A mechanistic pharmacokinetic model for simvastatin and its active metabolite simvastatin acid

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Introduction and objectives

- **Simvastatin** (SV) is a commonly used **HMG-CoA reductase inhibitor** to treat hypercholesterolemia and hypertriglyceridemia. It is a **prodrug** that needs conversion to the open acid form, **simvastatin acid** (SVA), in order to be active.
- This conversion is achieved **chemically** with non-enzymatic hydrolysis and **enzymatically** by tissue esterases or serum paraoxonases. SVA can be converted back to SV, while both SV and SVA undergo oxidative metabolism primarily by CYP3A4/5, (*Figure 1*), [1,2].
- **Several genetic polymorphisms** (SNPs) and **drug-drug interactions (DDIs)** have been reported to differentially **affect the PK of SV and SVA** [3].
- This research aims to **develop a population mechanistic PK model** for both SV and SVA.

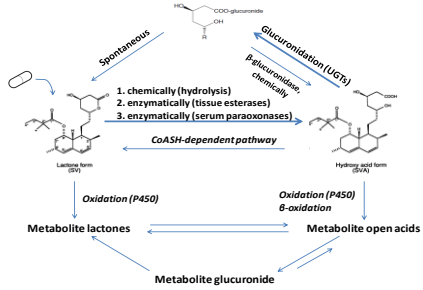


Figure 1: ***SV - SVA interconversion. Adapted from [2]***

Clinical data for analysis

- **Study A: 16 healthy** volunteers, two **40mg** doses separated by a 24h interval, **intensive sampling**
- **Study B: 18 healthy** volunteers, a single **20mg** dose, **intensive sampling**
- **Study C: 28 healthy** volunteers, a single **40mg** dose, **intensive sampling** [4]

Methods

Mechanistic model development:

- **Log-transformed SV** and **SVA plasma concentrations** from 34 healthy volunteers (**Study A & B**) were simultaneously analysed using nonlinear mixed effects software (**NONMEM 7.2**).
- The **mechanistic model** presented in **Figure 2** was coded as a system of **16 differential equations**.
- **Information** for **model parameters and** (when available) **their variability** was extracted from **physiology literature** (e.g. gastric residence time), ***in vitro*** **experiments** (e.g. clearance determined in human liver microsomes) and ***in silico*** **prediction methods** (e.g. tissue-plasma partition coefficients [5])
- Using the **prior functionality** in NONMEM, **prior information was integrated with the information from the analysed clinical data** to obtain maximum a posteriori (MAP) parameter estimates [6,7].
- A limited nonparametric bootstrap (n=25) was performed to assess bias and imprecision.
- Clinical data from **Study C** were used for the **external validation** of the **mechanistic** model.
- The developed model was finally employed to **simulate** concentration **profiles in plasma, liver and muscle** and investigate different scenarios , such as the **impact of an OATP1B1 polymorphism**.

Prior information:

- The **informative prior distributions** representing **prior uncertainty on fixed effects** are illustrated in Figure 3B. For 4 **unknown parameters** (Figure 3A), **uninformative** flat distributions **were assigned**.
- With regards to **inter-individual variability,** all priors assigned to drug related parameters were completely **uninformative**. For **gastric residence and small intestinal transit times, strongly informative** priors were assigned in order to produce physiologically realistic individual estimates which are in line with the variability reported in the literature (Figure 3C).
- **Variability in the other system-related parameters** was employed by ***a priori*** **relating them with covariates** such as weight of each individual:
  - $V_i = f_i \cdot WTE$,where f_i is the fractional volume of organ i with respect to total body weight.
  - $CO = 187 \cdot (WTE)^{0.81}$, where CO is the cardiac output in mL/min.
  - $Q_i = fq_i \cdot CO$,where fq_i is the fractional blood flow of organ i with respect to cardiac output.
  - **The radius of small intestinal lumen (R) was related to BSA of each individual** (Simcyp v.12)

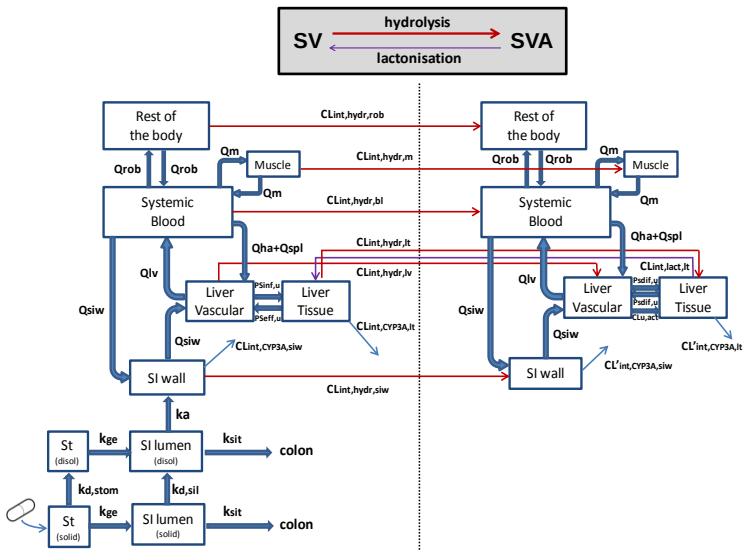


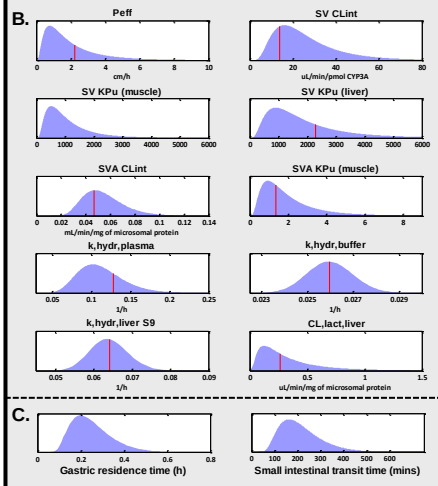
Figure 2: ***Schematic representation of the developed SV-SVA mechanistic model.***

PARAMETER ESTIMATES

A.

Model parameter	Informative Prior	NONMEM Estimate	Bootstrap mean (RSE %)
θ1: Peff (cm/h)	YES	2.22	2.20 (20.07)
θ2: SV CLint (μL/min/pmol CYP3A)	YES	14.01	14.46 (8.74)
θ3: SV KPu (muscle)	YES	4964.2	4757.2 (20.15)
θ4: SV KB (rest of body)	NO	16.95	16.58 (10.11)
θ5: SV KPu (liver)	YES	2275.6	2273.1 (12.42)
θ6: SVA CLint (mL/min/MMP)	YES	0.05	0.05 (7.11)
θ7: SVA KPu (muscle)	YES	1.36	1.47 (12.32)
θ8: SVA KB (rest of body)	NO	0.96	0.96 (35.77)
θ9: SVA CLact (L/h)	NO	7863.6	8031.9 (25.51)
θ10: k, hydr, plasma (h^{-1})	YES	0.13	0.13 (9.46)
θ11: k, hydr, muscle (h^{-1}) [prior from buffer]	YES	0.03	0.03 (0.003)
θ12: k, hydr, liver S9 (h^{-1})	YES	0.06	0.06 (0.55)
θ13: CL,lact,liver (μL/min/MMP)	YES	0.26	0.26 (1.67)
θ14: k, hydr, siw, rob (h^{-1})	NO	1.94	1.97 (16.93)
Inter-Individual Variability on θ1 (CV%)	NO	99.9	95.25 (38.68)
Inter-Individual Variability on θ2 (CV%)	NO	34.79	32.37 (34.14)
Inter-Individual Variability on θ4 (CV%)	NO	32.86	31.78 (40.72)
Inter-Individual Variability on θ6 (CV%)	NO	31.94	46.64 (184.16)
Inter-Individual Variability on θ8 (CV%)	NO	45.06	49.92 (69.38)
Inter-Individual Variability on θ9 (CV%)	NO	62.61	63.34 (63.42)
Inter-Individual Variability on θ14 (CV%)	NO	59.67	58.15 (43.29)
SV residual variability (nmol/L)	NO	0.45	0.45 (11.49)
SVA residual variability (nmol/L)	NO	0.25	0.24 (18.05)

B.



C.

Figure 3: ***(A): Table with parameter estimates (B): MAP estimates (red lines) plotted on top of the distributions that represent prior knowledge regarding uncertainty on a parameter. (C): Distributions that represent prior knowledge regarding the population variability of a parameter.***

MODEL VALIDATION

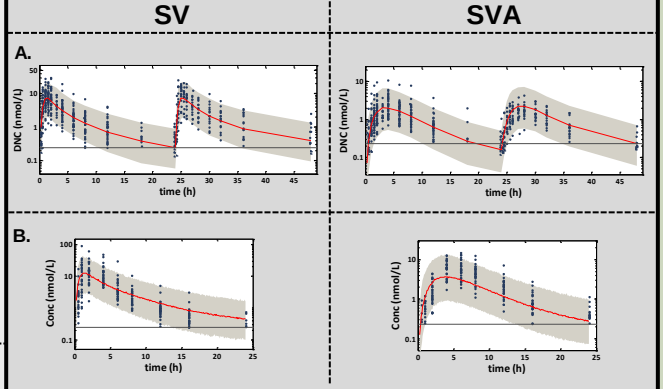


Figure 4: ***Validation of the mechanistic model. (A): Visual Predictive Check for SV (left) and SVA (right) using the observed concentrations of Study A and B after dose normalisation to a 20 mg dose. (B): External validation of the model using the independent (not fitted) data of study C. In both (A) and (B) grey areas represent 90% prediction intervals and the solid grey line represents the limit of quantification.***

MODEL SIMULATIONS

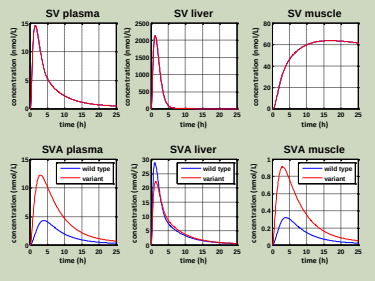


Figure 5: ***Model simulated SV (top) and SVA (bottom) concentration profiles and the effect of OATP1B1 polymorphism. For the simulations of the OATP1B1 polymorphism effect, SVA active uptake clearance (CLact) was optimised to observed plasma data reported in [8] for individuals homozygous for the SLCO1B1 c.521T>C polymorphism.***

Discussion

- The developed mechanistic model **provides good fit to the clinical data** with physiologically realistic parameter estimates.
- It illustrates the feasibility of **parameter estimation** in **complex physiologically based models**, where estimation is performed **without neglecting i) the variability** in key system and drug related parameters and **ii) the uncertainty** on the results of *in vitro* experiments or *in silico* predictions that are used to inform model parameters.
- The proof of concept simulation for the impact of an OATP1B1 polymorphism **is concordant with clinical observations** regarding the *SLCO1B1* c.521T>C SNP: **i)** It is **significantly associated with increased risk of muscle toxicity** (increased SVA muscle exposure) and **ii)** It **has not been associated with clinically significant alterations of the cholesterol lowering efficacy of SV** (unaltered SVA liver exposure).
- The developed model can be applied to **predict the effects of DDIs** or **genetic polymorphisms** on both SV and SVA disposition.

References and Acknowledgements

1. Prueksaritanont T., *et al,* Pharm Res, 2005. 22(7): p. 1101-1109
2. Prueksaritanont T., *et al,*Drug Metab Dispos, 2002. 30(5): p. 505-512
3. Elsby R., et al, Clin Pharmacol Ther, 2012. 92(5): p. 584-598.
4. Polli J.W., et al, Xenobiotica, 2013. 43(6): p. 498-508.
5. Rodgers T., *et al,* J Pharm Sci, 2006. 95(6): p. 1238-1257
6. Gisleskog P.O., *et al,* J Pharmacokinet Pharmacodyn, 2002. 29(5): p. 473-505
7. Langdon G., *et al,* Eur J Clin Pharmacol, 2007. 63(5): p. 485-498
8. Pasanen M.K., *et al,* Pharmacogenet Genomics, 2006. 16(12): p. 873-879.

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