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 Larsson1 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 CYP3A/4/5.

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 (Bjorkman3, Edginton4, Johnson5) 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\( CL_{int} \) 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 \( CL_{int} \) value of 29.35\( \text{L.h}^{-1} \) 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 deducing and renal CL, using (Equation 1).

\[
CL_{u, int} = \frac{CL_{max, u} \times Q_{u, int}}{Q_{u, int} \times (Q_{u} - CL_{u, int})} \quad \text{Equation 1}
\]

2. \( CL_{u, int} \) was then scaled to the unit of \( \mu l/min/mg \) 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 pediatrics 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](image1)

- The Bjorkman 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 \( CL_{int} \) using well stirred liver model assumptions (Figure 2).

![Figure 2](image2)

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