Physiologically Based Pharmacokinetic (PBPK) Modeling to Support Dosing Recommendations for Patients with Renal Impairment: Effects on Non-Renal Clearance

Stephen D. Hall
Eli Lilly and Co.
and
IQ Organ Impairment Working Group
IQ Organ Impairment Working Group

Goal: To evaluate the capability of existing PBPK models to predict the changes in drug PK in renal and hepatic impairment

1. ABBVIE  Mohamad Shebley
2. AMGEN  Vijay Upreti
3. ASTRAZENECA  Pradeep Sharma
4. BMS  Ming Zheng
5. Eisai  Vaishali Dixit
6. Genentech  Yuan Chen
7. GSK  Guoying Tai
8. J&J  Italo Pogessi
9. J&J  Jan Snoeys
10. Lilly  Stephen Hall
11. Merck  Ying-Hong Wang
12. Merck Serono  Sheila-Annie Peters
13. Novartis  Tycho Heimbach
14. Pfizer  Hugh Barton
15. Roche  Meret Martin-Facklam
16. Roche  Neil Parrott
17. Sanofi  Jun Chen
18. Takeda  Andy Zhu
19. Vertex  Shu-Pei Wu
Rate of Renal Excretion = Rate of Glomerular Filtration + Rate of Active Secretion - Rate of Reabsorption

Nephron

http://medcell.med.yale.edu/histology/urinary_system_lab.php

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Estimated GFR(^b) (ml/min/1.73 m(^2))</th>
<th>Estimated creatinine clearance(^c) (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Control (normal GFR)</td>
<td>(\geq 90)</td>
<td>(\geq 90)</td>
</tr>
<tr>
<td>2</td>
<td>Mild decrease in GFR</td>
<td>60–89</td>
<td>60–89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate decrease in GFR</td>
<td>30–59</td>
<td>30–59</td>
</tr>
<tr>
<td>4</td>
<td>Severe decrease in GFR</td>
<td>15–29</td>
<td>15–29</td>
</tr>
<tr>
<td>5</td>
<td>End-stage renal disease</td>
<td>(&lt;15), either not on dialysis or requiring dialysis</td>
<td>(&lt;15), either not on dialysis or requiring dialysis</td>
</tr>
</tbody>
</table>

GFR, glomerular filtration rate.

\(^a\)Stages of renal impairment are based on National Kidney Foundation KDOQI Clinical Practice Guidelines for Chronic Kidney Disease (http://www.kidney.org/Professionals/Kdqi/guidelines_ckd/toc.htm), 2002.\(^b\)Based on the Modification of Diet in Renal Disease study equation.\(^c\)Based on the Cockcroft–Gault equation.
Changes in Renal Insufficiency that May Alter Drug Exposure

- Reduced glomerular filtration and/or tubular secretion
- Increased α-acidic glycoprotein (AAG)
- Accumulation of uremia substances:
  - displacement of drugs bound to albumin
  - inhibition of transporters and enzymes
  - down-regulation of liver enzymes (inflammation?)
- Futile cycling of acyl glucuronides e.g. ketoprofen
- Reduced renal metabolism e.g. morphine glucuronidation
- Reduced hematocrit
- Reduced gastric emptying rate
Six oral NME drugs that are cleared mainly by drug metabolism and/or transport whose pharmacokinetics showed renal impairment effect that resulted in dosage adjustment

<table>
<thead>
<tr>
<th>Drug</th>
<th>ADME</th>
<th>Major enzymes/transporters</th>
<th>Effect of severe renal impairment on pharmacokinetics</th>
<th>Dosage adjustment in DOSAGE AND ADMINISTRATION section of the labeling</th>
</tr>
</thead>
</table>
| Duloxetine    | fe < 1% F > 80% | CYP1A2 and CYP2D6                                                                     | $C_{\text{max}} \uparrow 100\%$  
AUC $\uparrow 100\%$  
AUCs of the major circulating metabolites $\uparrow$ seven- to ninefold (in patients with ESRD receiving chronic intermittent hemodialysis) | Not recommended for patients with ESRD or severe renal impairment (estimated creatinine clearance ($CL_{\text{cr}}$) < 30 ml/min) |
| Tadalafil     | fe < 0.3% | Predominantly metabolized by CYP3A4 on extensively metabolized (~10%) CYP2C9       | $C_{\text{max}} \uparrow$ twofold  
AUC $\uparrow$ 2.7- to 4.1-fold (in subjects with ESRD on hemodialysis)                                                 | The maximum recommended dose is 5 mg not more than once in every 72 h in severe renal impairment           |
| Rosuvastatin  | fe = 6% F = 20% | OATP1B1  
Not extensively metabolized (~10%) CYP2C9                                           | Plasma concentrations $\uparrow$ threefold (in ESRD patients ($CL_{\text{cr}} < 30 \text{ ml/min}$)  
compared with healthy subjects ($CL_{\text{cr}} > 80 \text{ ml/min}$))  
Steady-state plasma concentrations 50% $\uparrow$ (in patients on chronic hemodialysis  
compared with healthy volunteer subjects with normal renal function) | For patients with severe renal impairment ($CL_{\text{cr}} < 30 \text{ ml/min}$) not on hemodialysis, dosing of  
rosuvastatin should be started at 5 mg once daily and not exceed 10 mg once daily |
| Telithromycin | fe = 13% F = 57% | 50% of its metabolism is mediated by CYP3A4 and the remaining 50% is cytochrome P450-independent | $C_{\text{max}} \uparrow$ 1.4-fold  
AUC $\uparrow$ 1.9-fold (in ESRD patients with $CL_{\text{cr}} < 30 \text{ ml/min}$, including patients who need dialysis, the dose should be reduced to 600 mg q.d. In the presence of severe renal impairment ($CL_{\text{cr}} < 30 \text{ ml/min}$), with coexisting hepatic impairment, the dose should be reduced to 400 mg q.d.) | In the presence of severe renal impairment ($CL_{\text{cr}} < 30 \text{ ml/min}$), including patients who need dialysis, the dose should be reduced to 600 mg q.d. In the presence of severe renal impairment ($CL_{\text{cr}} < 30 \text{ ml/min}$), with coexisting hepatic impairment, the dose should be reduced to 400 mg q.d. |
| Solifenacin    | fe < 15% F = 90% | CYP3A4                                                                                   | $C_{\text{max}} \uparrow$ 1.2-fold  
AUC $\uparrow$ 2.1-fold  
$T_{1/2} \uparrow$ 1.6-fold (in ESRD patients with $CL_{\text{cr}} < 30 \text{ ml/min}$, a daily dose of > 5 mg is not recommended) | For patients with severe renal impairment ($CL_{\text{cr}} < 30 \text{ ml/min}$), a daily dose of > 5 mg is not recommended |
| Tinidazole    | fe = 20–25% | ~40% metabolism by CYP3A4                                                               | No change in severe renal impairment patients not on dialysis; In presence of hemodialysis, clearance was significantly increased; $T_{1/2}$ reduced from 12 to 4.9 h; Approximately 43% of amount present in body was eliminated during a 6-h hemodialysis | If tinidazole is administered on the same day as and prior to hemodialysis, it is recommended that an additional dose of tinidazole equivalent to one-half of the recommended dose be administered after the end of the hemodialysis |

**ADME:** absorption, distribution, metabolism, and excretion  
**AUC:** area under the plasma concentration–time curve  
**$C_{\text{max}}$: peak plasma concentration  
**ESRD:** end-stage renal disease  
**fe:** percentage of drugs excreted unchanged in the urine  
**F:** absolute oral bioavailability  

Theoretical lowest R_CL < 1

Systematic and quantitative assessment of the effect of chronic kidney disease on CYP2D6 and CYP3A4/5

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Yoshida et al., Clin Pharmacol Ther 2016
FDA Guidance (2010)

A PK study should be conducted in patients with impaired renal function when the drug is likely to be used in such patients and when renal impairment is likely to mechanistically alter the PK of the drug and/or its active metabolites. This would most obviously be the case if the drug or a principal active metabolite is substantially eliminated renally (i.e., if the fraction of dose excreted unchanged in the urine is at least 30%), but it can also be the case if a drug is primarily metabolized or secreted in bile, because renal impairment can inhibit some pathways of hepatic and gut drug metabolism and transport. Therefore, a PK study in patients with renal impairment should be conducted for most drugs intended for chronic use.

EMA Guideline (2014)

A pharmacokinetic study in patients with decreased renal function should be conducted for most small-molecule drugs that are intended for repeated administration or continuous infusion, also when the drug/major active metabolite is not primarily eliminated by the kidneys.

5.7. Physiologically-based pharmacokinetic modelling (PBPK)

At time of revision of this guideline, the experience of using PBPK to predict the effect of decreased renal elimination capacity on drug elimination is limited. However, the field of PBPK is evolving and it is foreseen that PBPK modelling may become useful for predicting effects of decreased renal elimination capacity on drug disposition, in particular for drugs that are predominantly renally eliminated. When more knowledge on the effect of renal impairment on e.g. drug metabolism, transport and protein binding has been gained, it may become possible to use PBPK also for non-renally eliminated drugs.
Motivation to Model RI Studies

- Rationalize need, timing and design of resource intensive renal insufficiency studies.

- Fill in gaps when recruitment is incomplete.

- Predict how combinations of disease and other covariates would influence exposure.

- Particularly useful in oncology settings.

- Extend the insight gained from studies that have poor representation of some patient subsets.

- Can inform safety of P1/P2/P3 when patient data not available.
The tissues and organs of the body are arranged anatomically and connected via the vascular system, with Q denoting blood flow (Rowland et al., AAPSPharmSci 6:1-12, 2004).

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<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>GFR (ml/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>30–59</td>
</tr>
<tr>
<td>CYP1A2 (pmol/mg)</td>
<td>52 [58]</td>
<td>33 [63,129–131]</td>
</tr>
<tr>
<td>CYP2C8 (pmol/mg)</td>
<td>24 [58]</td>
<td>20 [64]</td>
</tr>
<tr>
<td>CYP2C9 (pmol/mg)</td>
<td>73 [58]</td>
<td>63 [65]</td>
</tr>
<tr>
<td>CYP2C19 (pmol/mg)</td>
<td>14 [58]</td>
<td>5.5 [66]</td>
</tr>
<tr>
<td>CYP2D6 (pmol/mg)</td>
<td>8.0 [58]</td>
<td>4.6 [67,132,133]</td>
</tr>
<tr>
<td>CYP3A4 (pmol/mg)</td>
<td>137 [58]</td>
<td>73 [68,134,135]</td>
</tr>
<tr>
<td>Albumin (g.l⁻¹) M</td>
<td>44.9 [205]</td>
<td>41.6 [136,137,205]</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>41.8 [205]</td>
</tr>
<tr>
<td>Hematocrit (%) M</td>
<td>43.0 [43]</td>
<td>39.7 [43]</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>38.0 [43]</td>
</tr>
<tr>
<td>Gastric emptying time (h)</td>
<td>0.40 [35]</td>
<td>0.55 [19]</td>
</tr>
</tbody>
</table>

F: Female; GFR: Glomerular filtration rate; M: Male.
Verification of Simcyp (v12) Renal Impairment Population for CYP2D6

Figure 1. Predicted and observed fold-increases in exposure ($C_{\text{max}}$ and AUC) after a single 30 mg dose of paroxetine in subjects with differing degrees of renal impairment (glomerular filtration rate <30 ml/min/1.73 m² and 30–59 ml/min/1.73 m²) relative to healthy volunteers based on the study design described by Doyle et al. [99].

Performance Verification – Oral Midazolam (2 mg)

Subjects from clinical study had ESRD (CrCL ~ 12 ml/min)
Simcyp Severe RI (CrCL<30 ml/min)

<table>
<thead>
<tr>
<th>Total</th>
<th>Unbound</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CL_{po} (L/h)</td>
</tr>
<tr>
<td></td>
<td>Predicted</td>
</tr>
<tr>
<td>Healthy</td>
<td>104.8</td>
</tr>
<tr>
<td>Severe RI</td>
<td>105.3</td>
</tr>
<tr>
<td>RI/Healthy</td>
<td>1.0</td>
</tr>
<tr>
<td>cf AUC</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Measured fu=0.039 in healthy subjects
Measured fu=0.065 in RI subjects (increased)
Observed fu ratio= 1.7 (predicted = 1.3)

Nolin et al., 2009
IQ Working Group Study Design

- Used the moderate and severe renal impairment populations in V15 of the Simcyp Simulator. Created a mild renal impairment group by setting creatinine clearance to 60–90 ml/min but unchanged CYP abundance.

- Match the control group to the age, weight, sex, ethnicity, genetics, extrinsic factors of the RI groups where possible.

- Select molecules not used in the construction of the Simcyp RI population. Focus on molecules not highly dependent on renal excretion.

- Account for protein binding changes by using measured or predicted fup in RI.

- Each company builds and verifies a Simcyp compound file in a non RI control group using company confidential studies such as radiolabel mass balance, bioavailability, DDIs, genetic polymorphisms.

- Each company predicts PK parameters in RI groups where observed data already exists.

- Observed and predicted PK parameters were submitted to IQ and anonymized. Only group level data was acceptable.
Relationship Between Predicted and Observed AUC for Control and Mild, Moderate and Severe RI for 20 Compounds

- **Observed AUC (ng*hr/ml)**
- **Predicted AUC**

Ratio P/O:
- 0.8-1.25 (56%)
- 0.5-0.8/1.25-2.0 (32%)

**AUC Ratio RI/Control**
- Mild: 0.8-1.25
- Moderate: 0.5-0.8/1.25-2.0
- Severe: 0.8-1.25

**Observed**

**Predicted**

N=57
Predicted vs Observed Ratios of Renal Impaired AUC to Healthy Control AUC

N=36

- Ratio 0.5-0.8/1.25-2: 36%
- Ratio 0.8-1.25: 47%

N=19

- Ratio 0.5-0.8/1.25-2: 36%
- Ratio 0.8-1.25: 47%

Mild, Moderate, Severe Renal Impairment

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Association of AUC Ratio Severe (RI / Control) with Major Clearance Pathways

- 100% Hepatic
- 95% CYP3A4; 2% Renal
- 90% CYP3A4
- 80% CYP1A2; 6% Renal
- 75% CYP2D6; 25% other hepatic met
- 85% UGT; 15% CYP3A4
- 80% CYP1A2; 20% CYP2D6
- 53% CYP3A4; 17% CYP2C19; 30% Renal
- 56% CYP3A4; 32% Biliary P-GP; Renal 11%
- 85% CYP2D6; 15% CYP1A2
- 70% CYP3A4; 30% CYP2C19
- 57% CYP1A2; 27% UGT; 8% CYP2C8; 7% UN
- 68% CYP3A4; Renal 16%; Biliary/Fecal 16%
- 53% Renal; 28% Hepatic; 19% Hydrolysis
- 45% Renal; 25% UGT; 10% CYP3A4
- 90% Hepatic

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Predicted vs Observed Ratios of Renal Impaired Cmax to Healthy Control Cmax

Predicted Cmax Ratio vs Observed Cmax Ratio

Cmax All RI

Predicted Cmax Ratio

N=32

Cmax Severe RI

Predicted Cmax Ratio

N=18

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Ratio 0.5-0.8/1.25-2.0

33%

Ratio 0.8-1.25

50%

Ratio 0.8-1.25

63%
Relationship Between Predicted and Observed Fraction Unbound in Plasma (fup)

- Ratio P/O 0.5-0.8/1.25-2.0
- Ratio P/O 0.8-1.25 68%

All Renal Impairment
N=37

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Relationship Between Cmax Ratio (Severe RI / Control) and AUC Ratio (Severe / Control)

N=19

Line of unity; solid line: 0.5 to 2.0 boundary; dashed lines
RI May Result in Increased Cmax and AUC Without a Change in t1/2

Duloxetine

- Patients with ESRD
- Healthy subjects

Plasma Duloxetine Concentration (ng/ml)

Mean, n=12

Olanzapine

- Severe RI
- Healthy

Olanzapine Plasma Concentration (ng/mL)

Mean (SE), n=6

Lobo et al., Clin Pharmacokinet 47: 191, 2008

Callaghan et al., Clin Pharmacokinet 37:177, 1999
Simcyp (v15) Predicted Effect of RI on the PK (reduced CYP)

Duloxetine

Olanzapine
Active Hepatic Uptake

Elimination:

\[
CL_{int} = \frac{(PS_{inf,act,B} + PS_{inf,pass,B}) \cdot (PS_{eff,act,A} + CL_{int,met})}{PS_{eff,act,A} + CL_{int,met} + PS_{eff,pass,B}}
\]

\[
CL_H = \frac{f_w \cdot CL_{int} \cdot Q}{f_w \cdot CL_{int} + Q}
\]

Distribution:

\[
Kpuu = \frac{PS_{inf,act,B} + PS_{inf,pass,B}}{PS_{eff,act,A} + CL_{int,met} + PS_{eff,pass,B}}
\]

\[
Vd,ss = Vp + V_T \cdot Kpuu \cdot Kpp
\]

\[
Kpuu = \frac{Cu,cell}{Cu,plasma}
\]

\[
Kpp = \frac{Ccell}{Cplasma} \text{ when } Kpuu \text{ is unity i.e. perfusion rate limited}
\]

Reduced \( CL_{int,met} \) reduces \( CL_H \) but increases \( Vd,ss \):
Increased AUC, increased t1/2

Reduced \( PS_{inf,act,B} \) reduces \( CL_H \) but reduces \( Vd,ss \):
Increased Cmax, t1/2 unchanged
Summary

- RI can cause decreases in clearance of drugs that are primarily eliminated by metabolism.

- The magnitude of the changes are modest but can be clinically significant: Observed AUC RI/Control was **1.2, 1.7 and 1.7 for mild, moderate and severe** respectively. For 25% of molecules the observed AUC ratio was 0.8 to 1.25 in severe RI.

- The prediction of these effects by Simcyp is reasonable and exceeded the observed by 0.5 to 2-fold only for one molecule in severe RI.

- Protein binding changes can be important but cannot be predicted without quantifying HSA and AAG contributions.

- The mechanistic basis for the effects are unlikely to reflect only reduced CYP abundance.

- A quantification of the reductions in transporter activity and the contribution of transport to drug clearance and volume distribution are required to progress to more accurate predictions.
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