ITC3 State of the Art in Clinical Transporter DDI Evaluation

Maciej Zamek-Gliszczynski, Ph.D.
4 Key References

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Transporters in Drug Development:

2018 ITC Recommendations for Emerging Transporters of Clinical Importance

Maciej J. Zamek-Gliszczynski⁴,#, Paresh P. Chothe², Xiaoyan Chu³, Kathleen M. Giacomini⁴, Richard B. Kim⁵, Adrian S. Ray⁶, Sophie L. Stocker⁷, Mitchell E. Taub⁸, Jashvant D. Unadkat⁹, Matthias B. Wittwer¹⁰, Cindy Xia¹¹, Sook-Wah Yee¹², Lei Zhang¹³, Yan Zhang¹⁴, on behalf of

Clinical Probe Drugs and Endogenous Biomarkers as Substrates for Transporter-Related Drug-Drug Interaction Evaluation: Perspectives from the International Transporter Consortium

Xiaoyan Chu¹ *, Mingxiang Liao², Hong Shen³, Kenta Yoshida⁴, Arik A. Zur⁵, Vikram Arya⁶, Aleksandra Galetin⁷, Kathy Giacomini⁸, Imad Hanna⁹, Hiroyuki Kusuhara¹⁰, Yurong Lai¹¹, A. David Rodrigues¹², Yuichi Sugiyama¹³, Maciej J. Zamek-Gliszczynski¹⁴, and Lei Zhang¹⁵ * on

ITC Commentary on Metformin Clinical Drug-Drug Interaction Study Design That Enables an Efficacy- and Safety-Based Dose Adjustment Decision.

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Dabigatran Eteplinate and Digoxin: Comparison as Clinical Probe Substrates for P-gp

Xiaoyan Chu¹*, Aleksandra Galetin², Maciej J. Zamek-Gliszczynski³, Lei Zhang⁴, and Donald J. Tweedie⁵
OATP2B1: An Emerging Transporter

Intestinal Epithelia

Blood → Lumen of Intestine

THTR1 → OATP2B1 → PEPT1, PEPT2 → ASBT → MCT1 → MRP2 → BCRP → MDR1 (P-gp)

OSTα/β → MRP3 → ENT1, ENT2

Hepatocytes

Blood → MRP4 → OAT2 → OCT1 → OAT7 → ENT1, OATP1B1 → OATP1B3 → OATP2B1 → NTCP

MRP3 → BSEP → MDR1 (P-gp) → ENT1, MRP2, MDR3 → MATE1

--- Intestinal OATP Isoform
...responsible for absorption of select drugs
...OATP substrate ≠ OATP2B1 absorption
...inhibitors decrease exposure (loss of efficacy)

--- One of Three Hepatic OATPs
...inhibitors increase exposure (safety)
Complex and Unexpected DDIs

--Decreased exposure of drugs absorbed via OATP2B1↓
  2X rosuvastatin, fexofenadine, aliskiren, celiprolol

--Asunaprevir increased rosuvastatin exposure
  ...DDI mainly due to hepatic OATP2B1 inhibition

Hepatic OCT1

- Key to metformin hepatic distribution and effect
  ...key to dose adjustment in metformin DDIs
  ...but not a PK determinant and poor clinical probe

- Rate-determining (PK/PD, PgX, DDIs) for:
  fenoterol, sumatriptan, O-desmethyl tramadol, tropisetron, ondansetron, and morphine

-6+ clinical probe drugs
-No specific inhibitors
-Polymorphic (9% inactive)
OCT1 Importance: Fenoterol

High in vitro activity with drug

No transport by OCT1 variants

2/3 hepatic uptake via OCT1

AUC ↑ 2X

Heart Rate ↑ 50%

Glucose ↑ 3.4X

OCT1 PK Importance

- Sumatriptan
  $AUC \uparrow 2.1X$
  Potential OCT1 Clinical Probe

- O-desmethyl Tramadol
  $AUC \uparrow 2.1X; AUEC (miosis) \uparrow 4.6X, \downarrow 30\% (self-dose)$

- Tropisetron
  $Plasma \uparrow 2-4X; Emesis \downarrow 10X$

- Ondasetron
  $Exposure \uparrow, PD \uparrow$

- Morphine(?)
  $PK \uparrow, PD \uparrow, but results inconsistent (PO codeine?)$

- NOTE: Metformin is NOT on this list!
Is hepatic elimination an important route of elimination of NME?  
**Criteria:** CL$_{h}$ > 0.25 CL$_{Total}$

**Yes**

Does the compound have active hepatocyte uptake?  
Do the drugs’ physiological properties (e.g. low passive membrane permeability*, high hepatic concentrations relative to other tissues, organic cation or anion/charged at physiological pH) support importance of active uptake into liver?

**Yes**

Investigate uptake mechanisms in transfected cell lines.

If an OATP or OCT1 substrate, consider a clinical DDI study with OATP or OCT1 inhibitor (or OATP1B1 or OCT1 pharmacogenetic study). Further consideration could be given to review clinical pharmacokinetics based on OATP1B1 or OCT1 genotyping.

**-Polymorphic (9% inactive)**
**-No specific inhibitors**

**No**

Hepatic clearance is not a sufficiently important determinant of drug levels
NME probably not an in vivo inhibitor of OATP or OCT1. Clinical study may not be needed.

No Clinical DDI study with sensitive or a clinically relevant substrate

Is the AUC or $C_{\text{max}}$ of DDI victim drug predicted to increase > 1.25-fold in the presence of the NME using extrapolation (e.g. #R-value ≥ 1.1)?

Yes

Clinical DDI study with sensitive or a clinically relevant substrate

e.g. Sumatriptan or relevant OCT1 co-med

No

NME probably not an in vivo inhibitor of OATP or OCT1. Clinical study may not be needed.
### Clinical Probes and Biomarkers

<table>
<thead>
<tr>
<th>Transporter</th>
<th>Probe Drug</th>
<th>Biomarker</th>
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<tbody>
<tr>
<td>OATP1B1/3</td>
<td>Pitavastatin Atorvastatin Rosuvastatin (2B1)</td>
<td>CP I &amp; III GCDCA-S HDA &amp; TDA UCB &amp; CB</td>
</tr>
<tr>
<td>OAT1/3</td>
<td>Adefovir Furosemide Benzylpenicillin</td>
<td>Taurine 6βHC</td>
</tr>
<tr>
<td>OCT1</td>
<td>Sumatriptan</td>
<td></td>
</tr>
<tr>
<td>OCT2/MATE1/2K</td>
<td>Metformin</td>
<td>Creatinine NMN</td>
</tr>
<tr>
<td>P-gp</td>
<td>Digoxin DABE Fexofenadine</td>
<td></td>
</tr>
<tr>
<td>BCRP</td>
<td>Rosuvastatin Sulfasalazine</td>
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Considerations for Probe Selection

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<td></td>
<td>UCB &amp; CB</td>
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- Pitavastatin
  ...most selective and specific $\rightarrow$ sensitive
  ...but not a common co-med

- Rosuvastatin or Atorvastatin
  ...not selective or specific (BCRP/OATP2B1 or 3A)
  ...common co-meds

- Considerations:
  1) what? (mechanism or specific DDI $\rightarrow$ perp dependent)
  2) extrapolation? (think beyond PK $\rightarrow$ PD and tox)
     ...biomarkers (collect data for future extrapolation)
Metformin: A Unique Molecule With Very Unique PK/PD Properties

OCT2/MATE1/2-K clinical probe
OCT1 is key to metformin hepatic distribution and effect
...key to dose adjustment in metformin DDIs
...but not a PK determinant and poor clinical probe
Absorption, Distribution, and Clearance are Transporter-Mediated Processes

Metformin Unexpected DDIs

Systemic PK ↔

Increased absorption???

Half Life = $\ln(2)/k$
$k = \text{CL/V}$
Both clearance and volume reduced to same extent???

F ↑
CLr ↑
PD ↑

Rational Design of Metformin Clinical DDI Studies

In addition to systemic PK, metformin DDI studies should include:
  • Systemic PK of high-dose metformin IR
  • Measurement of Renal Clearance and recovery
  • PD endpoint (HVNs: OGTT [75 g, 1 h], not FPG or HbA1C)
  • Safety endpoint (blood lactate as exploratory biomarker)

Study should design should be a 3-period design:
  • NME Alone → Does NME lower glucose AUC?
  • Metformin Alone
  • Metformin + NME

Rational Design of Metformin Clinical DDI Studies

Dabigatran Eteplolate and Digoxin: Comparison as Clinical Probe Substrates for P-gp

**a**

- Apical compartment
  - P-gp
  - Na-dep uptake
  - Na-dep endocytosis
  - Basolateral compartment
  - Paracellular flux

**b**

- GI lumen
  - P-gp
  - Na-dep uptake
  - Paracellular
  - Blood
  - Liver
  - Brain
  - BBB
  - Blood
  - OATP4C1 Na-dep uptake
  - Kidney
    - GFR
    - P-gp
    - Urine
  - PT

- Dabigatran etepolate (DE)
  - Absorption
  - CES1 CES2
  - Bioavailability 3%-7%

- Dabigatran glucuronides
  - 10% of total dabigatran in plasma

- Renal clearance of dabigatran primarily by glomerular filtration is 80% of total clearance
Increasing Consensus on Clinical Probes: BCRP Example

**Probe Substrates**
- Oral sulfasalazine (1000 mg IR) for intestinal BCRP
- Oral rosuvastatin (20 mg) for intestinal and hepatic BCRP
- Intravenous rosuvastatin (4 mg) for hepatic BCRP

**Inhibitors**
- Curcumin (2000 mg)
- Lapatinib (250 mg)

**PGx Considerations**
- Select BCRP c.421C/C subjects
- Select NAT2 intermeidate/rapid acetylators if using sulfasalzine
- Select OATP1B1 c.521T/T subjects if using RSV
- PD or PET for RSV dosing
## Transporter Clinical Probe Cocktails

### Table 2. Pharmacokinetic Properties* of the Proposed Transporter Cocktail Drugs

<table>
<thead>
<tr>
<th>BDDCS(^a)</th>
<th>Digoxin(^27)</th>
<th>Rosuvastatin(^36)</th>
<th>Furosemide(^37)</th>
<th>Metformin(^38)</th>
</tr>
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<tr>
<td><strong>Mode of Action</strong></td>
<td>Sodium–Potassium ATPase Inhibitor</td>
<td>HMG CoA Reductase Inhibitor</td>
<td>Sodium/Chloride Reabsorption Inhibitor</td>
<td>Increasing Peripheral Glucose Uptake and Utilization</td>
</tr>
<tr>
<td><strong>Clinical dose range (mg/day)(^b)</strong></td>
<td>0.125–0.25 (0.5)</td>
<td>5–20 (40)</td>
<td>40–80</td>
<td>850–2250</td>
</tr>
<tr>
<td><strong>Proposed dose in cocktail (mg)</strong></td>
<td>0.25</td>
<td>10</td>
<td>5</td>
<td>500</td>
</tr>
<tr>
<td><strong>Half-life (h)</strong></td>
<td>39</td>
<td>20</td>
<td>1.3 (0.5–2.4)</td>
<td>75 (41, 42)</td>
</tr>
<tr>
<td><strong>Oral bioavailability (%)</strong></td>
<td>70</td>
<td>20</td>
<td>61</td>
<td>52</td>
</tr>
<tr>
<td><strong>Unbound fraction (%)</strong></td>
<td>75</td>
<td>12</td>
<td>1.4</td>
<td>99.9</td>
</tr>
<tr>
<td><strong>Route of elimination</strong></td>
<td>i.v. Dosing: 51% urine, 15% faeces(^40)</td>
<td>i.v. Dosing: 28% urine; p.o. dosing: 90% faeces</td>
<td>i.v. Dosing: 83% urine, 7.5% faeces; p.o. dosing: 55% urine, 35% faeces(^41,42)</td>
<td>i.v. Dosing: 100% urine; p.o. dosing: 52% urine, 29% faeces(^42)</td>
</tr>
<tr>
<td><strong>Ratio of CL(_r)/GFR</strong></td>
<td>1.24 after i.v.(^43)</td>
<td>Minor</td>
<td>20 after i.v.(^44)</td>
<td>37–158 after i.v.(^45)</td>
</tr>
<tr>
<td><strong>In vitro transporter</strong></td>
<td>P-gp, OATP1B3,(^16,46,47) OCT2(^48)</td>
<td>P-gp,(^49) BCRP,(^50) OAT3,(^21) OATP1B1,(^50) OATP1B3(^50)</td>
<td>BCRP,(^51) OAT1,(^52) OAT3(^52)</td>
<td>About 3.5 after i.v.</td>
</tr>
<tr>
<td><strong>Used as clinical probe substrate</strong></td>
<td>Yes(^55)</td>
<td>Yes(^56,57)</td>
<td>No</td>
<td>Yes(^31,58)</td>
</tr>
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Biomarkers

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-Present

...insufficient validation (for drug development)
...internal decision making at best (early stages)

-Future

...some likely validated as replacement for DDI
...in vitro inhibition → biomarker → extrapolate DDI
...think ($4\beta$HC and CYP3A4)
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Deceptively Unchanged Systemic PK

Metformin & OCT1: It’s Complicated!

What Happens to Metformin PK, Distribution and PD Following Genetic Ablation of Oct1/2?

Metformin PK/PD in Oct1/2 KOs

AUC ↑ 2.9X
Liver Kp ↓ 4.2X
AUC, systemic ↑ 2.9X
AUC, liver ↓ 40%

ED₅₀ ↔ Emax ↔
August 11, 2014

Shares in Galapagos NV were down 9 percent Friday on news that Glaxosmithkline plc terminated development of its selective Janus kinase 1 (JAK1) inhibitor GSK2586184 in several chronic inflammatory conditions after a statin-associated drug-drug interaction became apparent in a phase I study.