Does birth have an effect on UGT2B7 activity in neonates?

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Background

Despite the increasing utility of physiologically based pharmacokinetic (PBPK) modelling approaches in adult and pediatric clinical pharmacology their application in preterm neonates remains limited. Preterm neonates further develop their metabolic capacity after birth, however, it is unclear whether maturation during postnatal life occurs at the same rate as *in utero* or at what postnatal age after birth the difference in metabolic capacity between full-term and preterm neonates diminishes.

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

Methods

Zidovudine clearance values were obtained in full-term and preterm neonates from the University of California. The step wise back calculation of unbound intrinsic metabolic clearance ($CLu_{int,H}$) is shown in Figure 1. The latter was used as marker of *in vivo* UGT2B7 activity.

$$GFR = 112 \times \left(\frac{BW(paed)}{70}\right)^{0.632} \times \frac{PMA^{3.3}}{55.4^{3.3} + PMA^{3.3}}$$

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

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

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

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

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

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

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

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

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

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.

In the deconvolution of clearance, 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.

To obtain the best fit for the ontogeny profile of UGT2B7, the $CLu_{int,H}$ pediatric relative to adult ratios data against PMA and GA 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. Intravenous clearance values of morphine in full term and preterm neonates were obtained from the literature and deconvoluted to achieve $CLu_{int,H}$ based on the methods described above and used as an external validation set. Finally, the UGT2B7 *in vivo*-based model was compared with the currently existing *in vitro* model. the latter is based on protein and mRNA expression in neonates (2).

Results

The zidovudine *in vivo* based ontogeny model as a function of postmenstrual age (weeks) is shown in figure 2a. Performance of the UGT2B7 *in vivo* based model in prediction of morphine $CLu_{int,H}$ ratios in preterm and full-term neonates is shown in figure 2b. Figure 2b reflects some under-prediction of morphine ratios using the model based on zidovudine data. Figure 3 compares the UGT2B7 *in vitro* and *in vivo*-based ontogeny models in the first month of postnatal life for full-term neonates born at 40 weeks of gestation (GA).

The new UGT2B7 ontogeny function can be used to predict chronological changes in activity of this enzyme with postnatal and gestational age. Figure 4 shows how UGT2B7 develops in neonates born at different gestational and postnatal ages (PNA).

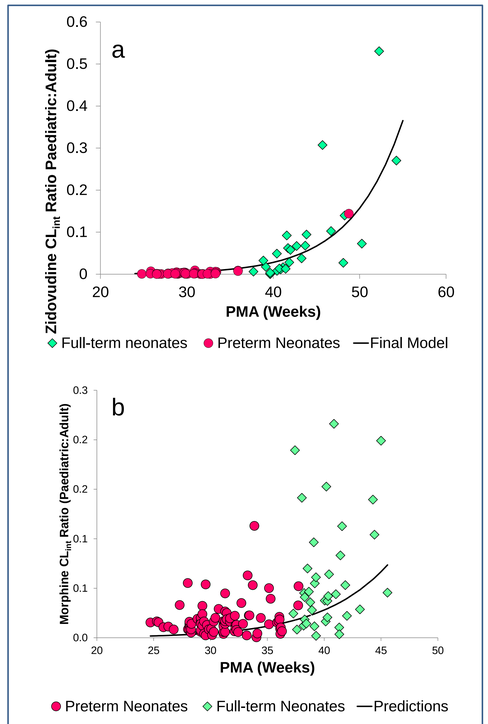

Figure 2. Zidovudine (a) and morphine (b) $CLu_{int,H}$ paediatric to adult ratios for full-term (diamonds) and preterm (circles) neonates. Solid line shows the UGT2B7 model fitted to zidovudine data and used for prediction in the morphine data set. PMA is postmenstrual weeks.

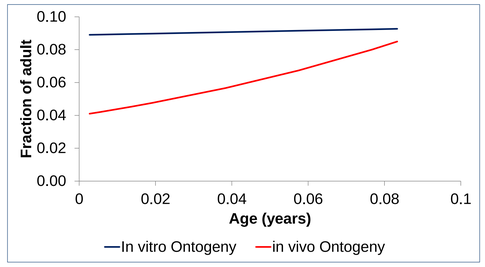

Figure 3. *In vivo* –based ontogeny model shows lower expression of UGT2B7 in preterm neonates (red line) compared to *in vitro* based model (blue line).

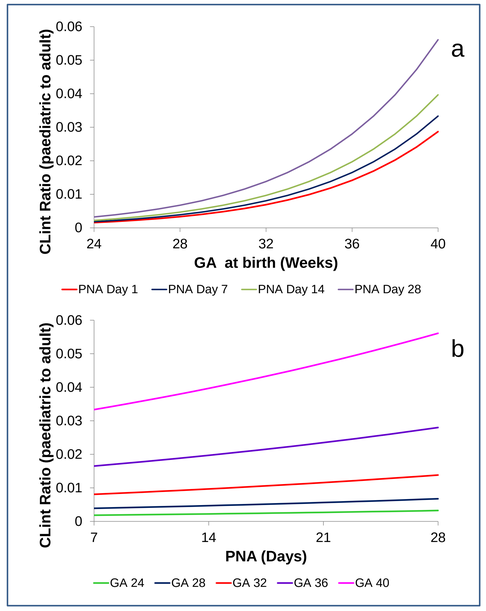

Figure 4. Changes in UGT2B7 activity with gestational (a) and postnatal (b) age in preterm and full-term neonates.

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.
- Morphine is a substrate of OCT1 uptake transporter (3). The under-prediction of morphine $CLu_{int,H}$ ratios by the zidovudine model might be explained by active uptake of morphine into hepatocytes.
- The difference between *in vitro* and *in vivo* models could stem from limitations of *in vitro* experiments (4) to reflect the *in vivo* situation.

References

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