Drug-drug interactions that really matter – focus on transporters

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Drug-drug interaction (DDI):
One drug (perpetrator) alters the intensity of pharmacological effects of another drug (victim) when administered concomitantly.

Exposure-response relation determines clinical relevance of pharmacokinetic drug-drug interaction.
Clinical relevance: high-priority drug-drug interactions

- **Electronic knowledge base utilized to generate clinical decision support (PHS MKB)**
  - Selection of high-priority DDIs out of 3327 DDI pairs by expert panel based on severity of clinical outcome, monitoring options, probability of occurrence, evidence from literature
  - 15 DDIs identified: 7 pharmacodynamic interactions, 8 pharmacokinetic interactions

- **Selected highly clinically significant pharmacokinetic drug-drug interactions**

<table>
<thead>
<tr>
<th>Victim drug</th>
<th>Perpetrator drug</th>
<th>PK and clinical consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triptans</td>
<td>MAO-A inhibitors</td>
<td>AUC ▲ up to 7-fold, cardiovascular ADRs</td>
</tr>
<tr>
<td>Ramelteon</td>
<td>Strong CYP1A2 inhibitors</td>
<td>AUC ▲ up to 190-fold, CNS ADRs</td>
</tr>
<tr>
<td>Tizanidine</td>
<td>CYP1A2 inhibitors</td>
<td>AUC ▲ up to 10-fold, hypotonia</td>
</tr>
<tr>
<td>Lova-/Simvastatin</td>
<td>CYP3A4 inhibitors</td>
<td>AUC ▲ up to 20-fold, rhabdomyolysis</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>CYP3A4 inhibitors</td>
<td>SN-38 AUC ▲ 2-fold, cytotoxicity</td>
</tr>
<tr>
<td>Ergot alkaloids</td>
<td>CYP3A4 inhibitors</td>
<td>Vasoconstriction, necrosis (ergotism)</td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td>Strong CYP3A4 inducers</td>
<td>AUC ▼ by 80%, lack of efficacy</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>Proton pump inhibitors</td>
<td>AUC ▼ by 60%, lack of efficacy</td>
</tr>
</tbody>
</table>

Drug transport proteins: gatekeepers of the body

> 400 membrane transport proteins in human genome

≈ 30 drug transporters

ABC transporters

SLC transporters

Absorption

Disposition

Uptake for metabolism and excretion

Excretion

Drug-drug interaction potential!

Alignment on relevant transporters for drug ADME

- **Goal 1**
  To provide overview of key drug transporters involved in drug ADME

- **Goal 2**
  To provide examples of various technologies in studies of transporter-related DDIs

- **Goal 3**
  To provide criteria for the design and conduct of clinical studies of transporter-related DDIs => decision trees

**Key milestones**

- FDA critical path initiative: ITC established in 2007
- First Workshop 2008, first White Paper 2010
- ITC recommendations taken up in revised draft of FDA Guidance for Industry on Drug Interaction Studies in February 2012
- Second Workshop March 2012, second set of White Papers 2013


Drug transporters of clinical importance selected by the ITC

### ABC transporters involved in drug absorption, disposition and excretion

<table>
<thead>
<tr>
<th>Transporter</th>
<th>Relevant tissue</th>
<th>Substrate (e.g.)</th>
<th>Inhibitor (e.g.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-glycoprotein</td>
<td>Intestinal enterocyte</td>
<td>Digoxin</td>
<td>Quinidine</td>
</tr>
<tr>
<td>(P-gp, MDR1)</td>
<td>Kidney proximal tubule</td>
<td></td>
<td>Clarithromycin</td>
</tr>
<tr>
<td></td>
<td>Hepatocyte (canalicular)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Brain endothelia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCRP</td>
<td>as P-glycoprotein</td>
<td>Topotecan</td>
<td>Elacridar</td>
</tr>
</tbody>
</table>

### SLC transporters involved in drug disposition and excretion

<table>
<thead>
<tr>
<th>Transporter</th>
<th>Relevant tissue</th>
<th>Substrate (e.g.)</th>
<th>Inhibitor (e.g.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OATP1B1</td>
<td>Hepatocyte (sinusoidal)</td>
<td>Pravastatin</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td>OATP1B3</td>
<td>Hepatocyte (sinusoidal)</td>
<td>Rosuvastatin</td>
<td>Lopinavir/ritonavir</td>
</tr>
<tr>
<td>OAT1</td>
<td>Kidney proximal tubule</td>
<td>Cidofovir</td>
<td>Probenecid</td>
</tr>
<tr>
<td>OAT3</td>
<td>Kidney proximal tubule</td>
<td>Furosemide</td>
<td>Probenecid</td>
</tr>
<tr>
<td>OCT2</td>
<td>Kidney proximal tubule</td>
<td>Metformin</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>MATE1, MATE2K</td>
<td>Kidney proximal tubule</td>
<td>Metformin</td>
<td>Cimetidine</td>
</tr>
<tr>
<td></td>
<td>Hepatocyte (MATE1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Drug transporters in the intestinal epithelia

Clinical relevance
- P-gp and BCRP limit oral bioavailability of drug substrates
- Inhibition of P-gp or BCRP => increased substrate bioavailability
- High gut concentrations of inhibitors lead to max. transport inhibition

Intestinal absorption interaction via P-gp: digoxin-clarithromycin

- **Digoxin-clarithromycin interaction trial**
  - Cross-over trial in 12 healthy subjects
  - Digoxin 0.75 mg SD p.o., in n=3 also i.v.
  - Clarithromycin 250 mg BID for 3 days

- **PK interaction results**
  - Digoxin AUC after p.o. ▲ 1.7-fold
  - Renal tubular digoxin secretion ▼ by 40%
  - Digoxin AUC after i.v. ▲ only 1.2-fold

Intestinal P-gp inhibition by clarithromycin: digoxin toxicity risk

- Inhibitor concentration effects
  - Highest interaction effect (digoxin ratios) during absorption phase of clarithromycin
  - Est. plasma / gut conc.: 2.7 / 1337 µM
  - In vitro IC₅₀ for interaction: 4.1 µM

- Clinical consequences
  - Digoxin therapeutic range: 0.9 – 2 µg/l
  - Due to narrow therapeutic index of digoxin AUC ▲ >1.25-fold clinically important
  - Clinically relevant DDI

Zhang L et al. Xenobiotica 2008;38:709-24
Drug transporters in brain capillary endothelial cells

Clinical relevance
- P-gp (and BCRP) constitute BBB for substrate drugs
- Transport inhibition => potential CNS ADRs
- Unbound concentrations of marketed inhibitors at BBB < in vitro IC₅₀ of transport => low risk for relevant DDI

Drug transporters in the hepatocytes

Clinical relevance

- Liver uptake transport basis for subsequent drug metabolism
- Inhibition of liver uptake => increased plasma exposure of substrate
- Drug inhibition of MRP or BSEP => DILI risk
- Canalicular MRP with sinusoidal salvage


Rosuvastatin-cyclosporine interaction
- 10 patients after heart transplantation
- Rosuvastatin 10 mg SD and MD
- Stable cyclosporin treatment
- Historic control with 21 healthy subjects
- Rosuvastatin AUC ▲ 7.1-fold after MD

Pharmacogenetic impact on statin PK
- OATP1B1 c.521T>C and BCRP c.421C>A both influence rosuvastatin AUC
- OATP1B1 SNP: Simvastatin AUC ▲ 3.2-fold in CC vs. TT; Odds ratio for myopathy after 80 mg simvastatin 16.9 in CC vs. TT
- Clinically relevant DDI between rosuvastatin and cyclosporine

Niemi M. Clin Pharmacol Ther 2010;87:130-33
Drug transporters in the renal proximal tubules

Clinical relevance

- Renal drug clearance = glomerular filtration + tubular secretion – tubular re-absorption
- Drugs with high tubular secretion at risk for renal transport DDIs
- Uptake inhibition may prevent nephrotoxicity

Drug interactions influencing renal tubular drug secretion

**DDIs via OAT1 and OAT3**

- Broad substrate overlap
- Probenecid potent inhibitor but extent of drug-drug interactions is moderate:
  - Cephradine AUC ▲ 3.6-fold
  - Acyclovir AUC ▲ 1.4-fold
  - Furosemide AUC ▲ 2.9-fold
  - Methotrexate Css ▲ 2-fold
- Beneficial use of probenecid interactions:
  - Increase of exposure and t\(_{1/2}\) of benzylpenicillin
  - Protection against cidofovir nephrotoxicity ➔ probenecid must be co-administered

**DDIs via OCT2 and MATE1 and 2K**

- Broad substrate overlap
- Cimetidine potent inhibitor (MATE > OCT) but extent of interactions is moderate:
  - Metformin AUC ▲ 1.4-fold
  - Dofetilide AUC ▲ 1.5-fold
  - Procainamide AUC ▲ 1.4-fold
  - Pindolol AUC ▲ 1.5-fold
- Interactions previously attributed to OCT2 may predominantly be mediated by MATEs due to higher inhibitor affinity

Evaluation of an investigational drug as substrate for drug transporters


All NMEs

- Determine whether NME is P-gp and/or BCRP substrate \textit{in vitro}
  - Refer to P-gp and BCRP decision tree for need to conduct \textit{in vivo} studies

- Hepatic or biliary secretion major? e.g. \geq 25\% of total clearance or unknown?
  - Yes
    - Determine whether NME is OATP1B1 and/or OATP1B3 substrate \textit{in vitro}
      - Refer to OATP1B1/1B3 decision tree for need to conduct \textit{in vivo} studies

- Renal active secretion major? e.g. \geq 25\% of total clearance or unknown?
  - Yes
    - Determine whether NME is OAT1, OAT3, OCT2 and/or MATE substrate \textit{in vitro}
      - Refer to OAT1/3 and OCT2/MATE decision tree for potential \textit{in vivo} studies

Giacomini KM and Huang SM. Clin Pharmacol Ther 2013;94:3-9
Physiologically based pharmacokinetic (PBPK) modeling and simulation
- Dynamic tool to predict PK of drugs and effects of intrinsic + extrinsic factors in humans

System component (drug-independent)

Drug-dependent component

**PBPK model**

**In vitro human ADME and MOA data**
- Physicochemical
- Absorption
- Distribution
- Metabolism and transport
- DDI
- MOA

**In vivo human PK data**
- Absorption and first pass metabolism
- Distribution
- Elimination
- PK of metabolite(s)
- PK-PD relationship

Lung
Rapidly perfused organs
Slowly perfused organs
Kidney
Liver
Intestines
Blood

Dosing Ellimination

PBPK modeling and drug-drug interactions – practice

Chances and limits of PBPK modeling

- Help optimizing clinical trials:
  - dosing regimens
  - sampling schemes
  - need for additional trials
- Prediction of complex DDIs involving transporters and metabolic enzymes
- Quality of \textit{in vitro} model information may limit utility of PBPK approaches
- Integration of \textit{in vivo} data to refine PBPK model: “predict, learn, confirm“ iterations
- 15 submissions to FDA containing PBPK analyses on DDIs (2008 – 2011)
- Specialized PBPK database software available, e.g. Simcyp Simulator

Prediction of transporter-mediated DDIs

- PBPK models to incorporate permeability-limited tissue compartments for intestine, liver and kidney with active transport
- Detailed kinetic characterization needed
- Transporter interaction related changes in tissue concentrations may be predicted
- Examples of successful prediction of transporter-mediated DDIs still limited:
  - Cyclosporine – repaglinide (OATP1B1)
  - Gemfibrozil – pravastatin (OATP1B1)
  - Verapamil – digoxin (P-glycoprotein)

Transporter-mediated drug-drug interactions: summary

- Transporter-mediated DDIs may have high clinical relevance, but their extent is rather lower than of DDIs mediated by metabolic enzymes.
- Transporter-mediated intestinal absorption, hepatic uptake and renal tubular secretion are main sites of transporter-mediated DDIs.
- Clinical relevance of transporter-mediated DDIs at BBB is still unclear.
- Emerging data on newly characterized transporters may change mechanistic understanding of clinically relevant DDIs.

**Relevance**

**Actions**

- Transporter-medicated DDIs are to be considered in drug development.
- NMEs are recommended to be investigated as potential substrates and/or inhibitors of relevant drug transporters according to decision trees.
- Results need to be reflected in drug labels in order to prevent adverse drug reaction or lack of efficacy caused by transporter-mediated DDIs.
- Well refined PBPK modeling may enable optimal predictions of transporter-mediated DDIs and help optimizing or even omitting clinical trials.