Imaging Hepatic Concentration and Biliary Excretion of Drugs

Yuichi Sugiyama
Sugiyama Laboratory, RIKEN Innovation Center, RIKEN, Research Cluster for Innovation,

DDI-2015
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Husky Union Building, University of Washington;
Seattle, WA, USA

I am enjoying my stay in Seattle;

Waterfront,
Ivar’s salmon house restaurant,
Starbucks Seattle first store.
1) Introduction; Rate-determining process (focusing on the liver) (Uptake, efflux, elimination, metabolism)

2) OATP1B1/1B3 mediated drug-drug interaction

3) Quantitative assessment of OATPs-mediated DDI and PGx using PBPK model.

4) Use of PET imaging

Gemfibrozil and Cerivastatin

52 patients died (US 31) after taking cerivastatin
Among 31 patients, 12 were given also gemfibrozil

Gemfibrozil glucuronide inhibited the CYP2C8-mediated metabolism (MBI) and OATP1B1-mediated uptake of CER. Dual inhibitor
Examples of the bisubstrate of hepatic uptake transporters and metabolic enzymes

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Transporter</th>
<th>Metabolic Enzymes</th>
</tr>
</thead>
<tbody>
<tr>
<td>atorvastatin</td>
<td>OATPs</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>cerivastatin</td>
<td>OATPs</td>
<td>CYP2C8, 3A4</td>
</tr>
<tr>
<td>repaglinide</td>
<td>OATPs</td>
<td>CYP2C8, 3A4</td>
</tr>
<tr>
<td>nateglinide</td>
<td>OATPs</td>
<td>CYP2C9, 3A4</td>
</tr>
<tr>
<td>bosentan</td>
<td>OATPs</td>
<td>CYP2C9, 3A4</td>
</tr>
<tr>
<td>telmisartan</td>
<td>OATP1B3</td>
<td>UGTs</td>
</tr>
<tr>
<td>torasemide</td>
<td>OATPs</td>
<td>CYP2C9</td>
</tr>
<tr>
<td>gimatecan</td>
<td>OATPs</td>
<td>CYP3A4</td>
</tr>
</tbody>
</table>

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**Overall Hepatic Intrinsic Clearance (Clint, all)**

Extended clearance concept

\[
\text{CL}_{\text{int, all}} = \frac{\text{PS}_{\text{inf}} \times \text{CL}_{\text{int}}}{\text{PS}_{\text{eff}} + \text{CL}_{\text{int}}}
\]

1) When \(\text{PS}_{\text{eff}} \ll \text{CL}_{\text{int}}\), (Case-1)

Degree of Sequestration (\(\beta\))

\[\beta = 1\] (anionic drugs, statins, sartans)

Only PS_{inf} influences the Clint_{all} value

2) When \(\text{PS}_{\text{eff}} \gg \text{CL}_{\text{int}}\), (Case-2)

All the intrinsic parameters (PS_{inf}, PS_{eff}, Clint) influence the Clint_{all} values (therefore, Css, AUC values)
PS_{inf} = 100, PS_{eff} = 2, CL_{bile} + CL_{met} = 500 (Case 1)

Impact of the function of each pathway on the overall intrinsic clearance

The determination of the relative importance of OATP1B1 and CYP3A4 in the PK of atorvastatin by drug-drug interaction MD study (Collaboration with Dr. Kumagai)

**Atorvastatin:** Substrates of OATP1B1, CYP3A4

→ Which is more important to determine the PK of atorvastatin?

**MD cassette administration**

<table>
<thead>
<tr>
<th>Term I</th>
<th>Term II</th>
<th>Term III</th>
</tr>
</thead>
<tbody>
<tr>
<td>atorvastatin,</td>
<td>+ rifampicin (p.o.)</td>
<td>+ itraconazole (i.v.)</td>
</tr>
<tr>
<td>midazolam,</td>
<td>(OATP inhibitor)</td>
<td>(CYP3A4 inhibitor)</td>
</tr>
<tr>
<td>pravastatin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Correlation between CYP3A4-mediated metabolism and PK of atorvastatin?

Correlation between OATP1B1-mediated transport and PK of atorvastatin?
Plasma concentrations of atorvastatin and pravastatin were greatly increased by rifampicin, but not by itraconazole.

Days of each substrates are 33 µg

<table>
<thead>
<tr>
<th></th>
<th>ATV</th>
<th>PRV</th>
<th>MDZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cont.</td>
<td>38.5</td>
<td>195</td>
<td>434</td>
</tr>
<tr>
<td>±17.5</td>
<td>±78.7</td>
<td>±122</td>
<td></td>
</tr>
<tr>
<td>+RIF</td>
<td>439***</td>
<td>949***</td>
<td>471</td>
</tr>
<tr>
<td>±134</td>
<td>±179</td>
<td>±168</td>
<td></td>
</tr>
<tr>
<td>+ITZ</td>
<td>36.0</td>
<td>386</td>
<td>755*</td>
</tr>
<tr>
<td>±19.2</td>
<td>±254</td>
<td>±276</td>
<td></td>
</tr>
</tbody>
</table>

***: P<0.0005
*: P<0.05

Effects of rifampicin and itraconazole on the PK of atorvastatin

CL of atorvastatin was inhibited only by rifampicin.

→ atorvastatin hepatic clearance is limited only by Hepatic uptake.
Mean plasma conc.-time profiles of bosentan when coadministered with rifampicin or itraconazole

In collaboration with PI clinic (Dr. Furihata)
\[ \beta = \frac{CL_{\text{bile}} + CL_{\text{met}}}{PS_{\text{eff}} + CL_{\text{bile}} + CL_{\text{met}}} \]

# ATV, Bosentan: Close to Case-1 (\( \beta \sim 1 \))
# CER, REPG, SIMP(simeprevir): (\( \beta \) intermediate)
# DAR(darunavir) (\( \beta \) small)

From the clinical DDI studies so far done and also from the Ki value of ITZ (CYP3A4 inhibitor), we can estimate the \( \beta \) values of each compound.

It is necessary for us to predict such \( \beta \) values from in vitro experiments (uptake, efflux and metabolism).

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4) Use of PET imaging

(12)
### The impact of OATP1B1 on the PK of drugs

Plasma conc. of drugs is increased in subjects with OATP1B1*15— (521C/T vs T/T)

<table>
<thead>
<tr>
<th>HMG-CoA reductase inhibitors</th>
<th>Anti-pulmonary hypertension drug</th>
<th>Anti-cancer drug</th>
<th>Chol-absorption inhibitor</th>
<th>Loop diuretics</th>
<th>Anti-allergic drug</th>
<th>Angiotensin receptor antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>pravastatin</td>
<td>Atrasentan (3A4)</td>
<td>irinotecan (SN-38)</td>
<td>Ezetimibe (glucuronidation)</td>
<td>Torasemide (2C9)</td>
<td>fexofenadine</td>
<td>Olmesartan</td>
</tr>
<tr>
<td>simvastatin acid (3A4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pitavastatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>atorvastatin (3A4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rosuvastatin</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

#### Anti-diabetes

repaglinide (2C8, 3A4)
nateglinide (2C9, 3A4)

#### Anti-allergic drug

fexofenadine

#### Anti-pulmonary hypertension drug

Atrasentan (3A4)

#### Anti-cancer drug

irinotecan (SN-38)

#### Chol-absorption inhibitor

Ezetimibe (glucuronidation)

#### Loop diuretics

Torasemide (2C9)

#### Anti-allergic drug

fexofenadine

### Relationship between OATP1B1 genetic polymorphism and Pharmacological effect and adverse effect of statins

**★ Pharmacological effect**

Target; HMG CoA-reductase in the liver

No effect or small effect if any


**★ Adverse Effect**

Target; Muscle (via plasma)

Simvastatin-induced myopathy

strong correlation with OATP1B1 polymorphism


<table>
<thead>
<tr>
<th>Odds ratio of this SNPs for simvastatin-induced myopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>521C/T vs T/T → 4.5 fold</td>
</tr>
<tr>
<td>521C/C vs T/T → 16.9 fold</td>
</tr>
</tbody>
</table>
Genome wide association study of LDL-cholesterol response to rosuvastatin in JUPITER Trial

Rosuvastatin 20mg/day (n=3523) or placebo (n=3466): Circ Cardiovasc Genet 2012;5:257-264

**ABCG2 (BCRP) is associated with LDL-C reduction** in SNP highly correlated with nonsynonymous 421C>A mutation (Linkage disequilibrium: $r^2=0.81$). Two additional reports supported the association of 421C>A mutation with efficacy.

421C>A mutation reduce excretion into intestine and secretion into bile => Increase plasma exposure and hepatic exposure

SLCO1B1 is (OATP1B1) not associated with LDL-C reduction in 521T>C mutation, which results in larger plasma exposure by the lower hepatic uptake activity.

Both mutations result in larger plasma exposure of rosuvastatin, while only mutation in **ABCG2** has association with efficacy.

>=Does difference in plasma exposure among races associate with efficacy?

<table>
<thead>
<tr>
<th>ABCG2</th>
<th>LDL-C reduction (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG</td>
<td>-53.0</td>
</tr>
<tr>
<td>GA</td>
<td>-59.0</td>
</tr>
<tr>
<td>AA</td>
<td>-64.0</td>
</tr>
</tbody>
</table>

Summary-1

# All of these pharmacogenetic and DDI studies on OATP1B1 suggested that the hepatic uptake plays an important role in the plasma clearance of therapeutically important drugs (mostly anionic drugs; statins, ARA, ACE inhibitors, anticancer drugs, etc).

Why did this polymorphism and/or DDI affect only side-effect (myopathy; muscle is a target tissue), and not pharmacological effect (lipid lowering effect; liver is a target organ) ?

To answer this question, PBPK modeling was performed.

PBPK model of pravastatin disappearance

PBPK model

Plasma conc-time profile of pravastatin in human

- i.v. 0.134mg/kg (observed)
- p.o. 0.26mg/kg (observed)

Blood

\[ V_i \frac{dC_i}{dt} = Q_b(C_i - C_s) - CL_i \cdot C_s \]

Capillary in the liver

\[ V_L \frac{dC_L}{dt} = Q_b(C_L - C_j) - f_{PS}PS_{inf}C_{ij} + f_{eff}PS_{eff}C_{ij} \]

Hepatocytes

\[ V_{H,j} \frac{dC_{H,j}}{dt} = f_{PS}PS_{inf}C_{H,j} - f_{eff}PS_{eff}\left(CL_{int} + PS_{eff}\right)C_{H,j} \]

Extrapolated parameters based on in vitro (animal, human) and in vivo (animal)

PBPK modeling of pravastatin disappearance

Effect of the transporters (influx, efflux) in the liver on the time-course and exposure of drugs in the plasma and target tissue.
Effect of functional alteration of metabolism/efflux process on the plasma and liver concentrations

\[ f_h \cdot AUC_b = \frac{Dose}{PS_{inf}} \]

\[ f_h \cdot AUC_h = \frac{Dose}{CL_{int}} \]

When PS\textsubscript{eff} < CL\textsubscript{int},\n(uptake limited)

When PS\textsubscript{eff} > CL\textsubscript{int},\n(intrinsic clearance-limited)

In either case, the change in PS\textsubscript{inf}(uptake clearance) does not influence the liver exposure (f\textsubscript{h} \cdot AUC\textsubscript{h}), but influence the blood exposure

“Extended Clearance Concept”

- enough to predict the change in AUC and/or Css both in plasma and tissue
  (PGx, DDI (at least for static analyses, and not for dynamic analysis)

“PBPK modeling”

- Appropriate model for describing the drug conc-time course both in plasma and tissue as well as AUC, Css
Summary-2:

1) Sensitivity analysis indicated that the change in hepatic uptake ability alters the plasma concentration profile sensitively (toxicity) and may not affect the profile in the liver, target tissue (pharmacological effect). GWAS for simvastatin in fact demonstrated it was the case.

2) Alteration in the biliary excretion ability (MRP2, BCRP) may affect the pharmacological effect much more sensitively than that of the uptake

⇒ This prediction is consistent with a most recent study published by other group.

How to predict the complicated DDI?
(transporter and enzymes are simultaneously inhibited)
Elevation of plasma pitavastatin (PIT) concentration by cyclosporine A (CsA)

Prediction by dynamic model (PBPK model)

Oral administration of CsA (average 131 mg) 1 hr before PIT

Oral administration of PIT (2 mg)

PIT (control)

PIT + CsA

Plasma concentration of PIT (ng/mL)

Time (hr)

AUC × 4.6

Cmax × 6.5

Pitavastatin

OATP1B1 substrate
(Hirano et al., 311:139-146(2004))

CL_{int,all} = PS_{int} \times \frac{CL_{bile} + CL_{met}}{PS_{eff} + CL_{bile} + CL_{met}}

\beta \text{ value}

(Hirano et al., 311:139-146(2004))

OATP1B1

Hirano et al.,

BCRP

(This can be neglected considering high FaFg value of PTV)
**PBPK model for DDI analyses (PIT, CsA)**

**Substrate**

Muscle, skin and adipose as rapid equilibrium compartments

**Inhibitor**

Five liver compartments (for better IVIVE of high clearance drugs) (Watanabe et al., JPET 2009)

**PIT: (Kp values; in silico method)**

Theoretical Equation of $K_{p,uu,ss}$ (Our Method)

\[
K_{p,uu,ss} = \left( \frac{C_{cell}}{C_{medium}} \right)_{37^\circ C} \left( \frac{C_{cell}}{C_{medium}} \right)_{4^\circ C}
\]

\[
= \frac{f_{o,ion} \cdot PS_{act,inf} + (\lambda \cdot f_{o,ion} + f_{o,union}) \cdot PS_{diff,inf,union}}{(\Phi \cdot \lambda \cdot f_{l,ion} + f_{l,union}) \cdot PS_{diff,inf,union}} \cdot \frac{1}{f_{cell,37^\circ C}}
\]

\[
= \frac{\lambda \cdot f_{o,ion} + f_{o,union}}{\lambda \cdot f_{l,ion} + f_{l,union}} \cdot \frac{1}{f_{cell,4^\circ C}}
\]

✓ Since $f_{cell}$ was not affected by temperature (Current study with equilibrium dialysis using human liver homogenate), $f_{cell,37^\circ C}$ and $f_{cell,4^\circ C}$ were cancelled out.

\[
K_{p,uu,ss} = \left( \frac{f_{o,ion} \cdot PS_{act,inf} + (\lambda \cdot f_{o,ion} + f_{o,union}) \cdot PS_{diff,inf,union}}{(\Phi \cdot \lambda \cdot f_{l,ion} + f_{l,union}) \cdot PS_{diff,inf,union}} \cdot \left( \frac{\lambda \cdot f_{l,ion} + f_{l,union}}{\lambda \cdot f_{o,ion} + f_{o,union}} \right) \right)
\]

\[
= K_{p,uu,true} \times \frac{\lambda \cdot f_{l,ion} + f_{l,union}}{\lambda \cdot f_{o,ion} + f_{o,union}}
\]

*Kp,uu (pitavastatin) value estimated by this method was 10.*
Analysis of DDI between PIT vs. CsA considering the inhibition of hepatic uptake process (Ki1)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Fitted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vb</td>
<td>L</td>
<td>4.92</td>
</tr>
<tr>
<td>ka</td>
<td>hr⁻¹</td>
<td>1.02</td>
</tr>
<tr>
<td>Lag</td>
<td>hr</td>
<td>0</td>
</tr>
<tr>
<td>f_P Sinf</td>
<td>L/hr</td>
<td>52.5</td>
</tr>
<tr>
<td>R</td>
<td>-</td>
<td>0.312</td>
</tr>
<tr>
<td>fhCLint</td>
<td>L/hr</td>
<td>7883</td>
</tr>
<tr>
<td>Fbile</td>
<td>-</td>
<td>0.338</td>
</tr>
<tr>
<td>Ktransit</td>
<td>hr⁻¹</td>
<td>0.707</td>
</tr>
<tr>
<td>Ki1 (total)</td>
<td>μM</td>
<td>0.204</td>
</tr>
<tr>
<td>Ki1 (unbound)</td>
<td>μM</td>
<td>0.0122</td>
</tr>
</tbody>
</table>

Reported in vitro Ki1 value (unbound): 0.24~0.69 μM. If preincubated with CsA, in vitro Ki1 value: 0.014 μM.

Proposal (Complicated DDI)

1) Almost impossible to obtain the accurate kinetic parameters (uptake, efflux, Clint) by top-down approach only from the plasma concentration-time profile even when the perturbed data (DDI etc.) are available. Pure bottom-up approach did not work well either (scaling factor necessary).

2) The important hybrid parameters in describing the clinical data (DDI, PGx etc.) are β value (to determine the rate-determining process) and Kpuu value for both substrate and inhibitors (or inducers).

3) Sandwich culture hepatocyte system may be appropriate to determine the uptake, efflux and Clint (metabolism + biliary excretion), and therefore β value and Kpuu value.

4) Keeping thus obtained in vitro parameters loosely fixed, we can determine all the parameters by fitting. ⇒ Cluster Newton method (CNM) is useful.
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Importance of the estimation of tissue concentration of drugs

Active transport, Metabolism etc.

1) Prediction of pharmacological/toxicological effects of drugs
   in the target tissue
   (e.g. Liver)
   HMG-CoA reductase inhibitors (statins) \(\rightarrow\) decrease in plasma cholesterol
   Biguanides \(\rightarrow\) decrease in blood glucose, lactic acidosis

2) Prediction of drug-drug interactions (DDIs) at the target tissue
   Inhibitor drugs are **actively accumulated** in the liver \(\rightarrow\) Underestimation
   of risks of DDIs involving the inhibition of CYPs/efflux transporters
PET probes for the analyses of transporter-mediated PK
(in collaboration with Dr. Yasuyoshi Watanabe (RIKEN, Kobe)

- **R(+)[^11]C Verapamil**: P-gp (BBB)
- **[^11]C Oseletamivir**: Ontogeny in BBB penetration
- **[^11]CTIC-Me**: OATP1B, MRP2
- **[^11]C Dehydropravastatin**: OATP1B1, MRP2
- **[^11]C Telmisartan**: OATP1B3
- **[^11]C SC-62807**: OATP1B1, 1B3, BCRP
- **[^11]C Metformin**: OCT?, MATE?
- **[^11]C Uric acid**: URAT1?

**Uptake and Metabolism**
- Brain penetration
- Renal excretion
- Hepatic uptake and metabolism
- Intestinal absorption

**Distribution to Targeting Organ**

**Drug Transporters**
- OATP1B, OATP1B3, MRP2
- BCRP

**Transporter-Mediated PK**

**Integration Plot**

**Human Studies**

**Baseline (rifampicin untreated)**
- Blood (venous blood)
- Liver
- Bile (gall bladder and bile duct)

**Blood (C\_t\_blood)**
- %dose/mL: 0.02 to 0.09

**Liver (X\_t\_liver)**
- Canalicular efflux

**Bile (X\_t\_bile)**

**Integration Plot**

**Determination of clearances for tissue uptake (OATP activity) and canalicular efflux (MRP2 activity) in the same subject using 15R[^11]CTIC**
15R-[11C]TIC-Me PET imaging

A) Healthy (male)

B) Dubin Johnson syndrome (male) - MRP2

In collaboration with Dr. Yasuyoshi Watanabe (RIKEN)

Coadministration of rifampicin with [11C]-15R-TIC in humans

Collaboration with Dr. Yasuyoshi Watanabe in Riken, Kobe

PET imaging of radioactivity after administration of [11C]-15R-TIC

Hepatic uptake

Biliary excretion
11C-Dehydropravastatin is accumulated in the liver followed by excretion into the bile, and urinary excretion

**BCRP/ ABCG2**
(Breast cancer resistance protein)

Functional PET probe for BCRP

Quantitative evaluation of BCRP-mediated transport in humans: Application to DDI and PGx

[\(^{11}\text{C}\)]SC-62807
(metabolite of celecoxib)

ATP-dependent uptake of SC-62807 by membrane vesicles expressing mBcrp or hBCRP

Comparison of canalicular efflux and brush border efflux of $[^{11}C]$SC-62807 between wild-type and Bcrp$^{-/-}$ mice

1) Integration plot (liver $\rightarrow$ bile)

$$X_{\text{bile}} = CL_{\text{int,bile,liver}} \times AUC_{\text{liver}} + X_0$$

<table>
<thead>
<tr>
<th></th>
<th>Wild-type</th>
<th>Bcrp$^{-/-}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL$_{\text{int,bile,liver}}$</td>
<td>4.5 ± 0.8 ml/min/kg</td>
<td>1.2 ± 0.1 ml/min/kg</td>
</tr>
</tbody>
</table>

2) Integration plot (kidney $\rightarrow$ urine)

$$X_{\text{urine}} = CL_{\text{int,urine,kidney}} \times AUC_{\text{kidney}} + X_0$$

<table>
<thead>
<tr>
<th></th>
<th>Wild-type</th>
<th>Bcrp$^{-/-}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL$_{\text{int,urine,kidney}}$</td>
<td>13 ± 2 ml/min/kg</td>
<td>0.12 ± 0.07 ml/min/kg</td>
</tr>
</tbody>
</table>

Preclinical studies

- **Phase I**
  - Analysis of tissue exposure using PET imaging
  - Prediction of PK
  - Measurement of drug exposure at the target tissues
- **Preclinical studies**
  - In vitro screening
  - ADME parameters (clearance etc)
  - PD/TD parameters (EC50 etc)
  - Integration by using mathematical modeling
  - Prediction of PD
  - Scaling factor validation
  - Measurement of drug exposure at the target tissues

PD vs exposure at the target sites
Proposal

1) Comparison of kinetic parameters (PSinf, Clbile) between in vivo (PET imaging) and in vitro (sandwich culture) is necessary for several different PET ligands.

2) Then, we can obtain more reliable scaling factors at least for uptake and biliary excretion process.
   (Consortium research is going to be held by inviting 5-8 Pharmas)

3) The PBPK based prediction using thus obtained scaling factors can be compared with that obtained PET imaging data (for example, the increase in drug exposure in the liver by inhibiting the biliary excretion (DDI/PGx))

Take home message

• It is essential to use the scaling factors for the hepatic uptake and biliary excretion clearances between in vitro (sandwich cultured hepatocytes and transporter expression systems and in vivo (PET) to make the IVIVE (including prediction of clearance and DDIs) successful.

• We are making the data base of drug-dependent PBPK parameters (uptake, metabolism, biliary excretion, urinary excretion, and inhibition and induction, and fm, ftransport) for as many drugs. These in vivo parameters will be obtained by optimization method (CNM) using clinical data.

• We then can predict any kind of DDIs (including complex DDIs) between the multiple drugs.
Sugiyama Lab  Main Members

Takashi Yoshikado (wet + dry, IVIVE DDI)
Kota Toshimoto (dry, VCT (Virtual clinical study))
Kim, Soo-Jin: (DDI, PGx, IVIVE)
Lee, Kyeong Ryo (Daewoong) (DDI, IVIVE)

Dec 2014

Kazuya Maeda, Hiroyuki Kusuhara (Univ of Tokyo)

May 2015