Theoretical Assessment of Metabolic Drug Interactions in Paediatric Population: The Impact of Age Related Fractional Metabolism (fm) and Its Disparity between Adults and Neonates

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Introduction

- Carrying out drug-drug interaction (DDI) studies in young children is fraught with ethical problems. The impracticality of such studies has led to a paucity of data and inability to extend observations from adults to paediatrics with adequate confidence.
- Modelling and simulation (M&S), combined with *in vitro in vivo* extrapolation (IVIVE) of information on ontogeny of various elimination routes (e.g. Fig. 1), can be used as a tool in understanding the potential for metabolic DDI in young children.
- The knowledge gained from M&S exercises may guide and justify the monitoring of pharmacotherapy for certain drug combinations in young children with the ultimate aim of providing definitive answers for the presence or absence of hypothetical mDDI.

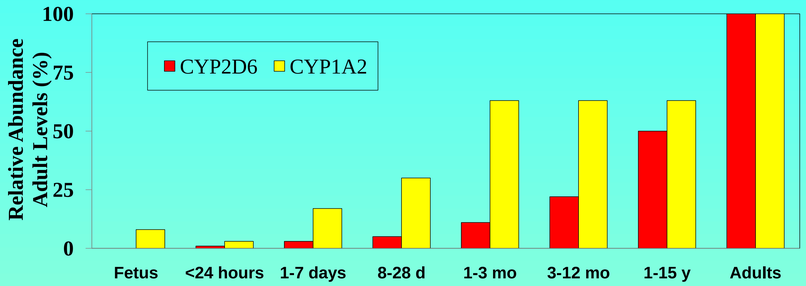

Fig. 1. Human hepatic enzyme abundance expressed as a percentage of the adult value[1]

Objective

To investigate theoretically conceivable differences in relative importance of metabolic routes between paediatric and adult individuals and its consequences for susceptibility to metabolic DDI.

Methods

The relative amount of each drug metabolising enzyme in whole liver was calculated and compared to adults as follows:

Age specific relative amount of total enzymes compared to adult =

$$= \frac{\left[Ontogeny\ Function \times Enzyme\ Abundance_{(Adults)}\right] \times MPPGL \times Liver\ Weight}{MPPGL_{(Adult)} \times Liver\ Weight_{(Adult)} \times Enzyme\ Abundance_{(Adults)}}$$

Where "Ontogeny Function" describes the enzyme abundance with age as a fraction of the adult value[2], MPPGL is microsomal protein per gram of liver calculated at each age[3], and liver weight is calculated with the knowledge of body surface area and tissue density[2]. Similarly, a relative renal function[1] was calculated at each age:

$$Relative\ Renal\ Function = \frac{Pediatric\ GFR\ at\ Given\ Age}{Adult\ GFR\ Value}$$

Where adult GFR value was assumed to be 120 ml/min[2].

Methods (continued)

Ratios for enzyme abundance and renal function were used to assess proportionality of ontogeny with age:

$$Fold\ Difference\ between\ Pathways = \frac{Route_{i,t}/Route_{i,20y}}{Route_{j,t}\ /\ Route_{j,20y}}$$

Where $Route_{i,t}$ and $Route_{j,t}$ are pathways "i" and "j" at the age of "t".

In order to evaluate the potential impact of DDI, we created two virtual compounds each being cleared only via two metabolic routes with the following characteristics:

Compound 1	V_{max}	K_m
CYP 3A4	10	17
CYP 1A2	68	10

Compound 2	V_{max}	K_m
CYP 3A4	100	10.5
CYP 2D6	50	21

V_{max} (pmol/min/pmol of enzyme) and K_m (µM) were used to calculate intrinsic clearance (CL_{int}) and scaled to hepatic clearance as reported previously[4].

Two different approaches[5,6] were followed to calculate the impact of DDI on these virtual compounds at different ages:

Method 1 (Mechanistic Static Model): Calculations were carried out with the assumption of selective and full inhibition of CYP3A4 at the given dose of inhibitor at all ages (3mg/kg). Increased exposure to substrate was calculated using the typical equation; area under the plasma concentration-time curve (AUC), in the presence and absence of an inhibitor:

$$R = \frac{AUC_{(inhibited)}}{AUC_{(uninhibited)}} = \frac{1}{\frac{fm}{1+\frac{[I]}{K_i}} + (1 - fm)}$$

where fm is the fraction of substrate clearance mediated by the inhibited metabolic pathway, [I] is the concentration of inhibitor at the enzyme site and K_i is the inhibition constant for inhibitor obtained from *in vitro* studies (note the equation applies only to orally administered drugs undergoing hepatic metabolism and it ignores, amongst other factors, the possibility of inhibition of gut "first-pass" metabolism and time-variant inhibitor concentration). By assuming that [I] has been adequately high, the level of DDI could be approximated by the following equation:

$$R = \frac{AUC_{(inhibited)}}{AUC_{(uninhibited)}} \approx \frac{1}{1 - fm}$$

With the knowledge of Cl_{int} in addition to metabolic and total blood clearance, fm was calculated.

Method 2 (Mechanistic Dynamic Model): Metabolic characteristics of the virtual compounds (K_m and V_{max}) were entered into Simcyp® Software Paediatric version 8.01 (Special Paediatric 2008 version TB3; www.simcyp.com). Both compounds were assumed to have similar permeability to that of alprazolam (i.e. low gut wall metabolism). The outcome of DDI with a strong inhibitor of CYP3A4 (Ketoconazole, K_i=0.015µM) was simulated for different age groups at a dose of 3mg/kg and the results were compared to the fold increase in AUC simulated in adults.

Results

Maximal discrepancies in "Fold Difference between Pathways" determined using Eq. 3 with the ages at which these were observed (majority neonates) are shown in Table 1.

The estimated level of DDI under inhibition of CYP3A4 from Methods 1 and 2 are summarised in Tables 2 and 3 and indicate variation in DDI susceptibility (higher: Compound 1 ; lower: Compound 2) in neonates compared to adults.

Table 1 – Maximum fold discrepancy in relative function of pathways compared to adults. Ages at which the maximal discrepancy was observed are provided and arrows indicate the direction of the relationship.

Ratio	CYP1A2	CYP2B6	CYP2E1	CYP2D6	CYP2C8	CYP2C9	CYP2C18/19	Renal
CYP3A4 *vs*	Day 1 108.9 ↑	Day 1 10.5 ↑	Day 1 4.6 ↓	Day 1 2.7 ↓	Day 1 16.4 ↓	Day 3 16.4 ↓	Day 1 9.9 ↓	Day 1 32.6 ↓
CYP1A2 *vs*		Day 1 10.3 ↓	Day 1 504.1 ↓	Day 1 289.7 ↓	Day 1 1784.2 ↓	Day 1 1786.4 ↓	Day 1 1072.8 ↓	Day 1 3550.8 ↓
CYP2B6 *vs*			Day 1 48.8 ↓	Day 1 28.0 ↓	Day 1 172.6 ↓	Day 1 172.8 ↓	Day 1 103.8 ↓	Day 1 343.5 ↓
CYP2E1 *vs*				Day 1 2.2 ↓	Week 1 3.6 ↓	Day6 4.1 ↓	Day 1 2.1 ↓	Week 1 7.0 ↓
CYP2D6 *vs*					Day 1 6.2 ↓	Day 1 6.2 ↓	Day 1 3.7 ↓	Day 1 12.3 ↓
CYP2C8 *vs*						Day 4 1.2 ↓	Week3 3.0 ↑	Week 1 2.0 ↑
CYP2C9 *vs*							Week 2 3.3 ↑	Day 1 2.0 ↑
CYP2C18/19 *vs*								Week 1 3.7 ↓

Table 2 –Estimated fm and DDI under inhibition of CYP3A4 as a function of age

Method 1	Compound 1			Compound 2		
Age	fm 3A4	fm 1A2	R_{AUC}	fm 3A4	fm 2D6	R_{AUC}
Year 20	28	72	1.38	78	22	4.49
Year 1	35	65	1.53	76	24	4.12
Day 1	50	50	2.00	50	50	2.00

Table 3 – Estimated fm and DDI under inhibition of CYP3A4 as a function of age

Method 2	Compound 1			Compound 2		
Age	fm 3A4	fm 1A2	R_{AUC}	fm 3A4	fm 2D6	R_{AUC}
Year 20	28	72	1.33	78	22	3.36
Year 1	35	65	1.37	76	24	2.67
Day 1	50	50	1.60	50	50	1.55

Conclusions

We were able to indicate the possibility of variable susceptibility to metabolic DDI in paediatric individuals compared to adults (both higher and lower depending on the characteristics of the drug). Further investigation of the findings is warranted via referral to case notes and future monitoring of certain cases of polypharmacy.

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