A mechanistic model to predict subcutaneous absorption of therapeutic proteins linked to a whole body PBPK model

Assigned AAPS Poster Number: T2042

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Purpose

Subcutaneous (SC) dosing is a common administration route for therapeutic proteins (TPs). This study aimed to expand an existing whole body PBPK model capable of predicting plasma and interstitial fluid concentrations of TPs in humans in order to mechanistically predict SC absorption.

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.

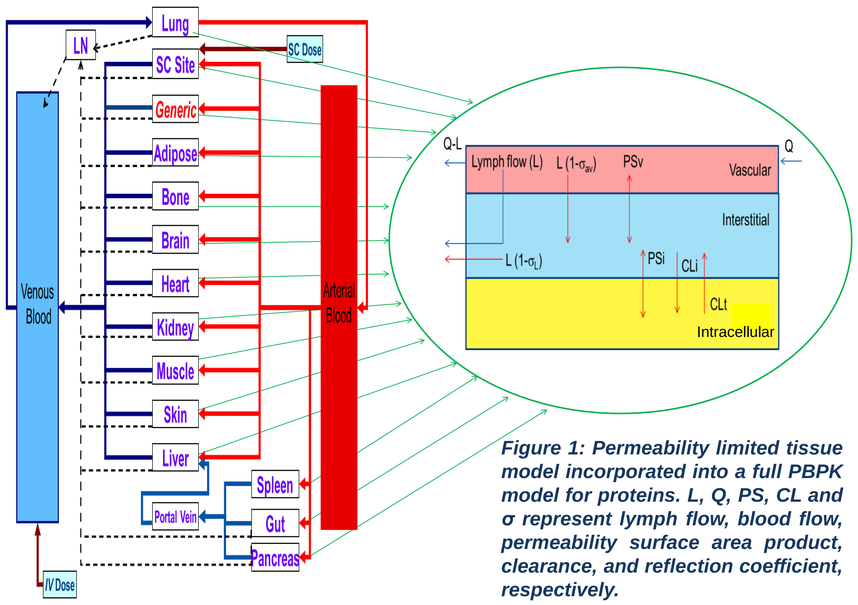

Figure 1: Permeability limited tissue model incorporated into a full PBPK model for proteins. L, Q, PS, CL and σ represent lymph flow, blood flow, permeability surface area product, clearance, and reflection coefficient, respectively.

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 as initial estimates for the SC dosing site. The model was optimised using percentage of dose absorbed in the lymph data reported for sheep [3] and observed data showing loss of radiolabelled IgG from the SC dosing site in humans [4-6] (Figure 2 B and 3). Final model parameters are shown in Table 1.

Table 1: Parameter values used for the SC dosing site.

Pore radius (nm)	Small = 5, large = 20, ratio large:small = 500
Fluid flows (L/h)	Blood = 0.0569, lymph = 0.000135 [4-6]
Volumes (mL)	Vascular space = 0.716, interstitial space = 3.12 [4-6], tissue space = 1.89

Steady-state plasma (Cp) and tissue interstitial fluid (Ci) concentrations for proteins with a range of hydrodynamic radii (1-11 nm) were simulated for the SC dosing site and compared with literature values [7-10] of lymph:plasma ratios in humans and experimental animals, with the assumption that lymph concentration is a measurable surrogate of tissue Ci.

In addition, the model was used to predict plasma concentration profiles for 8 TPs (MW: 8-150 kDa) following SC dosing and simulation results were compared with observed data (Table 2). 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.

Results

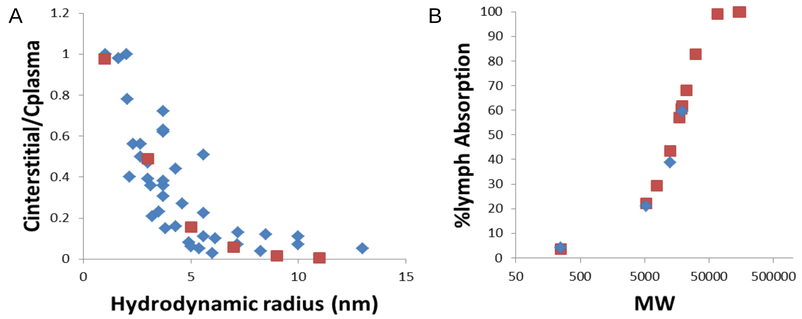

Figure 2: Predicted and observed Ci/Cp ratios at the SC site (A) and percentage of dose absorbed through the lymph (B) for proteins with a range of sizes. ♦ observed data [3,7-10]; ■ predicted data.

The model accurately recovered the observed Ci/Cp ratios (Figure 2 A) and percentage of dose absorbed through the lymph (Figure 2 B).

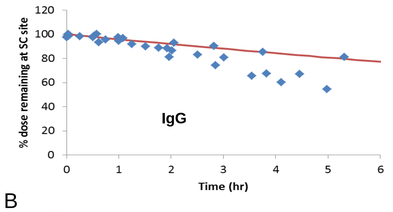

Figure 3: Predicted and observed % dose remaining at the SC site for IgG. ♦ observed data; – predicted data.

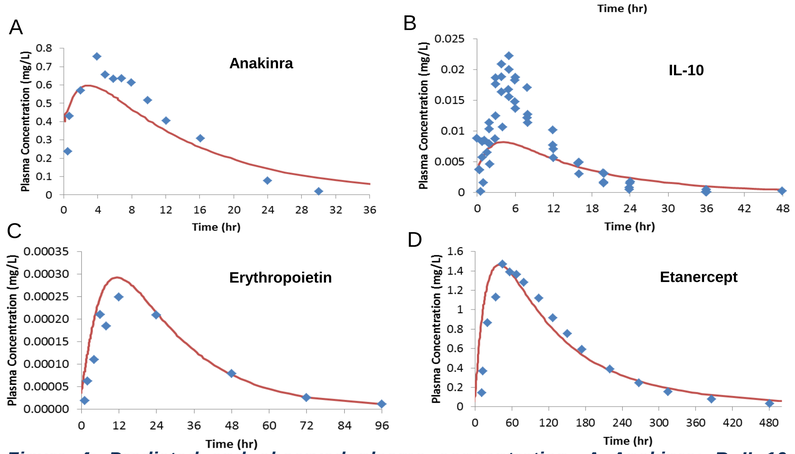

Figure 4: Predicted and observed plasma concentration. A Anakinra; B IL-10; C Erythropoietin; D Etanercept. ♦ observed data; – predicted data.

Plasma concentration profiles for a variety of TPs following SC dosing were similar to observed data for most of the tested TPs (examples in Figure 4).

T_{max} and C_{max} values were recovered by the model (Table 2), with predicted values generally within 30% of those observed. However, T_{max} for tralokinumab was under-predicted (68 vs 120 hr) and C_{max} values were under-prediction for IL-10, hGH and tralokinumab. A trend for increased under-prediction of T_{max} with increasing TP molecular size was observed, in contrast, no trend in prediction accuracy of C_{max} was apparent.

Table 2: Predicted and observed C_{max} and t_{max} for proteins with a range of sizes.

Drug	MW (kDa)	Rs (nm)	Dose (mg)	Observed		Predicted		Reference
				C_{max} (mg/L)	T_{max} (hr)	C_{max} (mg/L)	T_{max} (hr)	
IGF-1	7.6	1.56	3.228 +	0.169	7.4	0.179	6.9	Grahnen et al., 1993
IGF-1	7.6	1.56	6.456 +	0.304	6.6	0.358	6.9	Grahnen et al., 1993
Anakinra	17.3	2.16	100	0.773	4.0	0.594	4.0	Yang et al., 2003
IL-10	18.7	2.23	1.75	0.0186	5.0	0.00819	5.1	Radwanski et al., 1998
hGH	22.0	2.38	600 *	2.62 *	4.3	1.34 *	4.2	Janssen et al., 1999
hGH	22.0	2.38	1200 *	5.56 *	4.8	2.27 *	4.2	Janssen et al., 1999
hGH	22.0	2.38	1800 *	8.35 *	5.8	4.49 *	4.2	Janssen et al., 1999
Erythropoietin	30.4	2.70	0.0247	0.000225	13	0.000292	13	Salmonson et al., 1990
Albumin	67.0	3.55	100 $	7.9 $	48	9.63	42	Hollander et al., 1961
Tralokinumab	143.9	4.998	150	17.1	120	11.4	68	Oh et al., 2010
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** Dose and concentration units are mIU and mIU/L.*
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Conclusion

A whole body PBPK model for TPs has been expanded to describe the absorption of TPs following SC dosing via both direct diffusion through capillaries into blood and via lymphatic absorption.

The observed percentage of SC dose absorbed through lymph and the time of maximum plasma concentrations could be recovered for TPs covering a large range of molecular sizes.

The mechanistic whole body PBPK modelling approach described here can be applied to predict absorption of TPs into blood and movement into target tissues following SC dosing.

References

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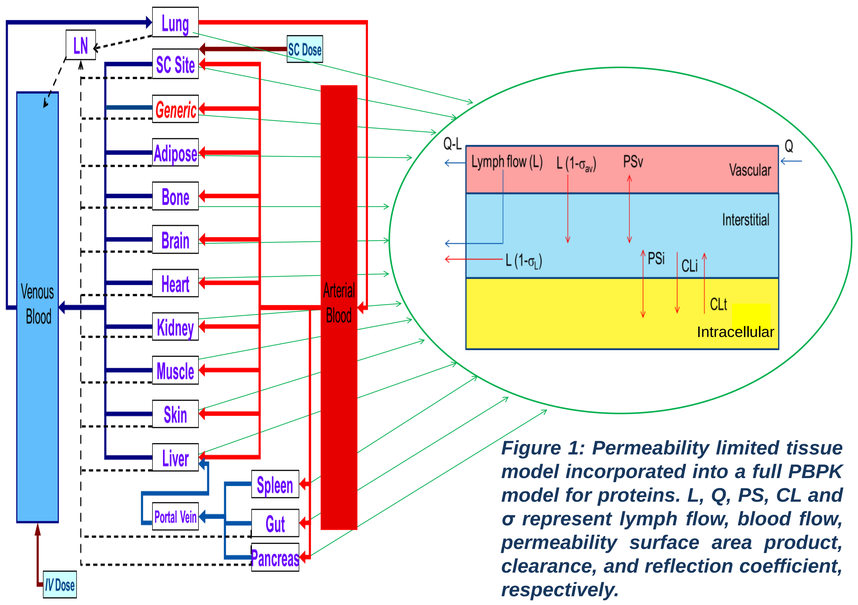

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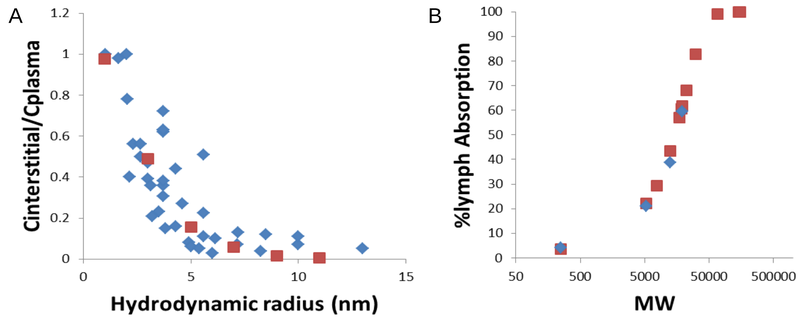

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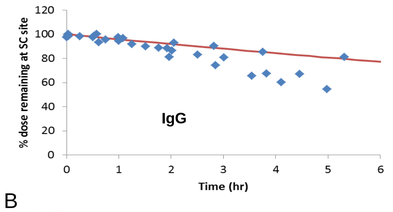

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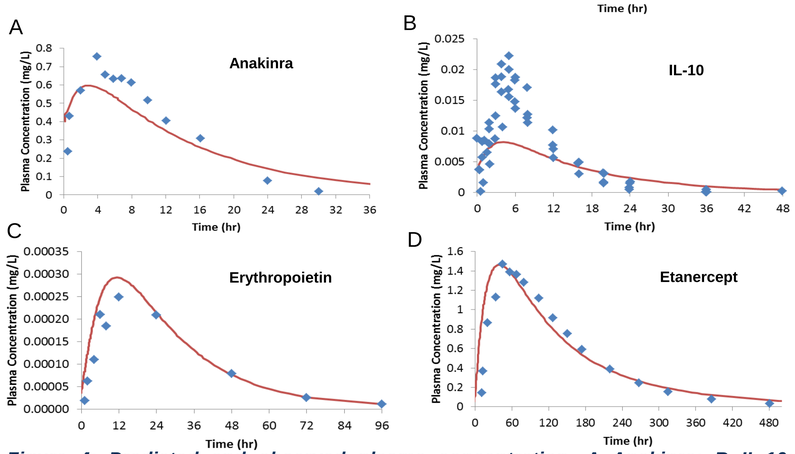

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