The purpose of this study was to identify and validate potential corrective models based on anatomy and physiology governing the blood supply at the site of sampling and incorporate them into a PBPK platform" Musther et al (2015).

Reference:

Musther, H., Gill, K.L., Chetty, M., Rostami-Hodjegan, A., Rowland, M. and Jamei, M. (2015) Are Physiologically Based Pharmacokinetic Models Reporting the Right Cmax? Central Venous Versus Peripheral Sampling Site. The AAPS Journal. June 23rd. .

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Abstract:

Physiologically based pharmacokinetic (PBPK) models can over-predict maximum plasma concentrations (Cmax) following intravenous administration. A proposed explanation is that invariably PBPK models report the concentration in the central venous compartment, rather than the site where the samples are drawn. The purpose of this study was to identify and validate potential corrective models based on anatomy and physiology governing the blood supply at the site of sampling and incorporate them into a PBPK platform. Four models were developed and scrutinised for their corrective potential. All assumed the peripheral sampling site concentration could be described by contributions from surrounding tissues and utilised

tissue-specific concentration-time profiles reported from the full-PBPK model within the Simcyp Simulator. Predicted concentrations for the peripheral site were compared to the observed Cmax. The models results were compared to clinical data for 15 studies over seven compounds (alprazolam, imipramine, metoprolol, midazolam, omeprazole, rosiglitazone and theophylline). The final model utilised tissue concentrations from adipose, skin, muscle and a contribution from artery. Predicted Cmax values considering the central venous compartment can over-predict the observed values up to 10-fold whereas the new sampling site predictions were within 2-fold of observed values. The model was particularly relevant for studies where traditional PBPK models over-predict early time point concentrations. A successful corrective model for Cmax prediction has been developed, subject to further validation. These models can be enrolled as built-up modules into PBPK platforms and potentially account for factors that may affect the initial mixing of the blood at the site of sampling.

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