Fitting PBPK Model Parameters within Simcyp Engine Using Simcyp-R Package

Anthonia Afuape, Janak Wedagedera and Masoud Jamei
Certara UK, Simcyp Division, Sheffield, UK

Introduction

Physiologically based pharmacokinetics (PBPK) models often need refining and optimisation based on clinical observations. For instance, a bottom-up PBPK model of Repaglinide without considering the organic anion transporting polypeptide 1B1 (OATP1B1) transporter mediated uptake into the liver will under predict the drug clearance. In order to incorporate OATP1B1 function a mechanistic permeability limited liver model in a PBPK model is required. Usually, these models are described using a set of ordinary differential equations (ODE's) involving large number of equations and parameters. Therefore, model development can be complex and tedious. The Simcyp Simulator links *in vitro in vivo* extrapolation (IVIVE) techniques with PBPK models and integrates drug and system parameters to simulate virtual populations. There are thousands of ready-made models available in the Simulator engine that can be accessed via a user-friendly graphical interface. These models can also be accessed and manipulated through a Simcyp-R package which provide easy access to the Simulator models and databases.

Objective

We aim to demonstrate the use of Simcyp-R (18.1.37) package to;

1. Run PBPK simulations directly from R and access the simulation results including PK profiles.
2. Perform parameter estimation, using the R's "optim" package, and fitting the intrinsic clearance (CLint) for OATP1B1 to match the observed data for Repaglinide.

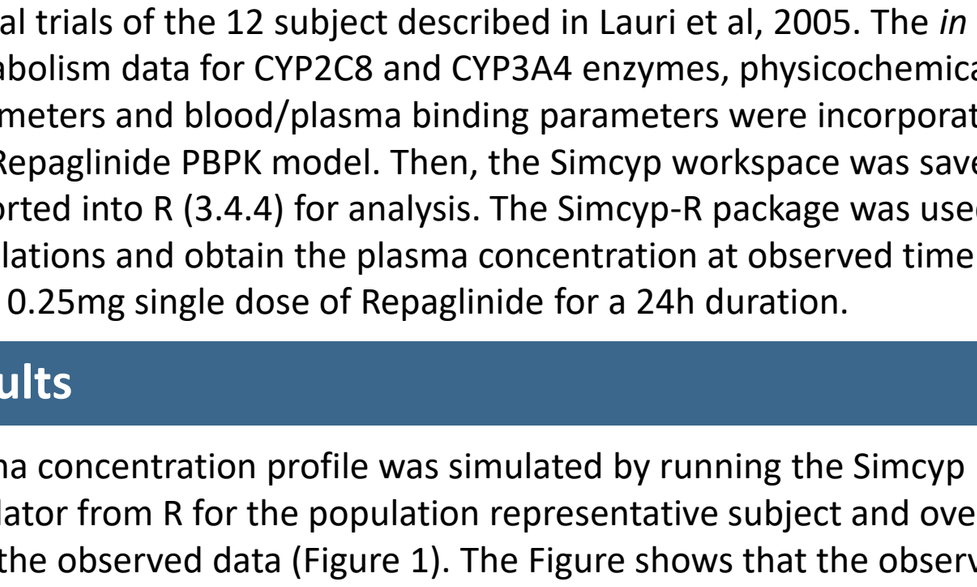
Methods

A simulation study was set up using the a population representative of the clinical study [2], (male subject, Age= 22.75 years, Weight=74.67 kg, Height=167.45 cm) in Simcyp V18's PBPK model for Repaglinide. The population representative subject was generated using the average of 50 virtual trials of the 12 subject described in Lauri et al, 2005. The *in vitro* metabolism data for CYP2C8 and CYP3A4 enzymes, physicochemical parameters and blood/plasma binding parameters were incorporated in the Repaglinide PBPK model. Then, the Simcyp workspace was saved an imported into R (3.4.4) for analysis. The Simcyp-R package was used to run simulations and obtain the plasma concentration at observed time points for a 0.25mg single dose of Repaglinide for a 24h duration.

Results

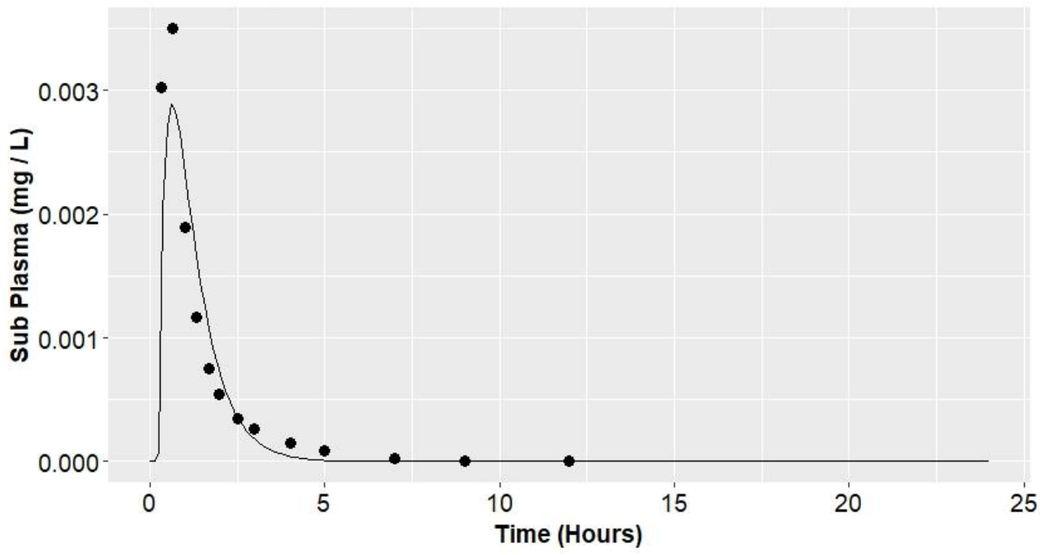
Plasma concentration profile was simulated by running the Simcyp Simulator from R for the population representative subject and overlaid with the observed data (Figure 1). The Figure shows that the observed data (black circles) are not well predicted. The plasma concentration is overestimated suggesting the under-prediction of the drug clearance. It has been previously suggested that OATP1B1 is a potential transporter involved in the hepatic uptake of Repaglinide [3]. However, there were insufficient *in vitro* data to fully characterise the hepatic uptake in the model resulting the overestimation of plasma concentration (Figure 1).

Figure 1. Simcyp predictions with observed values



Results

Figure 2. Fitted Plots with Observed values.



$$WLS_{Obj.Func} = \sum(obs_i - pred_i)^2 \qquad (1)$$

Subsequently, the intrinsic uptake clearance for OATP1B1 was incorporated and estimated using the 'Parameter Estimation' (PE) module available in the Simcyp Simulator and was also estimated using Simcyp-R using the R's "optim" package for comparison. In both cases, we used the Weight Least Squared (WLS) objective function (see Equation 1) and Nelder–Mead minimisation method. Figure 2 shows the plasma concentration profile after fitting the model to clinical data for Repaglinide using the optim package along with the Simcyp-R package. The estimated Clint OATP1B1 value was $2323.39\ \boldsymbol{\mu}L/\mathrm{min}/million\ cells$ (Table1). Incorporating this value in the permeability limited liver mode of the PBPK model improved the predictions.

Table 1. Estimated value of OATP1B1 via Simcyp PE and Simcyp-R + Optim

SLCO1B1 (OATP1B1) CLtrans (Sub)				
	Estimate (μL/min/million cells)		Residuals	RMSE
	With Variability	Without Variability		
Simcyp	2328.26	666.70	4.10E-06	4.10E-06
Simcyp-R	2323.39	923.72	2.02E-06	1.55E-07

Conclusions

The Simcyp-R package along with the R "optim" package successfully optimized the PBPK model using the WLS objective function. The determined estimate was consistent with the determined value using the Simcyp's built-in fitting tools (see Table 1). This demonstrates the capability of the Simcyp-R package as a powerful tool capable of using many of the Simcyp Simulator's compound/population parameters as well as PBPK model structures/parameters. Future applications may include using the Simcyp-R to perform parameter estimation with constraints or apply it to fit parameters across multiple studies. For example it is possible to estimate the induction parameters of an inducer across multiple interaction studies involving different victim drugs and a specific perpetrator. The same approach can be used to determine system parameters.

References

- [1] Cain T, Barnett A, Jamei M, 2015. Application of Simcyp's R Library Package in Simulation and Prediction of Metoprolol Compliance Using a Single Plasma Concentration Sample. 24th PAGE meeting, Crete, 2nd-5th June 2015 (poster presentation).
- [2] Lauri I. Kajosaari, MB, Mikko Niemi, MD, Mikko Neuvonen, MSc, Jouko Laitila, Pertti J. Neuvonen, MD, and Janne T. Backman. 2005. Cyclosporine markedly raises the plasma concentrations of Repaglinide. American Society for Clinical Pharmacology and Therapeutics. 388-398.
- [3] Niemi M, Backman JT, Kajosaari LI, Leathart JB, Neuvonen M, Daly AK, Eichelbaum M, Kivisto KT, Neuvonen PJ. Polymorphic organic anion transporting polypeptide 1B1 (OATP1B1) is a major determinant of repaglinide pharmacokinetics American Society for Clinical Pharmacology and Therapeutics ;77:468-78.