surface area and intestinal surface which increases with BSA [3]
  - Fraction unbound in plasma in children is calculated as: $f_u = \frac{1}{1 + \frac{(1 - f_{u,adult}) \times [P]_{pediatric}}{[P]_{adult} \times f_{u,adult}}}$ [4] with $[P]_{pediatric}$ [g/L] = 1.1287 × ln(*Age*[yr]) + 33.746 [3]
  - Tissue volumes are scaled based on BSA [5] and age [6]
    - V_H [L] = 0.722 × $BSA^{1.176}$
    - V_G [L] = 0.0467 × Age + 0.0901
  - Organ blood flows are a fixed percentage of cardiac output, which increases with BSA [7]
  - Central and peripheral volumes are linearly scaled from adults
  - Fraction midazolam metabolized into 1-OH-midazolam is 100%

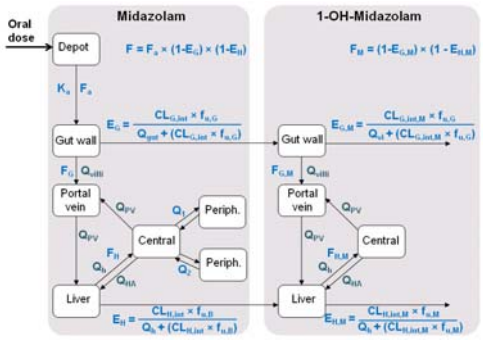

***Figure 1**. Schematic representation of the physiological population PK model for midazolam and the metabolite 1-OH-midazolam. E = extraction ratio, F = bioavailability in the gut wall (gut, G) and the liver (hepatic, H). CL_{int} = the whole-organ intrinsic clearance in the gut wall and liver. K_a = the absorption rate constant. The fraction unbound in blood and gut wall are described with $f_{u,B}$ and $f_{u,G}$ respectively. Q = blood flow; in the micro villi (Q_{villi}), portal vein (Q_{PV}), hepatic artery (Q_{HA}) and liver (Q_h). Q_1 and Q_2 = intercompartmental clearance between central and peripheral (Periph.) compartments. Parameters describing the metabolite are indicated with the subscript M.*

RESULTS

- The intrinsic clearance of midazolam in the gut wall and liver increase with body weight (**Figure 2A**), with exponents of 0.81 (RSE 10%) and 0.47 (RSE 16%) for $CL_{G,int}$ and $CL_{H,int}$, respectively.
- Intrinsic hepatic clearance per gram of liver decreases with age (**Figure 2B**), while no change with age is observed for gut wall intrinsic CYP3A activity per gram of small intestine.
- Plasma clearance increases from 9.3 L/h in infants to 24.2 L/h in adolescents (**Figure 3**).
- The fraction escaping gut wall metabolism (F_G) is lower than the fraction escaping hepatic metabolism (F_H) (**Figure 4**). The F_H increases with age, while F_G decreases to a lower extent. The resulting total bioavailability was found to be age-independent with a median of 21.6% in children (95%CI: 3.9-51.1%).
- Large inter-individual variability can be observed in F_G, F_H and F_{total} (**Figure 4**).

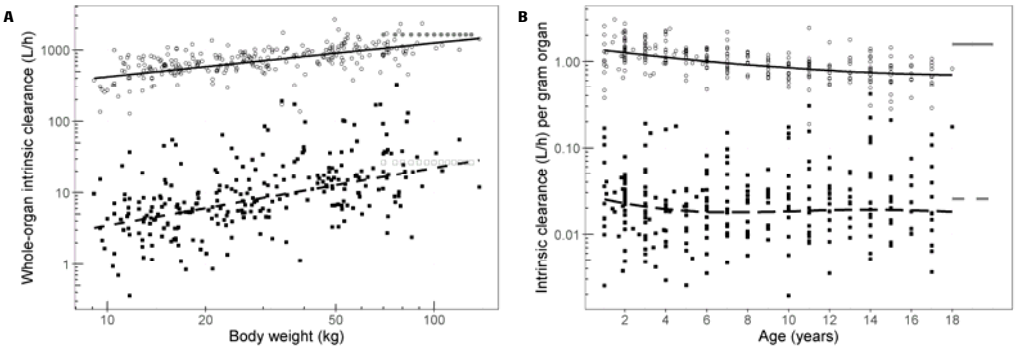

***Figure 2.** First-pass metabolism parameters in children. **A)** Whole-organ intrinsic intestinal (■) and hepatic (○) clearance versus body weight, both individually predicted (symbols) and the population predictions (lines). Reported literature values of 26.7 and 1640 L/h for intestinal (□) and hepatic (●) clearance in adults, respectively are also illustrated [2]. **B)** Intrinsic gut wall (■) and hepatic (○) clearance per gram of organ versus age for children in our study and for adults (–), both individually predicted (symbols) and a loess curve of the population predictions (lines).*

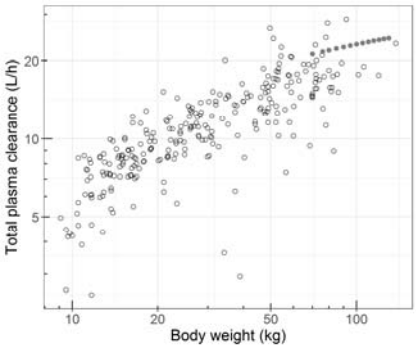

***Figure 3.** Total plasma clearance vs. body weight for children in our study (○) and calculated plasma clearance in adults (●) based on the reported hepatic intrinsic clearance of 1640 L/h, a hepatic blood flow increasing with body weight (Q_h = 3.75·$WT^{0.75}$), a fraction unbound of 0.0303 and a blood: plasma ratio of 0.66 [2].*

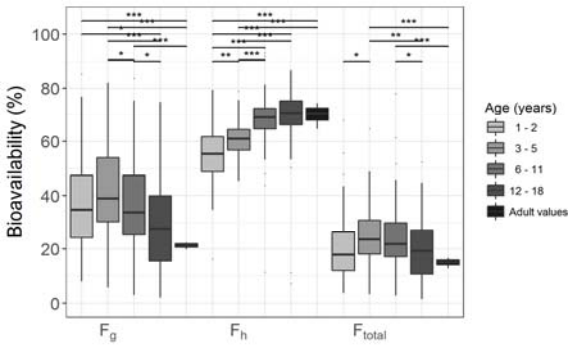

***Figure 4.** Bioavailability in in the gut wall (F_g), in the liver (F_h) and total bioavailability (F_{total}) in children of 1-2 years, 3-5 years, 6-11 years and 12-18 years of age (increasing grey scales) compared to reported adult values [2]. Significance was determined based on the Wilcoxon-Mann-Whitney Test, with *** indicating a p-value <0.001, ** for p<0.01, * for p<0.05 and 'NS' for p>0.05.*

CONCLUSIONS

- Intrinsic CYP3A-mediated gut wall clearance is substantially lower than the intrinsic hepatic CYP3A-mediated clearance throughout the pediatric age range.
- The intrinsic CYP3A-mediated gut wall clearance in children from 1-18 years of age contributes less to the overall first-pass metabolism compared to adults.
- Organ growth is the most important contributing factor to the increase in the whole-organ intrinsic CYP3A clearance in gut wall and liver with age, given the fact that the intestinal CYP3A activity per gram of organ remained relatively constant throughout childhood and the hepatic CYP3A activity per gram of liver even decreased.
- While intestinal bioavailability decreased with age in children >3 years of age, the hepatic bioavailability increased with age, resulting in no change in total bioavailability in children with increasing age and body weight, indicating an age-independent first-pass effect by intestinal and hepatic CYP3A enzymes in children from 1-18 years of age.

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[7] Simcyp (R) Simulator version 15.1. Certara, Sheffield, United Kingdom.

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