A mechanistic PBPK model to predict subcutaneous absorption of therapeutic proteins and monoclonal antibodies

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Purpose

Subcutaneous (SC) dosing is a common administration route for therapeutic proteins (TPs) including monoclonal antibodies. The ability to predict the absorption of TPs using a bottom up approach would be useful during pre-clinical and clinical development. Therefore, an existing whole body PBPK model capable of predicting plasma and interstitial fluid concentrations of TPs in humans has been expanded to mechanistically predict SC absorption. The prediction accuracy of C_{max} and t_{max} following SC dosing of TPs covering a large range of molecular sizes using the expanded PBPK model is assessed here.

Method

A human whole body PBPK model for TPs previously developed in Simulink (Matlab, Version R2013a) was expanded to include the SC dosing site. The model contains 12 tissues and each is described by three sub-compartments, representing vascular, interstitial and intracellular spaces (Figure 1). This tissue structure was also used to represent the SC dosing site. Movement of TPs between vascular and interstitial spaces was described mechanistically by considering both convection and diffusion processes based on a 2-pore framework [1,2]. SC dose was described as a bolus input to the interstitial compartment of the SC dosing site. Convection and diffusion rates were estimated for TPs using the hydrodynamic radius as an input parameter.

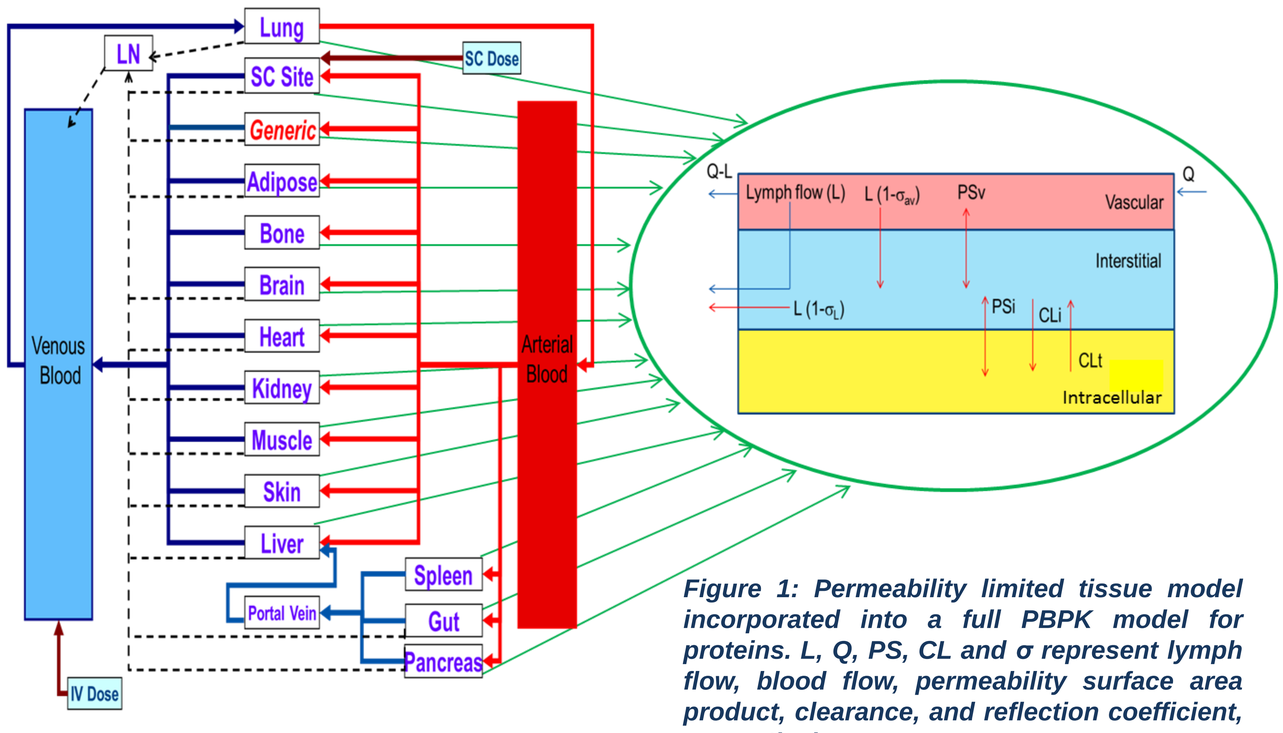

Figure 1: Permeability limited tissue model incorporated into a full PBPK model for proteins. L, Q, PS, CL and σ represent lymph flow, blood flow, permeability surface area product, clearance, and reflection coefficient, respectively.

Movement of protein into the intracellular space was not considered in these simulations, therefore PSi, CLi and CLt were set to 0. Physiological parameters for a 5 mL volume of skin were used for the SC dosing site. The model was optimised using data describing the percentage of dose absorbed in the lymph for a range of proteins dosed to sheep [3], literature values of SC site lymph:plasma ratios for a number of proteins in humans and experimental animals, and observed data showing loss of radiolabelled IgG from the SC dosing site in humans [4-6] (Figures 2 and 3).

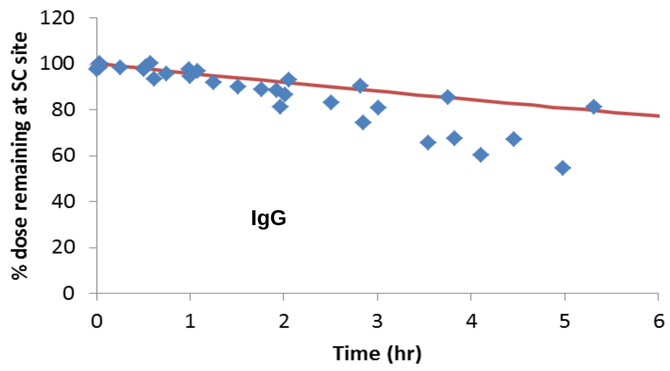

Figure 2 Predicted and observed % dose remaining at the SC site for IgG. ♦ observed data; – predicted data.

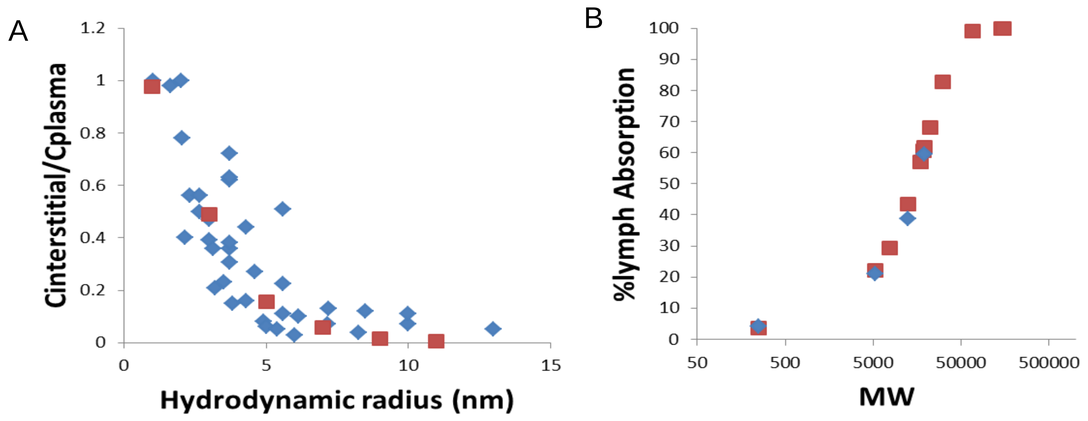

Figure 3: Predicted and observed interstitial/plasma concentration ratios at the SC site (A) and percentage of dose absorbed through the lymph (B) for proteins with a range of sizes. ♦ observed data [3,7-10]; ■ predicted data.

The model was then used to predict C_{max}, t_{max} and plasma concentration profiles for 12 TPs (molecular weight: 8-150 kDa) following SC dosing. Simulation results were compared with observed data collated from the literature. Observed bioavailability and intravenous clearance values for each TP were collated from the literature or calculated where unavailable, and were used in the model when predicting exposure following SC dosing. The observed dataset contained 54 studies/dose levels, with up to 14 sets of observed data per TP. Prediction accuracy for C_{max} and t_{max} were assessed using the fold error (predicted / observed). Correlations between prediction accuracy of C_{max} or t_{max} and protein size or isoelectric point were also assessed.

Results

Simulated plasma concentration profiles following SC dosing for the included TPs were generally similar to observed data (examples in Figure 4).

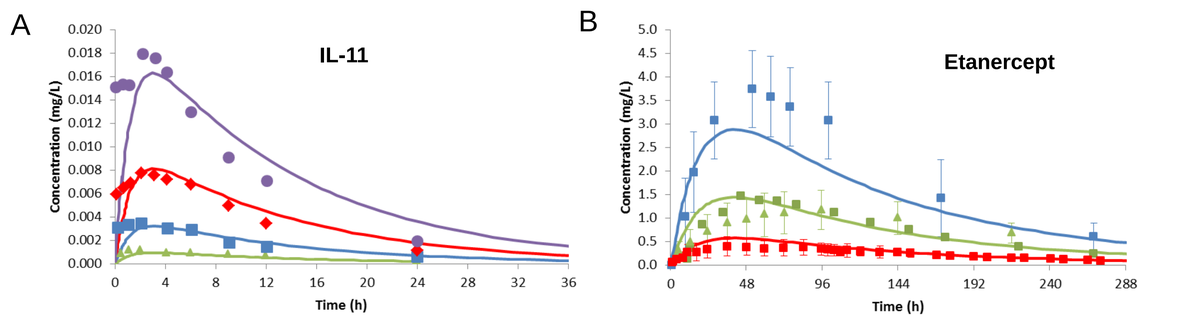

Figure 4: Predicted and observed plasma concentrations. A IL-11; B Etanercept. Symbols represent observed data; lines represent predicted data. A: Green, blue, red and purple symbols/lines = 3, 10, 25 and 50 µg/kg doses (Aoyama et al., 1997); B: Red, green and blue symbols/lines = 10 mg (Zhou, 2005), 25 mg (Korth-Bradley et al., 2000; Yi et al., 2012) and 50 mg (Sullivan et al., 2006) doses.

Table 1 summarises the prediction accuracy of C_{max} and t_{max} for the complete dataset. C_{max} was always predicted within 2.7-fold of observed values, with approximately half the C_{max} predictions falling within 1.25-fold of the observed values. 46% of t_{max} predictions were within 1.25-fold of observed values, with all predictions falling within 3.1-fold. There was no systematic bias for over or under prediction of C_{max}, although a general trend for under-prediction of t_{max} was apparent.

	C_{max}	t_{max}
No. of predictions	54	54
Mean fold error	1.01	0.84
Range of fold error	0.37 – 2.62	0.32 – 3.08
% predictions within 1.25-fold of observed	54	46
% predictions within 2-fold of observed	91	89

Table 1: Summary statistics for prediction accuracy of C_{max} and t_{max} following subcutaneous dosing of therapeutic proteins with a range of sizes.

No clear trend between prediction accuracy of C_{max} or t_{max} was apparent based on isoelectric point or molecular size (Figure 5).

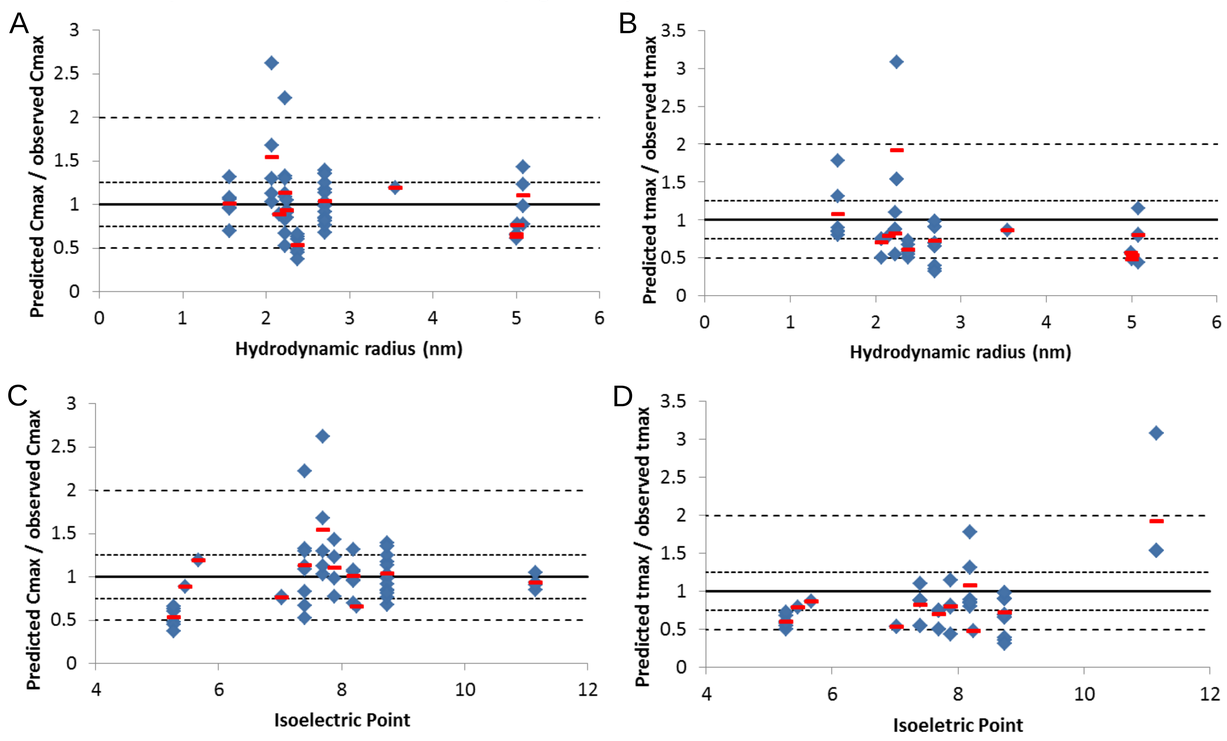

Figure 4: Prediction accuracy of C_{max} (A and C) and t_{max} (B and D) compared to hydrodynamic radius (A and B) or isoelectric point (C and D). ♦ prediction accuracy for individual studies/dose levels; ▬ mean prediction accuracy for each TP; ▬ line of unity; --- 1.25-fold prediction accuracy; - - - 2-fold prediction accuracy.

Conclusion

The mechanistic whole body PBPK modelling approach described here can be applied to predict absorption of TPs following SC dosing via both direct diffusion through capillaries into blood and lymphatic absorption into blood.

Approximately half the C_{max} and t_{max} predictions fell within 25% of the observed values.

A general trend for under prediction of t_{max} was observed, however no correlation with hydrodynamic radius or isoelectric point was apparent.

Further enhancement in the future, to include mechanistic prediction of dose transfer from the injection site to the interstitial space and catabolism at the injection site, will allow a true bottom up approach for prediction of SC absorption.

References

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