

SEMI-PHYSIOLOGICAL POPULATION PHARMACOKINETIC MODELLING OF RENAL TRANSPORTER-MEDIATED CLINICAL DRUG-DRUG INTERACTIONS



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Introduction

The once-separate disciplines of population pharmacokinetic (PPK) modelling and physiologically based pharmacokinetic modelling (PBPK) are becoming more frequently entwined. A major advantage of PBPK models is their ability to predict enzyme-mediated drug-drug interactions (DDI). More recently, PBPK models are being used to predict transporter-mediated DDI. Often, while the static approach ($[I]/K_i$ approach) may predict a 'clinically significant' increase in drug exposure, a dynamic approach (PBPK approach) which takes into account the time course of the inhibitor concentrations at the site of the interaction, predicts a lower DDI. This is consistent with the relatively few transporter DDI studies reported in the literature, which generally show low DDI even if the K_i is considered to be low with respect to the maximum plasma concentration of the inhibitor.

Objectives

To develop a semi-physiological population PK model for the Servier drug S1, which is a substrate of the renal transporter OAT3, in order to:

- simulate renal transporter-mediated DDI prior to a clinical study,
- estimate the inhibition constant K_i from the clinical data and compare with *in vitro* K_i

Methods

1. MODEL BUILDING

Study Data: Study 1 (dose finding)

Phase I clinical study (250 mg IV) – S1 plasma and urine concentrations, S1 *in vitro* $f_{u,plasma}$

Model

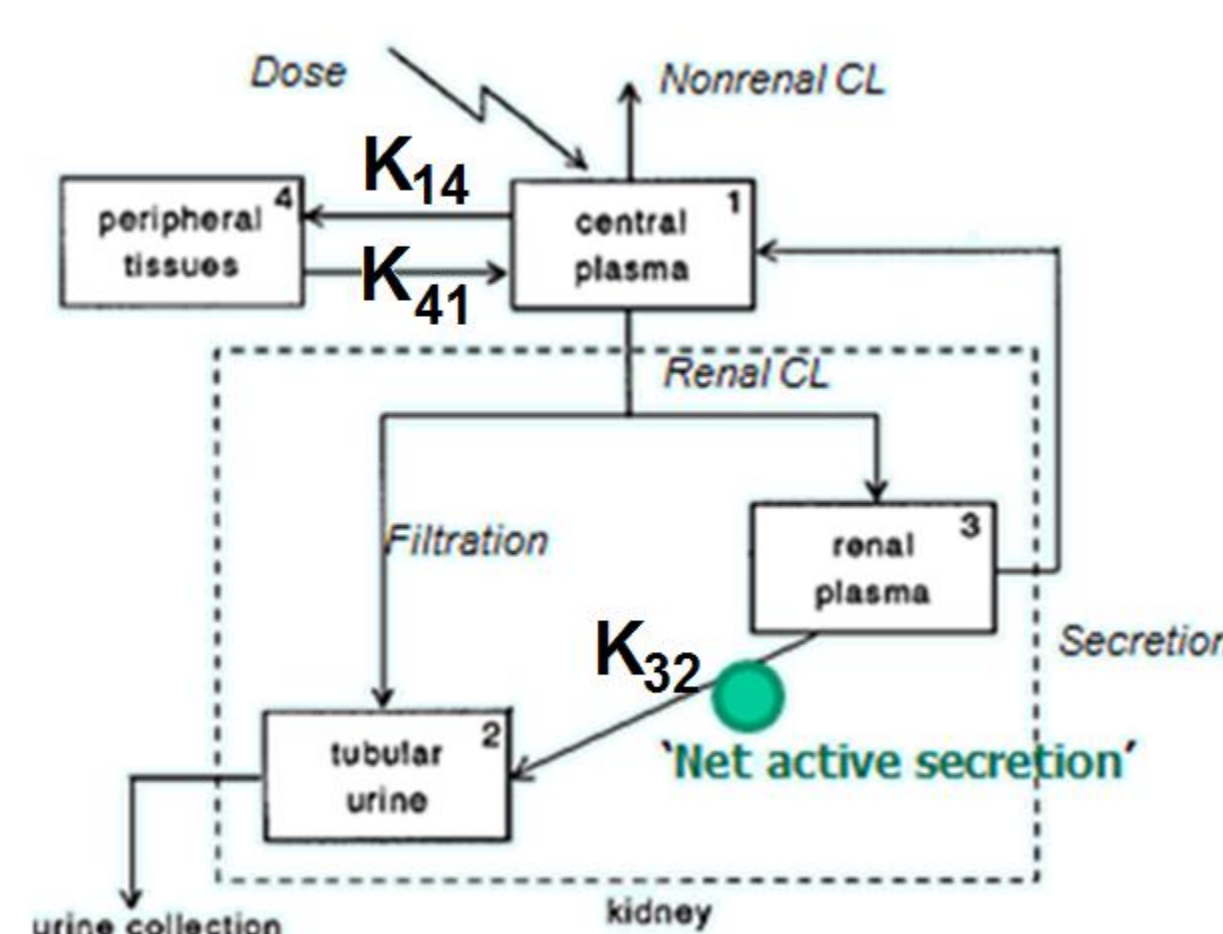
4-compartment model based on Boom *et al* [1]: central plasma, peripheral tissues, renal plasma, tubular urine. Physiological values for renal model parameters

Software

WinNonlin Phoenix NLME v1.3, FOCE estimation

Strategy

- Estimate distribution parameters, active renal secretion parameter
- Simulate using inhibitor model for $[I](t)$ and *in vitro* K_i



2. MODEL PREDICTION OF DDI

Data

Probenecid plasma concentrations and $f_{u,plasma}$ from literature

Model

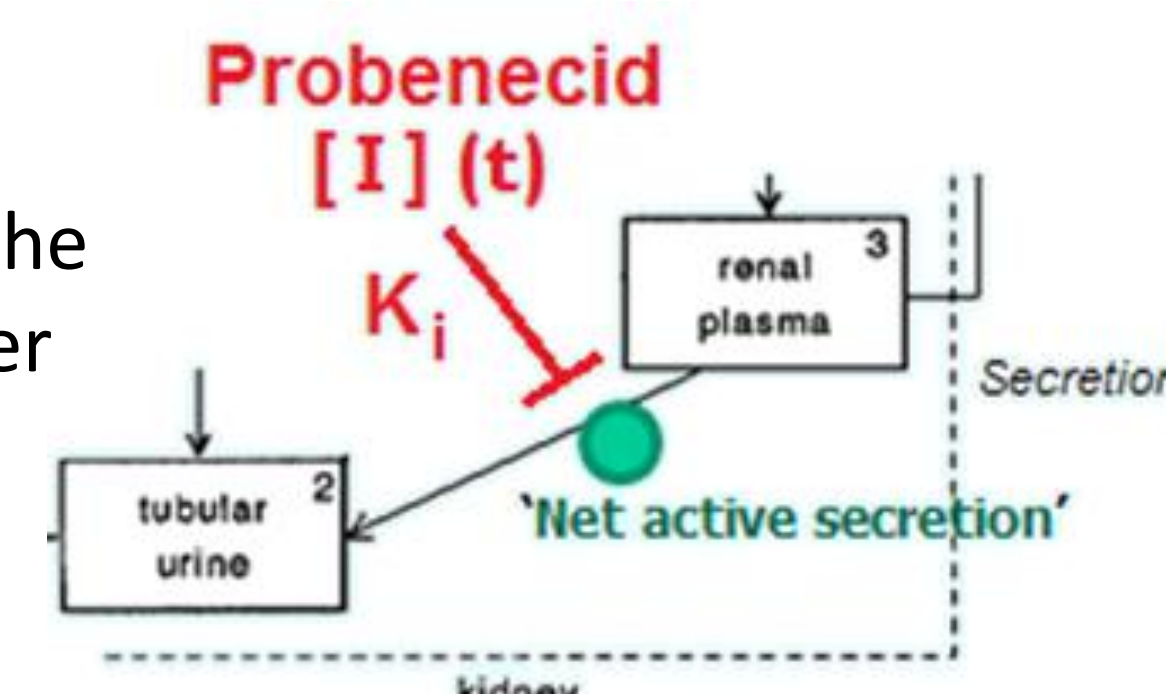
S1 model and data as described in Part 1, with the addition of K_i to inhibit the active secretion parameter

Software

WinNonlin Phoenix NLME v1.3, FOCE estimation

Strategy

- Estimate PK model parameters for probenecid
- Simulate using inhibitor model for $[I](t)$ and *in vitro* K_i of probenecid for OAT3 (**7.5 μ M**)



3. ESTIMATION OF 'IN VIVO' K_i

Study design: Study 2 (DDI)

- P1 : S1 alone (250 mg IV)
 P2 : S1 (250 mg IV) + probenecid (3 g PO)
 P3 : S1 (250 mg IV) + probenecid (1.5 g PO)

Data

S1 plasma and urine concentrations
 Probenecid plasma concentrations

Model

S1 model as described in Part 2

Software

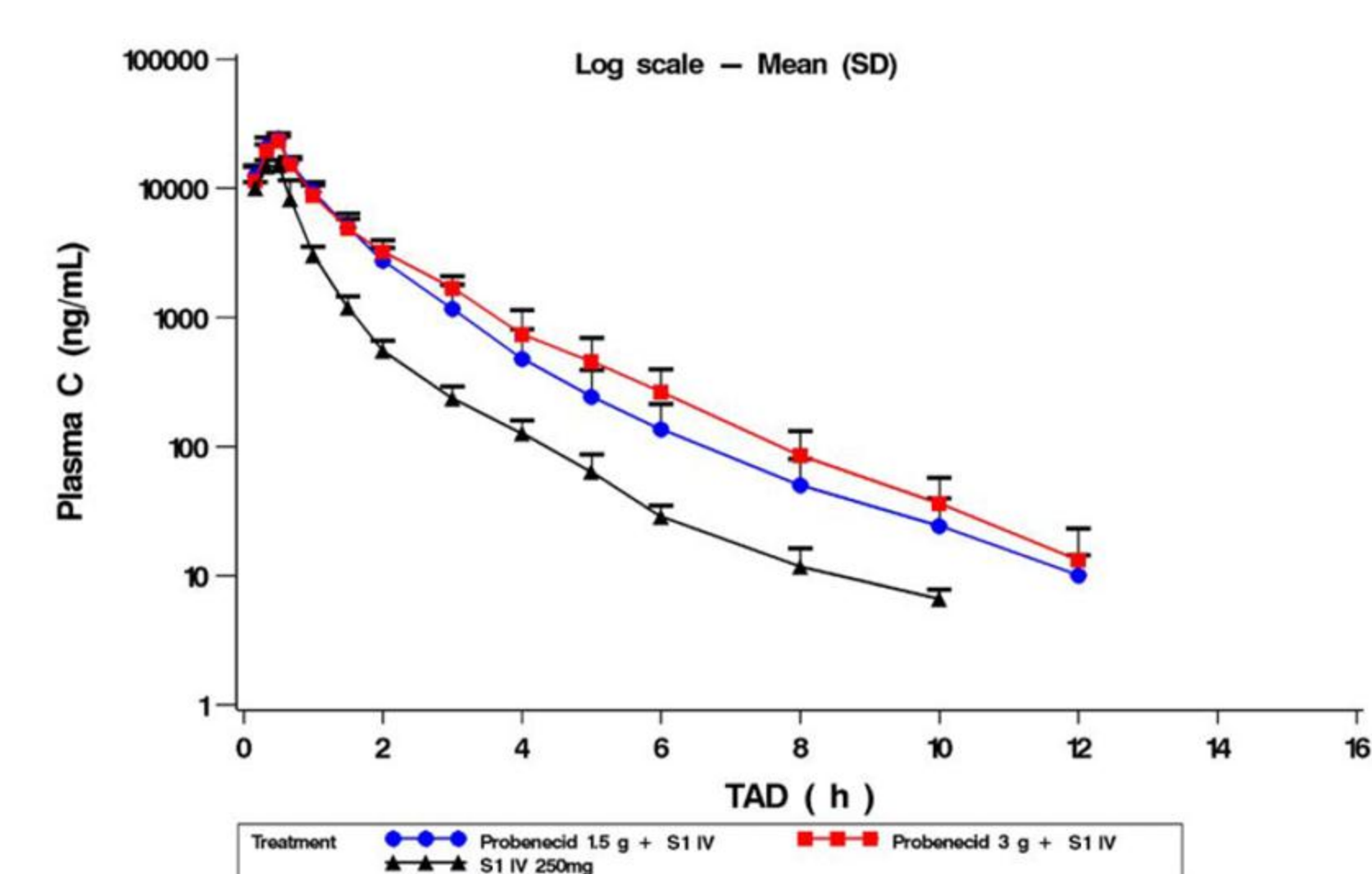
WinNonlin Phoenix NLME v1.3, FOCE estimation

Strategy

- Estimate distribution parameters, renal secretion parameter and K_i
- Compare estimated '*in vivo*' K_i with *in vitro* K_i

Results

DDI STUDY RESULTS



The observed data from the DDI study showed a difference in the slope of the S1 plasma concentration-time profiles between the two probenecid schedules (P2 and P3) which should be sufficient to allow the estimation of K_i

GOODNESS OF A PRIORI MODEL PREDICTIONS

Study part	<i>In vivo</i> AUC ratio	Simulated AUC ratio	<i>In vivo</i> C _{max} ratio	Simulated C _{max} ratio	<i>In vivo</i> CL _R ratio	Simulated CL _R ratio
P2: S1 + Probenecid (3 g) (Constant inhibition phase)	2.2	2.01	1.5	1.22	0.39	0.395
P3: S1 + Probenecid (1.5 g) (Dynamic inhibition phase)	2.0	1.98	1.6	1.24	0.42	0.406

P2 : Constant inhibition phase

The simulated AUC, C_{max} and CL_R DDI ratios were 1.1-fold, 1.2-fold and 0.99-fold of the observed DDI ratios, respectively.

P3 : Dynamic inhibition phase

The simulated AUC, C_{max} and CL_R DDI ratios were 1.0-fold, 1.3-fold and 1.0-fold of the observed DDI ratios, respectively.

ESTIMATION OF MODEL PARAMETERS USING

DDI STUDY DATA

Parameter	K_{32} (h ⁻¹)	K_{14} (h ⁻¹)	K_{41} (h ⁻¹)	K_i	ϵ_{plasma} (%)	ϵ_{urine} (%)
Description	Active renal secretion rate	Central-to-peripheral distribution rate	Peripheral-to-central distribution rate	Inhibition constant	Residual error (plasma)	Residual error (urine)
Estimate \pm SE	1626 \pm 240	0.14 \pm 0.014	0.51 \pm 0.020	6.9 \pm 1.9	52 \pm 3.6	37 \pm 1.9

NB. Fixed drug-specific parameters: CL_{NR} , central compartment volume, $f_{u,plasma}$
 Fixed physiological parameters: renal plasma volume, renal plasma flow, urine flow, glomerular filtration rate

The model did not converge when inter-individual variability was tested on these parameters, therefore no inter-individual variability was included in the final model. The model will be transposed to NONMEM, and these parameters obtained using the Naïve pool approach will be used as initial estimates.

COMPARISON OF 'IN VIVO' AND IN VITRO K_i

Estimated K_i *in vivo* = 6.9 \pm 1.9 μ M (estimate \pm SE)
 Measured K_i *in vitro* = 7.5 \pm 4.7 μ M (estimate \pm SE)

The 1.1-fold difference between the estimated '*in vivo*' K_i and the experimentally measured *in vitro* K_i can be considered to be close and gives confidence in using K_i measured *in vitro* in semi-physiological models of this type.

Conclusions

A good agreement was obtained between the *in vitro* (experimentally measured) and *in vivo* (model-estimated) inhibition parameter, which could give confidence in using this approach to predict renal DDI *a priori*. Although there are relatively few examples of renal DDI modelling in the literature, the extent of renal transporter-mediated DDI is generally low (due to non-total inhibition, the presence of glomerular filtration, and secretion by alternative transporters), so physiologically-structured population PK modelling could be used to replace clinical DDI studies when a negligible interaction is predicted [2], if this approach can be demonstrated to be reliable with further examples of this kind.

References :

- Boom SPA, Meyer I, Wouterse AC, Russel FGM. A physiologically based kidney model for the renal clearance of ranitidine and the interaction with cimetidine and probenecid in the dog. *Biopharm Drug Dispos.* 1998. 19 : p. 199-208.
- Shitara Y, Sato H, Sugiyama Y. Evaluation of drug-drug interaction in the hepatobiliary and renal transport of drugs. *Annu Rev Pharmacol Toxicol.* 2005. 45 : p. 689-723.