RENAL DRUG EXCRETION

Chairat Shayakul
Renal Unit, Department of Medicine
Faculty of Medicine Siriraj Hospital

cshayakul@hotmail.com  11-2011
**ADME:**
- Absorption (active transport, diffusion, metabolism)
- Distribution (active transport, diffusion)
- Metabolism (phase I, phase II enzymes)
- Excretion (active transport, diffusion)

**Pharmacokinetics**

**Pharmacodynamics**

**Safety**
The Permeability of Phospholipid Bilayer

- **Hydrophobic molecule:** 
  - $O_2$, $N_2$  
  - $CO_2$  
  - benzene

- **Small, uncharged polar molecule:** 
  - $H_2O$  
  - urea  
  - glycerol

- **Large, uncharged polar molecule:** 
  - glucose  
  - sucrose  
  - amino acids

- **Hydrophilic molecule:** 
  - ions: $H^+$, $Na^+$  
  - $K^+$, $Ca^{2+}$, $Mg^{2+}$  
  - $Cl^-$, $HCO_3^-$

**Exterior**
- Passive diffusion

**Hydrophobic**

**Interior**
Rosuvastatin pharmacokinetics and pharmacogenetics in white and Asian subjects residing in the same environment

CYP2C9 responsible for formation of N-desmethyl rosvastatin (10%)

Rosuvastatin also substrate for BCRP (ABCG2) transporter protein
ABCG2 Polymorphism Markedly Affects the Pharmacokinetics of Atorvastatin and Rosuvastatin

JE Keskišalo¹, O Zolk², MF Fromm², KJ Kurkinen¹, PJ Neuvonen¹ and M Niemi¹

Clinical Pharmacology & Therapeutics 2009; 86(2): 197
SCOPE

1. Summarized Concept in Drug Excretion in the Kidney
   - Renal drug transporters

2. Clinical application and common pitfall
   - Drug safety, efficacy, interaction
   - New drug discovery / labeling
Renal Drug Excretion

Three main mechanisms:

1. Glomerular filtration of unbound drug, small size (< 500 d)
2. Active secretion of (free & protein-bound) drug by transporters
3. Reabsorption by passive diffusion and/or transporters
Proximal tubule:
- Reabsorption of minerals and nutrients.
  < glucose, salt, amino acid, uric acid, phosphate, $\text{HCO}_3^-$ >
- Excretion of waste products and drugs.

Collecting duct

Distal tubule

Henle’s loop

Thick ascending limb

Thin descending limb
Drug dosage adjustment with renal insufficiency

Drug level correlates with creatinine clearance (CCr)

Cockcroft and Gault equation

\[
\begin{align*}
CCr \text{ Male} & = \frac{ABW \times (140 \text{ - age})}{SCr \times 72} \\
CCr \text{ Female} & = 85\% \text{ of male value}
\end{align*}
\]

. . . where SCr is the most recent serum creatinine (mg/dL)

. . . ABW = adjusted body weight (Kg)

Caution: 1) Alteration in plasma protein binding

2) Aging and alteration in renal blood flow
Renal Proximal Tubular Cells

- **Basolateral**
- **Apical**

**Driving force:**
- Electrochemical Gradient
- pH

**tight junction**

**Paracellular**

**Transcellular**

**Blood**
Transcellular Tubular Transport is Mediated by Selective Membrane Transport Protein

1) **Transporter**
   - Facilitated transport of substrate by interaction with protein: Uni-, Co-, or counter-transport

2) **Channel**
   - Rapid flow of molecules or ions via a specific pore
   - Passive, one-way

3) **Pump**
   - Active move of molecules or ions against the electrochemical gradient (uphill)
   - ATP use
Drug Transporters

- > 400 membrane transporters involved
- Epithelia of intestine, liver and kidney

Endothelia of blood brain barrier (BBB) and blood placental barrier (BPB)

- 2 major superfamilies and others
  1. ATP-binding cassette (ABC)
  2. Solute carrier protein (SLC)
ATP-binding Cassette (ABC) Transporter

1. P-glycoprotein (P-gp)  
   MDR-1, ABCB1

2. Breast cancer resistance protein (BCRP), ABCG2
P-glycoprotein, MDR-1

- Luminal membrane of small intestine, BBB, hepatocyte and apical membrane of kidney proximal tubular cell

- **Selected substrates:**
  - multiple anticancer drugs,
  - rifampicin, ketoconazole,
  - antihistamines, losartan,
  - talinolol, CNS drugs, digoxin,
  - diltiazem, loperamide

- **Selected inhibitors:** cyclosporine, quinidine, verapamil, tamoxifen, flavonoids
P-glycoprotein substrates

Neutral or cationic compounds with bulky structure

- Cancer Chemotherapy
  - Doxorubicin
  - Daunorubicin
  - Vinblastine
  - Vincristine
  - Paclitaxel
  - Teniposide
  - Etoposide

- Immunosuppressive Drugs
  - Cyclosporine A
  - FK506

- Antihistamine
  - Terfenadine

- HIV Protease Inhibitors
  - Amprenavir
  - Indinavir
  - Ritonavir
  - Saquinavir

- Cardiac Drugs
  - Digoxin
  - Quinidine
  - Posicor
  - Most statins

- Anti-thelmintics
  - Ivermectin
  - Abamectin

- Steroid-like
  - Aldosterone
  - Hydrocortisone et al.

- Miscellaneous
  - Loperamide
  - Colchicine
  - Ondansetron
  - Erythromycin
Ivermectin Toxicity in the Collies

- 50% of Collies display CNS toxicity when treated with normal doses of IVM (>60 μg/kg).
- IVM-sensitive Collies lack functional P-gp at the blood brain barrier.
- ABCB1 cDNA sequencing
  - Sensitive Collies (7/7)
    - 4-base pair deletion
    - homozygous
  - Non-sensitive Collies (6/6)
    - heterozygous (mutant/normal)
  - Other breeds (4/4)
    - normal/normal

http://www.awca.net/drug.htm
If the drug is a substrate of CYP3A4 and P-gp, ketoconazole or itraconazole represents the worse case scenario for a clinical DDI.
Breast Cancer Resistance Protein (BCRP)

- ABC subfamily 7 (G); member 2
- Mammary tissue, testis, placenta, luminal membrane of small intestine, muscle, BBB, BPB, liver, and apical membrane of kidney PXT cell
- In-vitro role in tumor drug resistance for Topo-1 and Topo-2 inhibitors (MXR, SN-38, Topotecan, J-107088)
- Emerging role in drug absorption of camptothecan analogues (Irinotecan and Topotecan)
Topotecan: BCRP Interaction

Jonker et al., JNCI, 2000

Jonker et al., PNAS, 2002

Jonker et al., JNCI, 2000

Kruijtzer et al., JCO, 2002
## Substrate and Inhibitors of BCRP

<table>
<thead>
<tr>
<th>Drugs/NMEs</th>
<th>Xenobiotics</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topotecan</td>
<td>PhIP</td>
<td>FTC</td>
</tr>
<tr>
<td>CPT-11/SN-38</td>
<td>Pheophorbide A</td>
<td>Ko134, 143</td>
</tr>
<tr>
<td>J-107088</td>
<td>Estrogen SO₄</td>
<td>Tryprostatin A</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>lysotracker (green)</td>
<td>GF120918</td>
</tr>
<tr>
<td>Flavopiridol</td>
<td>H33342</td>
<td>Lapatinib</td>
</tr>
<tr>
<td>Diflomotecan</td>
<td>Rhodamine 123</td>
<td>Erlotinib</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Bodipy-prazosin</td>
<td>Gefitinib</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Riboflavin (vitamin B2)</td>
<td>CI-1033</td>
</tr>
<tr>
<td>Prazosin</td>
<td></td>
<td>Novobiocin</td>
</tr>
<tr>
<td>Benzoylphenylurea</td>
<td></td>
<td>Imatinib</td>
</tr>
<tr>
<td>Cimetidine</td>
<td></td>
<td>Ritonavir</td>
</tr>
<tr>
<td>Imatinib</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ATP Transporter: Clinical Significance

• Drug-drug interaction

<table>
<thead>
<tr>
<th>Interacting drug</th>
<th>Affected drug</th>
<th>Clinical pharmacokinetic impact on affected drug†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidine</td>
<td>Digoxin</td>
<td>CL, ↓34–48%</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Digoxin</td>
<td>AUC ↑86%</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>Digoxin</td>
<td>AUC ↑157% and C_{max} ↑75%</td>
</tr>
<tr>
<td>Ranolazine</td>
<td>Digoxin</td>
<td>AUC ↑60% and C_{max} ↑46%</td>
</tr>
<tr>
<td>GF120918</td>
<td>Topotecan</td>
<td>AUC ↑143%</td>
</tr>
</tbody>
</table>

• Effect of Polymorphisms:

  Q141K variant → low BCRP expression levels
  - Gefitinib (Iressa®) induced diarrhea
  - Altered pharmacokinetics of rosvastatin, sulphasalazine, 9-aminocamptothecin, diflomotecan, irinotecan, topotecan
Altered Sulfasalazine Exposure in Q141K

SASP BCRP*3

Plasma Sulfasalazine (ng/mL)

Time (Hours)

CC (n=11)
CA (n=4)
Sulfasalazine Bioavailability by Curcumin

Graph showing the bioavailability of Sulfasalazine (SASP) and SASP + Curcumin over time (hr).

Bar chart comparing SASP levels in different genotypes: FVB WT, abcg2 KO, abcb1a KO, and FVB WT + Curcumin, abcg2 KO + Curcumin, abcb1a KO + Curcumin.

Pharm Res. 2008
Solute Carrier Protein (SLC)

• Solute Carrier (SLC) superfamily contains 43 families, 298 genes

• HUGO database
  (see www.gene.ucl.ac.uk/nomenclature/)
  – SLC root symbol
  – Followed by numeral (family)
  – Followed by letter
  – Followed by numeral (i.e. SLC22A1)
Solute Carrier Protein (SLC)

Excretion
1. Organic Cation Transporter (OCT)
2. Organic Anion Transporter (OAT)

Reabsorption or Bi-functional role
1. OAT4, URAT1
2. OCTN
Organic Cation Transporter

- Electrogenic transport of relatively hydrophilic, low mol. mass organic cations
  - OCT1, OCT2
  - OCTN1, OCTN2
Organic Cation Transporter

- **Selected substrates:** organic base at physiological pH
  endogenous compounds: choline, dopamine, N-methylnicotinamide
  TEA, metformin, oxaliplatin, pindolol, procainamide, ranitidine, amiloride, amantadine

- **Selected inhibitors:**
  quinine, quinidine, cimetidine, cetirizine, testosterone
Organic Anion Transporter

- Transport of relatively monovalent anion, low mol. mass < 500 dalton
  - basolateral: OAT1, OAT3
  - apical: OAT4, URAT1
Selected substrates: organic acid at physiological pH
PAH,
adefovir, lamivudine,
acyclovir, tenofovir,
ciprofloxacin,
methotrexate,
oestrone 3-sulphate, NSAID, cefaclor,
furosemide, bumetanide

Selected inhibitors:
probenecid
novobiocin

Organic Anion Transporter
Renal Excretion Factor and Pharmacokinetics

1. Changes in renal function and renal blood flow
   Prostaglandin inhibitors, ACEI, ARB

2. Changes in urinary pH
   ↑ excretion of weak acids (aspirin) at alkaline pH
   ↑ excretion of weak base (paracetamol) at acidic pH
   Strong acids and bases are not affected by pH changes

3. Changes in active renal tubular secretion
   Influence of proximal Na⁺ reabsorption DDI
   Lithium and loop diuretics
   Transporter - DDI
   Competition with the organic anion transporters-probenecid & penicillin, NSAIDs, ASA & methotrexate
Transporters for Liver Excretion

- OATP1B1 (OATP2/OATP-C)
- OATP1B3 (OATP8)
- OATP2B1 (OATP-B)
- OAT2
- OCT1
- NTCP

- MRP1 (ABCC1)
- MRP3 (ABCC3)
- MRP4 (ABCC4)
- MDR3 (ABCG4)
- BCRP (ABCG2)
- BSEP (ABCB11)

Blood

Bile canalicus

Sinusoidal membrane

Canalicular membrane
RFP inhibits Atorvastatin via OATP

- 600 mg rifampacin IV increases atorvastatin acid AUC 7-fold.
- Acutely, single dose rifampacin may inhibit OATP1B3, CYP3A4, and CYP2C8.
Drug Transporter Polymorphisms

- Polymorphisms in OCT and OAT have been identified in ethnically diverse human populations.

- Several polymorphisms exhibited altered kinetic properties when expressed *in vitro*.

These variants may lead to alterations in renal secretion of OCT and OAT substrates.

However, larger *in vivo* studies need to be confirmed.
SLCO1B1 Variants and Statin-Induced Myopathy — A Genomewide Study

The SEARCH Collaborative Group*

The genomewide scan yielded a single strong association of myopathy with the rs4363657 single-nucleotide polymorphism (SNP) located within SLCO1B1 on chromosome 12 (P=4×10⁻⁹). SLCO1B1 encodes the organic anion–transporting polypeptide OATP1B1, which has been shown to regulate the hepatic uptake of statins.

CONCLUSIONS

We have identified common variants in SLCO1B1 that are strongly associated with an increased risk of statin-induced myopathy. Genotyping these variants may help to achieve the benefits of statin therapy more safely and effectively. (Current Con-
### Examples of Transporter mediated DDI

<table>
<thead>
<tr>
<th>Interacting Drug</th>
<th>Affected Drug</th>
<th>Consequence</th>
<th>Fold Changes in Substrate Plasma AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidine</td>
<td>Digoxin</td>
<td>Digoxin Exposure 1.7-fold ↑</td>
<td>P-glycoprotein (P-gp, MDR1) Inhibition</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Digoxin</td>
<td>Digoxin Exposure 30% ↓</td>
<td>P-gp Induction</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>Digoxin</td>
<td>Digoxin Exposure 2.6-fold ↑</td>
<td>P-gp Inhibition</td>
</tr>
<tr>
<td>Probenecid</td>
<td>Cephradine</td>
<td>Cephradine Exposure 3.6-fold ↑</td>
<td>Organic Anion Transporter (OAT) Inhibition</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Metformin</td>
<td>Metformin Exposure 1.4-fold ↑</td>
<td>Organic Cation Transporter (OCT) Inhibition</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Rosuvastatin</td>
<td>Rosuvastatin Exposure 7-fold ↑</td>
<td>Organic Anion Transporting Polypeptide (OATP) Inhibition &amp; Breast Cancer Resistance Protein (BCRP) Inhibition</td>
</tr>
<tr>
<td>Lopinavir/Ritonavir</td>
<td>Rosuvastatin</td>
<td>Rosuvastatin Exposure 2-fold ↑</td>
<td>OATP Inhibition</td>
</tr>
</tbody>
</table>
Membrane transporters in drug development

The International Transporter Consortium

Abstract | Membrane transporters can be major determinants of the pharmacokinetic, safety and efficacy profiles of drugs. This presents several key questions for drug development, including which transporters are clinically important in drug absorption and disposition, and which in vitro methods are suitable for studying drug interactions with these transporters. In addition, what criteria should trigger follow-up clinical studies, and which clinical studies should be conducted if needed. In this article, we provide the recommendations of the International Transporter Consortium on these issues, and present decision trees that are intended to help guide clinical studies on the currently recognized most important drug transporter interactions. The recommendations are generally intended to support clinical development and filing of a new drug application. Overall, it is advised that the timing of transporter investigations should be driven by efficacy, safety and clinical trial enrolment questions (for example, exclusion and inclusion criteria), as well as a need for further understanding of the absorption, distribution, metabolism and excretion properties of the drug molecule, and information required for drug labelling.
Transporter information in labeling

- 23% for All NMEs approved between 2004-2009, with 28 transporter information and 95 no transporter information.
- 38% for Oral NMEs approved between 2004-2009, with 25 transporter information and 41 no transporter information.
Take Home Message

1. Membrane transporter proteins play a role in nearly all pharmacokinetic pathways.
Take Home Message

1. Membrane transporter proteins play role in nearly all pharmacokinetic pathways

2. Two major transporter superfamilies involved in proximal tubular secretion of drug in the kidney
   - ATP-binding cassette (ABC)
   - Solute carrier protein (SLC)

3. Physician should consider how drug excreted from the body for potential DDI, toxicity or non-beneficial effects even with appropriate dosage
Suggested Further Readings

1. **Transporter Whitepaper**

2. **Commentary.** Huang and Woodcock, Nature Reviews Drug Discovery 2010, 9, 175-176


4. **Drug Development and Drug Interactions.**
Thank you for your attention
Good luck with the flood!