Prediction of Erythropoietin Disposition in a Paediatric Population Using SimCYP®

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Background

There is a growing use of biologic drugs in paediatrics, but less is known about the ontogeny of their associated distribution and elimination pathways compared to small molecules [1]. Doses of therapeutic proteins in children are mainly estimated by allometry, which can lead to overdosing in these patients [2, 3]. The PBPK approach can offer a possibility to predict dose and disposition of biologics in a paediatric population if age-dependent system parameters are accounted for.

Objectives

To predict the disposition of erythropoietin in children using the Simcyp Paediatric Simulator.

Methods

The full PBPK model for other proteins was used to simulate erythropoietin distribution. It contains 13 organs, which are connected via the arterial and venous blood stream. Lymph flow from all organs except for bone and spleen is collected in a central lymph compartment and is circulated back to the venous blood stream. Each organ is further divided into vascular space, interstitial space and intracellular space. The Paediatric Simulator accounts for the age-dependency in the tissue volumes and flows to and from these organs, including vascular and endothelial volumes. Interstitial volume is calculated from the tissue volume, the age-dependent fraction of extracellular water and vascular volume according to the following equation:

$$V_{interstitium}[L] = (V_{tissue} \times f_{ECW}) - (V_{vascular} \times (1 - HCT))$$

where HCT is haematocrit. The lymph volume is a function of body weight. As there were no published values for lymph flow in the literature, it was scaled allometrically as shown below:

$$Lymph\ flow\ rate\ [{}^{L}/_{h}] = 0.287 \times \left(\frac{BW_{paed}}{BW_{adult}}\right)^{0.75}$$

All other parameters such as pore size and numbers of pores in a certain area are the same as in the adult model.

The compound file for erythropoietin was developed in adults by using a molecular weight of 30,400 g/mol and a clearance of 9.0 mL/min/kg. The model was verified using adult data from Salmonson et al. (1990), in which 6 healthy adult men received 50 U/kg of erythropoietin i.v. [4].

The model was then used to explore the exposure to the adult dose in paediatrics and also to replicate available studies in children at the received doses. Wu et al. (2012) administered different doses of erythropoietin i.v. to one day old neonates [3] and Braun et al. (1993) gave a dose of 4,000 U/m^2 to children aged 7-20 years [2].

Result

The model was able to predict the data in adults reasonably well (Fig. 1A). Simulations for the same dose (50 U/kg i.v.) in paediatrics aged 1 day, 6 years, 13 years and 18 years are given in Fig. 1B. Adolescents and adults have a perfect overlay, whereas neonates have a much higher plasma concentration.

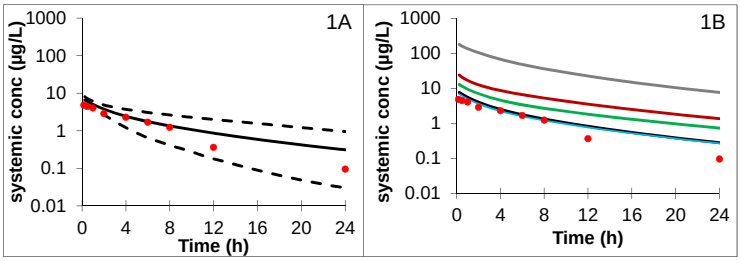

Fig 1A: Predicted (black line) with 95% CI (dashed lines) and observed data (red dots) of erythropoietin in healthy adult volunteers after 50 U/kg i.v. [4].

Fig 1B: Predicted lines at different ages (grey – 1 day old neonate, red – 6 years, green – 13 years, blue – 18 years and black – adults) receiving the same dose as adult and observed data (dots) of erythropoietin in healthy adult volunteers after 50 U/kg [4].

The predictions in 7 to 20 years olds are in close agreement with the observed data (Fig. 2). The model seems to over predict the clearance in the terminal elimination phase, but the data are within the 95% confidence interval.

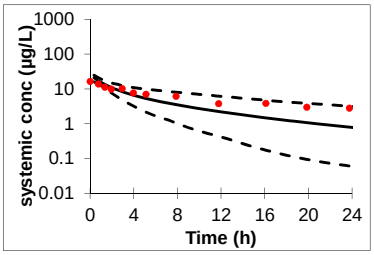

Fig. 2: Predicted (black line) with 95% CI (dashed lines) and observed data (red dots) from a clinical trial, where patients aged 7 to 20 years received 4,000 U/m^2 [2].

The model prediction of erythropoietin as an i.v. infusion given to 1 day old neonates receiving 500 U/kg, 1,000 U/kg or 2,500 U/kg is shown in Fig. 3.

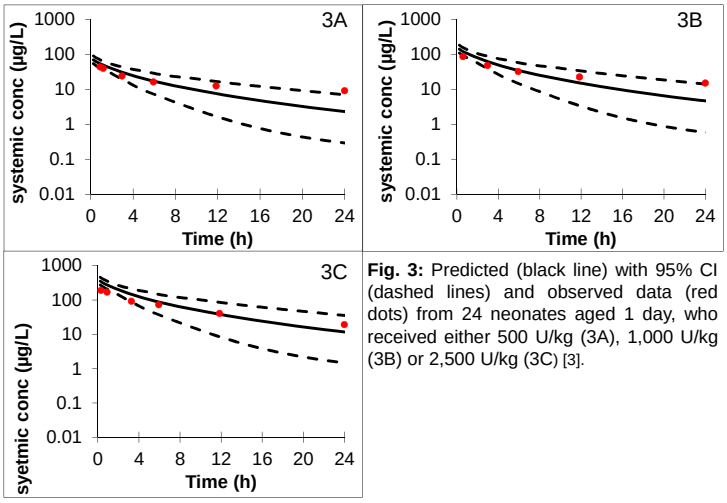

Fig. 3: Predicted (black line) with 95% CI (dashed lines) and observed data (red dots) from 24 neonates aged 1 day, who received either 500 U/kg (3A), 1,000 U/kg (3B) or 2,500 U/kg (3C) [3].

Discussion

The disposition of erythropoietin was predicted reasonable well by using the Simcyp Paediatric Simulator in the entire paediatric age range from one day old neonates to adolescents after administration of different doses. The model could be used to predict dose and disposition for other therapeutic proteins in paediatrics.

References

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3) Wu YW et al. Erythropoetin for neuroprotection in neonatal encephalopathy: saftey and pharmacokinetics. Paediatrics. 2012;130(4): 683-691.
4) Salmonson T et al. The pharmacokinetics of recombinant human erythropoietin after intravenous and subcutaneous administration to healthy subjects. British Journal of Clinical Pharmacology. 1990; 29(6): 709-713.