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

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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 TPs. The aim of this study was to develop a whole body PBPK model to predict plasma and interstitial fluid concentrations of TPs in humans and to assess the impact of plasma protein binding on tissue interstitial fluid concentrations for small TPs.

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 TPs from the vascular to the interstitial space was described mechanistically by considering both convection and diffusion processes. Convection and diffusion rates were estimated for TPs 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.

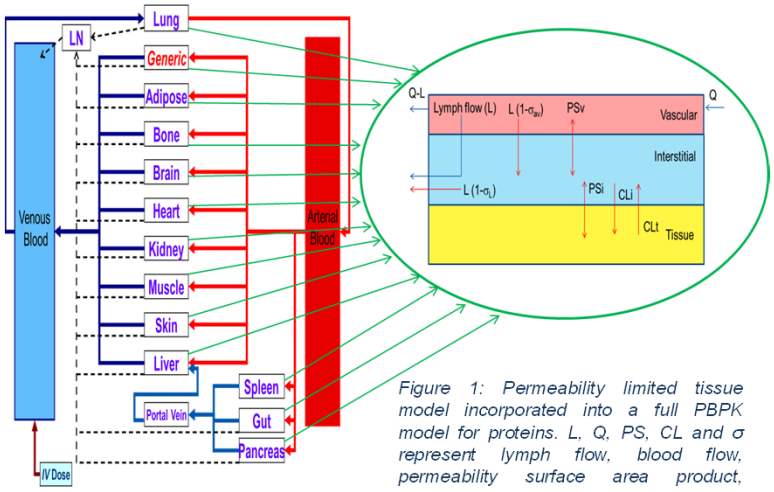

Figure 1: Permeability limited tissue model incorporated into a full PBPK model for proteins. L, Q, PS, CL and σ represent lymph flow, blood flow, permeability surface area product, clearance, and reflection coefficient, respectively.

Examples of predicted PSv and σ_{av} values are shown for the liver in Figure 2. Movement of protein into tissue cells was not considered in these simulations, therefore PSi, CLi and CLt were set to 0. Plasma (Cp) and tissue interstitial fluid (Ci) concentrations at steady-state were simulated and compared with literature values of lymph/plasma ratios for each tissue in humans and experimental animals, with the assumption that lymph concentrations are a measurable surrogate of Ci.

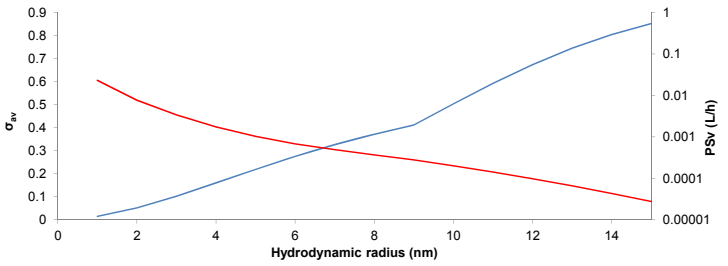

Figure 2: Predicted PSv and σ_{av} values for the liver for proteins with hydrodynamic radii ranging from 1 – 15 nm. — σ_{av} values; — PSv values.

To assess the impact of protein binding on Ci/Cp ratios, concentrations of a TP with molecular weight of 2450 Da (radius 1.0 nm) were simulated when differing degrees of plasma protein binding (0 – 99% bound) were assumed. The hydrodynamic radius of the bound protein complex was calculated using the equation:

$$\text{Radius (nm)} = 0.0458 \times \text{molecular weight}^{0.3951}$$

where molecular weight was the sum of protein and albumin (67000 Da) molecular weights.

Results

Predicted and observed Ci/Cp ratios for representative tissues (liver, gut, kidney, heart, lung, muscle, skin) are shown in Figure 3.

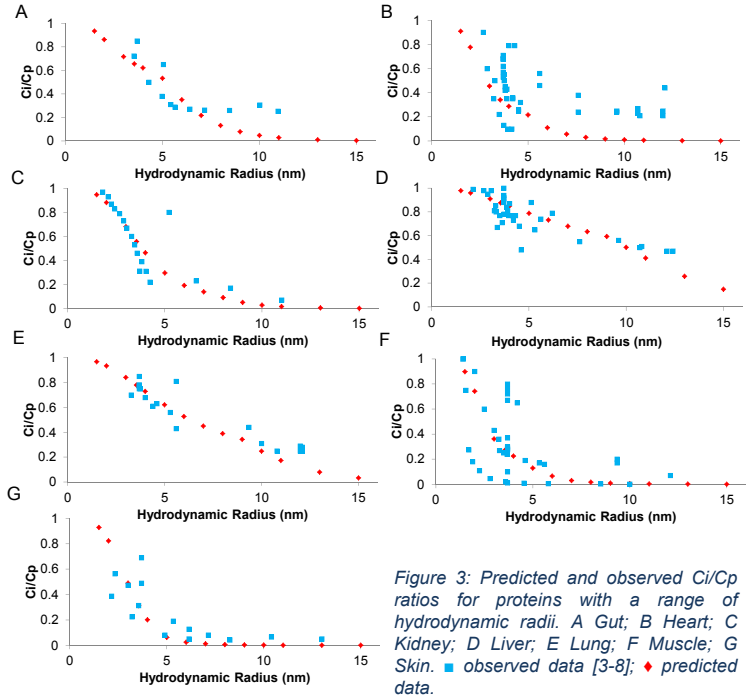

Figure 3: Predicted and observed Ci/Cp ratios for proteins with a range of hydrodynamic radii. A Gut; B Heart; C Kidney; D Liver; E Lung; F Muscle; G Skin. ■ observed data [3-8]; ♦ predicted data.

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.

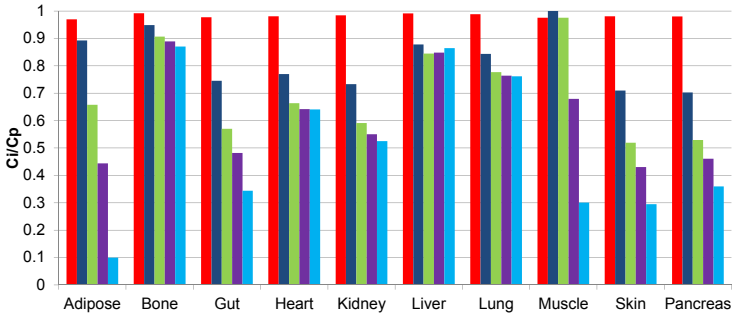

Figure 4: Predicted Ci/Cp ratios for a protein with hydrodynamic radius of 1 nm and varying plasma protein binding. % bound in plasma = 0 (■); 50 (■); 80 (■); 90 (■) or 99 (■).

For a TP with radius of 1.0 nm, increasing plasma protein binding from 0 to 99% reduced the Ci/Cp ratios by 12 to 90% depending on the tissue (Figure 4). For example, in bone the Ci/Cp ratio decreased from 0.99 to 0.87 when plasma protein binding increased from 0 to 99%, respectively, whereas for the adipose Ci/Cp decreased from 0.97 to 0.10.

Conclusion

A whole body PBPK model has been developed to describe the movement of small TPs 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 TPs in blood and target tissues.

References

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