A mechanistic minimal PBPK model to predict distribution and subcutaneous absorption of therapeutic proteins

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Kate Gill[1], Linzhong Li[1], Masoud Jamei[1], Iain Gardner[1]
[1] Simcyp (A Certara Company), Blades Enterprise Centre, Sheffield, UK
k.gill@simcyp.com

Abstract

Purpose: In parallel to mechanistic minimal PBPK (mPBPK) models developed for monoclonal antibodies (1-3), here a mechanistic human mPBPK model was developed to predict plasma and interstitial fluid concentrations of other therapeutic proteins (TPs) following intravenous (IV) and subcutaneous (SC) dosing.
Method: A human mPBPK model containing four physiological compartments, representing the blood, lymph node, tissue and SC dosing site was developed in Simulink (Matlab). The tissue and SC compartments are sub-divided into vascular, interstitial and intracellular spaces. Movement of TPs between vascular and interstitial spaces was described by considering both convection and diffusion processes based on a 2-pore framework [4]. Literature values of lymph/plasma concentration ratios for individual tissues in humans and experimental animals were used to calculate average whole body lymph/plasma ratios, weighted by tissue volume. Steady-state interstitial fluid (Ci)/plasma (Cp) concentrations for proteins of varying size were simulated and compared with average whole body lymph/plasma ratios, with the assumption that lymph concentration is a measurable surrogate of Ci. The resultant model was used to predict plasma concentration profiles for 5 TPs and simulation results were compared with observed data.
Results: The model recovered the observed whole body Ci/Cp ratios (Figure 1). Predicted plasma concentration profiles and PK parameters for 5 TPs following IV and SC dosing were generally similar to observed data (Table 1).
Conclusion: The mechanistic mPBPK model described here reduces the number of parameters needed for model construction when compared to whole body PBPK models. The model can be applied to predict distribution of TPs into interstitial fluid and SC absorption into blood. Future model expansion to include TMDD models driven by TP concentration in the blood and/or interstitial fluid will further extend the models utility.

Purpose

Minimal PBPK models have been developed for monoclonal antibodies [1-3]. In this study a human mechanistic minimal (mmPBPK) model was developed to predict plasma and interstitial fluid concentrations of other therapeutic proteins (TPs) following intravenous (IV) and subcutaneous (SC) dosing.

Method

A human mmPBPK model was developed in Simulink (Matlab, Version R2013a). The model contains four physiological compartments, representing the blood, lymph node, tissue and SC dosing site. The tissue and SC site compartments are sub-divided into vascular, interstitial and intracellular spaces (Figure 1). Movement of TPs between vascular and interstitial spaces was described mechanistically by considering both convection and diffusion processes based on a 2-pore framework [4,5].

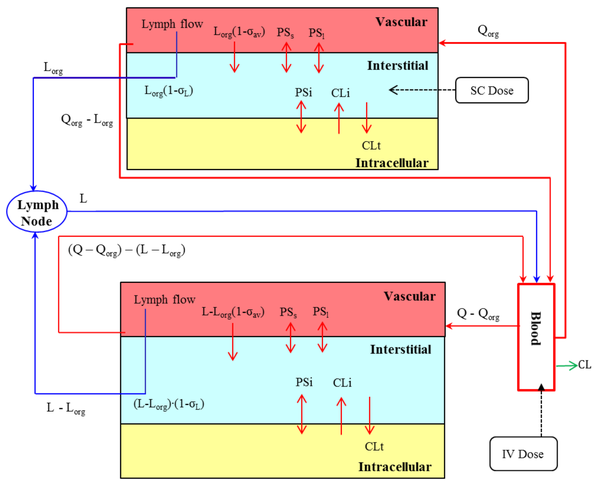

Figure 1: Permeability limited tissue model incorporated into a mmPBPK model for proteins. L, Q, PS, CL and σ represent lymph flow, blood flow, permeability surface area product, clearance, and reflection coefficient, respectively.

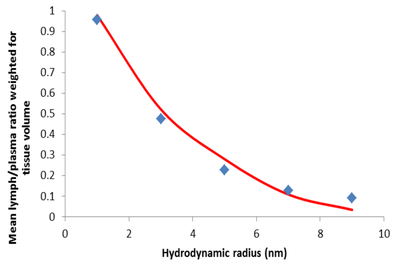

Figure 2: Predicted (—) and observed (♦) Ci/Cp concentration ratios for therapeutic proteins with a range of sizes. Average whole body Ci/Cp concentration ratios were calculated from reported experimental data for individual tissues, weighted by the tissue volume. Predicted Ci/Cp concentration ratios were simulated using the PBPK model.

Movement of protein into tissue cells was not considered in these simulations, therefore PSi, CLi and CLt were set to 0. 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 based on their hydrodynamic radius.

The SC dose was assumed to distribute into a 5 mL volume and physiological parameters for the SC dosing site were optimised as described previously [6].

Literature values of lymph/plasma concentration ratios for individual tissues in humans and experimental animals were used to calculate average whole body lymph/plasma ratios, weighted by tissue volume. Steady-state plasma (Cp) and tissue interstitial fluid (Ci) concentrations for proteins with a range of hydrodynamic radii (1-9 nm) were simulated and compared with the average whole body lymph/plasma ratios, 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 5 TPs following IV and SC dosing and simulation results were compared with observed data. Observed bioavailability and intravenous clearance values for each TP were collated from the literature and used in the model.

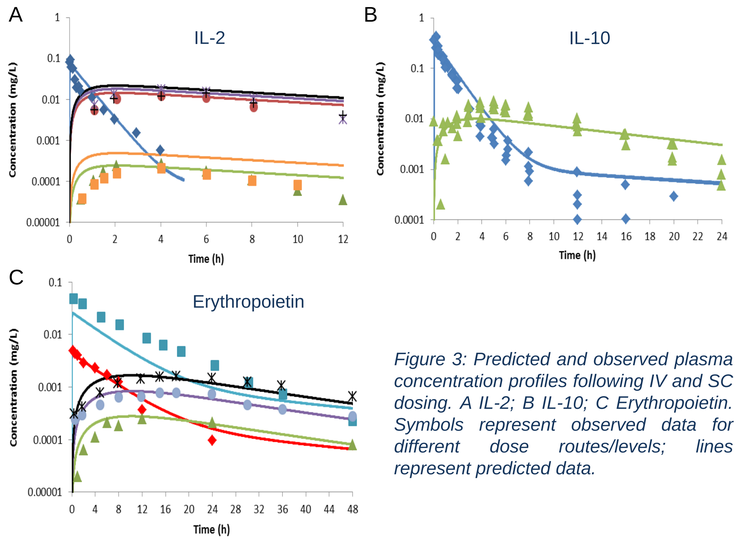

Figure 3: Predicted and observed plasma concentration profiles following IV and SC dosing. A IL-2; B IL-10; C Erythropoietin. Symbols represent observed data for different dose routes/levels; lines represent predicted data.

Results

The model accurately recovered the average whole body Ci/Cp ratios (Figure 2). Predicted and observed plasma concentration profiles for selected TPs are shown in Figure 3. Predicted plasma concentration profiles and PK parameters for 5 TPs following IV and SC dosing were generally similar to observed data (Table 1). 88% of AUC and C_{max} predictions were within 2-fold of observed values. Although a trend for under-prediction of t_{max} following SC dosing was observed, predicted values were generally within 2-fold of reported values.

Table 1: Predicted and observed C_{max}, t_{max} and AUC(0-t) for proteins with a range of sizes.

Drug	MW (kDa)	Dose route	Dose (mg/kg)	Observed			Predicted			Reference
				Cmax (mg/L)	Tmax (hr)	AUC(0-t) (mg/L.h)	Cmax (mg/L)	Tmax (hr)	AUC(0-t) (mg/L.h)	
IL-2	15.5	IV	0.25*	NR	NR	0.0941 $	0.0692	0.05	0.0494 $	Konrad et al., 1990
		SC	0.0583*	0.000260	4	0.00168	0.000243	2.11	0.00250	Kirschner et al., 1998
		SC	0.0292*	0.000210	4	0.00183	0.000486	2.07	0.00628	Kirschner et al., 1998
		SC	3+	0.0136	5	0.127	0.0144	2.06	0.187	Piscitelli et al., 1996
		SC	3.75+	0.0187	4.5	0.178	0.0180	2.06	0.233	Piscitelli et al., 1996
		SC	4.5+	0.0164	4	0.132	0.0217	2.06	0.280	Piscitelli et al., 1996
Anakinra	17.3	IV	1	22.4	NR	9.59 $	12.9	0.06	9.74 $	Yang et al., 2003
		SC	100+	0.773	4	10.2 $	0.615	2.15	12.4 $	Yang et al., 2003
IL-10	18.7	IV	0.025	NR	NR	NR	0.334	0.06	0.472	Radwanski et al., 1998
		SC	0.025	NR	NR	NR	0.00998	3.50	0.189	Radwanski et al., 1998
		IV	0.005	0.109	NR	0.0820	0.0668	0.07	0.0915	Huhn et al., 1996
		IV	0.01	0.227	NR	0.181	0.134	0.06	0.183	Huhn et al., 1996
		IV	0.025	0.584	NR	0.522	0.334	0.06	0.462	Huhn et al., 1996
		IV	0.05	0.961	NR	0.851	0.668	0.06	0.926	Huhn et al., 1996
		IV	0.1	2.18	NR	1.73	1.34	0.06	1.85	Huhn et al., 1996
		SC	0.001	0.00032	2	0.00435	0.000399	3.50	0.00387	Huhn et al., 1997
		SC	0.0025	0.00095	6.5	0.00945	0.000999	3.51	0.0129	Huhn et al., 1997
		SC	0.005	0.0022	4.92	0.0216	0.00200	3.49	0.0301	Huhn et al., 1997
		SC	0.01	0.00477	5.08	0.0518	0.00399	3.51	0.0679	Huhn et al., 1997
		SC	0.025	0.0172	3.83	0.171	0.00998	3.50	0.170	Huhn et al., 1997
		SC	0.05	0.0324	5	0.387	0.0200	3.50	0.363	Huhn et al., 1997
hGH	22.0	IV	0.00495	0.128	0.063	NR	0.0612	0.05	0.0262	Laursen et al., 1996
		SC	0.033	0.0140	5.30	NR	0.00712	1.48	0.0993	Laursen et al., 1996
		IV	1.3*	NR	NR	0.07	0.345	0.05	0.148	Zeisel et al., 1992
		SC	1.3*	0.0246	5.3	0.132	0.00601	1.47	0.0839	Zeisel et al., 1992
Erythro-poietin	30.4	IV	0.000313	NR	NR	0.0275	0.00432	0.08	0.0303	Salmonson et al., 1990
		SC	0.000313	0.000225	13	0.00921	0.000277	10.2	0.0107	Salmonson et al., 1990
		IV	0.00188	NR	NR	0.344 $	0.0259	0.08	0.181 $	McMahon et al., 1990
		SC	0.000934	0.0009	8-24	0.0254	0.000831	10.3	0.0256	McMahon et al., 1990
		SC	0.00188	0.0018	12-24	0.0533	0.00166	10.2	0.0512	McMahon et al., 1990

IV = intravenous; SC = subcutaneous; NR = not reported.
*+ dose in mg; * dose in mg/m²; $ AUC(0-inf).*

Conclusion

The mmPBPK model described here with a limited number of parameters can be applied to predict distribution of TPs into interstitial fluid and SC absorption into blood.

Future model expansion to include TMDD models driven by TP concentration in the blood and/or interstitial fluid will further extend the models utility.

References

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