Evaluation and Quantitative Prediction of Renal Transporter-Mediated Drug-Drug Interactions

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Outline

• Background of renal transporters.
• Clinically observed transporter-mediated renal DDIs.
• Quantitative prediction of renal DDIs.
• A case study to predict renal DDIs.
• Renal transporter inhibition and elevated serum creatinine.
Renal Clearance

If $CL_r > fu \times GFR$, transporter-mediated active secretion must be involved. Transporter interactions could lead to clinical DDIs.

$CL_r = fu \times GFR + CL_{secretion} - CL_{reabsorption}$
**Major Human Renal Transporters**

- **Blood Flow**
- **Proximal Tubular Cell**
- **Urine**

**Equations:**

- $CL_r = fu \times GFR + CL_{secretion} - CL_{reabsorption}$

**Transporters:**
- OAT1
- OAT3
- OCT2
- OAT4
- MRP2/4
- MDR1
- OCTN1
- OCTN2
- MATE1/2-K
- OAT3
- OCT2
- PepT2
- L-Carnitine
• Background of renal transporters.
• Clinically observed transporter-mediated renal DDIs.
• Quantitative prediction of renal DDIs.
• A case study to predict renal DDIs.
• Renal transporter inhibition and elevated serum creatinine.
Renal Transporter-mediated DDIs

Given the limitations of dosage and inhibitor concentrations relative to the inhibition potency against the transporters

- Cimetidine is one of the most potent OCT2 inhibitors *in vivo*.
- Probenecid is claimed as the most potent OATs inhibitor *in vivo*. 
**Renal Transporter-mediated DDIs**

- The magnitude of renal clearance reduction caused by cimetidine is lower compared with the renal clearance reduction from probenecid
  - The higher inhibition potency of probenecid compared with cimetidine.

- The magnitude of AUC changes from renal DDIs is much lower than the AUC changes from CYP DDIs and hepatic OATPs-mediated DDIs
  - Despite the fact that most of the market drugs have significant renal clearance, even complete inhibition of transporter is assumed, most renal DDIs are predicted to be <2-fold
  - Renal impairment causes weak or moderate effects.
Why AUC Changes from Renal DDIs are Small?

- About 30% of drugs have renal clearance as a major elimination pathway.
- Why don’t we observe significant renal DDIs due to the inhibition of renal transport?
  - No potent renal transporter inhibitors exist?
  - Renal clearance mechanism protect from DDIs, fraction of clearance inhibitable is low?
  - Significant renal DDIs have not been systemically documented?
Outline

- Background of renal transporters.
- Clinically observed transporter-mediated renal DDIs.
- Quantitative prediction of renal DDIs.
- A case study to predict renal DDIs.
- Renal transporter inhibition and elevated serum creatinine.
Static Models to Predict DDIs

- Basic model
- Mechanistic model
Renal OATs DDIs by Probenecid

• Compare probenecid inhibition potency towards hOAT1 and hOAT3 (Ki ~8 μM and ~3 μM, respectively) with unbound plasma concentration of probenecid.

• Using $CL_{sec,i} = CL_{sec}/(1+I/K_i)$, it is reasonable to estimate that probenecid at 2000 mg dose (unbound $C_{max} \sim 3-50 \mu M$) is able to inhibit about 80% of renal transport of victim drugs through OATs in vivo.

• Example: Victim drug A and probenecid DDI
  - Drug A: Control $CL_r, CL_{sec} = CL_r - fu*GFR$
  - With probenecid, $CL_{r,i} = fu*GFR + CL_{sec} \times 0.2$
  - Compare with the observed renal clearance of drug A with probenecid in clinical DDI trial
<table>
<thead>
<tr>
<th>Victim</th>
<th>Perpetrator</th>
<th>Control renal clearance (ml/min)</th>
<th>Renal clearance with perpetrator (ml/min)</th>
<th>Renal clearance reduction</th>
<th>Predicted renal clearance reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>Probenecid</td>
<td>248</td>
<td>168</td>
<td>32%</td>
<td>47%</td>
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<tr>
<td>Bumetanide</td>
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<td>44%</td>
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<td>21%</td>
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<td>270</td>
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<td>58%</td>
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<td>Cinoxacin</td>
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<td>61%</td>
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<td>65%</td>
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<td>61%</td>
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<td>107</td>
<td>64%</td>
<td>73%</td>
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<tr>
<td>Fexofenadine</td>
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<td>74.0</td>
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<td>65%</td>
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<tr>
<td>Furosemide</td>
<td>Probenecid</td>
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<td>20.3</td>
<td>72%</td>
<td>78%</td>
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<tr>
<td>Ganciclovir</td>
<td>Probenecid</td>
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<td>190</td>
<td>19%</td>
<td>40%</td>
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<td>Nafcilin</td>
<td>Probenecid</td>
<td>141</td>
<td>39.2</td>
<td>72%</td>
<td>73%</td>
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<tr>
<td>Oseltamivir</td>
<td>Probenecid</td>
<td>262</td>
<td>95.0</td>
<td>64%</td>
<td>44%</td>
</tr>
<tr>
<td>Zalcitabine</td>
<td>Probenecid</td>
<td>310</td>
<td>180</td>
<td>42%</td>
<td>50%</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Probenecid</td>
<td>333</td>
<td>209</td>
<td>37%</td>
<td>58%</td>
</tr>
</tbody>
</table>
Renal OCT DDIs through Cimetidine

- Compare cimetidine inhibition potency towards OCT2 ($K_i \sim 30 \, \mu M$) with unbound plasma concentration of cimetidine (unbound $C_{\text{max}} \sim 8.6-73 \, \mu M$).

- Using $\text{CL}_{\text{sec},i} = \text{CL}_{\text{sec}}/(1+I/K_i)$, it is reasonable to estimate that cimetidine is able to inhibit about 30% or more of renal transport of victims through OCT2 in vivo.
IVIVC of OCT2-mediated Renal DDIs

<table>
<thead>
<tr>
<th>Victim</th>
<th>Perpetrator</th>
<th>Control renal clearance (ml/min)</th>
<th>Renal clearance with perpetrator (ml/min)</th>
<th>Renal clearance reduction</th>
<th>Predicted renal clearance reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>Cimetidine</td>
<td>349</td>
<td>273</td>
<td>22%</td>
<td>22%</td>
</tr>
<tr>
<td>Amiloride</td>
<td>Cimetidine</td>
<td>358</td>
<td>299</td>
<td>16%</td>
<td>24%</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>Cimetidine</td>
<td>263</td>
<td>208</td>
<td>21%</td>
<td>18%</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>Cimetidine</td>
<td>274</td>
<td>238 or 184</td>
<td>13%-33%</td>
<td>25%</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>Cimetidine</td>
<td>230</td>
<td>152</td>
<td>34%</td>
<td>25%</td>
</tr>
<tr>
<td>Metformin</td>
<td>Cimetidine</td>
<td>728</td>
<td>403</td>
<td>45%</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>527</td>
<td>378</td>
<td>28%</td>
<td>23%</td>
</tr>
<tr>
<td>Procainamide</td>
<td>Cimetidine</td>
<td>466</td>
<td>297</td>
<td>36%</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ranitidine</td>
<td>Cimetidine</td>
<td>326</td>
<td>244</td>
<td>25%</td>
<td>21%</td>
</tr>
<tr>
<td>Varenicline</td>
<td>Cimetidine</td>
<td>133</td>
<td>100</td>
<td>25%</td>
<td>8.0%</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Cimetidine</td>
<td>478</td>
<td>210</td>
<td>56%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Feng, Mol. Pharmaceutics 2013
The basic model reasonably predicted the changes in CLr of OAT1/OAT3 and OCT2 substrates, when concomitantly dosed with probenecid and cimetidine, respectively.

- The prediction renal clearance changes with probenecid for 11 of 18 (61%) cases are within 25% error, and 17 of 18 (94%) cases are within 50% error of the observed CLr changes.
- The predicted renal clearance changes with cimetidine for 8 of 13 (61%) cases were within 25% and 12 of 13 (92%) cases within 50% of the observed CLr changes.

The basic model accounts for the inhibitory effect of a perpetrator at the high end of clinical relevant exposure range to predict the change in renal clearance of the victim drug.
A comprehensive mechanistic model was developed to examine the effect of inhibition of renal secretion transporters on plasma exposures of victim drug.

This is principally similar to Rowland–Matin equation proposed for prediction of CYP-related DDIs.

The mechanistic model takes into consideration the importance of renal clearance relative to the total clearance of a victim and the variation of a perpetrator’s concentration to predict the change in AUC of the victim.
Mechanistic Model

\[
\frac{AUC_i}{AUC_c} = \frac{CL}{CL_i} = \frac{1 + \frac{CL_{sec,c}}{CL_x}}{1 + \frac{CL_{sec,c}}{CL_x} \times \frac{1}{1 + ([I]/K_i)}}
\]

\[
= \frac{1 - \frac{CL_{sec,c}}{CL}}{1 - \frac{CL_{sec,c}}{CL} \times \frac{([I]/K_i)}{1 + ([I]/K_i)}}
\]

Where CL and CLi are total systemic clearance in the absence and presence of inhibitory drug, respectively. CLsec,c represents secretory clearance in control. CLx represents nonsecretory clearance (CLx = CL – CLsec,c).
The mechanistic model predicted 7 of 13 (54%) cases within 25% and 12 of 13 (92%) cases within 50% of the observed AUC ratios with probenecid.

Feng, Mol. Pharmaceutics 2013
AUC Changes as a Function of $\text{CL}_{sec}/\text{CL}$ at various $[I]/Ki$

AUC change from renal DDI is dependent on renal secretion pathway and inhibitor potency.

Feng, Mol. Pharmaceutics 2013
Summary from In vitro In vivo Analysis of Renal DDI

• Cimetidine is not only a renal OCT2 inhibitor, but also a potent inhibitor of MATEs. Prediction of cimetidine DDIs need to consider both OCT2 and MATEs inhibitions.

• The extent of renal clearance change of the affected victim drug can be predicted from the \textit{in vitro} IC$_{50}$ of the inhibiting perpetrator drug and its unbound therapeutic concentrations in the plasma.

• Based on the positive relationship from \textit{in vitro in vivo} renal DDI analysis, it is confident to predict \textit{in vivo} renal DDIs based on \textit{in vivo} PK and \textit{in vitro} transporter interaction.
Conclusions

• If a NCE is identified as a substrate of renal transporters, its renal clearance reduction and AUC change with transporter inhibitors can be predicted with its human renal clearance and other PK parameters.

• If re-absorption process is involved in the renal clearance
  – Underestimate the contribution of active secretion in renal clearance
  – Underestimate renal clearance reduction in vivo.

• Many drugs may be handled by multiple transporters with overlapping substrate and inhibitor specificities.
  – The reduction of renal active secretion due to the inhibition of a transporter may be overestimated.

• The magnitude of AUC change caused by renal DDIs is dependent on the contribution of active secretion clearance in total clearance, as well as inhibitor potency compared with systemic concentration.
  – Clinical significant interactions occur only when the affected transporter represents the major pathway for overall elimination.
Conclusions (con’t)

• Because of the involvement of multiple renal processes including filtration, tubular secretion and tubular reabsorption in renal drug handling, and the functional redundancy of some renal drug transporters, sever clinical DDIs at the renal level seem to be not very common.

• However, clinical relevance of renal DDIs needs to be evaluated in the context of efficacy and safety profile of the affected drug.
  – Awareness of the possibility of transporter-mediated DDIs is necessary for drugs that are on the current market and for compounds in clinical development.

• To better predict transporter-mediated DDIs from in vitro data, the quantitative contribution of each individual transporter to the total drug clearance in vivo needs to be determined.
Outline

• Background of renal transporters.
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• Quantitative prediction of renal DDIs.
• A case study to predict renal DDIs.
• Renal transporter inhibition and elevated serum creatinine.
Case Study: Prediction of renal DDIs associated with OAT1 inhibition by Compound A

• Unchanged renal excretion is the major route of elimination for compound A in humans.
  • >90% of the dose was excreted unchanged in urine in clinical studies
• Transporter Inhibition.
  – No inhibition was observed up to 1000 μM for P-gp/BCRP/OAT3/OCT2/OATP1B1/OATP1B3
  – OAT1 Inhibition IC₅₀ = 281 μM
• Static DDI Estimation.
  • Clinical Plasma Concentrations
    • Loading Dose free Cₘₐₓ = 43 μM
    • Maintenance Dose Cₘₐₓ = 26 μM
  • Free Cₘₐₓ /IC₅₀
    • 0.15 (>0.1) based on loading dose
    • 0.09 based on maintenance dose
Predicted change in Renal clearance and plasma AUC of OAT1 substrate drugs when co-dosed with Probenecid

- **Probenecid** inhibit OAT1/3 and show maximum reported renal DDIs.
- A maximum AUCR of ~3 was predicted for nafcillin as victim drug, and cimetidine, furosemide and zidovudine show ~2, while majority of the interactions are predicted to be <2-fold.
- Mechanistic models were validated with the clinical data.
Predicted change in Renal clearance and plasma AUC of OAT1 substrate drugs when co-dosed with compound A

- In relation to DDIs noted with probe inhibitors (probenecid), compound A may show no impact on both the changes in plasma AUC and Renal CL of OAT1 substrates.

- A maximum AUCR of ~1.25 was predicted for nafcillin as victim drug, while majority of the interactions are predicted to be <10% change.

- The risk of OAT1-mediated interactions by compound A was predicted to be minimal.
**Prediction of Renal DDI by Compound A**

- Mechanistic renal DDI model predicts maximum interaction of ~25% AUC increase when co-administered compound A, while the majority of interactions with OAT1 substrates < 10% change.
  - OAT1 substrates, e.g., zidovudine, acyclovir, tenofovir, methotrexate, etc. are not common co-medications for the patient population.
  - OAT1 substrates are not narrow TI compounds, so no limitations to concomitant medication.
  - Magnitude of known OAT1 DDIs is small.
    - Probenecid OAT1 inhibitor- 3.6 x increase w/Cephradine, 1.5 x increase w/Cidofovir, 1.4 x increase w/Acyclovir, 2.9x increase in Furosemide (both OAT3 and OAT1)
- No Clinical OAT1 DDI studies are planned.
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• A case study to predict renal DDIs.
• Renal transporter inhibition and elevated serum creatinine.
Creatinine Interacts with Renal Transporters

Mathialagan, J Pharm Sci 2017
## Renal Transporter Inhibition and Free Cmax

<table>
<thead>
<tr>
<th>Inhibitors</th>
<th>$C_{\text{max},u}$ (µM)</th>
<th>$C_{\text{max},u}/IC_{50}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>hOCT2</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>3.9</td>
<td>0.151</td>
</tr>
<tr>
<td>Pyrimethamine</td>
<td>0.299</td>
<td>0.322</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>9.60</td>
<td>0.264</td>
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<tr>
<td>Cobicistat</td>
<td>0.05</td>
<td>0.005</td>
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<tr>
<td>Vandetanib</td>
<td>0.03</td>
<td>0.055</td>
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<tr>
<td>Dolutegravir</td>
<td>0.13</td>
<td>0.016</td>
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<td>Ranolazine</td>
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<td>Dronedarone</td>
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<td>Amiodarone</td>
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<tr>
<td>Ritonavir</td>
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<td>0.003</td>
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<tr>
<td>Telaprevir</td>
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<td>0.023</td>
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<td>Famotidine 40mgs</td>
<td>0.312</td>
<td>0.011</td>
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<tr>
<td>Ranitidine</td>
<td>3.16</td>
<td>1.311</td>
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<tr>
<td>Nizatidine</td>
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<td>0.522</td>
</tr>
<tr>
<td>Quinidine</td>
<td>0.52</td>
<td>0.033</td>
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Using free Cmax will generate false negatives and false positives
Renal Transporter Inhibition and **Total Cmax**

Using total Cmax will generate false positives

<table>
<thead>
<tr>
<th>Inhibitors</th>
<th>Total C&lt;sub&gt;max&lt;/sub&gt; (µM)</th>
<th>Total C&lt;sub&gt;max&lt;/sub&gt;/IC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>hOCT2</th>
<th>hMATE1</th>
<th>hOAT2</th>
<th>hMATE2K</th>
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</thead>
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<tr>
<td>Trimethoprim</td>
<td>6.9</td>
<td></td>
<td>0.267</td>
<td>4.259</td>
<td>0.069</td>
<td>11.897</td>
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<td>Pyrimethamine</td>
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<td>2.473</td>
<td>13.529</td>
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<td>6.571</td>
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<td>3.175</td>
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<td>1.269</td>
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<td>5.143</td>
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<td>0.052</td>
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<td>5.82</td>
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<td>0.222</td>
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<tr>
<td>Famotidine 40mgs</td>
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<td>0.014</td>
<td>1.444</td>
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<td>0.053</td>
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<td>0.664</td>
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<td>1.094</td>
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<td>0.809</td>
<td>2.731</td>
<td>0.178</td>
<td>0.127</td>
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<tr>
<td>Quinidine</td>
<td>4</td>
<td></td>
<td>0.256</td>
<td>0.202</td>
<td>0.018</td>
<td>0.506</td>
</tr>
</tbody>
</table>
Summary

- Creatinine was used as the common substrate to assess inhibition potency against renal OCT2, MATE1, MATE2K and OAT2 transporters.
- When $C_{\text{max}}/IC_{50} \geq 0.1$ is used as a cutoff, all of the 11 compounds with elevated serum creatinine can be attributed to the inhibition of at least one of the 4 renal transporters.
  - Unfortunately, the 4 negative controls without elevated serum creatinine also demonstrated inhibition of at least one renal transporter.
- Renal transporter inhibition studies are useful to rationalize the cases where elevated serum creatinine are observed in human.
  - Assessment of renal function marker other than creatinine is helpful.
- Although creatinine is a substrate of OAT2 in vitro, more in vivo data are needed to gain a better understanding of the role of OAT2 in creatinine renal secretion in vivo.
Acknowledgments

- Manthena Varma
- Yasong Lu
- Sumathy Mathialagan
- David Rodrigues