Mapping *in vitro* and *in vivo* derived CYP2C9 and CYP2C19 ontogeny functions: A critical comparison between various ontogeny models
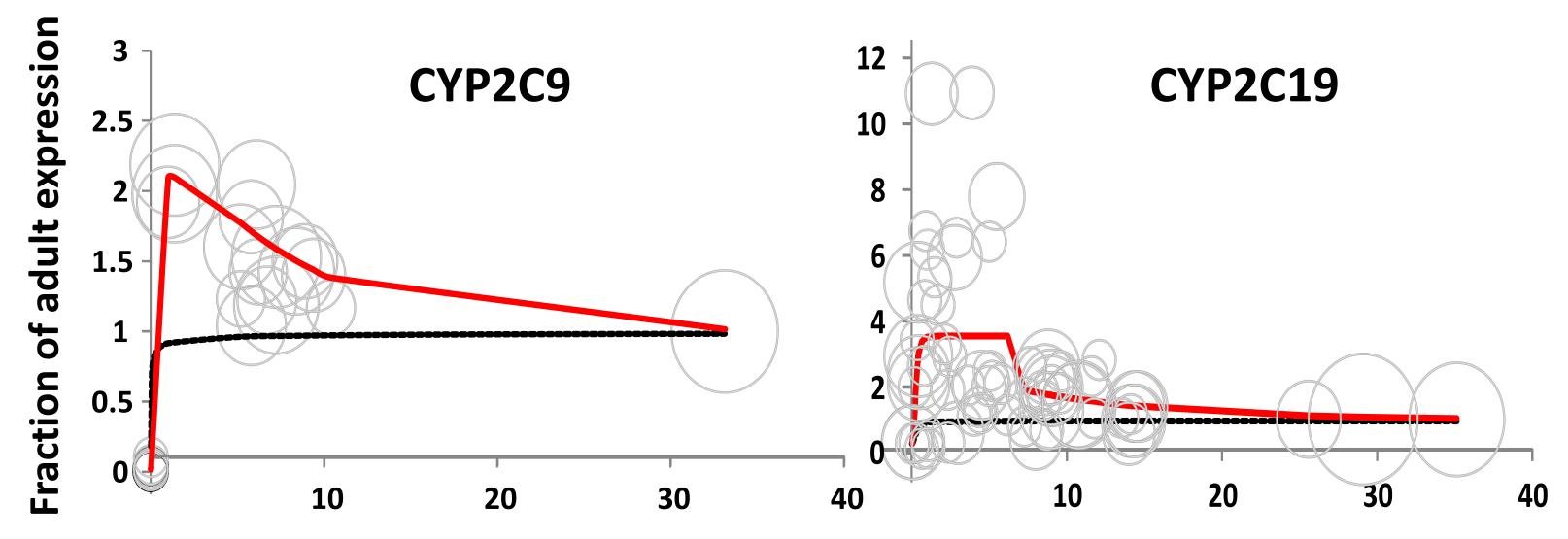
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Background

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 paediatric PBPK platforms are based on data derived from *in vitro* studies of enzyme abundance (mRNA or protein) or activity. Recently, it has been shown that *in vitro* derived ontogeny profiles for CYP2C19, when incorporated in p-PBPK models, under-predict CL values in infants and young children[2]. Previously, *in vivo* derived ontogeny profiles have been successfully developed for CYPs 1A2 and 3A4/5 after deconvolution and removing the effect of size. These have been shown to result in more accurate ropivacaine and alfentanil CL prediction in neonates, infants and children when applied within a paediatric PBPK platform[3].

The aim of this study is to extend this approach to create ontogeny models based on the reported *in vivo* CL of probe drugs for CYPs 2C9 (ibuprofen) and 2C19 (lansoprazole and pantoprazole) across the paediatric age range

Methods

Data collection and analysis of data

A literature review was undertaken to collect oral and intravenous CL data for CYP2C9 and CYP2C19 probes ibuprofen and lansoprazole/pantoprazole across the paediatric age range from birth to 18 years. Considering the gestational or post menstrual age, the individual or geometric mean values were deconvoluted with known developmental functions related to organ size, microsomal protein, plasma protein binding and renal CL to yield intrinsic CL (CL_{int}) values (per mg of liver microsomal protein)[3]. Data from poor metabolisers were excluded where genotype information was available. 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 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 v14 and examined for prediction of diclofenac concentration-time profiles and s-warfarin CL with age. For CYP2C19 there is a lack of suitable validation compounds due to lack of data with a possibility of using omeprazole or voriconazole.

Results

CYPs 2C9 and 2C19 enzyme activities per mg of microsomal protein showed an increase with age to values higher than adults in children between ages 2 months to 2 years for CYP2C9 and 3.9 years for CYP2C19 before declining to typical adult levels. Figure 1 compares the new ontogeny models with those reported by Johnson et al in 2006[4].

Comparison of plasma concentration-time profile and CL predictions from new *in vivo*-based ontogeny models for diclofenac and s-warfarin showed improvement compared to in vitro-based ontogeny models (figures 2&3).

Figure 1. *Comparison between the in vivo-based CYP2C9 and CYP2C19 ontogeny models (solid red line) and Johnson in vitro-based ontogeny models[2] (broken black line). Results from individual clinical studies are shown by the ellipses where size corresponds to study n.*
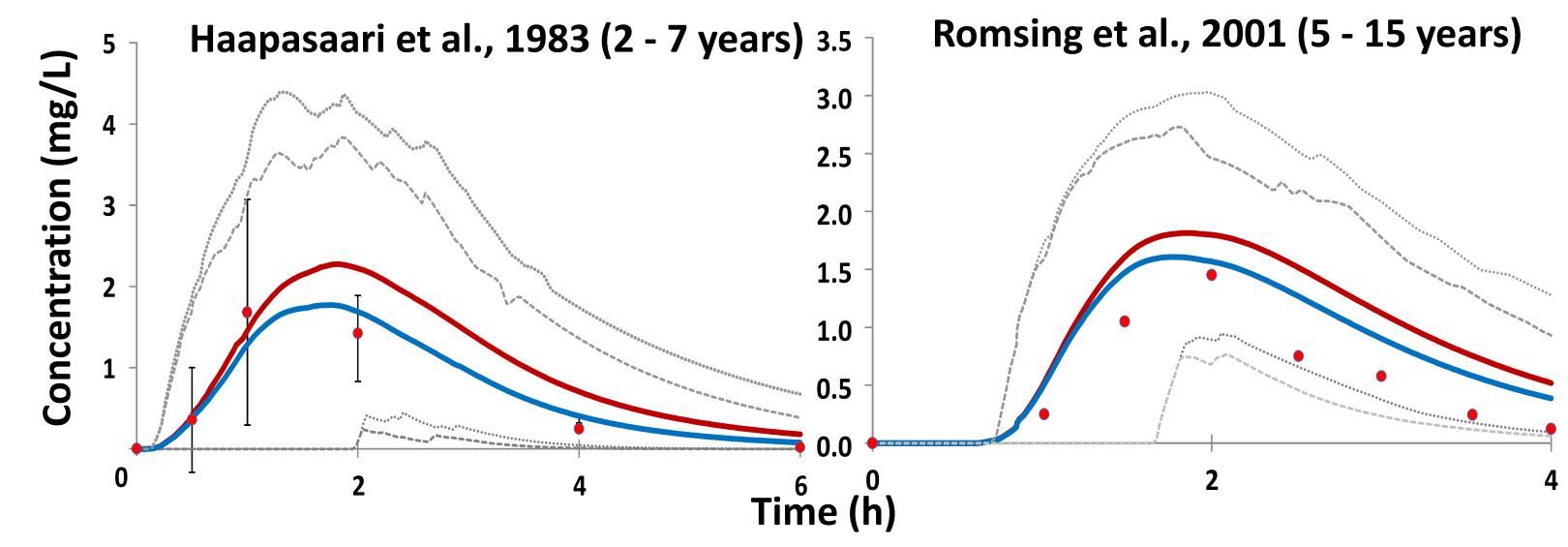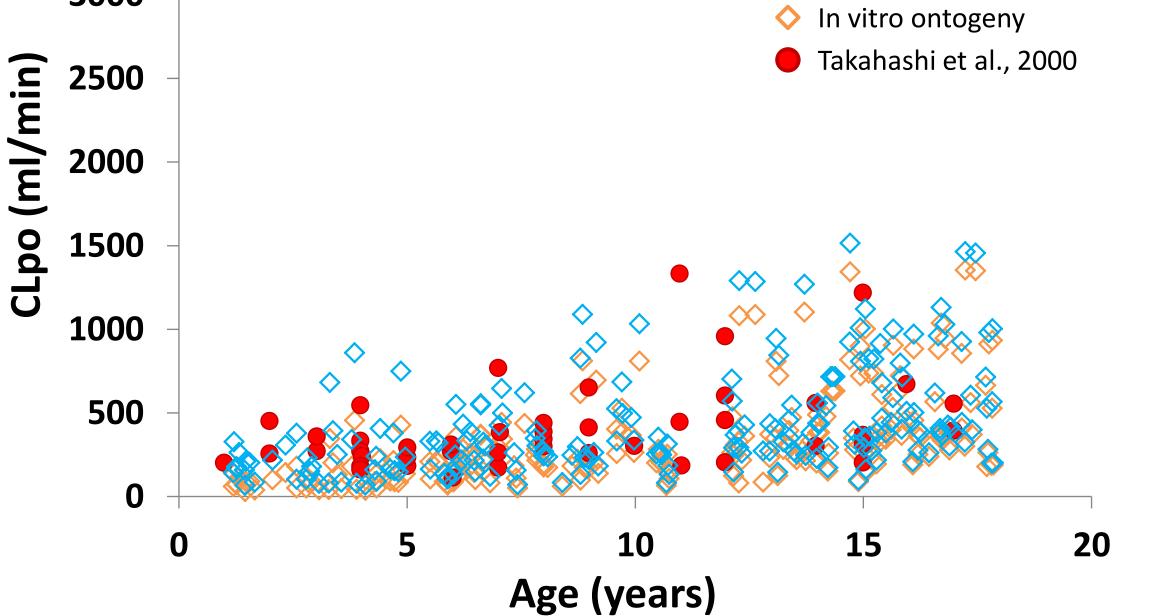

Figure 2. *Comparison between the predictions of plasma concentration-time profiles for diclofenac from in vivo-based CYP2C9 ontogeny model (blue line) and Johnson in vitro-based ontogeny model[4] (red line). Clinical data is shown by solid red circles, dashed and solid grey lines are 5th and 95th percentiles for in vivo and in vitro ontogeny models, respectively.*

Figure 3. *Comparison between the predictions of S-warfarin clearance from in vivo-based CYP2C9 ontogeny model (blue diamonds) and Johnson in vitro-based ontogeny model[4] (orange diamonds) against the in clinical data from Takahashi (solid red circles).*

Conclusions

The new *in vivo* based ontogeny models derived from analysis of observed CL showed improvement in prediction of plasma concentration-time profile and CL for the compounds examined. The improvement is significant for CYP2C9 but there is lack of validation set for CYP2C19 probes. Ideally, independent data sets should be used to examine the new models but finding such data across the paediatric age range is challenging. The currently available data sets are restricted by the wide paediatric age range and limited data in neonatal age range. The *in vivo* based ontogeny models require further refining including the effects of clinical condition and genotype and also their interface with adult expression. The reasons for discrepancy between *in vitro* and *in vivo* derived ontogeny profiles requires further investigation.

References

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