PBPK modeling of renal impairment – what is missing?

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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 $\text{CL}_R$

Prediction of renal tDDIs and nephrotoxicity

- Recent examples – cidofovir, rivaroxaban, metformin, lesinurad\textsuperscript{1-3}
- \textit{In vitro} transporter kinetic data and certain system parameters still sparse\textsuperscript{4}

\textsuperscript{1}Hsu Clin Pharmacokinet 2014, \textsuperscript{2}Grillo BDD 2012, \textsuperscript{3}Burt EJPS 2016, \textsuperscript{4}Scotcher AAPS J 2016
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

Information Availability
Utility of Model Based Approaches for Informing Dosing Recommendations in Specific Populations:
- Report from the Public AAPS Workshop
- Islam R. Younis, PhD, J. Robert Powell, PharmD, Amin Rostami-Hodjegan, PharmD, PhD, Brian Corrigan, PhD, Norman Stockbridge, MD, PhD, Vikram Sinha, PhD, Ping Zhao, PhD, Pravin Jadhav, PhD, MPH, Bruno Flamion, MD, PhD, Jack Cook, PhD

Jadhav J Clin Pharmacol 2015
Younis J Clin Pharmacol 2016
Changes in system parameters in CKD

**KIDNEY**

1-5 \( \downarrow \) CL\(_R\)

\( \downarrow \) Q\(_R\) and kidney weight

\( \downarrow \) GFR
Stages 1-5: \( \geq 90 \text{ to } <15 \text{ mL/min/1.73m}^2 \)

Changes in tubular surface area?

\( \downarrow \) Tubular secretion
  - \( \downarrow \) Transporter expression/activity
  - Inhibitory effect of uremic solutes
  - \( \downarrow \) Proximal tubule cell number

\( \downarrow \) Renal metabolism – UGT?

**LIVER**

2,6-8

\( \downarrow \) CL\(_H\) for nonrenally cleared drugs

- Downregulation or inhibition of CYPs
- \( \downarrow \) activity OATP (SN-38)
- \( \downarrow \) UGT1A9, -2B7

**GI**

2

- \( \uparrow \) Gastric emptying time
- \( \uparrow \) pH
- Expression of CYPs?

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

- 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, sildenafil
- 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

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

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

LoH, DT and CD cells - sparse/negligible microvilli

\[
(\text{mL/min}) \quad \text{CL}_{R,\text{int,reat},i} = (\text{cm/min}) \quad P_{\text{app}} \times (\text{cm}^2) \quad \text{TSA}_i
\]


Tubular surface area - collecting duct requires special consideration!

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

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

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

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

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
### Performance of the mechanistic tubular reabsorption model – *in vivo* data from healthy

*gmfe (% predicted within 3-fold of observed)*

<table>
<thead>
<tr>
<th></th>
<th>Proximal tubule only</th>
<th>No correction for microvilli</th>
<th>Reabsorption model</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All drugs</strong> (n = 45)</td>
<td>2.17 (76%)</td>
<td>5.35 (27%)</td>
<td>1.96 (87%)</td>
</tr>
<tr>
<td><strong>Low F_{reab}</strong> (n = 17)</td>
<td>1.59 (94%)</td>
<td>5.02 (35%)</td>
<td>1.97 (88%)</td>
</tr>
<tr>
<td><strong>Medium F_{reab}</strong> (n=12)</td>
<td>1.44 (92%)</td>
<td>8.52 (17%)</td>
<td>1.90 (92%)</td>
</tr>
<tr>
<td><strong>High F_{reab}</strong> (n = 16)</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

**Scaling of kinetic parameters**

- REF \( \frac{V_{\text{max}}}{\text{CL}_{\text{int}}} \)
- ft \( \text{IC}_{50}/\text{Ki} \)

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

**Proximal tubule cell number**
\( \frac{V_{\text{max}}}{\text{CL}_{\text{int}}} \)
30 – 209 million PTC/ g kidney

**Kidney weight** \( (\text{CL}_{\text{int}}) \)

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Transfected cells
- HEK, HeLa

Immortalised cells
- LLC-PK1, ciPTEC, HK-2

Primary cultured renal tubule cells

Kidney slices

Kidney-on-a-chip

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

Relative expression factor =

OAT3 expression \textit{in vivo} / OAT3 expression \textit{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><strong>Kidney weight/ volume</strong></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td><strong>Renal blood flow</strong></td>
<td>✔</td>
<td>✔</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GFR</strong></td>
<td>✔</td>
<td>✔</td>
<td>Inter-study variability</td>
<td>✔</td>
</tr>
<tr>
<td><strong>Nephron number</strong></td>
<td>✔</td>
<td>No change after birth</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td><strong>Regional tubule length/ diameter</strong></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><strong>PTCPGK</strong></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) 1 study rat</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 $CL_R$ 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**
  - Calculated using Cockcroft-Gault eq. from serum creatinine
  - $f_{u,p}$ from meta-analysis of reported data

- **$CL_{PD}$**
  - Same value for all tubular regions

- **Transporter kinetics**
  1. IVIVE
     - P-gp – in vitro $K_m$ and $V_{max}$, REF
     - OATP4C1 – not successful
  2. OATP4C1 $CL_{int,T}$ estimated using clinical $CL_R$ data
     - (19 clinical studies, 214 healthy subjects)

**Model verification**

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

**Model application**

- Elderly
- Renal impairment

Scotcher et al, JPET 2017
Digoxin mechanistic kidney model verification

A

B

C

D

E

F

Plasma concentration

Urinary excretion rate
Mechanistic digoxin kidney model: prediction of $\text{CL}_R$ in renal impairment

Scenarios tested in digoxin model:

1. Reduction in GFR alone

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

* Reflects also $\downarrow$ transporter activity due to inhibition by uremic solutes

Scotcher et al, JPET 2017, ASCPT – Quantitative Pharmacology, PII-122
Prediction of digoxin $CL_R$ in moderate to severe renal impairment – reduction in GFR

Assumption:
- NO changes in active secretion in renal impairment

Over-estimation of $CL_R$ 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

![Graph showing CL ratio changes](image)

Change in GFR only
(severe renal impairment; GFR = 15 – 30 mL/ min)

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

- Different mechanisms considered for active secretion in RI-PBPK model
  - Comparable NET effect on the predicted systemic exposure and CLR
  - 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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