DOES BIRTH HAVE AN EFFECT ON GESTATIONAL TRAJECTORY OF UGT2B7 ACTIVITY IN NEONATES?

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Background

There has been an ongoing debate as to the effect of birth versus gestational age (GA) on the ontogeny of drug metabolising enzymes. This may have clinical implications in determining the dosage in young infants who have similar post-natal age (PNA) but varying GA due to being born prematurely. Despite the increasing utility of physiologically based pharmacokinetic (PBPK) modelling approaches in adult and pediatric clinical pharmacology, their application in preterm neonates remains limited. In preterm neonates the rate of postnatal development of metabolic enzymes and the age by which there is no difference between full-term and preterm neonates is largely unknown.

The aim of this study is to derive an *in vivo* ontogeny function for UGT2B7 that accounts for differences in activity in preterm and full-term neonates by considering gestational age at birth (GA_B) and postnatal age (PNA) using zidovudine.

Methods

Zidovudine clearance was used as marker of *in vivo* UGT2B7 activity. Values were obtained in full-term and preterm neonates from the University of California. The step wise back deconvolution of unbound intrinsic metabolic clearance ($CLu_{int,H}$) is shown in Figure 1. The relevant values of renal clearance (CL_R), Blood to plasma ratio (B:P), hepatic blood flow (Q_H), liver weigh, unbound fraction of drug in plasma (f_u) and albumin concentration [P] were applied (1). An in house GFR model using inulin clearance based on GA_B and PNA in paediatrics was used. Zidovudine renal clearance is through glomerular filtration and active tubular secretion. Adult renal clearance (CL_R) was reduced by 60% to account for the immature function of OAT1 in proximal tubule (2).

To obtain the best fit for the ontogeny profile of UGT2B7, the $CLu_{int,H}$ pediatric relative to adult ratios data against GA_B and PNA were fitted with a variety of functions in Phoenix NLME 64 (Pharsight, Cary, NC: Phoenix NLME), the best fit model was selected based on AIC and -2LL.

$$CL_R(\text{paed}) = \frac{GFR(\text{paed})}{GFR(\text{adult})} \times CL_R(\text{adult})$$

$$CL_{R,B} = \frac{CL_R}{B:P}$$

$$CL_B = \frac{CL}{B:P}$$

$$CL_{H,B} = CL_B - CL_{R,B}$$

$$CLu_{int,H}(L/h) = \frac{Q_{H,B}(L/h) \times CL_{H,B}(L/h)}{fu_B(Q_{H,B}(L/h) - CL_{H,B}(L/h))}$$

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

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

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

$$CL_{int\,H,b}(\mu l/\min/mg) = \frac{CL_{int\,H,b}(L/h) * 10^6}{Liver \quad Weight * MPPGL * 60}$$

Figure 1. Deconvolution of zidovudine systemic clearance to remove the effect of body size in order to attain *in vivo* activity of UGT2B7 to the unit of µl/min per mg of microsomal protein per gram of liver.

Results

The zidovudine *in vivo* based ontogeny model as a function of postmenstrual age (PMA in weeks) is shown in figure 2. The new UGT2B7 ontogeny function can be used to predict chronological changes in activity of this enzyme with postnatal and gestational age at birth (GA_B). Figure 3 shows how UGT2B7 develops in neonates born at different gestational and postnatal ages.

UGT2B7 activity in new-borns and infants born at 24, 28, 30, 35 and 40 weeks of GA is presented in figure 4. the figure shows with a fixed PMA, subjects born more premature has higher UGT2B7 activity.

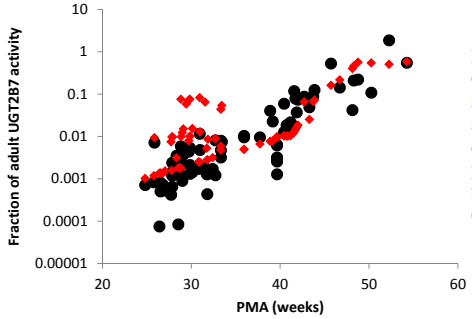

Figure 2. Zidovudine $CLu_{int,H}$ paediatric to adult ratios for full-term and preterm neonates. Red diamonds show the predictions from the model fitted to zidovudine data (black circles).

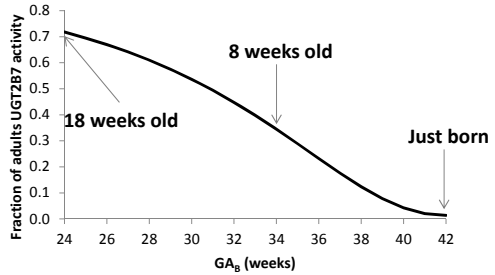

Figure 3. Changes in UGT2B7 activity at a fixed PMA of 42 weeks for babies born at different GA.

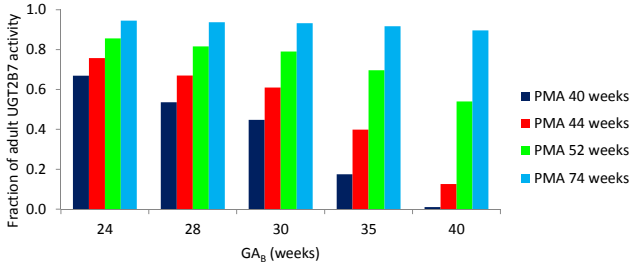

Figure 4. Changes in UGT2B7 activity with GA and PNA in preterm and full-term neonates.

Conclusions

- In very preterm neonates UGT2B7 activity is low regardless of PNA. The difference in activity against PNA becomes more evident in the neonates born at higher GA weeks.
- UGT2B7 activity increases with postnatal age. Subjects born for a longer time have higher activity by a certain PMA regardless of gestational age.
- However by 74 weeks PMA, all neonates have 90% UGT2B7 activity regardless of being born preterm or full-term.

References

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2. Hedaya, M., et al. Pharm Res, 1990; 7: 411-417

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