A Whole Body PBPK Model to predict Plasma and Tissue Interstitial Fluid Concentrations in Humans for Proteins with a Range of Sizes

Kate Gill1, Krishna Machavaram1, Linzhong Li2, Rachel Rose1, Manoranjeni Chetty1, Iain Gardner1

1 Simcyp (A Certara Company), Blades Enterprise Centre, Sheffield, UK

Purpose

The binding of small therapeutic proteins (TP) to plasma proteins may potentially influence the movement of the TP throughout the body but has generally not been considered in previous PBPK models for TP. The aim of this study was to develop a whole body PBPK model to predict plasma and interstitial fluid concentrations of TP in humans and to assess the impact of plasma protein binding on tissue interstitial fluid concentrations for small TP.

Method

A human whole body PBPK model was developed in Simulink (Matlab, Version R2013a). The model contains 12 tissues and each is described by three compartments, representing vascular, interstitial and intracellular spaces (Figure 1). Movement of free and plasma protein bound TP from the vascular to the interstitial space was described mechanistically by considering both convection and diffusion processes. Convection and diffusion rates were estimated for TP covering a range of hydrodynamic radii (1.0 – 15 nm) using a 2-pore model [1, 2]. For estimating these parameters, blood to plasma ratio was assumed to be 1, while clearance and plasma protein binding were set to 0.

Predicted and observed Ci/Cp ratios for representative tissues (liver, gut, kidney, heart, lung, muscle, skin) are shown in Figure 3. For example, for a TP with radius of 3.55 nm, the predicted Ci/Cp ratio was 0.88 for the liver compared to Ci/Cp ratios of 0.78 – 1.00 reported in vivo.

Predicted Ci/Cp ratios were generally similar to observed data (Figure 3). For example, for a TP with radius of 3.55 nm, the predicted Ci/Cp ratio was 0.88 for the liver compared to Ci/Cp ratios of 0.78 – 1.00 reported in vivo.

Conclusion

A whole body PBPK model has been developed to describe the movement of small TP between the blood and tissues, while accounting for plasma protein binding.

The importance of accounting for plasma protein binding during prediction of small TP pharmacokinetics has been highlighted.

The mechanistic modelling approach described here can be applied to predict the concentration of small TP in blood and target tissues.

References