Prediction of metabolic drug clearance in pediatric subjects and its sensitivity to different models of the development of CYP enzymes

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INTRODUCTION

The paediatric version of Simcyp® software (www.simcyp.com) incorporates a mechanistic PBPK model for *in vitro - in vivo* extrapolation of ADME properties (Figure 1). The software has already been used successfully to predict drug clearance (CL) and its associated variability in neonates, infants and children[1]. The underlying algorithms within Simcyp incorporate current information on demographics, developmental physiology and the ontogeny of enzyme systems involved in drug elimination. A number of patterns of CYP3A development have been suggested in the literature[2-4]. The aim of this study was to assess the sensitivity of CL predictions for three CYP3A substrates to different models of the time course of CYP3A development within Simcyp Pediatric.

METHODS

The derivation of the sigmoidal (SIG) hyperbolic (HYP) and logarithmic (LN) models for CYP3A development have been described previously[5]. In addition to these, a biphasic model was included, based on the data of Stevens *et al*[4]. Three drug substrates commonly used clinically across the pediatric age range were chosen for the simulations (IV midazolam, oral cisapride and oral carbamazepine) Twelve simulations were run (4 CYP3A models on each of the 3 drug substrates) incorporating 2000 virtual pediatric subjects from birth to 18 years. The impact of changing the default SIG model to alternative models was assessed based on the precision and bias of median CL prediction across the 3 drugs and also on the percentage of median and variability values within 2-fold of the experimentally observed values.

RESULTS

The overall results for all three drugs are shown in Table 1.

Table 1. Precision and bias of clearance predictions based on different models of CYP 3A development.

CYP	Model	Precision	Bias	2-fold (%)	
				Med	*Var*
3A4/5	Sigmoidal	0.011	0.066	93	79
	Hyperbolic	0.011	0.064	93	86
	Nat Log	0.013	0.055	86	79
	Biphasic	0.034	0.139	79	79

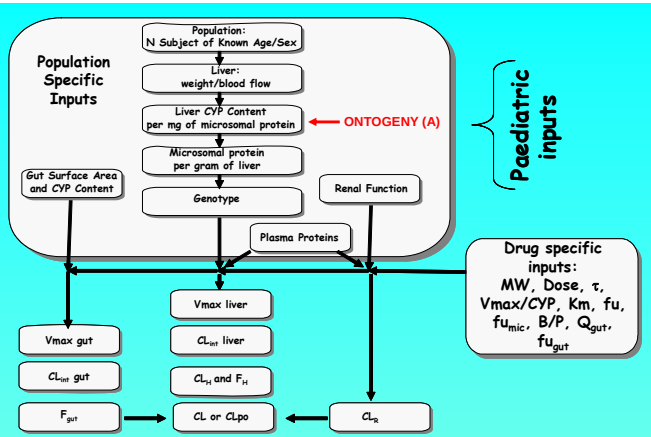

Figure 1. Schematic representation of the basic Simcyp algorithm indicating the input of data specific to pediatrics

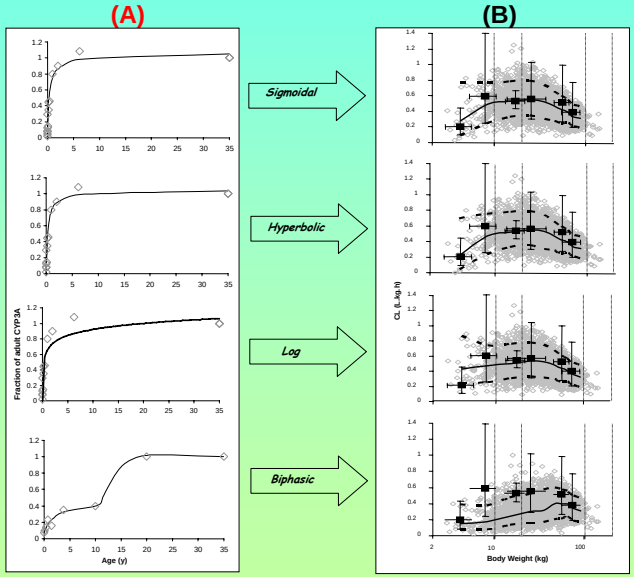

Figure 2. (A) Different models of the age related change in CYP3A expression / activity as a fraction of adult values. Grey diamonds indicate experimental in vitro data; lines indicate 'best' fits to the experimental data. (B) Changes in weight normalized MDZ clearance versus body weight predicted by the SIG, HYP, LN and biphasic models. The grey points indicate data for 2000 virtual subjects; the solid and dashed lines are median predicted clearance and its 95% CI, respectively; the data points and error bars represent mean and 95% CI values from in vivo studies.

The HYP model performed better than the default SIG model with less bias and a greater percentage of predicted variability values within 2-fold of the observed values. The LN model had less bias than the SIG and HYP models but was less precise and predicted fewer median CL values within 2-fold of observed. The biphasic model was the worst model. The effect of changing the models of CYP3A development on the prediction of clearance of IV MDZ across the pediatric weight range is shown in Figure 2.

CONCLUSIONS

Although the HYP model of CYP3A ontogeny performed better than the SIG model (the default model in Simcyp pediatric), the improvement was not clinically significant. The biphasic model represents the case where there is an initial sharp increase in CYP3A expression during the first few months of life followed by a second rise during puberty. The results of the current study (deviation between observed and predicted CL) suggest that the biphasic pattern is incorrect and that CYP3A reaches adult levels at an early age (1 – 2 years or 10 – 15kg).

The use of PBPK models such as Simcyp pediatric provide a useful tool to assess the sensitivity of predicted PK parameters to changes in underlying determinants, in this case CYP3A development.

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