

Extended Validation of a Peripheral Sampling Site in PBPK modelling using Clarithromycin, Dextromethorphan, Dextrorphan, Erythromycin, Lidocaine and Tramadol

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Objectives

A corrective model to account for the observation that physiologically-based pharmacokinetic (PBPK) models often over-predict C_{max} for intravenous (i.v.) administration compared to *in vivo* sampling data has previously been presented [1]. The initial validation was limited to seven compounds. The objective of this study was to extend the validation to additional compounds with varying physicochemical properties.

Methods

A peripheral site model has been developed and implemented within the Simcyp Simulator (V14) based on anatomy and physiology governing the blood supply at the site of sampling. This model utilises the tissue-specific concentration-time data reported by the full-PBPK model, and tissue "conc" fractions (Table 1). Tissues used in defining the peripheral site are Adipose, Muscle, Skin and a "Shunt" compartment comprised of Skin and an arterial contribution (Figure 1). The Shunt describes the arterio-venous anastomoses in the skin of the hand.

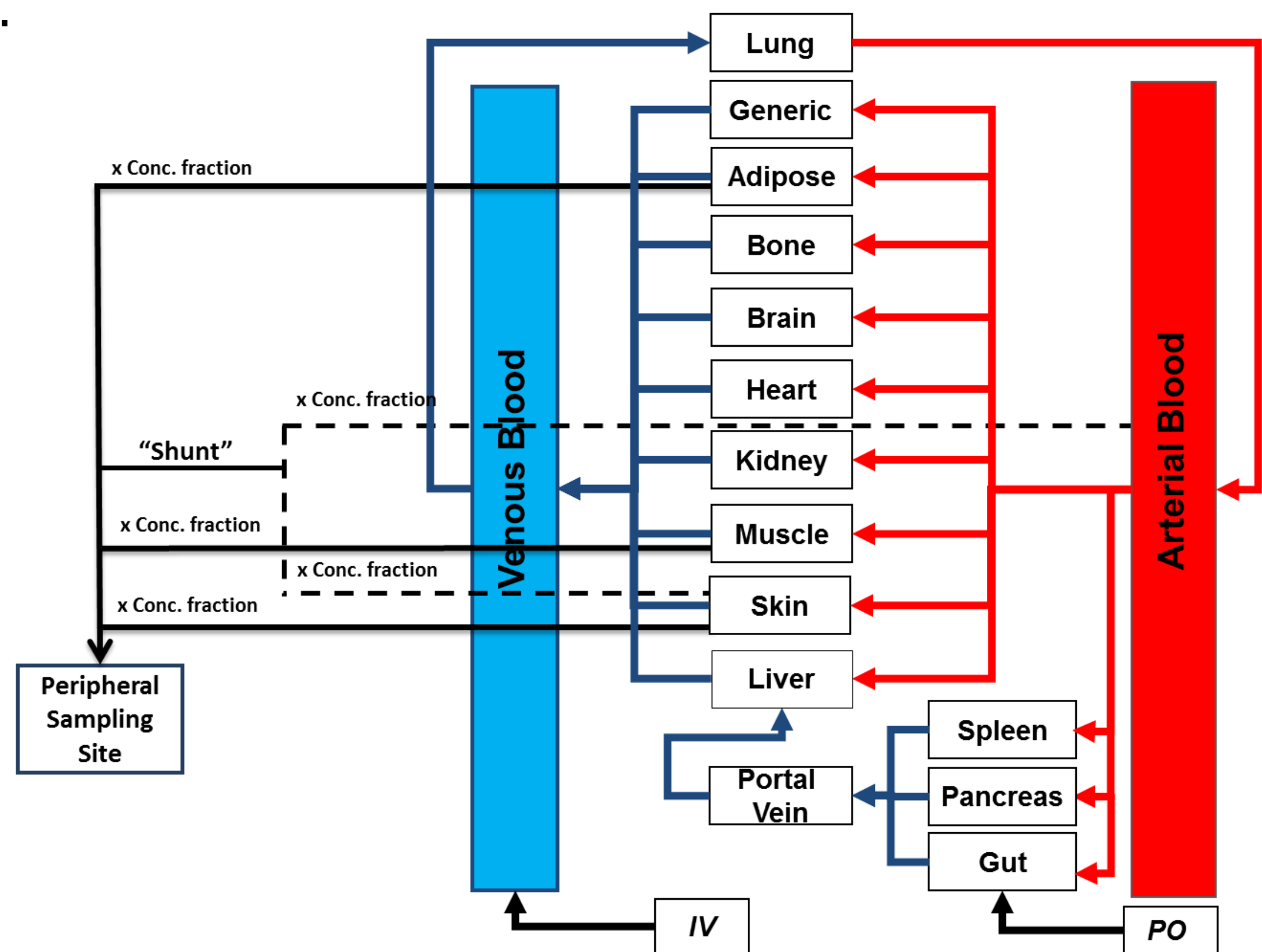


Figure 1: Full-PBPK model within Simcyp with schematic representation of peripheral sampling site model

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

Tissue	Adipose	Muscle	Skin	Shunt	
				Arterial	Skin
Conc. fraction	0.075	0.05	0.25	0.1	0.525

Initial validation was performed for seven compounds [1], however, to illustrate the full utility of the model early sampling time points were required in the *in vivo* study. It was noted that the model may have a different impact for compounds with differing properties, and also for different administration scenarios (e.g. bolus vs. long infusion, multiple vs. single dose), these options have been explored further herein.

Additional compound datasets were identified where data required for modelling a compound and clinical studies with i.v. dosing and early sampling time points were available. Comparisons were made between *in vivo* observed C_{max} values and the predicted central venous and peripheral site concentrations.

Results

Physicochemical and *in vitro* metabolism data for six compounds (Clarithromycin, Dextromethorphan, Dextrorphan, Erythromycin, Lidocaine and Tramadol) with at least one relevant clinical i.v. study were collated for further performance verification.

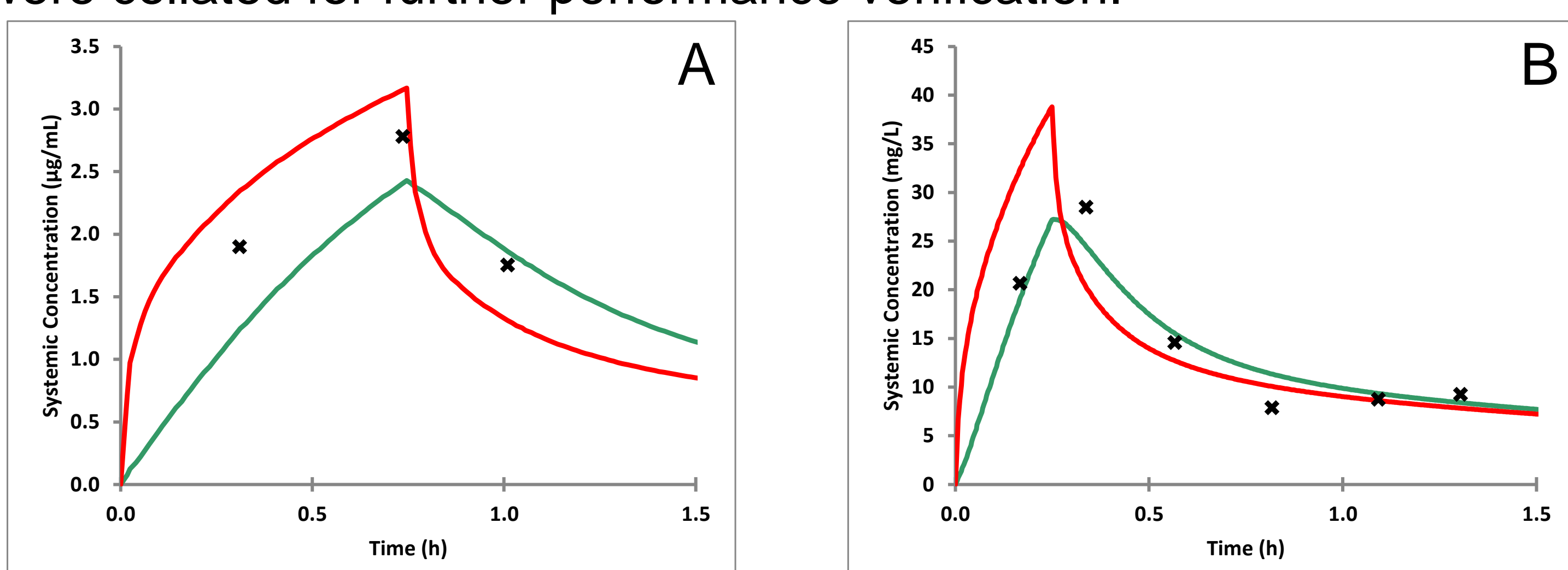


Figure 2: Predicted and observed plasma concentration profiles for A) Clarithromycin - 250mg (45min infusion) [2] and B) Erythromycin - 900mg (15min infusion) [3]. X *in vivo* data, - predicted central venous, - predicted peripheral site.

References

[1] Gill et al., 2014 PAGE meeting. [2] Chu 1992. Antimicrob. Agents. Chemother. 36:1147-1150 [3] Austin 1980 BJCP. 10:273-279. [4] Duedahl 2005. Pain. 113:360-368. [5] Dixon 1983. Res Commun Chem Pathol. Pharmacol. 41:3-17 [6] Orlando et al. 2003. BJCP 55:, 86-93 [7] Isohanni et al., 2005. Eur. J. of Anaesthesiol. 22: 795-799. [8] Kottayil et al. 2013. Patent application.

In the case of Clarithromycin and Erythromycin (Figure 2), both with low observed V_{ss} values (1.75 and 0.75 L/kg, respectively), an improvement can be seen from the use of the peripheral model. However, observed time points must be early to ensure redistribution has not already occurred.

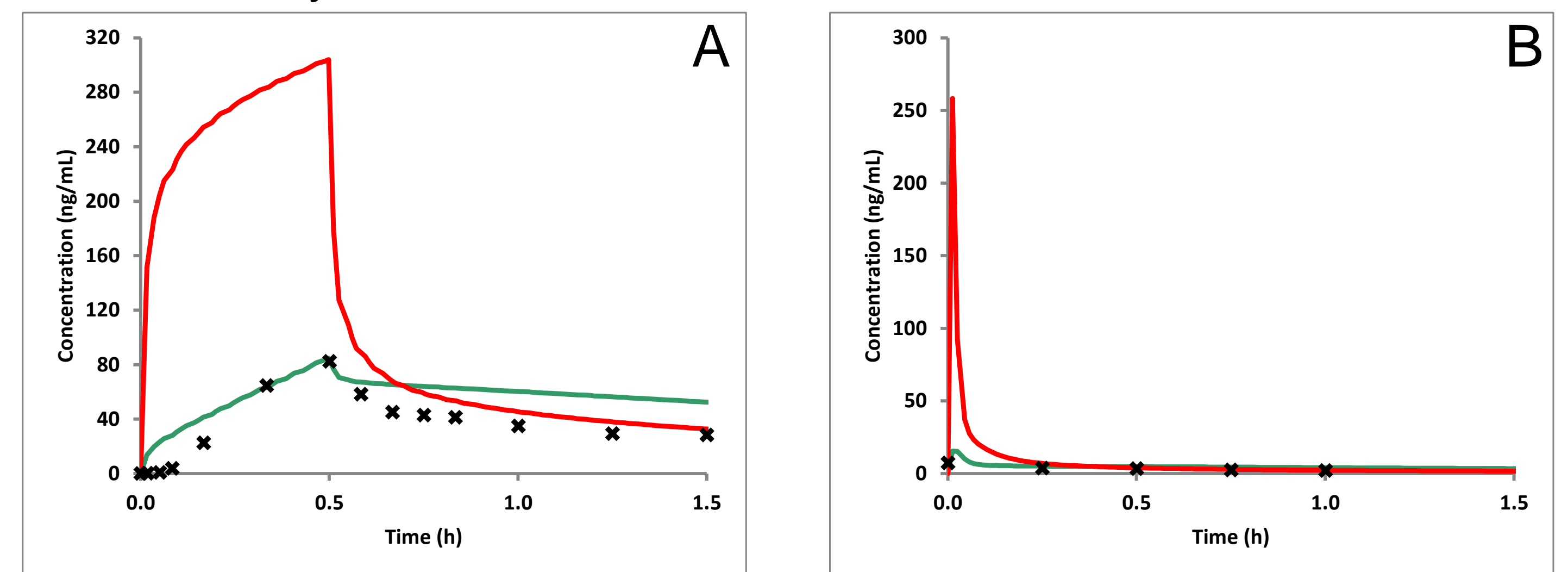


Figure 3: Predicted and observed plasma concentration profiles for A) Dextromethorphan - 0.5mg/kg (30min infusion) [4] and B) Dextrorphan - 2mg (bolus) [5]. X *in vivo* data, - predicted central venous, - predicted peripheral site.

For both Dextromethorphan and Dextrorphan (Figure 3), with higher V_{ss} values (14.3 and 11.5 L/kg, respectively), significant improvement by using the peripheral model can be seen.

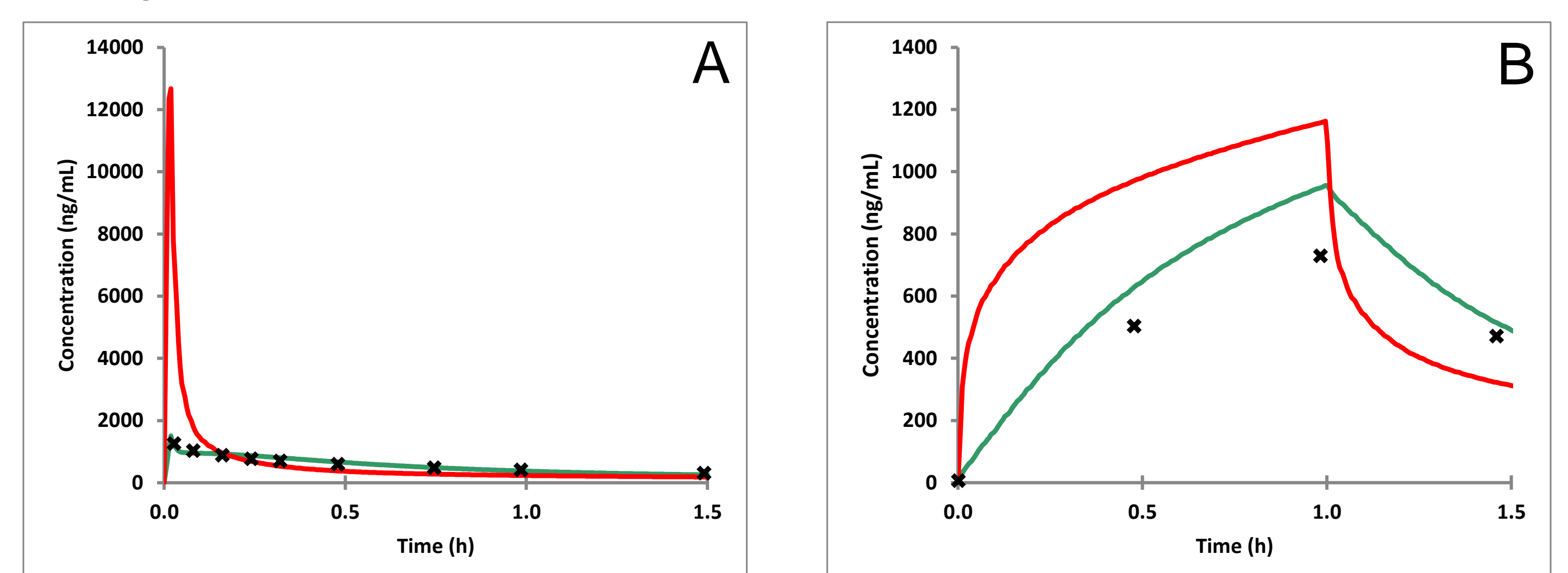


Figure 4: Predicted and observed plasma concentration profiles for A) Lidocaine 1mg/kg (bolus) [6] and B) 1.5mg/kg (60min infusion) [7]. X *in vivo* data, - predicted central venous, - predicted peripheral site

For Lidocaine (Figure 4), a more marked improvement using the peripheral model can be seen for an i.v. bolus c.f. a long infusion.

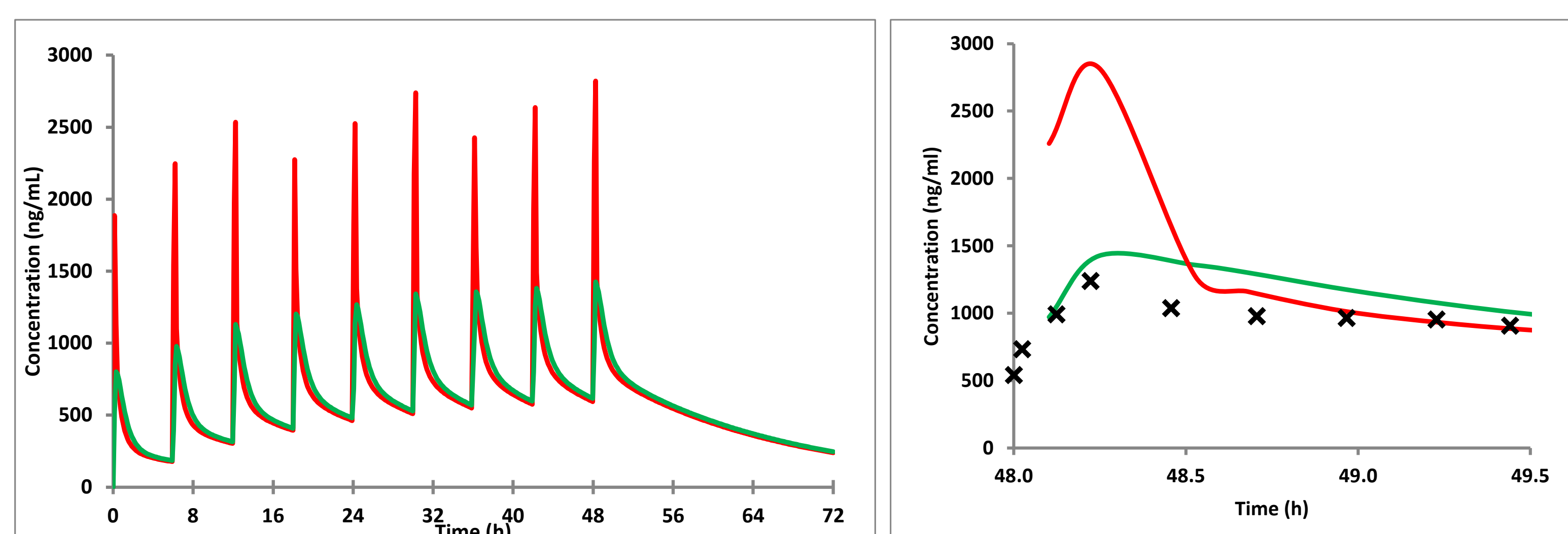


Figure 5: Predicted and observed plasma concentration profiles for Tramadol multiple dose 100mg (15min infusion) [8] X *in vivo* data, - predicted central venous, - predicted peripheral site.

For Tramadol (Figure 5), the peripheral site model allowed the C_{max} to be accurately captured following a multiple dose study.

All studies investigated showed a C_{max} prediction within 2-fold of the observed values when using the peripheral site concentration, with many showing a marked improvement compared to the central venous concentration. The impact of using the corrective model may depend on the compound properties and the length of the i.v. administration.

Conclusions

Additional successful validation was performed for a model that allows a more realistic comparison of the predicted concentrations at a peripheral sampling site to those taken in clinical trials, particularly at early sampling time points and for compounds known to significantly distribute into tissues.

These models can be built into PBPK platforms to improve C_{max} predictions and potentially account for factors (such as effect of heat, variation in adipose and muscle content of the body) that may affect the initial mixing of the blood at the site of sampling and hence the simulated drug concentrations in blood or plasma at early time points.