Prediction of Large Molecule Clearance in Children using Allometry *vs.* PBPK – Erythropoietin as a case example.

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Background & Objective

Therapeutic proteins (TP) are increasingly given to paediatric patients with doses based on allometric scaling of the clearance from adults to children without accounting for underlying nonlinear processes such as the specific binding of a TP to its target.
The aim of this study was to compare two erythropoietin (EPO) models in a virtual paediatric population, one with a total clearance value scaled from adults to neonates and one with a physiologically-based pharmacokinetic (PBPK) model including a quasi-equilibrium (QE) model, which accounts for age-dependent system parameters.

Methods

Allometry model: In this model the total adults clearance of EPO (552 mL/h) [1,2] was scaled to one day old neonates using the three-quarter exponent approach.
PBPK model: The full PBPK model for other proteins implemented in the Simcyp Paediatric Simulator V15R1 has been used. The quasi-equilibrium (QE) model was used to describe the specific binding to the erythropoietin receptor (EPOR) and was parameterised with values from the literature (Table 1). The QE model accounts for age-dependent changes in system parameters, although no EPOR abundance has been described in the literature for neonates and therefore the adult value was taken.
Model verification: The two EPO models were developed in a virtual adult population receiving doses from 10 to 500 IU/kg (Figure 1) [1,2]. The model was then used to replicate a clinical study [3] to predict EPO disposition in one day old neonates after administration of four different doses (250, 500, 1000 and 2500 IU/kg).

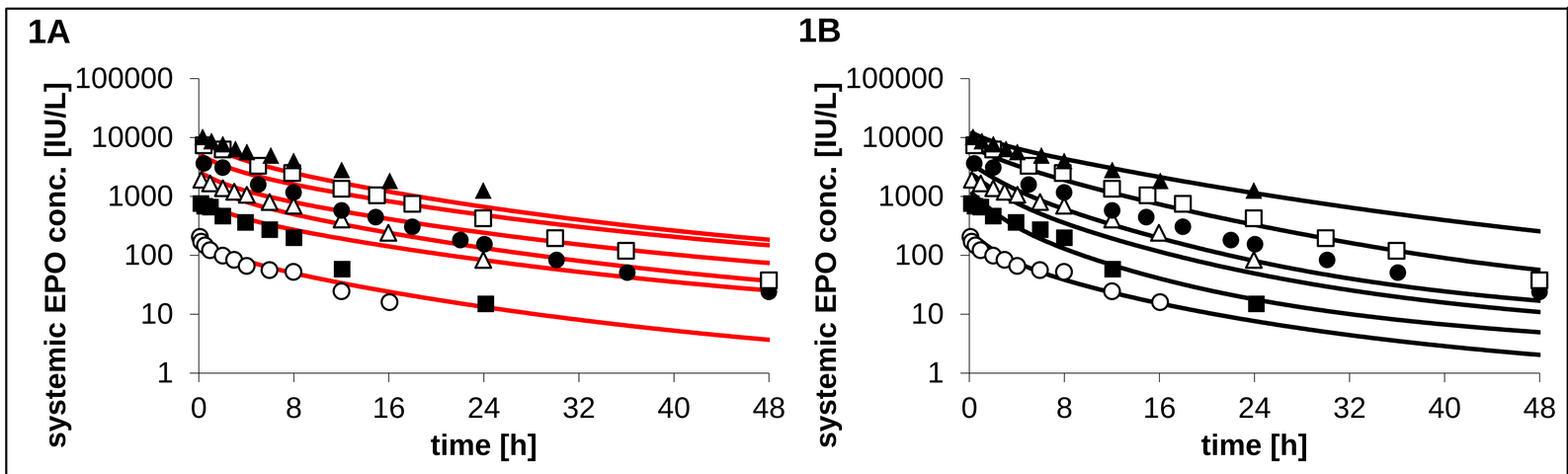

Figure 1: Predictions of EPO in adults (A: allometry and B: PBPK) *vs.* observed data points of different doses.

Parameter	Value	Reference
EPOR abundance [µM]	3.62E-05	optimised in adults
k_{deg} [1/h]	2.49	[4]
k_{int} [1/h]	1.85	[4]
KD [µM]	4.8E-05	[4]

Table 1: Input parameter for the used QE model.

Results

While the allometric model showed adequate prediction for the lowest dose only, the nonlinearity of EPO disposition in one day old neonates was better predicted by the QE model across the different doses (Figure 2). All clearance predictions for one day old neonates made by the QE model were within two folds of the observed data (Table 2).

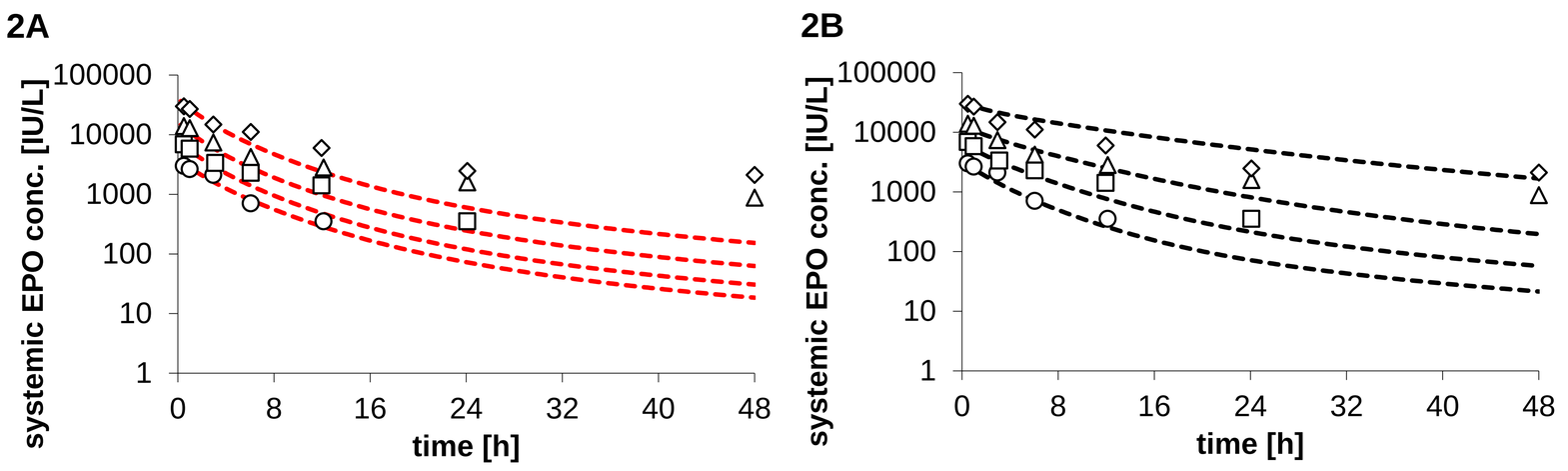

Figure 2: Predictions of EPO in one day old neonates (A: allometry and B: PBPK) *vs.* observed data points of different doses.

Clearance [mL/h]			
Dose (IU/kg)	Observed	Allometry	QE model
250	51.5	55.4	35.8
500	33.3	55.4	29.2
1000	25.4	55.4	21.4
2500	26.1	55.4	13.2

Table 2: Clearance prediction in neonates

Discussion

The mechanistic QE model was able to predict the clearance of EPO in neonates within two folds of the observed values and captured the nonlinearity of EPO disposition adequately. The age-dependent scalar of the EPOR target abundance might not describe reality, but it is a starting point towards a more mechanistic approach to predict the fate of EPO in paediatrics. PBPK models could be a useful tool to predict doses for TPs to be administered in paediatrics.

References

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