A Critical Comparison between CYP1A2 and 3A4 Ontogeny Profiles Used in Pediatric PBPK Models

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Background and Objectives

Pediatric physiologically based pharmacokinetic models (p-PBPK) incorporate available data describing the ontogeny of CYPs. However, there are uncertainties rin deciphering the true ontogeny of metabolism from the observed kinetics of probe compounds. Since CYP1A2 is a major metabolic pathway for caffeine (CAF) & theophylline (THEO) and CYP3A is a main determinant of midazolam (MDZ) kinetics, the age related changes in elimination of these compounds may reflect the ontogeny of CYP1A2 and CYP3A after necessary corrections for changes in body size.

The aim of this study is to compare the performance of some existing ontogeny functions nested within p-PBPK models[1-3] . Some of these were derived from *in vitro* information on CYP1A & CYP3A ontogeny whilst *in vivo* ontogeny from the deconvolution of 'top down' clearance (CL) data of appropriate probe substrates were used for others.

Methods

CYP1A2 and CYP3A ontogeny models[1-3] were used as input into the whole organ metabolic CL option of Simcyp v11 and population simulations performed to predict CAF, THEO and MDZ CL in 250 neonates, infants, children and adolescents. CL predictions were compared with those from *in vivo* data expressed as ml/min and allometrically scaled to 70 kg using an 0.75 exponent. For CYP3A CL predictions were compared the publication of Anderson[4] who fitted the *in vivo* ontogeny profile from iv MDZ CL data in NONMEM. An age fixed milligrams of 40 mg/g microsomal protein per gram of liver (MPPGL) values was used in all p-PBPK simulations.

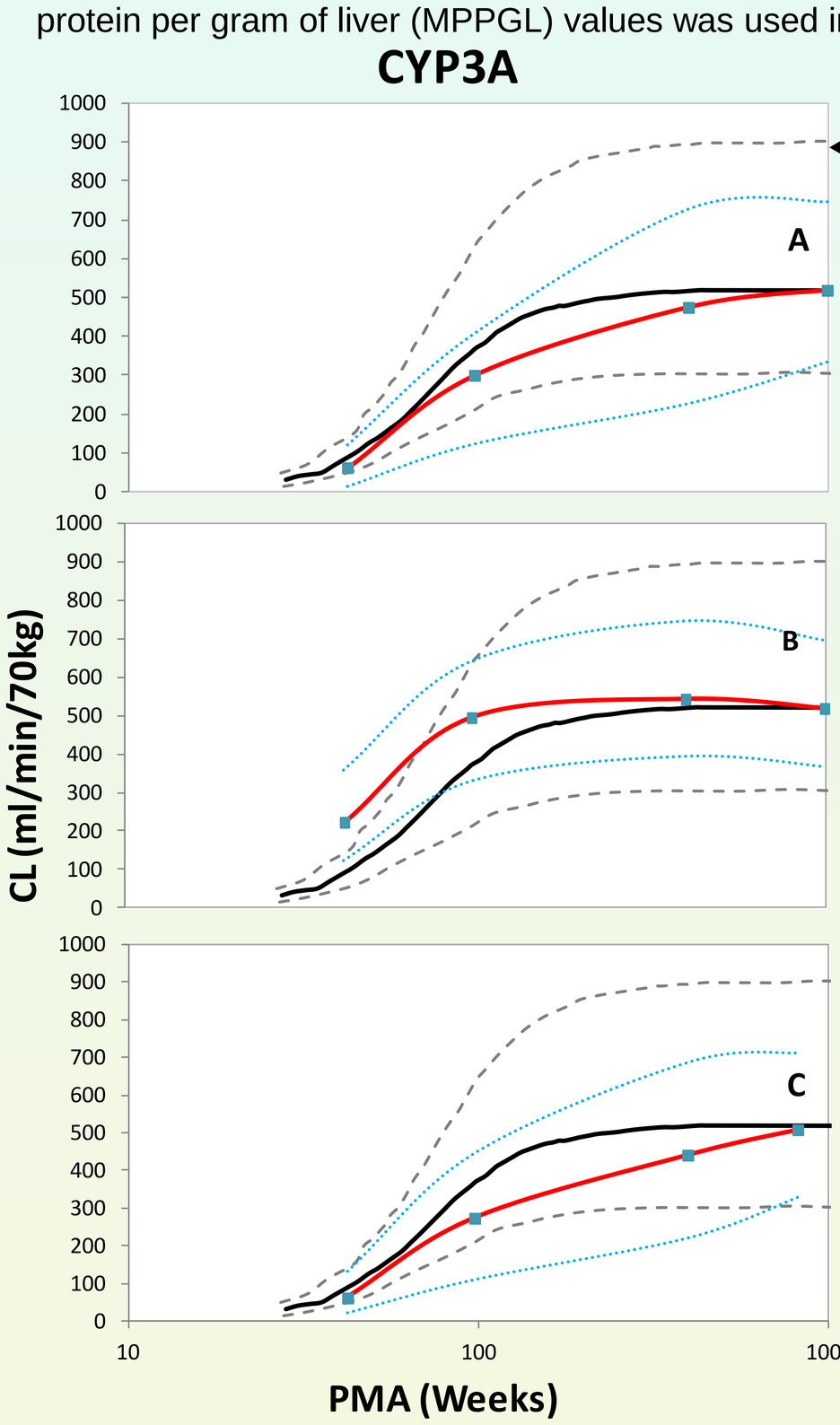
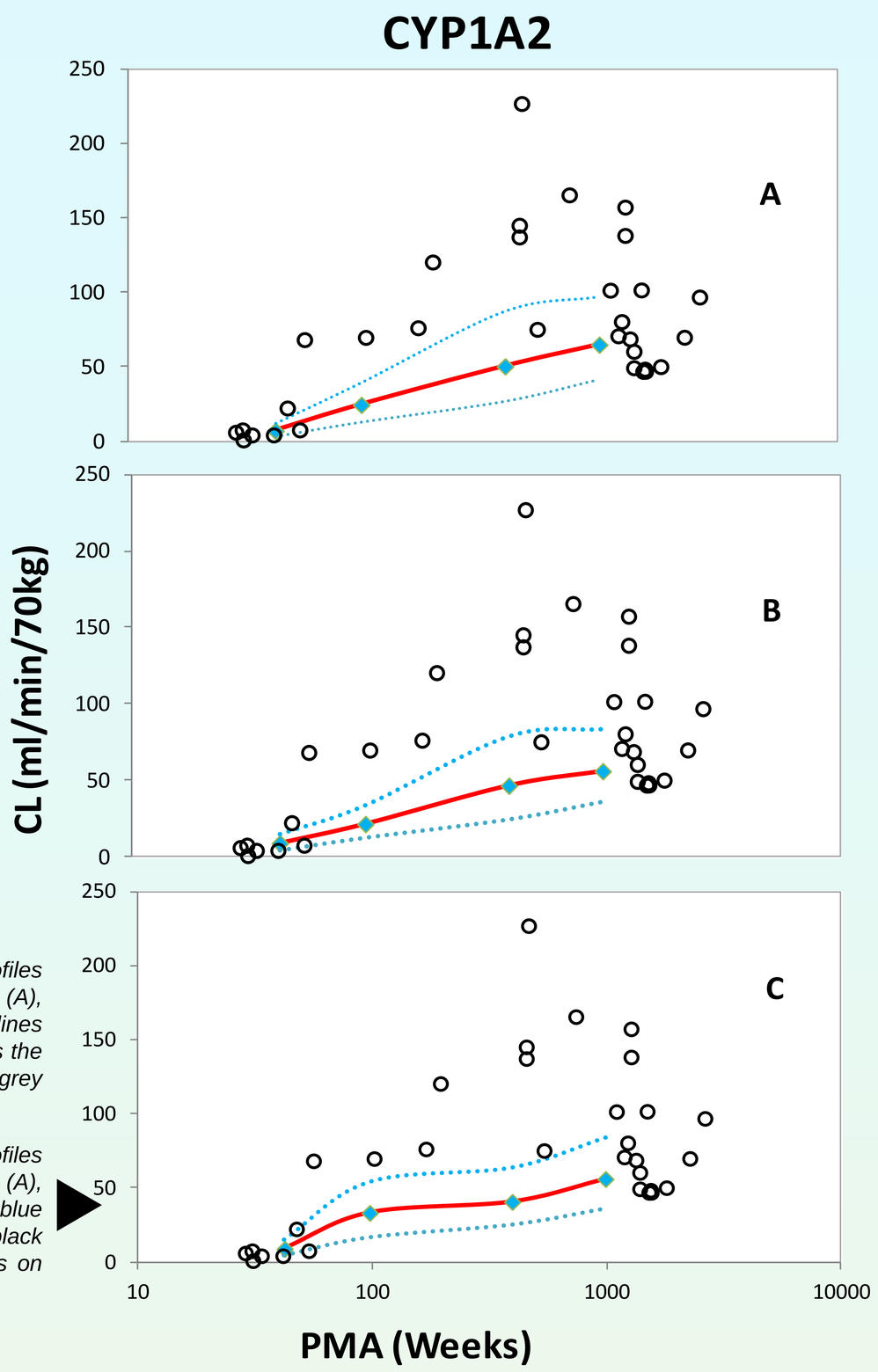


Figure 1. Comparison of the mean ontogeny profiles for CYP3A4 (red line) described by Johnson (A), Edginton (B) and Bjorkman (C). The blue dotted lines are 5th and 95th percentiles, the solid black line is the best fit line to the clinical data [4] and dotted grey lines are the 5th and 95th percentiles for this data.

Figure 2. Comparison of the mean ontogeny profiles for CYP1A2 (red line) described by Johnson (A), Edginton (B) and Bjorkman (C) ontogenies. The blue dotted lines are 5th and 95th percentiles and the black circles are the mean values from clinical studies on CAF/THEO



Results

For CYP3A, the Johnson and Bjorkman models underpredicted MDZ CL by 13% and 17% respectively across the age range while the Edginton model over predicted by an average of 50%. The Johnson model gave the best prediction in neonates, infants and children.

For CYP1A2, comparison between models and observed CL values showed that all models predicted CAF/THEO CL reasonably well in neonates and adults but that there was significant under prediction (1.5 to 5.6-fold) between 100 and 400 weeks PMA.

Discussion and Conclusions

A major shortcoming of current models is the fact that probe compounds are considered a pure marker of enzyme activity. The inconsistency between the existing models illustrates the need for developing more robust models from the allometrically scaled *in vivo* derived CL values after separating the effects of other elements which influence the overall CL. An ongoing exercise using CAF/THEO CL data to present CYP1A2 ontogeny may show the value of this approach, particularly when there is some evidence of over expression of CYP1A2 in children and adolescents compared to adults due to influenced by growth hormone secretion[5] and the puberty[6].

New optimised models (such as those for CYP3A4 in this study or ongoing effort on CYP1A2) can be implemented within commonly used p-PBPK (e.g. Simcyp) and assessed for wider validation on other drugs.

References

1.Bjorkman. *Br J Clin Pharmacol* 2005;**59:**691-704. 2.Edginton *et al* . *Clin Pharmacokinet* 2006;**45:**683-704. 3.Johnson et al. *Clin Pharmacokinet* 2006;**45:**931-956. 4. Anderson BJ, Larsson P. Ped Anesthesia 2011; **21**: 302 – 308. 5.Levitsky *et al.* Dev Pharmacol Ther 1989; **12**: 90 – 95. 6.Lambert GH. Dev Pharmacol Ther 1986; **9**: 375 – 388.