Application of the target-mediated drug disposition approach within a minimal PBPK model to investigate pharmacokinetics of therapeutic proteins

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Background

Drugs such as therapeutic proteins which bind with high affinity to pharmacologic targets often exhibit a decrease in the volume of distribution and clearance (CL) as the dose is increased. Mager and Jusko (2001) [1] developed a general pharmacokinetic model for describing such 'Target Mediated Drug Disposition' (TMDD), as shown schematically in Figure 1. This phenomenon is particularly important for therapeutic proteins because they bind with high affinity to the target receptor and the drug-target complex is prone to degradation once internalised within the cell. Gibiansky et al (2008) [2] provided an equivalent Quasi-Equilbrium (QE) approximation to this model for when k_{on} and k_{off} >>> k_{deg} in which k_{off}/k_{on} is given by an equilibrium disocciation constant K_D.

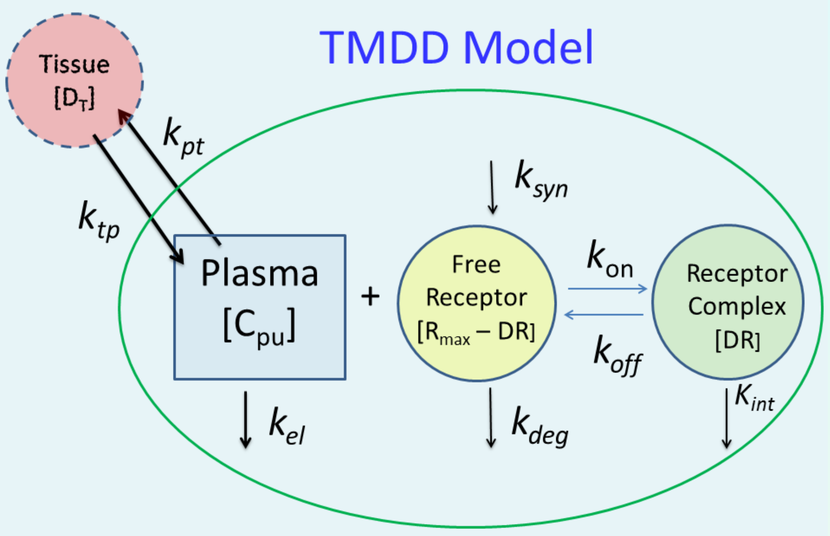

Figure 1. Schematic diagram of the TMDD model proposed by Mager and Jusko 2001 [1]

Objectives

We demonstrate how an equivalent dynamic representation to the target mediated drug disposition (TMDD) model proposed by Mager and Jusko [1] can be achieved through 'embedding' the TMDD model within the systemic compartment of the minimal-PBPK model with single adjusting compartment (SAC) employed in the Simcyp simulator[3] as shown in Figure 2.

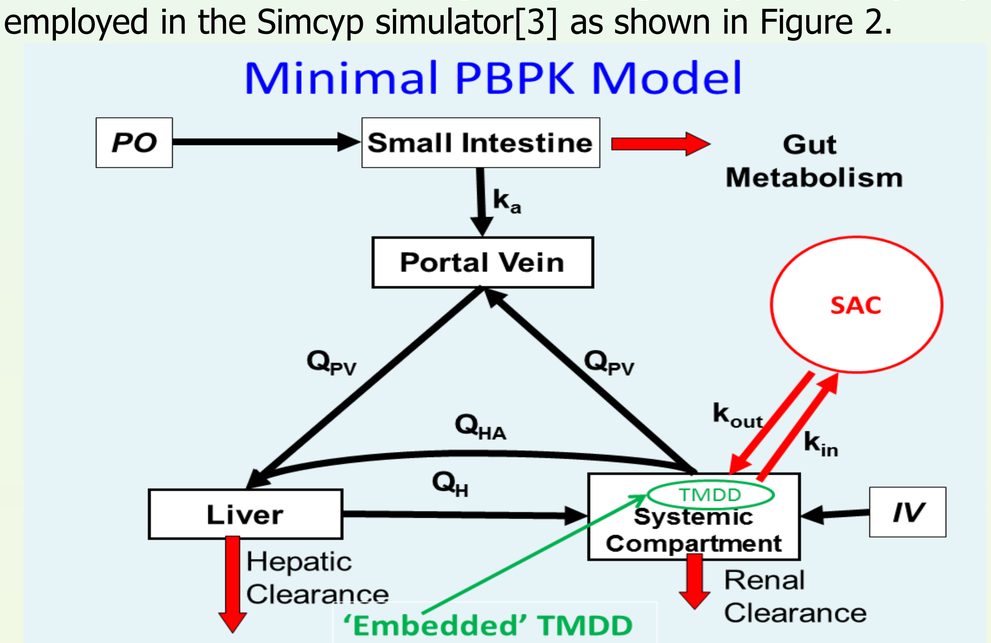

Figure 2. The minimal PBPK model (MPBPK) with embedded TMDD model

Methods

The TMDD model was 'embedded' into the systemic compartment of the minimal-PBPK model by coupling the drug concentration within that compartment with the input concentration into the TMDD model. The TMDD and minimal-PBPK models were parameterized with data obtained for the therapeutic protein Erythropoetin (EPO), a glycoproteine hormone, from [4]. Profiles of concentrations in plasma and SAC versus time were generated with and without TMDD to demonstrate the significance of TMDD in the PK of this drug (Figure 3).

Results

A comparison of the PK profiles generated by the minimal-PBPK with embedded TMDD model with those of the separate TMDD model confirmed that both representations produced equivalent output. The plasma concentration profiles with TMDD and SAC operative gave good matches to the published clinical data for Erythropoetin [4] for doses ranging from 0.0625 to 3.125 microg/kg as shown in Figure 3 (A) below.

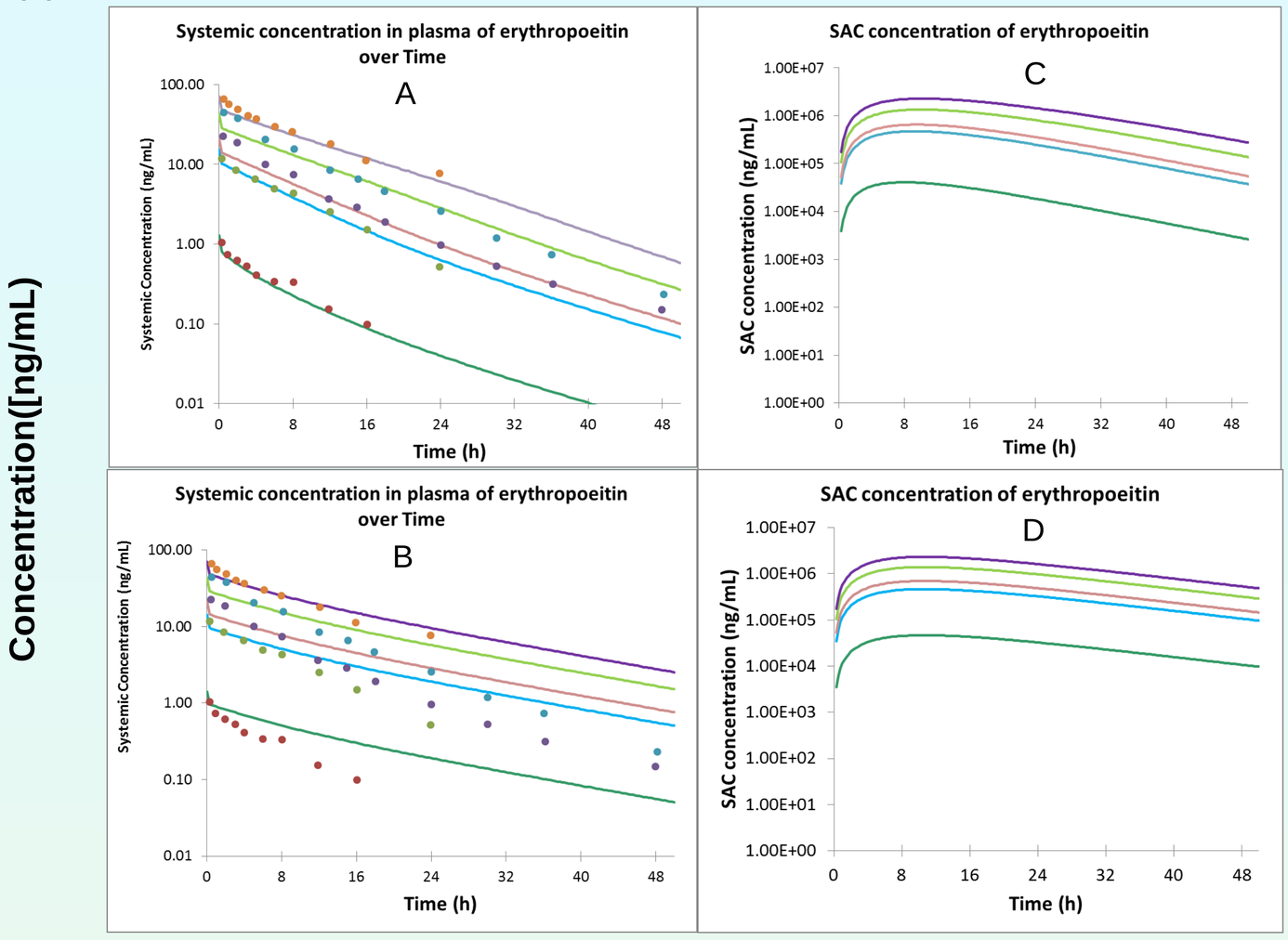

Figure 3. Profiles generated by the MPBPK with embedded TMDD (QE) model , parameterized for EPO at doses from 0.0625 to 3.125 microg/kg as in Woo et al (2007) , illustrating the significance of TMDD on plasma and tissue concentrations with time. Vertical Scale: Logarithmic Base 10. Systemic (or central) compartment with superimposed EPO data obtained by Woo et al (2007) [4] (circles): (A) with TMDD and (B) without TMDD. Respective tissue (or SAC) compartment profiles are shown in (C) with TMDD and (D) without TMDD.

Parameter	Description		
TMDD model		**EPO**	**units**
R_{max}	Total binding capacity in blood	0.000136	[microM]
k_{pt}	Rate constant of non-specific tissue binding	0.0359	[per h]
k_{tp}	Rate constant of non-specific tissue distribution	0.1151	[per h]
k_{int}	Rate constant of DR internalisation and degradation	0.2216	[per h]
k_{syn}*#	Apparent zero order production of free receptors	0.0000586	[microM per h]
K_D*	Equilibrium dissociation constant	0.00002	[microM]
k_{deg}	Degradation rate of free receptors	0.8974	[per h]
MPBPK model			
B:p	Blood:plasma ratio	1	[dimensionless]
fu	Fraction unbound in plasma	1	[dimensionless]
Vss	Volume of distribution at steady state	0.05	[L/kg]
CL	Clearance rate	0.35	[L/h]

Table 1. Parameter values used in simulations. All parameter values as reported in Woo et al (2007) [4] except for those * asterisked.

Conclusions

This study demonstrates that the minimal-PBPK model with SAC as used within the Simcyp simulator can be parameterized for therapeutic proteins to be dynamically equivalent to the TMDD model of Mager and Jusko (2001) [1]. Hence the minimal-PBPK model within the Simcyp simulator can be employed to explore the influence of key TMDD parameters (such as Rmax, Kint and affinity of binding to target) on compound disposition. In addition inclusion of the single adjusting compartment allows distribution into tissues other than the liver to be accounted for. The systems approach adopted here will enable semi-mechanistic modelling of many therapeutic proteins.

References

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[3] Rowland-Yeo K. Jamei M., Yang J., Tucker G.T., Rostami-Hodjegan A. (2010). Physiologically based mechanistic modelling to predict complex drug-drug interactions involving simultaneous competitive and time-dependent enzyme inhibition by parent compound and its metabolite in both liver and gut - the effect of diltiazem on the time-course of exposure to triazolam, *Eur J Pharm Sci* **39**, 298-309.
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Abstract amendment : AMG 317 has been removed from the analysis of this poster