Are PBPK models reporting the right C_{max}? Central venous versus peripheral site

Kate Gill [1], Helen Musther [1], Manoranjenni Chetty [1], Masoud Jamei [1], Malcolm Rowland [2] and Amin Rostami-Hodjegan [1,2]

[1] Simcyp (A Certara Company), Blades Enterprise Centre, Sheffield, UK
[2] The University of Manchester, Manchester, UK
k.gill@Simcyp.com, h.musther@Simcyp.com

Purpose

PBPK models often report over-predicted maximum concentration (C_{max}) for doses administrated intravenously (IV) compared to observed *in vivo* sampled data. It is suggested that this discrepancy may be due to PBPK models reporting the concentration in the central venous compartment, rather than the concentration at the sampling site. The objective of this project was to develop a corrective model describing a "peripheral site" to improve the predicted concentration-time profile and in particular C_{max}.

Method

A peripheral site model was developed assuming that the tissues surrounding the sampling site contribute, to different degrees, to its concentration. The model utilised the tissue-specific concentration-time profiles output by the full-PBPK model in the Simcyp population-based simulator (V13), and tissue "flow" fractions (Fr) as defined by Levitt (2004) [1]. Tissues used in defining the peripheral site were Skin, Adipose, Muscle and a "Shunt" to describe arterio-venous anastomoses (Figure 1).

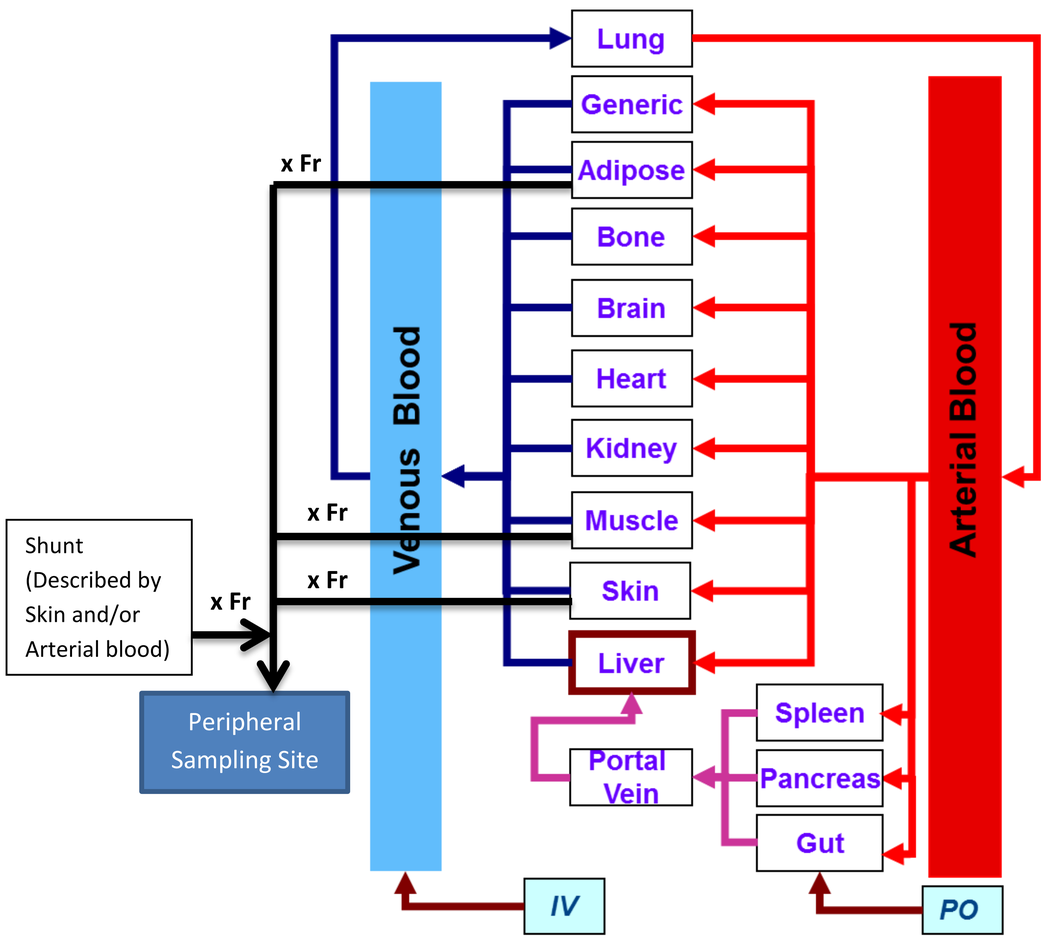

Figure 1: Current full-PBPK model in Simcyp with schematic representation of peripheral sampling site

The Fr values used for each tissue are shown in Table 1.

Tissue	Adipose	Muscle	Skin	Shunt	
				Arterial	Skin
Fr	0.075	0.05	0.25	0.1	0.525

Table 1: Tissue 'flow' fractions used in the peripheral site model

Fr values for the adipose, muscle and skin were based on Levitt et al., 2004 [1]. The concentration in blood exiting the lung in the PBPK model was used as a surrogate for arterial concentration. Fr values for the shunt were varied based on assumptions made on the arterial contribution to the "Shunt", where arterial Fr was varied from 0.02 to 0.625.

The model was applied to 7 different compounds where a Simcyp compound library file and *in vivo* literature data following IV dosing were available: alprazolam, imipramine, metroprolol, midazolam, omeprazole, rosiglitazone and theophylline (n = 4, 3, 1, 2, 2, 1 and 2 sets of observed data, respectively). Predicted C_{max} concentrations using the peripheral site model were compared to the observed C_{max} at the same time point. The difference in prediction accuracy of the peripheral site was compared to that of the central venous compartment concentration ("pooled venous return sampling").

Results

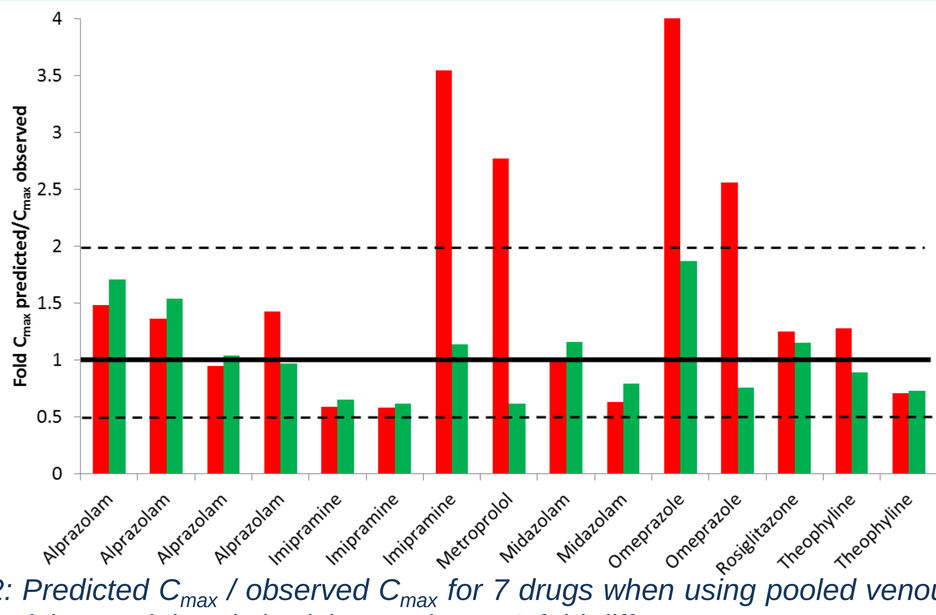

Figure 2: Predicted C_{max} / observed C_{max} for 7 drugs when using pooled venous return sampling (■) or peripheral site (■). ▬ unity; - - 2-fold difference.

Application of the peripheral model improved predictions of the observed C_{max} value compared to the "venous sampling" (see Figure 2). This was most noticeable for drugs where *in vivo* studies with early sampling time points following IV dosing were available (Examples are shown in Figure 3).

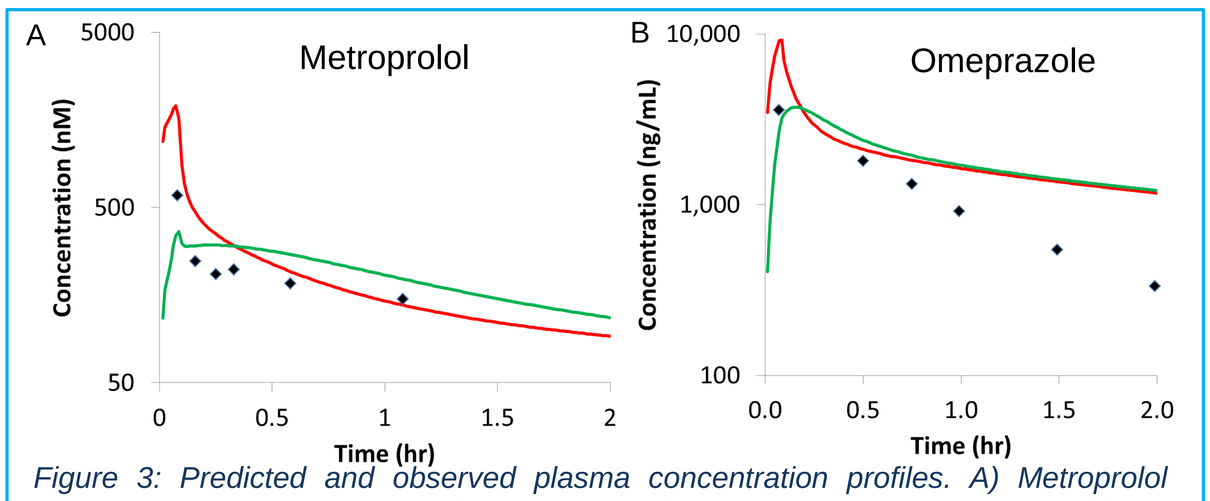

Figure 3: Predicted and observed plasma concentration profiles. A) Metroprolol (observed data supplied by Prof Rowland); B) Omeprazole (observed data for 80 mg dose level [2]). ♦ observed data; – predicted data using central venous compartment; – predicted data using peripheral site model.

Changing the fractional contribution of the arterial concentration to the shunt resulted in an improvement for some compounds, bringing the C_{max} predictions within a 0.8-1.25-fold range, while other compounds moved outside the 2-fold range. All studies investigated showed a C_{max} prediction within 2-fold of the observed value when using the peripheral site model with a fraction of 0.1 for arterial contribution (Figure 4). This suggests that the original fraction of 0.1 for arterial contribution was preferable in the model selected.

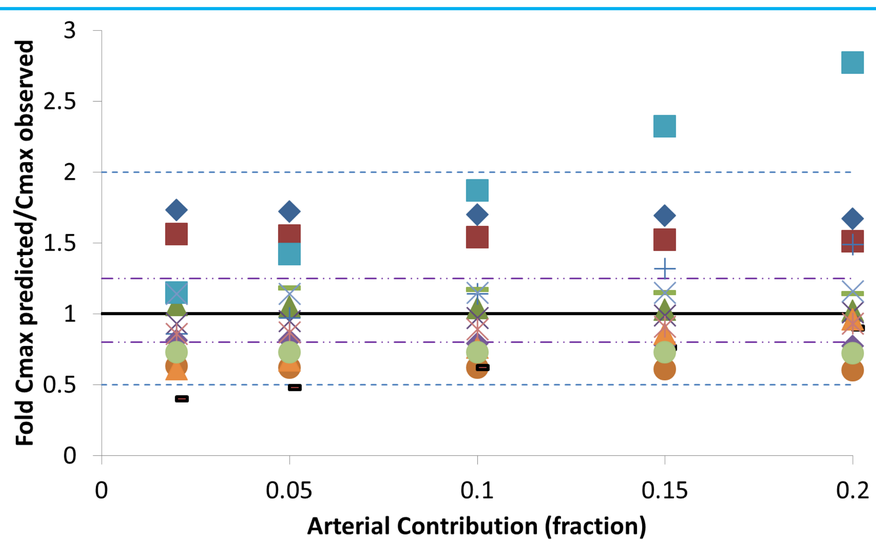

Figure 4: Predicted C_{max} / observed C_{max} for 7 drugs when using differing contributions of arterial concentration to the shunt (0.02 – 0.2). ▬ unity; - - 2-fold difference; - ·· - 0.8 to 1.25-fold difference. Symbols represent different clinical trials.

Conclusion

The developed peripheral site model significantly improved predictions of C_{max} after IV dosing for the compounds tested.

The results suggest this model should be used when comparing the predicted values from PBPK models with the observed C_{max} values.

References

1. Levitt DG., 2004, BMC Clin Pharmacol, 4:2;

2. Oosterhuis B., 1992, J Clin Pharmacol, 32:470-5;