An Overview of Drug Transporters in ADME & Drug Action

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Principles of Clinical Pharmacology
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Implications of Drug Transport in Drug Development

• Impact of Drug Transport on ADME
  – Oral absorption of drug
  – Drug Distribution and elimination
  – Drug-Drug Interactions
  – Influence of Pharmacogenomics (PGx on Drug Transport)

• Impact of Drug Transport on Response & Toxicology
  – Over expression of drug transporters may be a major factor in tumor, bacterial, and fungal multi-drug resistance (MDR).
The rate-determining process

“To understand transporter-mediated drug-drug interactions, we have to know the rate-determining process of a substrate in the overall clearance.”

uptake, basolateral efflux, apical excretion, and metabolism

Professor Sugiyama, Keynote address AAPS, November 2007

Lecture Objectives

At the end of this lecture and workshop, the student will be able to:

- List the 7 transporters currently identified by the International Transporter Consortium (ITC) as clinically important in drug absorption and disposition
- Explain why transporters can be major determinants of the pharmacokinetic, efficacy, and safety profiles of drugs
- Describe the process of transport induction, its time course, and how induction influences pharmacokinetic variability
- Describe the process of transport inhibition, its time course, and how induction influences pharmacokinetic variability
- Given a target drug(s), predict the effects on F, CL, exposure (AUC, Cmax) when a second agent (drug, natural product, etc) is administered that is an:
  • Inducer of transporters of the target drug
  • Inhibitor of transporters of the target drug
When Is an Interaction Clinically Significant?

**Wide Therapeutic Range**

- Drug Response
- Efficacy Curve
- Safety Curve (Adverse Effect)
- Dose, AUC, or Concentration [Exposure]

**Narrow Therapeutic Range**

- Drug Response
- Efficacy Curve
- Safety Curve (Adverse Effect)
- Dose, AUC, or Concentration [Exposure]

Adapted from S-M. Huang/FDA


By the International Transporter Consortium (ITC): Academia, FDA, Industry

**Key Issues Addressed:**

- Which transporters are clinically important and should be considered for evaluation during drug development for induction and/or inhibition studies?
- Which methods for studying transporters should be used?
- When are evaluations recommended (decision trees)?

Membrane transporters in drug development

The International Transporter Consortium

In the process of developing new drugs, it is important to understand the potential impact of transporters on drug pharmacology. Which transporters should be considered for evaluation during drug development for induction and/or inhibition studies? Which methods should be used? When are evaluations recommended (decision trees)? These questions are addressed in this white paper, which provides a comprehensive guide for understanding the role of membrane transporters in drug development.
Drug Transporters of Interest from ITC2 Meeting

The Original ITC - 7 Transporters of Interest
P-gp (ABCB1), BCRP (ABCG2), OAT1, OAT3, OCT2, OATP1B1, and OATP1B3
Role of Transporters in Drug Absorption

**Intestinal Epithelial Transporters**

**Transporters in the Intestinal Epithelia**

Efflux (efflux into lumen): P-gp (MDR1), BCRP

PK consequences of induction/inhibition of intestinal transporters

- Inhibition of intestinal uptake transporters or induction of efflux transporters may decrease intestinal absorption of drugs
- Inhibition of intestinal efflux transporters may increase the oral bioavailability of drugs

**Diagram**

- OCT1, OCT2, OCT3
- MRP1, MRP2, MRP3
- BCRP
- MRP1, MRP2
- ASBT
- MCT1

**Absorption**

**Efflux**
**P-glycoprotein Substrates**

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

- **Immunosuppressive Drugs**
  - Cyclosporine A
  - FK506

- **Antihistamine**
  - Terfenadine

- **Steroid-like**
  - Aldosterone
  - Hydrocortisone et al.

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

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

- **Anti-thermints**
  - Ivermectin
  - Abamectin

- **Miscellaneous**
  - Loperamide
  - Colchicine
  - Ondansetron
  - Erythromycin

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**Drug Metabolizing Enzyme - Drug Transporter Interplay**

*Substrate overlap with multiple CYPs and Drug Transporters complicates in vitro to in vivo predictions*

However, if your drug is a substrate of CYP3A4 and P-gp, Ketoconazole or Itraconazole represents the worse case scenario for a Clinical DDI study

*Mol. Pharmaceutics, 2009, 6 (6), pp 1766–1774*
Consequences of Inducing Intestinal Efflux Transporters

Expression of P-gp in Human Duodenal Biopsy

P-gp expression before rifampin administration.

P-gp expression after rifampin administration.

Consequences of Inhibiting Intestinal Efflux Transporters

Xifaxan (rifaximin) Label Information

- Rifaximin is a gut-targeted, minimally absorbed, broad-spectrum, oral antibiotic that is well suited for the treatment of GI-based conditions. Absolute BA is ~ 0.4%

- Concomitant administration of drugs that are P-glycoprotein inhibitors substantially increase the systemic exposure to rifaximin. Caution should be exercised when concomitant use of rifaximin and a P-glycoprotein inhibitor such as cyclosporine is needed.

- An in vitro study suggested that rifaximin is a substrate of P-glycoprotein. Co-administration of cyclosporine, a potent P-glycoprotein inhibitor, with rifaximin resulted in 83-fold and 124-fold increases in rifaximin mean Cmax and AUC in healthy subjects. The clinical significance of this increase in systemic exposure is unknown.
Effect of P-gp Inhibitors on Plasma Digoxin Concentrations

Mean digoxin plasma concentration time curves in 28 patients before (closed circles) and at least 14 days after the start (open circles) of an antiretroviral therapy containing 400 mg lopinavir + 100 mg ritonavir twice daily. The patients received 0.5 mg digoxin orally at both occasions. Error bars indicate standard deviations.

Clinical Pharmacology & Therapeutics (2008); 84, 1, 75–82

Digoxin: Label Information

-------------------------DRUG INTERACTIONS-------------------------
- PGP Inducers/Inhibitors: Drugs that induce or inhibit PGP have the potential to alter digoxin pharmacokinetics. (7.1)
- There are numerous drug interactions associated with digoxin. The potential for drug-drug interactions must be considered prior to and during drug therapy. See full prescribing information for a complete listing of pharmacokinetic (7.2) (12.3) and pharmacodynamic interactions (7.3).
### Digoxin: Label Information

**7.2 Pharmacokinetic Drug Interactions on Serum Digoxin Levels in Adults**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Change in Serum Digoxin Levels (%)</th>
<th>Recommendations</th>
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### Digoxin: Safety Concerns

- Therapeutic conc ~ 1.5 ng/mL
- 33% change in Digoxin Exposure ($C_{max}$) ~ 2.0 ng/mL → Safety concerns
- 25% change in exposure might be clinically relevant

Fenner et al., Clinical Pharmacology & Therapeutics (2009); 85, 173–181
P-gp Mediated Digoxin DDIs

- <2-fold change in digoxin Cmax or exposure were observed in the majority of published cases
  - I/IC50 > 0.1 is predictive of positive clinical digoxin DDI related to P-gp
  - I2/IC50 < 10 is predictive of no clinical digoxin DDI
- For Digoxin or NMEs that have a narrow T.I. (similar to digoxin), P-gp may be an important determinant of PK and response.
- Additional work is needed to fully understand the mechanism of false (-)'s observed with I/IC50 or false (+)'s with I2/IC50

Role of P-gp in the Blood-Brain Barrier and the Placenta (murine studies)

- Mdr1a/b (-/-) were found to be:
  - Viable
  - Fertile
  - Without observable phenotype until pharmacological challenge with IVM.
    - mdr1a -/- LD50 = 0.7 mg/kg
    - mdr1a +/- LD50 = 60 mg/kg
- CF-1 mice were found to be spontaneously mutant in mdr1a by MSD Scientists. The degree of chemical exposure of fetuses within each litter was inversely related to expression of placental P-gp and cleft palate susceptibility
  - mdr1a +/- 100% cleft palate
  - mdr1a +/- 50% cleft palate
  - mdr1a +/- 0%

Figure from A.H. Schinkel et al., Cell, Vol.77, 491-501, 1994
Ivermectin Toxicity in the Collie

- 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

ABCG2 (alias BCRP, MXR, ABCP,BMDP)

- Expressed endogenously in the intestine (small & large), liver, kidney, placenta, skeletal muscle, brain, and in hematopoietic stem cells
- 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).

| ABC subfamily 7 (G);member 2 (related to Drosophila White proteins) |
| 655 amino acid protein |
| ABCP isolated from human placenta R482 WT (Allikmets, 1996) |
| BCRP breast cancer resistance protein R482 T (Doyle et al., 1998) |
| MXR: Mitoxantrone resistance protein R482G (Bates et al., 1999) |
| BMDP: Brain multidrug resistance protein (Eisenblatter et al., 2003) |
## Substrates & Inhibitors of ABCG2

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<thead>
<tr>
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<th>Xenobiotics</th>
<th>Endobiotics</th>
<th>Inhibitors</th>
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<td>Topotecan</td>
<td>PhIP</td>
<td>Pheophorbide A</td>
<td>FTC</td>
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<tr>
<td>CPT-11/SN-38</td>
<td>Estrogen SO₄</td>
<td>lysotracker (green)</td>
<td>Ko134, 143</td>
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<td>H33342</td>
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<td>Tryprostatin A</td>
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<td>Imatinib</td>
<td></td>
<td></td>
<td>Curcumin</td>
</tr>
</tbody>
</table>


- Bcrp-/- ADME Phenotype
  - Mice displayed diet-dependent phototoxicity
  - Protoporphyria
  - Enhanced oral absorption of topotecan
  - ABCG2 is expressed in bone marrow stem cells.

---

**Expression BCRP in mammary gland across species**

- *Mouse*  
  - BCRP substrates reported concentrated into milk of each of these species

- *Cow*  
  - MRP1-5, P-glycoprotein not upregulated in lactating mouse mammary gland

- *Human*  
  - Not shown
Of mice and men: Topotecan:BCRP interaction

Absorption, metabolism, and excretion of salicylazosulfapyridine in man

Fig. 2. Serum concentrations of SASP after ingestion of a single 4 Gm. dose of SASP on Day 1 (10 subjects) and 3 x 1 Gm. dose of SASP on Days 2 to 19 (9 subjects).

Hans Schröder and Ove E. S. Campbell. Upsala, Sweden
Department of Toxicology, University of Upsala, Pharmacia AB, Box 604, 751 23
**Sulfasalazine (SASP) Disposition**

- Indications: Rheumatoid arthritis (RA), Long term therapy of ulcerative colitis, and Crohn's disease
- Bioavailability (F) of SASP in humans is low (F<15%) and highly variable
- Low %F primarily attributed to SASP's low permeability and poor solubility (thus, poor absorption)
- Azo-reduction is the primary route of metabolic clearance
- Metabolism occurs in distal small intestine and large intestine via bacterial flora

**Sulfasalazine (SASP) Hypothesis**

*Inter-individual differences in intestinal expression and function of ABCG2 (BCRP) contribute to variability in drug bioavailability, exposure and pharmacological response to SASP.*
Bcrp is Major Determinant of SASP Absorption in the Mouse

P-gp does not contribute to SASP Bioavailability or Clearance in the Mouse
Altered SASP PK in ABCG2 (BCRP) Q141K
North American Healthy Volunteers
SASP BCRP*3

Time (Hours)

Plasma Sulfasalazine (ng/mL)


Figure 2 Effect on pharmacokinetics of Plasma profiles of oral administration of a mg conventional SASP tablet subjects circles, = subjects (open triangles, n = 12), 421C/A subjects (closed diamonds, n = 9).

Yamasaki et al., CPT January 2, 2008

SASP PK in Healthy Japanese Volunteers
421C>A SNP Changes Surface ABCG2 Expression

<table>
<thead>
<tr>
<th>Total Protein</th>
<th>Cell Surface</th>
</tr>
</thead>
<tbody>
<tr>
<td>kDa</td>
<td></td>
</tr>
<tr>
<td>Vector control</td>
<td>Wild-type</td>
</tr>
<tr>
<td>75</td>
<td>BCRP (V5)</td>
</tr>
<tr>
<td>105</td>
<td>Calnexin</td>
</tr>
<tr>
<td>75</td>
<td></td>
</tr>
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</table>


ABCG2 Polymorphisms and Ethnic Distribution of SNPs.

- The ABCG2 Q141K genotype significantly affected the pharmacokinetics of irinotecan (Clin Pharmacol Ther. 2004).
- Gefitinib-induced diarrhea correlates with Q141K (J Natl Cancer Inst. 2006).
- ABCG2 expression correlates with flavopiridol-induced myelotoxicity.

<table>
<thead>
<tr>
<th>Allelic variant</th>
<th>Caucasians</th>
<th>African-Americans</th>
<th>Asians</th>
<th>Hispanics</th>
<th>Africans</th>
<th>Middle Easterns</th>
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<td>V129M</td>
<td>2</td>
<td>4</td>
<td>20-45</td>
<td>40</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Q141K</td>
<td>11-14</td>
<td>2.3-5.0</td>
<td>15-35</td>
<td>10</td>
<td>1.0</td>
<td>13</td>
</tr>
<tr>
<td>T206L</td>
<td>10</td>
<td>15-35</td>
<td>10</td>
<td>1.0</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>N590Y</td>
<td>10</td>
<td>15-35</td>
<td>10</td>
<td>1.0</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

Figg et al., Anticancer Drugs. 2007
Role of Intestinal Efflux Transporter
BCRP/ABCG2 Uric Acid excretion and Gout

- Gout is a common disease with a genetic predisposition
- In Japanese subjects, GWAS showed that serum uric acid levels relate to ABCG2/BCRP gene, which locates in a gout-susceptibility locus revealed by a genome-wide linkage study. Risk was observed in those with ≤1/4 function (OR, 25.8; 95% CI, 10.3-64.6; \(p = 3.39 \times 10^{-21}\)). (Nucleosides Nucleotides Nucleic Acids. 2011 and Science Translation 2009)
- In addition to renal secretion of UA, intestinal efflux (secretion) is an important determinant of UA clearance. Efflux is mediated by BCRP (ABCG2)

Curcumin (Tumeric)
Curcumin: from ancient medicine to current clinical trials

- Many ongoing clinical investigations including:
  - 89 trials listed in Clinicaltrials.gov
  - anti-inflammatory, antioxidant, age-associated Cognitive impairment, chemopreventive and chemotherapeutic activity

Curcumin increases SASP Bioavailability in Mouse

Clinical SASP/Curcumin Interaction

- SASP absorption enhanced with curcumin
- Greater curcumin interaction after higher dose of SASP likely the impact of intestinal update and SASP efflux

Kusuhara et al., Br J Pharmacol. 2012 Jul;166(6):1793-803
Sulfasalazine BCRP (ABCG2)

- SASP may be a useful probe to investigate the impact of ABCG2 PGx on human PK
  - SASP **dose** and **formulation** are important determinants of ABCG2's impact on drug absorption.
  - SASP still used in various inflammatory diseases (RA and IBD). Can knowledge of SASP PGx provide insight into SASP PK/PD?

- The abcg2 KO mouse in combination with ABCG2 (BCRP) assay cluster may be best way to define ABCG2 substrates and inhibitors.
  - abcg2 KO mouse significantly over-predicted clinical impact of ABCG2 variants

- ABCG2-transfected LLC-PK1 or MDCK cells may be useful to evaluate the interaction of this transporter with NCEs or Drugs, however, many BCRP (ABCG2) substrates require a basolateral uptake transporter.

Oncology Drug Development Challenges

- Despite significant progress in the understanding of genetic determinants of cancer, only 1 in 10 oncology molecules that entered phase III drug trials from 2004-2009 were approved by the FDA.

- The therapeutic index for many molecular-targeted agents is quite narrow.
  - MTD approach to determine dose and schedule versus exposure-driven cancer biological response.
  - A ‘personalized’ approach is needed to define optimal dose and schedule to achieve maximal efficacy with an acceptable safety profile.

- Each Cancer patient represents a ‘special population’.
  - Cancer patients may take up to 20 concomitant medications + multiple complimentary alternative medicines.
  - Some cancer patients have had significant gastric surgery and/or develop hepatic metastases leading to altered drug aborption and variable hepatic clearance.
Intrinsic and Extrinsic Factors Impacting Drug Absorption and Pharmacokinetics

**Intrinsic (Host Dependent)**
- Disease
- Age, Gender, Ethnicity
- Special populations and PGx
- *H. pylori* is known to cause hypochlorhydria
- Ethnic differences in hypochlorhydria (Japanese ~ 60%, European ~ 10%)

**Physicochemical and CMC Properties**
- Biopharmaceutical
  - Solubility, permeability, pKa
  - Tablet compression, coating and matrix
  - Excipients
  - Particle size

**Extrinsic Factors**
- Environment

S Undevia, Nature Reviews Oncology, 2005

---

Influence of pH-dependent Solubility on Maximum Absorbable Dose (MAD) of a Weakly Basic Drug or NME

**Normal**

**Hypochlorhydric**

+ ARA (e.g. PPI, H2RA)
+ Disease

0 1 2 3 4 5 6 7 8 9

pH

Maximum Absorbable Dose

Normal

Hypochlorhydric
Many Molecular Targeted Agents Display pH-dependent Solubility

<table>
<thead>
<tr>
<th>Drug</th>
<th>pHa</th>
<th>pH-dependent solubility?</th>
<th>BCA/BCDO Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crizotinib</td>
<td>9.4</td>
<td>Yes</td>
<td>II</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>5.42</td>
<td>Yes</td>
<td>NA</td>
</tr>
<tr>
<td>Panitumab</td>
<td>2.1 and 5.4</td>
<td>Yes, but no documented effect</td>
<td>II</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>0.01  and 0.001</td>
<td>Yes, but no documented effect</td>
<td>IV</td>
</tr>
</tbody>
</table>

- Approximately 50-70% of recently approved orally administered targeted cancer therapies display pH-dependent solubility.

- We hypothesize that a decrease in the overall exposure of an orally administered cancer therapy may occur due to concomitant ARA use and this could lead to compromised efficacy and overall patient outcomes.

Budha et al., CPT Aug, 2012

Proton Pump Inhibitor (PPI) Pharmacology

- All PPI's are substituted benzimidazoles.  
  - Undergo chemical activation within parietal cell.  
  - Only active parietal cells are inhibited (approximately 70-80% following meal).  
  - Maximum inhibition at 3-4 days.

- Activated molecule irreversibly inhibits Proton Pump (H+K+ ATPase).  
  - Long off rate (up to 1 week to wash out).  
  - Rebound acid hypersecretion when PPI's are discontinued.

- H2-receptor antagonists (H2RA) competitively inhibit and wash out quickly.

- Altered intestinal pH is known to impair drug absorption and has been reported in multiple therapeutic areas (CV, antiviral, and oncology).
**Prevalence of Acid-Reducing Agent Use in Different Cancer Populations - Results**

ARA Prevalence in
MarketScan Population

Cancer Type

**Part 2: Dasatinib PK (control, plus PPI, plus PPI/betaine-HCl reacidification)**

N = 10 Subjects
(9 male, 1 female)

**Treatment A**

7-Day Washout

Day 1:
100mg Dasatinib PO

**Treatment B**

7-Day Washout

Days 1-3:
20mg Rabeprazole PO, BID

Day 4:
20mg Rabeprazole PO 2hrs prior to 100mg Dasatinib PO

**Treatment C**

7-Day Washout

Days 1-3:
20mg Rabeprazole PO, BID

Day 4:
20mg Rabeprazole PO 2hrs prior to 100mg Dasatinib PO + 1500mg HCl

Marc Yago, PhD Candidate UCSF
Rabeprazole Significantly Decreases Dasatinib Exposure in Healthy Volunteers

Betaine-HCl Increases Dasatinib Exposure in Subjects with Pharmacologically-induced Hypochlorydria

Yago et al., ASCPT 2013
Long term tolerability of BHCI in Cancer patients with GERDs is unknown

Regimen adherence may be challenging
- Combo formulation limited by tablet size and dose adjustment options
- BHCI w/out PPI may significantly enhance dasatinib exposure
  • Many patients take BHCI as digestive aid

Additional research needed to determine whether low dasatinib exposure results in the development of drug resistance and loss of dasatinib efficacy

Points to Consider to Evaluate Impact of pH-dependent Solubility on PK/PD

- pH-dependent solubility curve (weak base pKa)
- Maximal Absorbable Dose (MAD)
- Clinical Dose
- Bioavailability
- Therapeutic Index
  - Narrow TI
  - Therapeutic range
- Prevalence of acid-reducing agent (ARA) use in cancer patients
The SLC Superfamily

- Solute Carrier (SLC) superfamily contains
  - 43 families
  - 298 genes
- HUGO database (see http://www.gene.ucl.ac.uk/nomenclature)
  - SLC root symbol
  - Followed by numeral (family)
  - Followed by letter
  - Followed by numeral (ie SLC22A1)
  - Further elaborated in the SLC21/SLOC

Major Renal Transporters

Blood Flow

Filtration (GFR) *fu

\[ \text{CL}_{r} = \text{GFR} + \text{secretion} - \text{reabsorption} \]

\[ \text{CL}_{r} = \text{GFR} \]

Filtration only

\[ \text{secretion} = \text{reabsorption} \]

\[ \text{CL}_{r} < \text{GFR} \text{ (net reabsorption)} \]

\[ \text{CL}_{r} > \text{GFR} \text{ (net secretion)} \]

Urine

Renally-Mediated DDIs

Penicillin/Probenecid one of the earliest examples of ATS (Active Tubular Secretion) inhibition.

Drugs that have labeling precautions relating to renally-mediated drug transport:

- Dofetilide (Tikosyn™)
  - Concomitant administration OCT inhibitors increase potential for cardiac toxicity
- Cidofovir (Vistide™)
  - Concomitant administration of OAT inhibitors decrease potential for nephrotoxicity
Package Inserts: Clinical Studies and DDI Potential

<table>
<thead>
<tr>
<th>Drug (CL_{R})</th>
<th>Results (Bedside)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mirapex (400 mL/min) + cimetidine + probenecid</td>
<td>N=12 subjects/treatment arm. 50% ↑ in AUC; 40% ↑ in T 1/2 No effect on PK</td>
</tr>
<tr>
<td>Tikosyn (420 mL/min) + cimetidine + probenecid</td>
<td>Narrow TI 40% ↑ in AUC; CLR ↓ 33%; QTc ↑ 17-19 ms No effect</td>
</tr>
<tr>
<td>Metformin (600 mL/min) + cimetidine + probenecid</td>
<td>Narrow TI 40% ↑ in AUC and 60% ↑ in Cmax No effect</td>
</tr>
<tr>
<td>Oseltamivir + cimetidine + probenecid</td>
<td>N=12-18/treatment (see Hill et al.) No change on PK 2.5-fold AUC of Ro64-0802 (active metab)</td>
</tr>
</tbody>
</table>

Dofetilide:Drug Label

Drug-Drug Interactions (see CONTRAINDICATIONS) Because there is a linear relationship between dofetilide plasma concentration and QTc, concomitant drugs that interfere with the metabolism or renal elimination of dofetilide may increase the risk of arrhythmia (torsade de pointes). TIKOSYN is metabolized to a small degree by the CYP3A4 isoenzyme of the cytochrome P450 system and an inhibitor of this system could increase systemic dofetilide exposure. More important, dofetilide is eliminated by cationic renal secretion, so that inhibitors of this process can increase systemic dofetilide exposure. The magnitude of the effect on renal elimination by cimetidine and ketoconazole (both contraindicated concomitant uses with dofetilide) suggests that extreme caution should be taken when any inhibitor of cationic transport is co-administered with TIKOSYN (see PRECAUTIONS, Potential Drug Interactions). Where possible, appropriate alternatives not dependent on cationic renal transport should be employed.
Metformin – 1st line therapy for newly diagnosed Type II Diabetics (T2D)

- The only oral antidiabetic agent proven to reduce diabetes-related and total mortality in obese T2D (UK Prospective Diabetes Study Group, 1998)
- Metformin is eliminated unchanged in the urine (CLR>>GFR)
- Adverse reactions:
  - Most common: GI effects (~50%)
  - Lactic acidosis (extremely rare: 3/100,000 patients)
- Recent evidence suggests an anti-cancer benefit

Metformin is Predominately Eliminated in the Proximal Tubule of the Kidney
Consequences of Blocking Organic Cation Elimination

Slide from Kari Morrissey, Ph.D. UCSF KM Giacomini Lab.
Impact of Cimetidine on the PK of Metformin Depends on OCT2 Genotype

Fig 1

Fig 2

Pharmacogenetics and Genomics Vol 18 No 7

OCT1 transports metformin into the liver, the major site of its hypoglycemic activity

Transport into the liver

Pharmacologic Activity

Metformin uptake

AMPK activation

↓ Gluconeogenic enzymes

↑ Uptake of gluconeogenic substrates

↑ Glycolytic enzyme activation

↓ Gluconeogenesis

↑ Glucose uptake

↑ Glucose metabolism

Slide from Kari Morrissev UCSF & GNE
Hepatic Uptake/Efflux Transporters

Basolateral membrane

Hepatic permeability

Nucleus

Etoposide-glucuronide

Antibiotics, taxol, dextran, large-hydrophilic NN drugs

Nucleus

Uptake (from blood into hepatocytes): OATP1B1, OATP1B3
Efflux (excretion to bile): P-gp, BCRP, MRP2

PK consequences of inhibition of hepatic transporters
- Inhibition of hepatocellular uptake transporters increase area under concentration curve and maximal plasma concentration
- Inhibition of drug efflux transporters at the canalicular membrane may decrease the secretion of drug into the bile and significantly increase hepatic drug levels
Rosuvastatin Calcium (Crestor) Pharmacokinetics and Prescribing Information

FDA ALERT [03/2009]
Rhabdomyolysis (serious muscle damage) has been reported in patients taking Crestor as well as other statin drugs. To date, it does not appear that the risk is greater with Crestor than with other marketed statins. However, the labeling for Crestor is being revised to highlight important information on the safe use of Crestor. To reduce the risk for serious muscle toxicity (myopathy/rhabdomyolysis), especially at the highest approved dose of 40 mg. The labeling will also be revised to reflect the results of a large pharmacokinetic study involving a diverse population of Asian patients compared to a Caucasian control group that found drug levels to be elevated approximately 2-fold. Kidney failure of various types

Impact: Start patients of Asian descent at lowest dose of Rosuvastatin (5 mg)

Influence of SLC01B1 T521>C Genotype on Rosuvastatin AUC

CYP2C9 responsible for formation of N-desmethyl rosuvastatin (10%)
Rosuvastatin also substrate for BCRP (ABCG2)
Figure 1. Results of Tests for a Trend in the Association between Myopathy and Each SNP Measured in the Genome-wide Association Study.
P-values are shown for each SNP measured among 85 participants with myopathy and 90 matched controls who were taking 80 mg of simvastatin daily. Analyses are based on 316,184 of the 318,237 SNPs (99.4%) on the Sentrix HumanHap550-Duo BeadChip (Illumina). A result above the horizontal red line indicates strong evidence of an association (P<5×10^{-6}).


**CPIC Guidelines for Simvastatin based on SLCO1B1 Phenotype**

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Implications for Simvastatin</th>
<th>Dosing recommendations for simvastatin</th>
<th>Classification of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal function</td>
<td>Summary: phenotype risk</td>
<td>Decreased initial dosing and increase dose by weight based specific guidelines</td>
<td>Strong</td>
</tr>
<tr>
<td>Intermediate phenotype</td>
<td>Top</td>
<td>Decrease dose每日 or consider alternative dose or follow-up for higher drug exposure</td>
<td></td>
</tr>
<tr>
<td>Low function</td>
<td>High myopathy risk</td>
<td>Follow-up</td>
<td></td>
</tr>
</tbody>
</table>

Guidelines for Simvastatin based on SLCO1B1 Phenotype. Recommendations are based on data from the Supplementary Material and are consistent with the CPIC guidelines for simvastatin based on SLCO1B1 Phenotype.
Drug Label: Atorvastatin

7.3 Cyclosporine: Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g., cyclosporine) can increase the bioavailability of atorvastatin. Atorvastatin AUC was significantly increased with concomitant administration of LIPITOR 10 mg and cyclosporine 5.2 mg/kg/day compared to that of LIPITOR alone [see Clinical Pharmacology (12.3)]. In cases where co-administration of LIPITOR with cyclosporine is necessary, the dose of LIPITOR should not exceed 10 mg [see Warnings and Precautions, Skeletal Muscle (5.1)].
When Should You Look and at What!

If a compound is cleared primarily through bile, identify the transporters responsible (BCRP, P-gp, MRPs, BSEP).

If $\text{Cl}_r > \text{fu} * \text{GFR}_{\text{free}}$, have active tubule secretion. Identify transporter responsible (OCT2, OAT1, OAT3, MATE's).

Summary and Conclusions

Transporters are membrane proteins that move substrates (including) drugs into or out of cells.

The ITC has currently identified 7 transporters that are currently considered to be clinically important in PK and response:

- **Efflux**: P-gp, BCRP
- **Uptake**: OATP1B1, OATP1B3, OCT2, OCT1, OAT3

Transporter mediated drug-drug interactions (caused by induction and inhibition) have the potential to influence pharmacokinetics and pharmacodynamics (efficacy and toxicity) of many drugs.

Transporter mediated drug-drug interactions are now routinely taken into account in drug development and drug labeling now usually includes information about transporter DDIs.

PGx-dependent impact of drug transporter function is an important consideration for OATP1B1 (SLCO1B1) and BCRP (ABCG2).

The transporter field is a dynamic area of research and new data continues to emerge at a rapid pace. Drug transporter biology impacts the PK and PD of many drugs.

Slide from K. Hillgren, 2012 CACO

Acknowledgment(s) and Contributors

Genentech Research and Early Development, Development Sciences, Laboratory of Clinical Pharmacology (Mark Dresser, Amita Joshi, Sharmila Rajan, Eric Reyner, Gillian Smelick, Bert Lum and Karl Morrissey), ED-PK/PD, SA, and DMPK (Laurent Salphati, Harvey Wong and Marcel Hopp)

ITC and Research Collaborators

<table>
<thead>
<tr>
<th>Academia</th>
<th>Industry</th>
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<tbody>
<tr>
<td>Les Benet</td>
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<td>Raymond Evers</td>
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<td>Volker Fischer</td>
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<td>Kate Hillgren</td>
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<td>Shiew Mei Huang</td>
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<tr>
<td>Kari Morrissey</td>
<td>Lei Zhang</td>
</tr>
<tr>
<td>Marc Anthony Yago</td>
<td>FDA</td>
</tr>
</tbody>
</table>

References

Transporter mediated drug uptake and efflux
Clinical Pharmacology & Therapeutics (2011) 89 6, 798–805
Clinical Pharmacology & Therapeutics (2012) 92 5,

Transporter-mediated drug-drug interactions

Membrane transporters in drug development

UCSF-FDA Drug Transporter Portal (website)
http://dxr.ucsf.edu/fdtransportal/

Transporter Mediated Drug-Drug Interactions (DDIs)
Presentation slides by Lei Zhang, PhD (OCP, FDA)
Clinical Pharmacology Advisory Committee (March 2010)
Thank-you!!

Transporter Nomenclature

<table>
<thead>
<tr>
<th>SLC Family</th>
<th>ABC Family</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basolateral</td>
<td>Apical</td>
</tr>
<tr>
<td>- OCT2 = SLC22A2</td>
<td>- MDR1 = ABCB1</td>
</tr>
<tr>
<td>- OAT1 = SLC22A6</td>
<td>- MRP2 = ABCC2</td>
</tr>
<tr>
<td>- OAT3 = SLC22A8</td>
<td>- MRP4 = ABCC4</td>
</tr>
<tr>
<td>- System L = SLC7A5/8</td>
<td>- BCRP = ABCG2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Apical</th>
</tr>
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<tbody>
<tr>
<td>- PepT2 = SLC15A2</td>
</tr>
<tr>
<td>- OCTT1N1 = SLC22A4</td>
</tr>
<tr>
<td>- OCTN2 = SLC22A5</td>
</tr>
<tr>
<td>- OAT4 = SLC22A11</td>
</tr>
<tr>
<td>- hMATE1 =SLC47A1</td>
</tr>
<tr>
<td>- hMATE2=SLC47A2</td>
</tr>
</tbody>
</table>
Drug Interactions: CYP Mediated

• Significant CYP mediated drug interactions based on AUC ratio

\[
\text{N} = 115 \text{ Studies} \\
\text{CYP2C9, 2D6, 3A4}
\]


CYP Summary

• CYP interactions were complex when first recognized
• Largest CYP-mediated DDIs
  - Increase AUC 20X, C_{max} 12X
• Mechanism of CYP inhibition
  - Competitive or non-competitive
  - Potent inhibitors in sub-nanomolar range
• Many CYP liabilities are thought to be 'screened' out at an early stage of preclinical development, however, what liabilities are we selecting for?
ABC Substrate/Inhibitor Overlap

Distinct but Overlapping Substrate Specificities

Figure adapted from Thomas Litman

Sulfasalazine (SASP) Resistance *in-vitro*
Regulated by BCRP (ABCG2)

van der Heijden et al., Ann Rheum Dis. 2004
Gefitinib-enhanced SASP Bioavailability in the mouse

Plasma concentrations versus time curve after oral administration of SASP (20 mg/kg) alone or combined with gefitinib (50 mg/kg) gavage 2 hrs prior to SASP administration in wt-type mice.

When is it Important to Study Renal Transporters?

• Does scientific evidence suggest that it is necessary to investigate renal transport DDI potential for NMEs?
  – Toxicologic significance
  – Primary determinant of systemic CL
  – NME inhibits the CLR of compound with narrow TDI

• Is there a need to perform both probenecid and cimetidine studies in healthy volunteers if in vitro and preclinical data support that compound is a prototypical transport substrate?
Hepatic Transporters

Question 1. Is uptake transport the rate-limiting step of total clearance (assume low/no metabolism).

Question 2. Is it possible to predict the DDI potential mediated through hepatic uptake or efflux or are we only able to define potential mechanisms of a PK observation?

Question 3. Toxicological significance of bile acid uptake, synthesis, or efflux inhibition

Pravastatin Css Disposition in WT vs Slco1b2−/− Mice

Do not over interpret the efflux ratio.

In transporter assays, for in Caco-2 or polarized epithelial cell lines, is the net flux ratio of NME 2?

- Net flux ratio $\geq 2$
  - Is efflux significantly inhibited by 1 or more P-gp inhibitors?
    - Yes
    - No

- Net flux ratio $< 2$
  - Poor or non-P-gp substrate

If net flux ratio is $\geq 2$, complete an assessment of pharmacological and clinical information to determine whether an in vivo study is warranted.

Many drugs that are efflux substrates are extensively absorbed ($fa > 80\%$).

Factors that contribute to efflux limited absorption are high Km, Vmax, low solubility, low permeability, metabolic stability and low dose.

Slide courtesy from Joe Polli and ITC

### Pgp/BCRP Inhibitor Decision Tree

#### Need to "calibrate" in vitro systems using clinical data

- Bi-directional transporter assay with a probe P-gp substrate, for example, in Caco-2 or P-gp-overexpressing polarized epithelial cell lines
- Net flux ratio of a probe substrate decreases with increased concentrations of the investigational drug
- Net flux ratio of the probe substrate is not affected with increased concentrations of the investigational drug

#### Determine $K_i$ or $IC_{50}$ of the inhibitor

- Partially
  - Probable a Pgp inhibitor
  - Poor or non-inhibitor

- Complete an in vivo drug interaction study with a P-gp substrate such as digoxin is recommended
  - An in vivo drug interaction study with a P-gp substrate may not be needed

**False Positives (unnecessary clinical studies)**
- Alert for $[I]/IC_{50} \geq 0.1$ or $[I]/IC_{50} > 10$
- $[I]$ is steady-state total Cmax at the highest clinical dose
- $[I]$ is the GI concentration calculated as dose (mg)/250 ml
- $[I]/IC_{50} > 10$ will be exceeded at a dose of $\sim 12 \text{ mg}$ for a drug with inhibition potency of $\sim 10 \mu\text{M}$ in vitro (MW $\sim 500$).
- False Negatives (safety concerns for NTI drugs like digoxin and topotecan)

**Special Cases**

Slide courtesy from Joe Polli and ITC
OATP Inhibitor Decision Tree

Is the IC50 of the NME ≤ 10 times unbound Cmax?

- Yes
  - Is the AUC or Cmax of statin (e.g. rosuvastatin, pravastatin, pitavastatin) predicted to increase > 2 fold in presence of the NME using extrapolation (e.g. R-value > 2)?
    - Yes
      - Clinical DDI study with sensitive substrate (e.g. rosuvastatin, pravastatin, pitavastatin)
    - No
      - Clinical study may not be needed
      - Clinical study with sensitive substrate (e.g. rosuvastatin, pravastatin, pitavastatin)
- No
  - NME likely not to be an in vivo inhibitor of OATP.

*R-value = 1 + (fu / is) * IC50, where IC50 is the estimated maximum inhibitor concentration at the site to the liver and is equal to IC50 = P * Cmax / G, i.e. Cmax is the maximum systemic plasma concentration of inhibitor, P is the fraction of the dose of inhibitor Cmax, which is absorbed, fu is the absorption rate constant of the inhibitor and G, i.e. the hepatic blood flow (e.g., 1500 mL/min).

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