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 Interaction
  - Influence of Pharmacogenomics (PGx on Drug Transport)
- Impact of Drug Transport on Response & Toxicology
  - Emerging Role in Toxicology
    - Over expression of drug transporter 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 inhibition 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

Narrow Therapeutic Range

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)?
Drug Transporters of Interest from Second ITC Meeting

Transporters in Drug Absorption

*Intestinal Epithelial Transporters*
Absorption vs Efflux

**PK consequences of induction/inhibition of intestinal transporters**
- Inhibition of intestinal uptake transporters or induction of efflux transporters may decrease intestinal absorption of drugs.
- Induction of intestinal efflux transporters may increase the oral bioavailability of drugs.

**Transporters in the Intestinal Epithelia**

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

**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
  - Saquinavir

- **Cardiac Drugs**
  - Digoxin
  - Quinidine
  - Procainamide
  - Moxidazone

- **Anti-thelmintics**
  - Ivermectin
  - Abamectin

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

**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 oritraconazole 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

Consequences of Inhibiting Intestinal Efflux Transporters
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---

- P-gp inducers/inhibitors: Drugs that induce or inhibit P-gp 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

---Pharmacokinetic Interactions of Digoxin with other Drugs---

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Interactions</th>
</tr>
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<tbody>
<tr>
<td>Enzyme Inducers</td>
<td>++</td>
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<tr>
<td>Enzyme Inhibitors</td>
<td>++</td>
</tr>
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</table>
Digoxin: Safety Concerns

1.00
1.50
2.00
2.50
3.00
3.50

Valspodar
Quinidine
Cyclosporin
Quinidine
Itraconazole
Clarithromycin
Alprazolam
Ranolazine
Verapamil
Amiodarone
Diltiazem
Conivaptan
Captopril
Mibefradil
Propafenone
carvedilol
Cimetidine
Nifedipine
Ritonavir
Telmisartan
Talinolol
Felodipine
Atorvastatin
Nitrendipine
Omeprazole
Isradipine
Sertraline
Nicardipine
Losartan
Troglitazone
Varenicline

AUC or Cmax,i

• Therapeutic conc ~ 1.5 ng/mL
• 33% change in Digoxin Exposure (Cmax) ~ 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/−/− 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

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).

Substrates & Inhibitors of ABCG2

<table>
<thead>
<tr>
<th>Drugs/NMEs</th>
<th>Xenobiotics</th>
<th>Endobiotics</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topotecan</td>
<td>PhIP</td>
<td>Pheophorbide A</td>
<td>FTC</td>
</tr>
<tr>
<td>CPT-11/SN 38</td>
<td>Estrogen SO 3</td>
<td>lysotracker (green)</td>
<td>Ko134, 143</td>
</tr>
<tr>
<td>J-107088</td>
<td>Mitoaxantone</td>
<td>H33342</td>
<td>Tryprostatin A</td>
</tr>
<tr>
<td>Mitoaxantone</td>
<td>Flavoperidol</td>
<td>Rhodamine 123</td>
<td>GF120918</td>
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<tr>
<td>Diflomotecan</td>
<td>Diflomotecan</td>
<td>Bodipy-prazosin</td>
<td>Lapatinib</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Prazosin</td>
<td>Riboflavin (vitamin B2)</td>
<td>Erlotinib</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Prazosin</td>
<td>Riboflavin (vitamin B2)</td>
<td>Gefitinib</td>
</tr>
<tr>
<td>Nazosin</td>
<td>Benzoylphenyleurea</td>
<td>Riboflavin (vitamin B2)</td>
<td>CI-1033</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Cimetidine</td>
<td>Uric Acid</td>
<td>Novobiocin</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Imatinib</td>
<td>Imatinib</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Ritonavir</td>
<td>Curcumin</td>
<td>Curcumin</td>
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</table>

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

Of mice and men: Topotecan:BCRP interaction

Absorption, metabolism, and excretion of salicylazosulfapyridine in man
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

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

van der Heijden et al., Ann Rheum Dis. 2004

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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 PK in Healthy Japanese Volunteers**

![Graph](image)

**421C>A SNP Changes Surface ABCG2 Expression**

<table>
<thead>
<tr>
<th>kDa</th>
<th>Vector Control</th>
<th>wild-type 560A</th>
<th>560C-A</th>
<th>Cell Surface</th>
</tr>
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<tbody>
<tr>
<td>75</td>
<td></td>
<td></td>
<td></td>
<td>BCRP (V5)</td>
</tr>
<tr>
<td>105</td>
<td></td>
<td></td>
<td></td>
<td>Calnexin</td>
</tr>
<tr>
<td>75</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>


**ABCG2 Polymorphisms and Ethnic Distribution of SNPs.**

- The ABCG2 Q141K genotype significantly affected the pharmacokinetics of diflomotecan (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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</thead>
<tbody>
<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>T490Y</td>
<td>1</td>
<td>1</td>
<td>15</td>
<td>10</td>
<td>1.0</td>
<td>10</td>
</tr>
</tbody>
</table>

Pigg 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 × 10^-21). (Nucleosides Nucleotides Nucleic Acids. 2011 and Science Translation 2009)
- In addition to renal secretion of UA, intestinal efflux is an important determinant of UA clearance. Efflux is mediated by BCRP (ABCG2)

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.

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

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 PK provide insight into how inflammation impacts 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 prediction 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 develop liver metastasis or have had significant gastric surgery.

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
  - Drug-Drug Interaction (DDI)
  - pH-dependent absorption
  - Drug Metabolism and Drug Transport
  - Food-effect

Influence of pH-dependent Solubility on Maximum Absorbable Dose (MAD) of a Weakly Basic Drug or NME
Many Molecular Targeted Agents Display pH-dependent Solubility

Budha et al., CPT Aug, 2012

- 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.

Proton Pump Inhibitor (PPI) Pharmacology (aka “Nexium Nation”)

- All PPIs are substituted benzimidazoles.
  - Undergo chemical activation within parietal cell.
  - Only active parietal cells are inhibited (approximately 70-85% 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 PPIs 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

Smelick et al., 2013
Part 2: Dasatinib PK (control, plus PPI, plus PPI/betaine-HCl reacidification)

N = 10 Subjects (9 male, 1 female)

Rabeprazole Significantly Decreases Dasatinib Exposure in Healthy Volunteers

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

Marc Yago, PhD Candidate UCSF

Yago et al., ASCPT 2013
Dasatinib-Rabeprazole-BHCI provides Clinical PoC: Translation of Single dose HV to Chronic Administration is Needed

- 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 SLC22/SLCO

**Major Renal Transporters**

- **Blood Flow**
- **Filtration (GFR) = fu**
- **CLᵣ = GFR + secretion – reabsorption**
- **CLᵣ = GFR**
- **Filtration only**
- **secretion = reabsorption**
- **CLᵣ < GFR** (net reabsorption)
- **CLᵣ > GFR** (net secretion)

**Urine**

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**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?
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™) increase potential for cardiac toxicity
  - Cidofovir (Vistide™) decrease potential for nephrotoxicity

Dofetilide: Drug Label

Drug-Derug Interactions (see CONTRAINDICATIONS)
Because there is a linear relationship between dofetilide plasma concentration and Q5, 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 administered with TIKOSYN (see PRECAUTIONS, Potential Drug Interactions). Where possible appropriate alternatives not dependent on cationic renal transport should be employed.

Package Inserts: Clinical Studies and DDI Potential

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

Impact of Cimetidine on the PK of Metformin Depends on OCT2 Genotype

OCT1 transports metformin into the liver, the major site of its hypoglycemic activity
Hepatic Uptake/Efflux Transporters

Hepatic permeability

Glucuronide-, sulfate-, GS-conjugates, anionic

ABCB1
ABCB11
ABCB3
ABCC2
ABCC3

Bile canaliculus

Vinblastine, taxol
doxorubicin, large hydrophobic MW drugs

Taurocholate, bile acids

PC (flipase)

Basolateral membrane

Canalicular membrane

ABCG2

Nucleus

NTCP

Na+

OATP1B1

Etoposide-glucuronide

OATP2B1

OATP1B3

BPS 121; Nov.7, 2011

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
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 coadministration of LIPITOR with cyclosporine is necessary, the dose of LIPITOR should not exceed 10 mg [see Warnings and Precautions, Skeletal Muscle (5.1)].
Influence of SLCO1B1 T521>C Genotype on Rosuvastatin AUC

P3: Mordhorst et al., Clinical Therapeutics, vol.25, No. 11, 2003.

CYP2C9 responsible for formation of N-desmethyl rosuvastatin (10%).
Rosuvastatin also substrate for BCRP (ABCG2).

Effect of Gemfibrozil on the PK of Rosuvastatin via uptake transporter OATP1B1 inhibition

Fig 1. Plasma concentrations of rosuvastatin over time

Fig 2. In vitro uptake of [3H]rosuvastatin into cells expressing OATP2

Fig 3. Effect of gemfibrozil on the kinetics of OATP2-mediated [3H]rosuvastatin uptake in vitro

Clinical Pharmacology & Therapeutics 2004;75(5):455-63

Effect of Gemfibrozil on the PK of Rosuvastatin via uptake transporter OATP1B1 inhibition

When Should You Look and at What!

Clearance Pathways For Top 200 Drugs

If Clr > fu * GFRfree
Have active tubule secretion
Identify transporter responsible (OCT2, OAT1, OAT3, MATE's)

If >25% of drug is cleared hepatically determine if it is actively taken up into hepatocytes
(OATP1B1, OAT1B3, OCT1)


Slide from K. Hilgren, 2012 CACD
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, OAT1, 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.

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

The transporter field is a dynamic area of research and new data continues to emerge at a rapid pace. It is important to keep up to date with reviews in the literature and transporter information in drug labels.

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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://bts.ucsf.edu/fdatransportal

Transport Mediated Drug-Drug Interactions (DDIs)

Presentation slides by Lei Zhang, PhD (OCP, FDA)

Clinical Pharmacology Advisory Committee (March 2010)

Examples of Mechanisms Underlying Adverse Drug Reactions Due to Modifications in Transport Processes

Transporter Nomenclature

**SLC Family**
- **Basolateral**
  - OCT2 = SLC22A2
  - OAT1 = SLC22A6
  - OAT3 = SLC22A8
  - System L = SLC7A5/8
- **Apical**
  - PepT2 = SLC15A2
  - OCTN1 = SLC22A4
  - OCTN2 = SLC22A5
  - OAT4 = SLC22A11
  - hMATE1 = SLC47A1
  - hMATE2 = SLC47A2

**ABC Family**
- **Apical**
  - MDR1 = ABCB1
  - MRP2 = ABCC2
  - MRP4 = ABCC4
  - BCRP = ABCG2

Thank-you!!
Drug Interactions: CYP Mediated

- Significant CYP mediated drug interactions based on AUC ratio
  
  N= 115 Studies
  CYP2C9, 2D6, 3A4
  
  AUCi/AUC related to P-gp DDI


CYP Summary

- CYP interactions were complex when first recognized
- Largest CYP-mediated DDIs
  - Increase AUC 20X, C<sub>max</sub> 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
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.

**Pgp/BCRP Inhibitor Decision Tree**

- False Positives (unnecessary clinical studies)
- Alert for \([I_1]/IC_{50} ≥ 0.1\) or \([I_2]/IC_{50} ≥ 10\),
  - \([I_1]\) is steady-state total Cmax at the highest clinical dose
  - \([I_2]\) is the GI concentration calculated as dose (mg/250 mL).
  - \([I_2]/IC_{50} ≥ 10\) will be exceeded at a dose of ~12 mg for a drug with inhibition potency of ~10 µM in vitro (MW ~ 500).
- False Negatives (safety concerns for NTI drugs like digoxin and topotecan)

**Special Cases**

- More information from Joe Polli and ITC
OATP Inhibitor Decision Tree

Nature Reviews Drug Discovery 9, 215-236 (March 2010)