PBPK modeling of renal impairment – what is missing?

Aleksandra Galetin

Centre for Applied Pharmacokinetic Research, University of Manchester, UK
Outline of the presentation

- Physiological changes in renal impairment
- PBPK modelling of RI
  A. Nonrenally cleared drugs
  B. Renally eliminated drugs
    ▪ System data needed for mechanistic kidney models
    ▪ Drug-transporter interaction in renal impairment - digoxin example
Renal elimination of drugs

- Active uptake via OAT1/3, OCT2 paired with efflux transporters MRP2/4, MATEs
- Proximal tubule cells also express drug metabolising enzymes
- Reabsorption - generally passive, active reabsorption via OAT4, PEPT1/2
Integrated bottom up and top down approach for mechanistic prediction of $CL_R$

Prediction of renal tDDIs and nephrotoxicity

- Recent examples – cidofovir, rivaroxaban, metformin, lesinurad
  
- In vitro transporter kinetic data and certain system parameters still sparse

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Where we can expect PBPK modelling to inform drug labelling in the future?

- Large % of drug labels for FDA approved drugs in 2013-14 lack dose recommendations in RI

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Utility of Model Based Approaches for Informing Dosing Recommendations in Specific Populations: Report from the Public AAPS Workshop

Islam R. Younis, PhD\(^1\), J. Robert Powell, PharmD\(^2\), Amin Rostami -Hodjegan, PharmD, PhD\(^3\), Brian Corrigan, PhD\(^4\), Norman Stockbridge, MD, PhD\(^5\), Vikram Sinha, PhD\(^6\), Ping Zhao, PhD\(^1\), Pravin Jadhav, PhD, MPH\(^7\), Bruno Flamion, MD, PhD\(^8\), Jack Cook, PhD\(^4\)
Changes in system parameters in CKD

**KIDNEY**

1-5 ↓ CLR

↓ QR and kidney weight

↓ GFR
Stages 1-5: ≥ 90 to <15 mL/min/1.73m²

Changes in tubular surface area?

↓ Tubular secretion
  - ↓ Transporter expression/activity
  - Inhibitory effect of uremic solutes
  - ↓ Proximal tubule cell number

↓ Renal metabolism – UGT?

**LIVER**

2,6-8

↓ CLH for nonrenally cleared drugs
- Downregulation or inhibition of CYPs
- ↓ activity OATP (SN-38)
- ↓ UGT1A9, -2B7

**GI**

2

↑ Gastric emptying time
↑ pH
Expression of CYPs?

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1 FDA Renal impairment Guidance  
3 Nolin Am J Kidney Dis 2003  
4 Scotcher AAPS J 2016  
5 Hsueh Mol Pharm 2016  
6 Fujita Pharm Res 2014  
7 Zhao J Clin Pharmacol 2012  
Changes in plasma protein binding in CKD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Healthy</th>
<th>GFR &lt;30 mL/min/1.73m²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>44.9</td>
<td>41.8</td>
</tr>
<tr>
<td></td>
<td>37.6</td>
<td>35.0</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>43.0</td>
<td>38.0</td>
</tr>
<tr>
<td></td>
<td>39.7</td>
<td>33.2</td>
</tr>
</tbody>
</table>

- Other factors that may affect protein binding:
  - Conformational changes in albumin structure/binding sites
  - Competition for binding sites by uremic solutes
  - Limited data suggest elevated $\alpha$-acid glycoprotein

- Important to measure fu in RI population for highly bound drugs

\[ fu_i = \frac{1}{1 + \frac{(1-fu) \times [P]_i}{[P] \times fu}} \]

1 Rowland Yeo Expert Rev Clin Pharmacol 2011
Systematic evaluation of the CKD effect on CYPs

CYP2D6

- CYP2D6-mediated clearance decreased in parallel with the severity of CKD
- No apparent relationship between the severity of CKD and CYP3A4/5-clearance

Effect on CYP1A2, CYP2C8, CYP2C9 and CYP2C19 – Poster Tan et al.

Yoshida Clin Pharmacol Ther 2016
PBPK modelling of RI - nonrenal CYP-mediated clearance

- Retrospective analysis\(^1\) – repaglinide, telithromycin, slidenafil

- CYP abundance in RI extrapolated from clinical data

Bosutinib PBPK\(^2\)

- Step wise PBPK model development and verification

- RI Virtual population:
  i. Reduced GFR, kidney weight and Q\(_R\)
  ii. Reduced hepatic CYP3A4 expression
  iii. Reduced serum albumin and hematocrit

\(^1\)Zhao J Clin Pharmacol 2012 \(^2\)Ono DMD 2017
Effect of CKD on OATP

- Decrease in clearance in parallel with CKD severity

- Challenges:
  - Lack of binding data in RI subjects
  - Overlap between CYP2C8 and OATP drugs

Poster Tan et al. - ITCW and ASCPT PT-020
PBPK modelling of RI – renally eliminated drugs

System parameters for mechanistic kidney models - healthy vs. RI?
Tubular surface area – accounting for microvilli

Nephron tubule considered as a cylinder

\[ \text{Area} = 2\pi rh \times \text{number of nephrons} \]

Both PT cells and Caco-2 cells have extensive microvilli (apical membrane) - \( \uparrow \) surface area.

LoH, DT and CD cells - sparse/ negligible microvilli

\[ \text{CL}_{\text{R,int, reb,i}} = \text{P}_{\text{app}} \times \text{TSA}_i \]

Cortical Collecting Ducts formed by merging of app. 10 tubules (i.e. 900,000 nephrons/kidney → 90,000 CCD/kidney)

Inner Medulla Collecting Ducts undergo successive dichotomous fusions (i.e. 90,000 IMCD/kidney → 360 Ducts of Bellini/kidney)

No merging in Outer Medulla Collecting Ducts (i.e. 90,000 OMCD/kidney)

Tubular surface area - collecting duct requires special consideration!

\[ C_x = (d_0 \times NCD_0 \times \pi)e \left( \frac{x \times F}{n} \times \ln \left( \frac{2}{d_0 F} \right) \right) \]

Scotcher, Eur J Pharm Sci 2016
Minimal tubular reabsorption model

IVIVE – Scaling $P_{app}$ to $CL_{R,int}$

- pH gradient (6.5 - 7.4)
- Transporter inhibitor cocktail

$$CL_{R,int,i} = P_{app} \times TSA_i$$

Regional differences in TSA and tubular flow

Scotcher, Eur J Pharm Sci 2016
Performance of the mechanistic tubular reabsorption model – *in vivo* data from healthy

<table>
<thead>
<tr>
<th>gmfe (% predicted within 3-fold of observed)</th>
<th>Proximal tubule only</th>
<th>No correction for microvilli</th>
<th>Reabsorption model</th>
</tr>
</thead>
<tbody>
<tr>
<td>All drugs <em>(n = 45)</em></td>
<td>2.17 (76%)</td>
<td>5.35 (27%)</td>
<td>1.96 (87%)</td>
</tr>
<tr>
<td>Low $F_{reab}$ <em>(n = 17)</em></td>
<td>1.59 (94%)</td>
<td>5.02 (35%)</td>
<td>1.97 (88%)</td>
</tr>
<tr>
<td>Medium $F_{reab}$ <em>(n = 12)</em></td>
<td>1.44 (92%)</td>
<td>8.52 (17%)</td>
<td>1.90 (92%)</td>
</tr>
<tr>
<td>High $F_{reab}$ <em>(n = 16)</em></td>
<td>4.11 (44%)</td>
<td>4.03 (25%)</td>
<td>2.01 (81%)</td>
</tr>
</tbody>
</table>

- Proximal tubule can be used as surrogate for low-med $F_{reab}$ (<75%)
- Consideration of correct tubular surface area of key relevance
In vitro-in vivo extrapolation of active renal secretion

Increasing system complexity

- Transfected cells: HEK, HeLa
- Immortalised cells: LLC-PK1, ciPTEC, HK-2
- Primary cultured renal tubule cells
- Kidney slices
- Kidney-on-a-chip

Scaling of kinetic parameters

- REF ($V_{\text{max}} / CL_{\text{int}}$)
- ft ($IC_{50}/Ki$)

Tubular surface area ($P_{\text{app}}$)

Proximal tubule cell number

($V_{\text{max}} / CL_{\text{int}}$)

30 – 209 million PTC/ g kidney

Kidney weight ($CL_{\text{int}}$)

PBPK model

Scotcher et al, AAPS J, part I 2016
Implementation of transporter expression data in PBPK models

Relative expression factor =

\[ \text{OAT3 expression}_{\text{in vivo}} / \text{OAT3 expression}_{\text{in vitro}} \]

- Emerging proteomic data for renal transporters/UGTs
- Missing data:
  - Large cohort of individuals and special populations
  - Regional and species differences
  - Expression vs. functional activity
- Current REFs – estimated using plasma or urinary excretion data
  - 5.3 - HEK-OAT3 (pemetrexed)
  - 2.3 - HEK-OCT2 (metformin)
  - 3 - HEK-MATE1 (metformin)

Scotcher AAPS J 2016 Part II; Prasad Drug Metab Dispos 2016; Knights Br J Clin Pharmacol 2016; Posada Drug Metab Dispos 2015; Burt EJPS 2016
### Renal PBPK models – special populations

<table>
<thead>
<tr>
<th>System Parameters</th>
<th>Young adults</th>
<th>Paediatrics</th>
<th>Elderly</th>
<th>Renal impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney weight/volume</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Renal blood flow</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>GFR</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Nephron number</td>
<td>✔️ Highly variable</td>
<td>✔️ No change after birth</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>Regional tubule length/ diameter</td>
<td>✔️ Variability within and between studies</td>
<td>❌ Proximal tubule only (1 study)</td>
<td>✔️ Mainly proximal tubule</td>
<td>❌ Limited reports (qualitative)</td>
</tr>
<tr>
<td>PTCPGK</td>
<td>❌ Rat data only</td>
<td>❌</td>
<td>❌ Limited reports (qualitative)</td>
<td>❌ Limited reports (qualitative)</td>
</tr>
<tr>
<td>Transporter abundance *</td>
<td>❌ 1 study human (pooled HKM)</td>
<td>❌ Mouse/ rat data</td>
<td>❌</td>
<td>❌ Limited rat data</td>
</tr>
</tbody>
</table>

Data available (quantitative, human) | Limited or conflicting data

Scotcher et al AAPS J 2016
Mechanistic digoxin kidney model: prediction of $\text{CL}_R$ in moderate to severe renal impairment

- Existing PBPK model for digoxin incorporates transport by P-gp in liver and intestine (Neuhoff et al, J Pharm Sci, 2013)
- Consider role of P-gp and OATP4C1 (uptake) in kidney
- Availability of clinical data in healthy, elderly and different stages of RI
Development, verification and application of digoxin mechanistic kidney model

Model development

- Glomerular filtration
- \( CL_{PD} \)
- Transporter kinetics

Model verification

- Simulated vs. observed digoxin plasma concentration- and urinary excretion-time profiles

Model application

- Elderly
- Renal impairment

Scotcher et al, JPET 2017
Mechanistic digoxin kidney model: prediction of CL\textsubscript{R} in renal impairment

Scenarios tested in digoxin model:

1. Reduction in GFR alone

2. Modification of both GFR and active secretion
   a. ↓OATP4C1 expression per million proximal tubule cells*
   b. ↓P-gp expression per million proximal tubule cells*
   c. ↓proximal tubule cellularity (PTCPGK)
   d. ↓OATP4C1 expression or proximal tubule cellularity proportional to changes in GFR

* Reflects also ↓transporter activity due to inhibition by uremic solutes

Scotcher et al, JPET 2017, ASCPT – Quantitative Pharmacology, PII-122
Prediction of digoxin $\text{CLR}_R$ in moderate to severe renal impairment – reduction in GFR

Assumption:
- NO changes in active secretion in renal impairment

Over-estimation of $\text{CLR}_R$ in RI

Scotcher et al, JPET 2017
Mechanistic digoxin kidney model: prediction of $\text{CL}_R$ in severe renal impairment

Additional mechanisms considered: i) ↓ transporter expression or ii) ↓ number of tubular cells

\[
\text{CL}_R \text{ ratio} = \frac{\text{CL}_R (\text{renal impairment})}{\text{CL}_R (\text{healthy subjects})}
\]

Change in GFR only (severe renal impairment; GFR = 15 – 30 mL/ min)
Mechanistic kidney model for digoxin: renal impairment

- OATP4C1 abundance and PTCPGK parameters changed proportionally to the change in GFR from the population representative

Scotcher et al, JPET 2017
Take home message

- Assumption that secretion does not change in renal impairment over-estimated digoxin CL$_R$

- Different mechanisms considered for active secretion in RI-PBPK model
  - Comparable NET effect on the predicted systemic exposure and CL$_R$
  - Predicted dynamics inside proximal tubule cells different – implications for nephrotoxicity or transporter-mediated DDIs

- Integrated bottom up-top down approaches important for step-wise RI-PBPK model development and verification
  - Enhanced clinical trial design/adequate clinical data
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