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

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Introduction

Most paediatric physiologically based pharmacokinetic models (p-PBPK) incorporate algorithms describing the known ontogeny of major hepatic drug metabolizing enzymes based *in vitro* data. However, there are uncertainties around the consistency of predictions from these ontogeny algorithms with the observed kinetics of probe compounds. Since CYP3A is a major metabolic pathway for midazolam (MDZ), the age related changes in elimination of this compound, after correcting for changes in body size, may reflect the ontogeny of CYP3A. Anderson and Larsson[1] have collated reported literature values for MDZ iv clearance (CL) from birth to adulthood and report a maturation function (ontogeny) model based on allometrically scaled CL values . Their model reflects the pattern of size corrected CL changes with age for MDZ, because this drug is >90% eliminated by CYP3A it is also likely to reflect the *in vivo* ontogeny pattern of CYP3A4/5.

Aims

The aims of this study are to

- Evaluate the performance of three existing p-PBPK models containing different *in vitro* derived CYP3A ontogeny profiles (Bjorkman[3], Edginton[4], Johnson[5]) in predicting size corrected MDZ CL values and to compare these against the *in vivo* ontogeny of Anderson and Larsson.
- Produce a new ontogeny function for CYP3A abundance based on MDZ $CL_{u,int}$ using deconvoluted CL_{iv} data.

Methods

Comparing the performance of three available ontogeny models for CYP3A in the prediction of MDZ CL

1. The retrograde model with an adult CL_{iv} value of 29.35[6] $L.h^{-1}$ for MDZ was used to predict the whole organ metabolic CL_{int} within Simcyp paediatric.
2. A 'User defined' ontogeny function was used to apply each of the three ontogeny profiles to the scaling of the CL_{int} within the model in order to predict MDZ iv CL with age.
3. 1000 population simulations with 250 subjects in each subpopulation within the neonatal, infant, children and adolescent age ranges were performed with proportion of male/female set on 0.5.
4. Individual predicted CL values were scaled to 70 kg of body weight using allometric scaling with a power of 0.75, mean values and the 90% confidence interval around the mean were calculated for the four discrete age groups.
5. Predicted CL (ml/min/70kg) from the three ontogeny models were compared with those derived from *in vivo* data by Anderson and Larsson. The discrepancy between predictions and fitted model to *in vivo* data was used to calculate error in prediction at each age group. The overall lowest sum of squares error was used to determine the best ontogeny model.

Building a CYP3A ontogeny model based on MDZ CL_{iv}

1. Unbound intrinsic clearance ($CL_{u,int}$) for MDZ was calculated from CL_{iv} values from the literature by applying the retrograde model, after first deducting and renal CL, using (Equation 1).

$$CL_{u,int} = \frac{CL_{met,b} * Q_{(h)}}{f_{(u)} * (Q_h - CL_{met},b)} \qquad \text{Equation 1}$$

2. $CL_{u,int}$ was then scaled to the unit of µl/min/mg by dividing by the relevant age related values for liver size and milligrams microsomal protein per gram of liver (MPPGL).
3. The ratio of $CL_{u,int}$ in paediatrics to adults was used from deconvolution stage to derive a new ontogeny function for CYP3A.
4. A model was fitted to these data points using Graphpad Prism V5.04.
5. This ontogeny model was entered to the whole organ metabolic CL feature in Simcyp Paediatric using the 'User defined' ontogeny function as a new ontogeny model for CYP3A4.
6. Steps three to five from the previous section were repeated to predict and compare CL with Anderson and Larsson.

Result

The Johnson model for CYP3A ontogeny gave the best agreement with the data of Anderson with an average < 5% difference between the two across all ages (Figure 1).

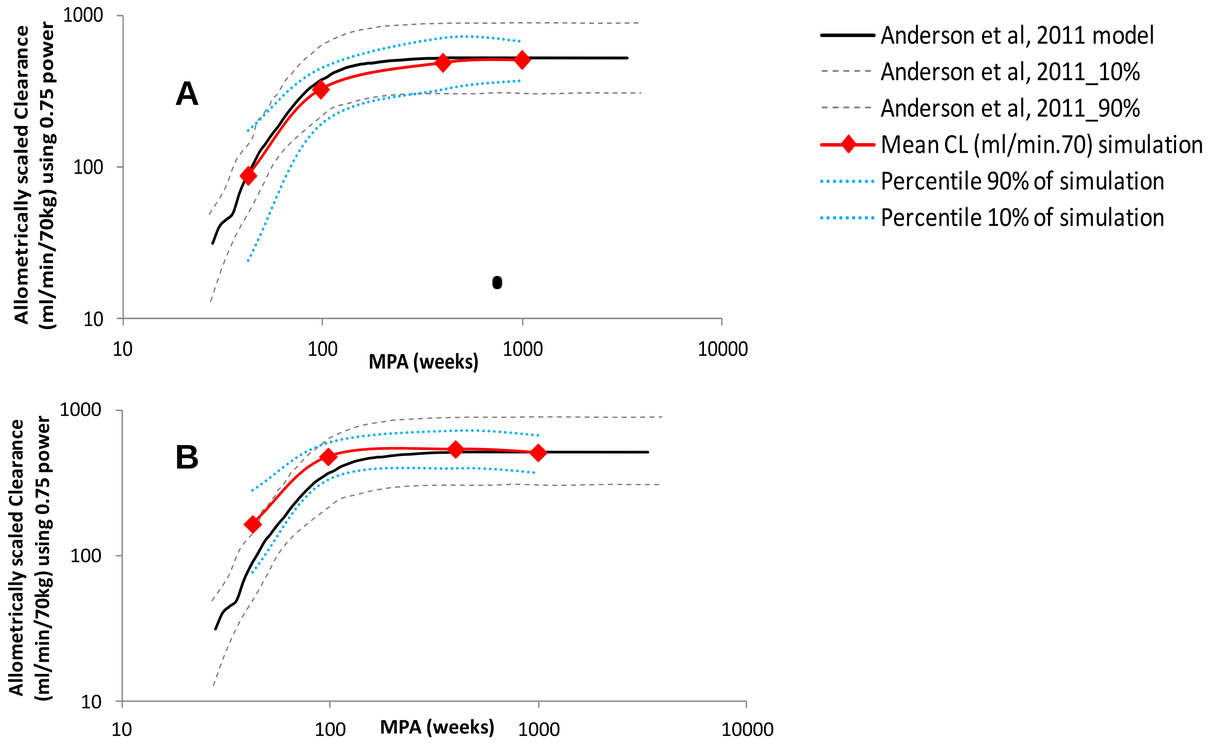

Figure 1. CL predictions from Johnson (A) and Edginton (B) ontogeny as input to Simcyp with CL_{iv}=29.35 (L/h) from Cubit, MPPGL fixed at 40 mg/g across the paediatric range

- The Bjorkmann ontogeny model gave a slight under-prediction in CL in the infants group (data not shown).
- The Edginton ontogeny model over predicted MDZ CL up to 100 weeks post menstrual age (Figure 1)
- A new model for ontogeny of $CL_{u,int}$ was successfully derived by deconvolution of CL_{iv} using well stirred liver model assumptions (Figure 2).

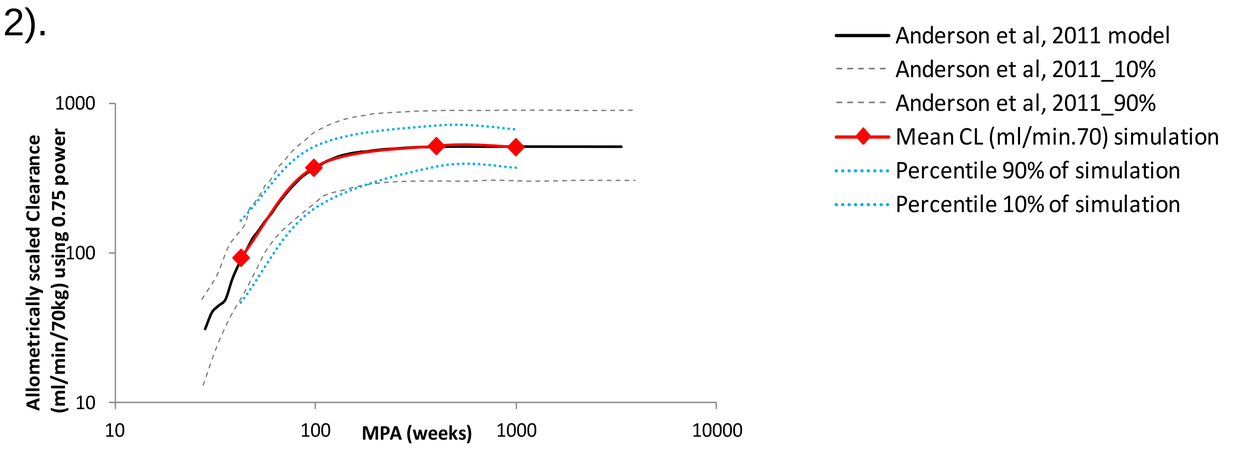

Figure 2. CL predictions from $CL_{u,int}$ ontogeny as input to Simcyp with CL_{iv}=29.35 (L/h) and MPPGL fixed at 40 mg/g across the paediatric range.

Conclusion

Although the existing model within Simcyp paediatric performed well, the new model combines existing knowledge from clinical observations and could be used with more confidence to predict age dependent CL of other drugs where CYP3A has a substantial role. Application of this model and deriving similar ontogeny models for other enzymes warrant further studies.

References

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