New Developments in Renal Drug Transport

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Renal Elimination
Contribution of Secretion and Filtration

Proximal Tubule
Transporter Expression

Adapted from Lepist E.I. and Ray A.S. Expert Opin Drug Metab Toxicol 2012, 8:433-48
Creatinine Renal Transport is Complex
Uptake, Secretion and Reabsorption

Over a half dozen transporters have been implicated

# Clinical Relevance

## Drugs Reported to Affect Serum Creatinine

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antacid</td>
<td>Cimetidine</td>
</tr>
<tr>
<td></td>
<td>Famotidine</td>
</tr>
<tr>
<td>Antibiotic</td>
<td>DX-619</td>
</tr>
<tr>
<td></td>
<td>PA-824</td>
</tr>
<tr>
<td></td>
<td>Trimethoprim</td>
</tr>
<tr>
<td>Antiparasitic</td>
<td>Pyrimethamine</td>
</tr>
<tr>
<td>Antiviral</td>
<td>Dolutegravir</td>
</tr>
<tr>
<td></td>
<td>Rilpivirine</td>
</tr>
<tr>
<td>Pharmacoenhancer</td>
<td>Cobicistat</td>
</tr>
<tr>
<td></td>
<td>Ritonavir</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Amiodarone</td>
</tr>
<tr>
<td></td>
<td>Dronedarone</td>
</tr>
<tr>
<td></td>
<td>Ranolazine</td>
</tr>
<tr>
<td>Thrombin inhibitor</td>
<td>AZD0837</td>
</tr>
<tr>
<td>Oncology</td>
<td>Imatinib</td>
</tr>
</tbody>
</table>

Clinical Relevance of Renal Interactions
Adverse Drug-Drug Interactions

Dofetilide Pharmacokinetics

- Cimetidine (400 mg) reduced dofetilide renal clearance by 33%
- Increased ΔQTc corresponding with exposure

Relative Contribution of Tubular Secretion
Effect of Renal Impairment

Contribution to Creatinine elimination:

- 16% Glomerular Filtration
- 36% Glomerular Filtration
- 48% Glomerular Filtration

Shemesh O. et al. Kidney Int. 1985,28:830-8
In mice, cisplatin induced nephrotoxicity is increased by MATE1−/− and the inhibitor ondansetron

Adapted from Li Q. et al. Toxicology Applied Pharmacol. 2013
Regulatory Guidance
Renal Transporters

Blood (Basolateral)  Proximal Tubule  Urine (Apical)

OCT2  OCT2  FDA  EMA  PMDA
OAT1,3  OCT2  EMA  PMDA
OA-  OA-  OA-  PMDA
OC+  OC+  OC+  H+

P-gp  BCRP  MATE1, MATE2-K

<table>
<thead>
<tr>
<th>Cut-Off</th>
<th>FDA</th>
<th>EMA</th>
<th>PMDA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;1.10 (10x)</td>
<td>&gt;1.02 (50x)</td>
<td>&gt;1.25 (4x)</td>
</tr>
</tbody>
</table>

1 + [I₁]/IC₅₀
[I₁] = Fraction unbound (Fᵤ) plasma Cᵥₐₓ where Fᵤ < 1% use 1%

Creatinine Renal Transport is Complex
Basolateral Uptake – Role of OAT2?

- Efficient transport by OAT2 >> OCT2

Creatinine Transport

Kinetics

- OAT2 is ~30-fold more efficient creatinine transporter than OCT2

<table>
<thead>
<tr>
<th></th>
<th>Vmax (pmol/min/mg)</th>
<th>Km (µM)</th>
<th>Efficiency (µL/min/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OAT2</td>
<td>24,987</td>
<td>795</td>
<td>31.4</td>
</tr>
<tr>
<td>OCT2</td>
<td>17,546</td>
<td>18,771</td>
<td>0.93</td>
</tr>
</tbody>
</table>

Shen H. et al. Drug Metab Dispos 2015, 45(2), 228-36
Kidney Transporters
Quantitative Proteomics

8-fold

OCT2
OAT1
MATE1
OAT3
P-gp
MRP2
OCTN1
OCTN2
OAT2
MRP4
OAT4

Prasad B. et al. Drug Metab Dispos. 2016, 44:1920-4
# Clinical Evidence for a Role of OAT2

**Creatinine versus Metformin**

<table>
<thead>
<tr>
<th>Perpetrator</th>
<th>Most Affected Transporter</th>
<th>Creatinine (mg/dl)</th>
<th>Metformin ((\Delta)AUC)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrimethamine</td>
<td>MATE1/2-K</td>
<td>(\uparrow0.24)</td>
<td>(\uparrow35%)</td>
<td>Kusuhara et al. Clin Pharmacol Ther 2011</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>MATE1/2-K</td>
<td>(\uparrow0.28)</td>
<td>(\uparrow37%)</td>
<td>Grun et al. Br J Clin Pharmacol 2013</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>MATE1</td>
<td>(\uparrow0.37)</td>
<td>(\uparrow50%)</td>
<td>Somogyi et al. 1987</td>
</tr>
<tr>
<td>Famotidine</td>
<td>MATE1</td>
<td>(\uparrow0.11)</td>
<td>(\leftrightarrow)</td>
<td>Hibma et al. Clin Pharmacokinet 2016</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>MATE2-K</td>
<td>(\uparrow0.10)</td>
<td>(\leftrightarrow)</td>
<td><a href="http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002264/WC500118874.pdf">Link</a></td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>OCT2</td>
<td>(\uparrow0.11)</td>
<td>(\uparrow79%) (QD) (\uparrow145%) (BID)</td>
<td>Song et al. J Int AIDS Soc 2014</td>
</tr>
<tr>
<td>Ranolazine</td>
<td>OCT2</td>
<td>(\uparrow0.10)</td>
<td>(\uparrow37%) (500 mg) (\uparrow79%) (1000 mg)</td>
<td>Zack J. et al. Clin Pharmacol Drug Dev 2015</td>
</tr>
</tbody>
</table>
Clinical Drug-Drug Interaction
Famotidine Effect on Creatinine and Metformin

H₂N
N
H₂N
S
S
NH₂
O
O
H₂N
H₂N

Effect of 800 mg Famotidine in Healthy Volunteers (n = 12)

<table>
<thead>
<tr>
<th>Transporter</th>
<th>IC₅₀ (µM)</th>
<th>[I₁]/IC₅₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCT1</td>
<td>19</td>
<td>0.015</td>
</tr>
<tr>
<td>OCT2</td>
<td>66</td>
<td>0.053</td>
</tr>
<tr>
<td>MATE1</td>
<td>0.25</td>
<td>4.0</td>
</tr>
<tr>
<td>MATE2</td>
<td>2.5</td>
<td>0.40</td>
</tr>
</tbody>
</table>

[I₁] = unbound Cₘₙₙ 1.0 µM

<table>
<thead>
<tr>
<th>Serum Creatinine (mg/dL)</th>
<th>Metformin (ΔAUC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑0.11**</td>
<td>↔</td>
</tr>
</tbody>
</table>

Bioavailability

↑1.24-fold**

Renal Secretion

↑1.36-fold*

*P<0.05, **P<0.01

Significant increase in Metformin pharmacodynamic effect also observed

Renal Transporter Inhibition
Decision Tree Analysis

<table>
<thead>
<tr>
<th>Transporter</th>
<th>IC₅₀ (µM)</th>
<th>([I_1]/IC_{50})</th>
</tr>
</thead>
<tbody>
<tr>
<td>OAT1</td>
<td>2.12</td>
<td>0.04</td>
</tr>
<tr>
<td>OAT3</td>
<td>1.97</td>
<td>0.04</td>
</tr>
<tr>
<td>OCT2</td>
<td>1.93</td>
<td>0.04</td>
</tr>
<tr>
<td>MATE1</td>
<td>6.34</td>
<td>0.01</td>
</tr>
</tbody>
</table>

\([I_1] = \text{Unbound } C_{\text{max}} = 80 \text{ nM}\)

- Little or no potential for clinically relevant inhibition
  - Lack of OAT1/3 interaction confirmed by lack of effect on PAH and TFV in clinical studies

Reese M.J. et al. Drug Metab Dispos 2013,41:353-61
Transporter Inhibition
Dolutegravir Inhibition of OCT2

OCT2 Inhibition

More than 20-fold more potent than published value
- Similar MATE1 IC$_{50}$ (4.67 μM) to that previously reported

Transporter Inhibition
Effect of Serum Protein

Dolutegravir Inhibition of OCT2-Dependent Metformin Transport

<table>
<thead>
<tr>
<th>Serum</th>
<th>IC$_{50}$ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0% (Buffer)</td>
<td>0.085</td>
</tr>
<tr>
<td>5%</td>
<td>0.10</td>
</tr>
<tr>
<td>10%</td>
<td>0.20</td>
</tr>
<tr>
<td>25%</td>
<td>0.71</td>
</tr>
<tr>
<td>100%</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Estimated IC$_{50}$ = 11 µM (F$_u$ 0.8%)

- Cimetidine has same IC$_{50}$ in buffer and 100% serums (~ 80 µM)
Inhibition of OCT2 by Dolutegravir
Prediction Based on IC$_{50}$ in Human Serum

Dolutegravir Pharmacokinetics

Based on metformin total clearance (0.4 L/h/kg) and GFR (0.11 L/h/kg), inhibition of tubular secretion of 60% for 1.79-fold increase in metformin

Multidose pharmacokinetics from Greener B.N. J Acquir Immune Defic Syndr 2013, 64:39-44
Renal Transporter Inhibition

Decision Tree Analysis

<table>
<thead>
<tr>
<th>Transporter</th>
<th>IC$_{50}$ (µM)</th>
<th>[I$<em>1$]/IC$</em>{50}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>OAT1</td>
<td>&gt;100</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OAT2</td>
<td>&gt;100</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OAT3</td>
<td>6.6</td>
<td>0.014</td>
</tr>
<tr>
<td>MRP2</td>
<td>71</td>
<td>0.0012</td>
</tr>
<tr>
<td>MRP4</td>
<td>24</td>
<td>0.0037</td>
</tr>
</tbody>
</table>

[I$_1$] = unbound C$_{max}$ 90 nM

<table>
<thead>
<tr>
<th>Transporter</th>
<th>IC$_{50}$ (µM)</th>
<th>[I$<em>1$]/IC$</em>{50}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCT2</td>
<td>14</td>
<td>0.0064</td>
</tr>
<tr>
<td>OCT3</td>
<td>12</td>
<td>0.0075</td>
</tr>
<tr>
<td>OCTN1</td>
<td>2.5</td>
<td>0.036</td>
</tr>
<tr>
<td>MATE1</td>
<td>1.9</td>
<td>0.047</td>
</tr>
<tr>
<td>MATE2-K</td>
<td>34</td>
<td>0.0026</td>
</tr>
</tbody>
</table>

Little or no potential for clinically relevant inhibition
- Weak inhibition of cationic transporters

Inhibition of Creatinine Secretion

Cobicistat

- Reversible decrease in creatinine secretion in the absence of an effect on renal function

Facilitated Inhibitor Accumulation
Cobicistat Transport by OCT2

Mean ± SD; N = 3 independent experiment
**, P < 0.005; ****, P < 0.0001; Students t-test

Assay Systems
Multiple Transfection Model

Creatinine Secretion

- OCT2 potentiates cimetidine inhibition of MATE1

Zhang, X.et al.  AAPS Workshop, Bethesda, MD, March 17-20, 2013
Proximal Tubule Model Systems
Primary Proximal Tubule Cells

Secretory transport of Tenofovir

Billington S. et al. AAPS, San Diego, California, November 2-6, 2014
Proximal Tubule Model Systems
3D Bioprinting

- Basal interstitium
  - Renal fibroblasts and Endothelial cells (HUVEC)
- Epithelium
  - Monolayer of primary polarized proximal epithelium cells

King SM. Front Physiol 2017, in press
Conclusions

- Clinically significant renal DDIs are rare but are difficult to predict, underappreciated and may be more severe in **sensitive populations**

- Renal transport pathways are **complex**
  - Fractional transport ($f_t$) often spread across multiple transporters
  - Involvement of transporters not often studied

- Need for more **holistic models** to study potential for renal drug-drug interactions
  - Actual victim/perpatrator
  - Addition of plasma proteins
  - Multiple transfection and PPT systems
Acknowledgements

Thank you for your attention!

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