Development of population based approaches to describe the complex pharmacokinetics of simvastatin in different individuals.

“Bridging the gap between population and PBPK modelling”

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Motivation

• Simvastatin (SV) is an HMG-CoA reductase inhibitor, used to treat lipid disorders.

• SV was the most commonly prescribed medication in England with 39.9 million items dispensed in 2013.[1]

• Why do we care about the PK of SV?
  - The risk for myopathy (the main adverse effect) is at least partly of a PK origin
  - SV is involved in clinically significant DDIs that arise at the PK level (e.g. CYP inhibition)
  - Several SNPs in enzyme/transporter genes have been clinically identified to affect its PK and subsequently PD (efficacy or safety)
  - Inter-conversion between SV and its main active metabolite simvastatin acid (SVA)

• However, population PK model-based approaches that can indicate individuals susceptible to DDIs and myopathy have not been widely developed.

Simvastatin: A prodrug with complex pharmacokinetics

1. chemically (hydrolysis)
2. enzymatically (tissue esterases)
3. enzymatically (serum paraoxonases)

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CoASH-dependent pathway

Glucuronidation (UGTs)

8-glucuronidase, chemically

Spontaneous

Lactone form (SV)

Hydroxy acid form (SVA)
Simvastatin: A prodrug with complex pharmacokinetics

1. chemically (hydrolysis)
2. enzymatically (tissue esterases)
3. enzymatically (serum paraoxonases)

CoASH-dependent pathway

Oxidation (P450)

Lactone form (SV)

Hydroxy acid form (SVA)

Metabolite lactones

Metabolite open acids

Metabolite glucuronide

SV pharmacogenetics

• Several factors reported to increase myopathy risk: **clinical** (e.g. DDIs), **demographic** characteristics (e.g. age and ancestry) and **genetic predisposition**

• The c.521 T>C (**rs4149056**) SNP in **SLCO1B1** is strongly associated with elevated SVA plasma levels\[^1\] and increased risk of myopathy\[^2\]

• Recent guidelines\[^3\] recommend PG testing of this SNP to aid dose adjustment

• Additional SNPs in disposition related-genes have been clinically identified to affect SV/SVA PK/PD (e.g. **CYP3A4**, **CYP3A5**, **ABCG2**, **ABCB1**)

• PK studies test single gene variant effects analysed with NCA

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**Objective**

Develop a joint population SV/SVA PK model that incorporates the effects of multiple polymorphisms and clinical/demographic characteristics
Clinical data

Study 1: 16 healthy volunteers, two 40mg doses with 24h interval, rich sampling

Study 2: 18 healthy volunteers, a single 20mg dose, rich sampling

Study 3: 40 patients, 40mg daily, sparse sampling (peak and trough)
Clinical data

**Study 1:** 16 healthy volunteers, two 40mg doses with 24h interval, rich sampling

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Study 1: 16 healthy volunteers, two 40mg doses with 24h interval, rich sampling

Study 2: 18 healthy volunteers, a single 20mg dose, rich sampling

**Study 3:** 40 patients, 40mg daily, sparse sampling (peak and trough)
Model development

- SV/SVA plasma concentrations from 74 individuals were analysed (NONMEM 7.2)

- **Ethnicity:** Caucasian (n=47), Japanese (n=19), African (n=5), other (n=3)

- **18 SNPs** were genotyped in all participants: $ABCB1$ (3), $ABCG2$ (3), $CYP3A4$ (1), $CYP3A5$ (1), $SLCO1B1$ (7), $SLCO2B1$ (2), $PPARA$ (1)

- Base model that best fits the data:

- Covariate selection with a forward inclusion - backward elimination process, the degree of correlation between SNPs was also assessed.
• **Linkage disequilibrium (LD)** is the non-random association in a population of alleles at closely linked loci.

LD plot for OATP1B1 SNPs
• Linkage disequilibrium (LD) is the non-random association in a population of alleles at closely linked loci.

ANOVA statistical significance
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ANOVA statistical significance
Linkage disequilibrium (LD) is the non-random association in a population of alleles at closely linked loci.
The final model included the effect of:

**Genetic polymorphisms:**
- rs4149056 \((SLCO1B1)\)
- rs776746 \((CYP3A5)\)
- rs12422149 \((SLCO2B1)\)
- rs2231142 \((ABCG2)\)
- rs4148162 \((ABCG2)\)
- rs4253728 \((PPARA)\)
- rs35599367 \((CYP3A4)\)
- rs4149056 \((SLCO1B1)\)
- rs776746 \((CYP3A5)\)
- rs12422149 \((SLCO2B1)\)
- rs2231142 \((ABCG2)\)
- rs4148162 \((ABCG2)\)
- rs4253728 \((PPARA)\)
- rs35599367 \((CYP3A4)\)

**Demographic characteristics:**
- Age
- Weight
- Japanese ethnicity

**Reference:**
Identification of the Effect of Multiple Polymorphisms on the Pharmacokinetics of Simvastatin and Simvastatin Acid Using a Population-Modeling Approach
N Tsamandouras¹, G Dickinson², Y Guo², S Hall², A Rostami-Hodjegan¹,³, A Galetin¹ and L Aarons¹
Clinical Pharmacology & Therapeutics, advance online publication, 2 April 2014; doi: 10.1038/clpt.2014.55
Covariate effects plasma exposure

• Using the developed model we can separately investigate the effects of different genetic and demographic characteristics

• What if these risk factors co-exist in a high-risk individual?

• The effects of multiple genetic and demographic risk factors co-occurrence can be assessed by analysing extensive combinations
  
  (-) Combinatorial explosion          (-) Some are not physiologically plausible

• A physiologically realistic population (n=100,000) was simulated and then using a script that identifies risk factor combination patterns examine their effects on SVA plasma exposure and the frequency that these might occur.
Effect of multiple risk factors combinations

<table>
<thead>
<tr>
<th>Factors Combinations</th>
<th>AUC Fold Increase from Reference</th>
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<tbody>
<tr>
<td>Japanese</td>
<td>1.52</td>
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<tr>
<td>Age &gt; 65</td>
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<tr>
<td>Weight &lt; 70</td>
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<tr>
<td>rs35599367 (TT or TC)</td>
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<tr>
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<td>6.39</td>
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</tbody>
</table>
Effect of multiple risk factors combinations

- We reported as clinically interesting only those patterns (188) that increase SVA exposure > 3-fold and thus have high chance to predispose for myopathy

- Only in 3.5% of the simulated population, however absolute numbers matter
Empirical compartmental approach

• Advantages of this approach:
  - **Simple** model, number of parameters is small
  - **Fast** runs, crucial if covariate model building is stepwise
  - **Mechanistic enough**, to allow genotype information to be incorporated as a covariate on a model parameter

• Disadvantages:
  - **Physiologically not accurate**: It does not capture the pre-systemic formation of SVA or the inter-conversion between the two forms
  - **Not assumption-free**: Despite simplicity, model is structurally unidentifiable
  - It cannot predict concentration profiles in **clinically relevant tissues** (liver, muscle)
  - Difficult to incorporate *in vitro* information and **extrapolate** outside the studied population and conditions (e.g. predict the magnitude of a DDI / polymorphism).
Development of a SV/SVA mechanistic population model

SI lumen (solid)

SI lumen (disol)

Sto (solid)

Sto (disol)

Rest of the body

Systemic Blood

Liver Vascular

Liver Tissue

Muscle

SI wall

Qrob

CLint, CYP3A, siw

PSinf, u

PSeff, u

Qm

Qrob

Ql

Qa+Qspl

QL

Qsiw

kge

kd, sto

kd, sil

ka

kge

ksit

kge

ksit

colon

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kge

ksit

kge

ksit

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colon
SV/SVA mechanistic population model

• The model was implemented as a system of 16 ODEs (NONMEM 7.2, ADVAN13)

• Most of the model parameters can be *a priori* informed:
  - Physiology/biology: e.g. Blood flows, organ volumes
  - *In vitro* experiments: e.g. SV/SVA metabolism/stability assays
  - *In silico* predictions: e.g. SV/SVA tissue-plasma partition coefficients

• The prior functionality in NONMEM was applied to integrate prior information for model parameters and (when available) their variability with clinical data[^1,2]

• SV/SVA plasma concentrations from Study 1 & 2 were simultaneously analysed

Parameter estimates

- Model parameters were precisely estimated (RSE < 25% and RSE < 50% for all fixed and random effects accordingly)
MAP estimates relatively to informative priors

- Several model parameters were informed from the plasma data updating prior knowledge
  - e.g. SV metabolic clearance, partition coefficients

- Parameters which cannot be informed from plasma data shrink towards prior mean
  - e.g. inter-conversion inside liver, hydrolysis in muscle
Visual Predictive Check

Study 1

Study 2

SV

SVA
OATP1B1 rs4149056 CC effects (tissues)
Agreeing with clinically observed\textsuperscript{[1]} PD effects of the \textit{SLCO1B1} rs4149056 SNP:

- Has been robustly and repeatedly \textbf{associated} with increased risk of \textbf{myopathy}
- Has not been \textbf{associated} with clinically significant alterations in the \textbf{cholesterol lowering efficacy}. LDL reduction was only 2.56\% smaller in CC subjects (n=16,664)

Prediction of DDI effects

• The developed model was also able to successfully predict the effects of a range of clinically significant SV DDIs (clarithromycin, erythromycin, itraconazole, diltiazem)

• Clarithromycin (CLR) is a mechanism-based CYP3A inhibitor. Co-administration with SV leads to a severe DDI that can cause lethal rhabdomyolysis [1,2].

SV 40mg q.d. alone or SV 40 mg q.d. + CLR 500mg b.i.d. AUC and Cmax are reported in nmol·h/L and nmol/L respectively and they refer to plasma and the last dosing interval. Observed DDI effect data (OBS ratio) are extracted from Jacobson 2004

<table>
<thead>
<tr>
<th></th>
<th>SV</th>
<th>SV + CLR</th>
<th>PRED ratio</th>
<th>OBS ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>SV AUC</td>
<td>102.54</td>
<td>1027.90</td>
<td>10.02</td>
<td>9.95</td>
</tr>
<tr>
<td>SV Cmax</td>
<td>15.81</td>
<td>102.54</td>
<td>6.49</td>
<td>7.14</td>
</tr>
<tr>
<td>SVA AUC</td>
<td>53.13</td>
<td>608.99</td>
<td>11.46</td>
<td>12.17</td>
</tr>
<tr>
<td>SVA Cmax</td>
<td>5.02</td>
<td>44.98</td>
<td>8.97</td>
<td>10</td>
</tr>
</tbody>
</table>
Conclusions

• The developed population-based approaches overall provide further insight into the PK of SV/SVA and the related population variability.

• These approaches could be of clinical application due to the widespread use of SV and the clinical burden of muscle toxicity.

• Revealed interesting PG associations. Indicated features that could explain myopathy cases which can not be solely attributed to $SLCO1B1$ genotype.

• An integrated modelling approach where PBPK and population methods are combined to develop a mechanistically sound model with clinical relevance.

• Conditionally on the modelling purpose such an approach can provide advantages:
  - Extrapolation outside the studied population and experimental conditions
  - Efficacy and toxicity (PD) is not linked to the surrogate plasma concentrations
  - It can inform design of PG or DDI studies in early stages of drug development
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