Mapping *in vitro* and *in vivo* derived CYP1A2 and CYP3A ontogeny functions: A critical comparison between various ontogeny models

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Background

The application of paediatric physiologically based pharmacokinetic (p-PBPK) models during paediatric drug development has increased in the last few years as shown by the rising number of related submissions to the FDA's office of clinical pharmacology[1]. The ontogeny models implemented into most of the PBPK platforms are based on data derived from *in vitro* studies of enzyme activity or abundance. Data from either adult systemic CL or enzyme kinetic parameters (K_m and V_{max}) are used as input in these models to extrapolate paediatric CL. Recently, it has been shown that these *in vitro*-derived ontogeny profiles for CYP1A2 and CYP3A, when incorporated in p-PBPK models, under-predict CL values in infants and young children[2]. Therefore a novel approach is considered to create ontogeny models based on the reported *in vivo* CL of probe drugs for CYP1A2 and -3A4 (i.e. caffeine, theophylline and midazolam) across the paediatric age range after deconvolution and removing the effect of size.

Methods

Data collection and analysis of data

A literature review was undertaken to collect intravenous CL data for CYP1A2 and CYP3A4 probes caffeine/theophylline and midazolam across the paediatric age range from birth to 18 years. The values were deconvoluted with known developmental functions related to organ size, microsomal protein, plasma protein binding, renal CL to yield intrinsic CL (CL_{int}) values (per mg of liver microsomal protein)[3]. Ratio of paediatric CL_{int} to mean adult CL_{int} was calculated and plotted against age.

Data fitting and model building

Classical fitting techniques were undertaken using Graphpad Prism 5 and Matlab v7.12 to obtain the best fit for ontogeny models through an iterative process by minimising the weighted least square. Additional weighting based on the number of subjects was applied to the objective function, to account for the differences in the study size. Several statistical tests were carried out and the best fitted model was selected.

Model validation

New *in vivo*-based ontogeny models were input to Simcyp v12 whole organ metabolic CL section and examined for prediction of theophylline and midazolam CL. CL data for these compounds were compared against CL predictions by Leong et al.,[2] for theophylline and midazolam in Simcyp v10 using Johnson[3] ontogeny model. Another CYP3A4 substrate, alfentanil, was used to examine the CL predictions for new CYP3A4 ontogeny.

Results

CYP1A2 enzyme activity per mg of microsomal protein showed an increase with age to values higher than adults in children between ages 1 to 12 years before declining to typical adult levels by about 27 years. There was a monotonic increase of CYP3A activity with age from the neonatal period to adulthood with activity reaching adult levels at about 2 years. Figure 1 compares the new ontogeny models with those reported by Johnson et al in 2006[3].

Comparison of CL predictions from new *in vivo*-based ontogeny models for caffeine and theophylline showed improvement across the paediatric age range (figure 2).

Alfentanil CL predictions from new ontogeny model showed improvement compared to Johnson model[3] however, there is still significant under-prediction in neonatal age (figure 3).

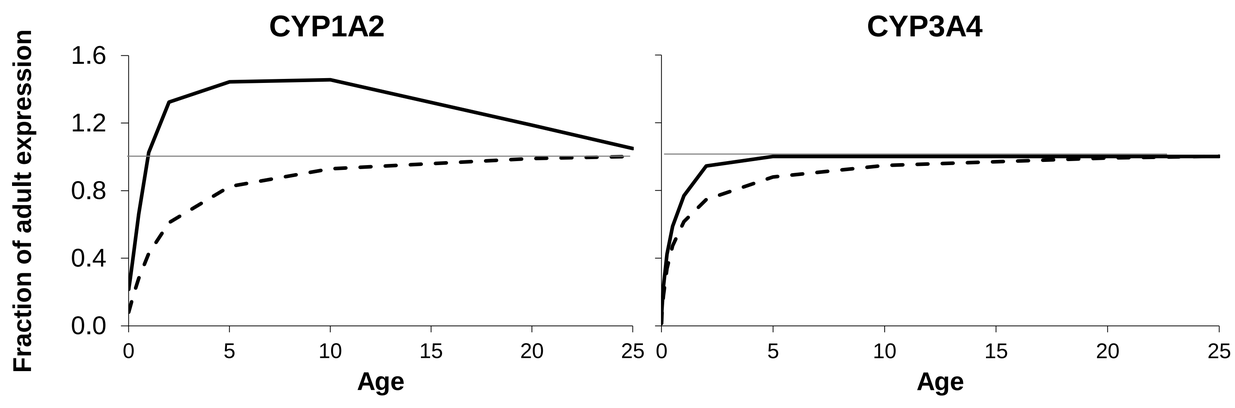


Figure 1. Comparison between the *in vivo*-based CYP1A2 and -3A4 ontogeny models (solid line) and Johnson *in vitro*-based ontogeny models[3] (broken line).

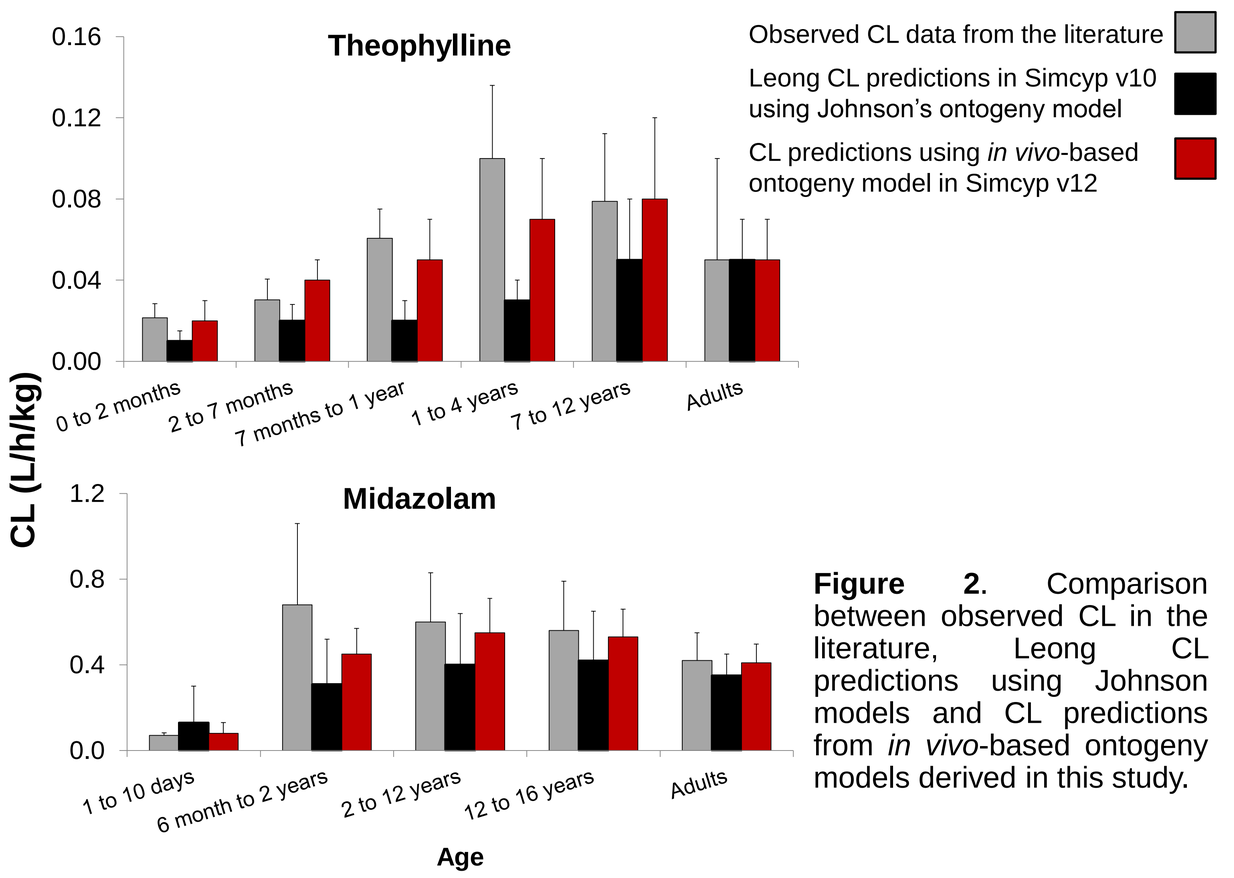
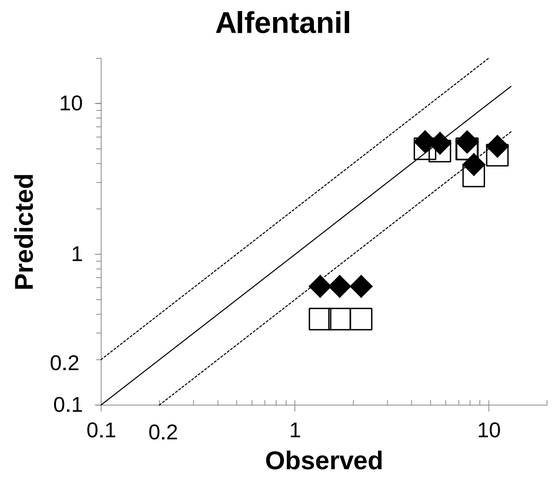


Figure 2. Comparison between observed CL in the literature, Leong CL predictions using Johnson models and CL predictions from *in vivo*-based ontogeny models derived in this study.



Predicted CL from new *in vivo*-based CYP3A4 ontogeny model

Predicted CL from Johnson[3] *in vitro*-based CYP3A4 ontogeny model

Figure 3. Predicted *vs.* observed CL for alfentanil from Johnson and new ontogeny models.

Conclusions

The new *in vivo*-based ontogeny models derived from analysis of observed CL showed improvement in prediction of CL across the paediatric age range for all three compounds examined. The improvement is significant for CYP1A2 but there is still under-prediction of CL for CYP3A probes. Ideally, independent data sets should be used to examine the new models but finding such data across the paediatric age range is challenging. CYP3A4 under-prediction might be explained by recent findings that suggest factors such as the clinical condition (critical illness, inflation and infection) of patients affect the activity of CYP3A4[4,5] and therefore the new CYP3A4 model should be refined by considering these factors.

The reasons for discrepancy between *in vitro* and *in vivo* derived ontogeny profiles requires further investigation considering re-analysis of the observed data used in building the model in relation to clinical condition.

References

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