Physiologically-Based Pharmacokinetic Modelling of Cyclosporine A in Rat

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Background

Cyclosporine A (CsA) is an immunosuppressive medication used to prevent rejection in organ transplants. However, therapeutic monitoring is required to prevent drug-induced nephrotoxicity [1], such as damage to Renal Proximal Tubule Epithelial Cells (RPTECs) [2]. *In vitro* CsA has been shown to cause toxicity and oxidative stress in RPTEC cells but transcriptome changes consistent with oxidative stress were not observed in the rat *in vivo* [3]. In this study we used PBPK models to investigate whether the pharmacokinetics of CsA could explain this discrepancy. The drug shows non-linearity in clearance as well as blood and tissue binding [4]. Although non-linearity in clearance can be considered in the Simcyp Rat simulator, non-linearity in blood and tissue binding can not. Therefore, as well as performing simulations with a perfusion-limited PBPK model, a full body PBPK model incorporating this non-linearity in binding was developed. The model combines the Simcyp permeability-limited model with the model proposed by Kawai et al [5] and Tanaka et al [4] for tissue binding in all the organs. The performance of the model to predict systemic plasma and kidney concentrations has been compared with the perfusion-limited model currently available in the Simcyp Rat simulator.

Methods

The non-linear binding model was developed in Simulink (Matlab, Mathworks) by integrating the Simcyp full PBPK model for rat with nonlinear intracellular drug binding [4]. The Simcyp permeability-limited equations describe the disposition of the drug in extracellular water by equilibrium with blood and exchange with the intracellular space, Intracellular drug binding was modelled as [4]:

- Muscle, adipose and brain - Non-instantaneous exchange between non¬specific and specific binding in the cell
- Lung, heart, bone, and skin - Saturable specific binding in the cell with instantaneous exchange
- Kidney, spleen, liver, gut - Saturable specific binding in the cell with non-instantaneous exchange

Hepatic clearance was determined using the well-stirred model [6] with assumption that intrinsic clearance follows Michaelis-Menten kinetics. Oral absorption was described using a first order model. Intestinal metabolism was estimated using the Qgut model [7].

Results

The model predicts well the blood CsA concentration following intravenous administration when comparing with observed data – Cmax of 17.4 vs 15.8 mg/L and AUC of 32.5 vs 26.9 for arterial blood, and Cmax of 43.2 vs 54.5 mg*hr/L and AUC of 238.5 vs 242.7 mg*hr/L for kidney (Fig.I).

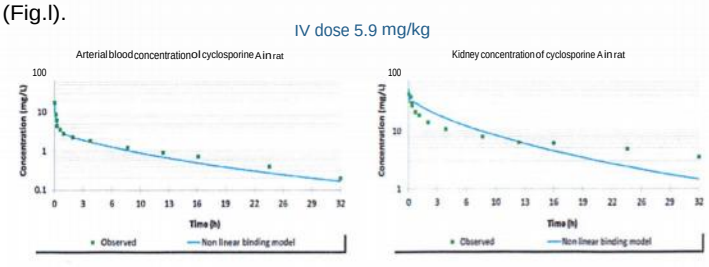

Figure 1. Intravenous (IV) observed data from Kawai et al 1998 [5] versus predicted using the nonlinear binding model.

The predicted plasma and kidney concentrations using the non-linear binding model following a daily oral administration of CsA is presented in Figure 2. With additional non-linear blood and tissue binding the new model predicts higher peak plasma and kidney exposures for the lower dose regimens, i.e. 10 and 30 mg/kg/day; but lower exposure for the highest dose of 100 mg/kg/day.

Results

In vitro experiments suggest that extracellular concentrations of 5pM and 15pM are, respectively, non-toxic and toxic for Renal Proximal Tubule Epithelial Cells (RPTECs) [3]. These extracellular concentrations result in kidney cell concentrations above 1000 mg/L, (Figure 2 last panel). The PBPK model developed predicts a peak kidney concentration of 194 mg/L, which is well below this threshold.

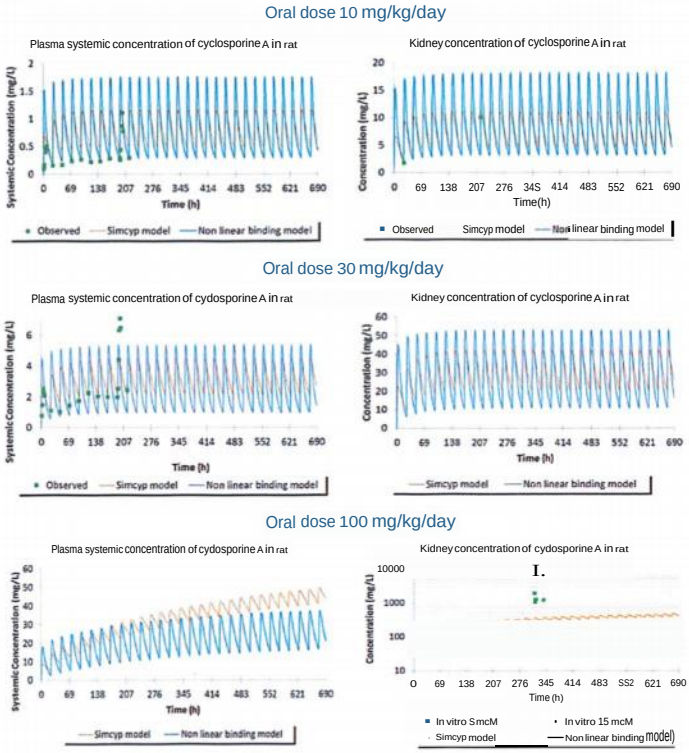

Figure 2. Oral observed data [8] versus predicted with Simcyp and the nonlinear binding model for three dose regimens. Extracellular CsA concentrations to which RPTECs cells were exposed *in vitro* are shown in the last graph as a reference [3].

Conclusions

The predictions of plasma and kidney concentrations are comparable between the new model and the initial PBPK model for the lowest dose of 10 mg/kg/day. However, the predictions for a higher dose of 30 mg/kg/day have been improved by accounting for the nonlinear properties of the blood and tissue binding of CsA. At the higher dose, where no observed data is available for comparison, the two models show differing behaviour with the non-linear binding model predicting lower exposure than the initial PBPK model. For both models the predicted concentrations in kidney tissue is lower than the concentrations causing toxicity and oxidative stress *in vitro*. These simulations may help to explain why despite the *in vitro* findings oxidative stress was not observed *in vivo* in the TG-Gates study [3].

References

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