Experience In Using PBPK Models in Clinical Pharmacology Reviews

Ping Zhao, PhD

Office of Clinical Pharmacology
Office of Translational Sciences
Center for Drug Evaluation and Research Food and Drug Administration

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The Views expressed in this presentation do not reflect the official policy of the FDA
Outline

- Why PBPK
- Application of PBPK in clinical pharmacology review
Physiologically-based Pharmacokinetic models (PBPK)

The model

Effect of absorption kinetics

Teorell, Arch Intern Pharmacodym, 1937

History: One of the Earliest PK Models “Was a PBPK Model”
Increased Interest in Using PBPK


From the Office of Clinical Pharmacology, FDA--


Can Model Provide Desired Insights?

1-Compartmental PK

Oral Dose

\[ C_a, V_a \]

\[ K_a \]

\[ C, V \]

\[ CL_h + CL_r \]

\[ V \cdot \frac{dC}{dt} = K_a \cdot V_a \cdot C_a - (CL_h + CL_r) \cdot C \]

\[ V_a \cdot \frac{dC_a}{dt} = -K_a \cdot V_a \cdot C_a \]

System component (drug-independent)

Drug-dependent component

ADME, PK, PD and MOA

Metabolism
Active transport
Passive diffusion
Protein binding
Drug-drug interactions
Receptor binding

PBPK Model

Blood

Lung

Rapidly perfused organs

Slowly perfused organs

Kidney

Liver

Intestines

Blood

Dosing

Elimination

\[ C = \frac{K_a \cdot \text{Dose}}{V \cdot (K_a - \frac{CL_h + CL_r}{V})} \cdot (e^{-\frac{(CL_h + CL_r) \cdot t}{V}} - e^{-K_a \cdot t}) \]

\[ C_{\text{plasma}} \]

\[ C_{\text{liver}} \]

\[ C_{\text{kidney}} \]

\[ C_{\text{muscle}} \ldots \ldots \]

And…
Blood
Lung
Rapidly perfused organs
Slowly perfused organs
Kidney
Liver
Intestines

PBPK: Systems Clinical Pharmacology

Other rapidly perfused organs
Heart
Clinical Pharmacology

- Central role: to assess PKPD in specific patient groups

- To make more informed decision on drug dosing

- To guide our decisions:
  - In theory, all situations can be tested clinically. However, ethical and practical issues may limit the numbers of studies one can conduct
  - Can some situations be predicted using current knowledge?

Huang and Temple, Clin Pharmcol Ther, 2007
A. Patient Factors

Intrinsic factors
Extrinsic factors

B. PBPK Model components

System component (drug-independent)

Drug-dependent component

Physiology
Anatomy
Biology

PBPK Model

Drug disposition
Drug action

Predict, Learn, Confirm

Huang and Temple, 2008

Adapted from Zhao P, et al Clin Pharmacol Ther 2011
Outline

- Why PBPK
- Application of PBPK in clinical pharmacology review
Investigational drug

- is a substrate of CYP3A4 AND (polymorphic) CYP2D6, what exposure change can be expected when a moderate CYP3A4 inhibitor is used in CYP2D6 PM?

- is renally AND hepatically cleared, what exposure change can be expected when a CYP inhibitor is used in patients with decreased renal function?

- forms an active/toxic metabolite whose exposure was increased in subjects with renal impairment, what are the effect of renal impairment AND drug interactions on the exposure of this metabolite?

- has dose- and time- dependent PK, what is its potential as an enzyme inhibitor?

How much do we know about the compound
DDI Prediction

Interacting drug

ADME, PK, PD and MOA
Metabolism
Active transport
Passive diffusion
Protein binding
Drug-drug interactions
Receptor binding

PBPK Model: Interacting Drug

Parameters can be altered by DDI
Extrapolating effect of CYP2D6 PM + CYP3A4 moderate inhibitor when data on PGx with strong inhibitor are available

<table>
<thead>
<tr>
<th>Observed</th>
<th>Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUCR</td>
</tr>
<tr>
<td>EM +/- Ketoconazole</td>
<td>2.3 [a]</td>
</tr>
<tr>
<td>PM +/- Ketoconazole</td>
<td>2.5 [a]</td>
</tr>
<tr>
<td>PM / EM</td>
<td>2.3</td>
</tr>
<tr>
<td>PM + Keto / EM</td>
<td>5.7 [a]</td>
</tr>
<tr>
<td>EM +/- Fluconazole</td>
<td>1.3 [b]</td>
</tr>
<tr>
<td>PM + Fluconazole / EM</td>
<td>-</td>
</tr>
</tbody>
</table>

Fesoterodine case
Polymorphic vs Non-polymorphic enzyme ~ 1:1

Each contributes > 25% CLs
Question #1 for Audience, with available clinical data, can PM + fluconazole be predicted?

No. Clinical study should be conducted
Yes. Prediction can be used to design clinical study
Yes. Clinical study is not necessary

<table>
<thead>
<tr>
<th></th>
<th>Observed</th>
<th>Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUCR</td>
<td>CmaxR</td>
</tr>
<tr>
<td>EM +/- Ketoconazole</td>
<td>2.3  [a]</td>
<td>2.0  [a]</td>
</tr>
<tr>
<td>PM +/- Ketoconazole</td>
<td>2.5  [a]</td>
<td>2.1  [a]</td>
</tr>
<tr>
<td>PM / EM</td>
<td>2.3</td>
<td>2.1</td>
</tr>
<tr>
<td>PM + Keto / EM</td>
<td>5.7  [a]</td>
<td>4.5  [a]</td>
</tr>
<tr>
<td>EM +/- Fluconazole</td>
<td>1.3  [b]</td>
<td>1.2  [b]</td>
</tr>
<tr>
<td>PM + Fluconazole / EM</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Apparaju et al, DCP3; Vieira et al, ASCPT Annual Meeting, National Harbor, MD, March 2012
Organ Impairments

Parameters altered by Organ impairment: importance of “INTERPLAY”

Systems:
- Blood
  - Lung
  - Rapidly perfused organs
  - Slowly perfused organs
- Kidney
- Liver
- Intestines

Parameters:
- $f_p$, $B/P$, $Vss$
- $CL_r$
- $F_h$, $CL_h$
- $F_g$

Components:
- System component (drug-independent)

Substrate:
- ADME, PK, PD and MOA
  - Metabolism
  - Active transport
  - Passive diffusion
  - Protein binding
  - Drug-drug interactions
  - Receptor binding

PBPK Model: Substrate

Renal impairment

Hepatic impairment
Organ Dysfunction: The Interplay

Effect of liver impairment on renal clearance

<table>
<thead>
<tr>
<th>Table I. Physiological changes associated with liver cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Blood flow</td>
</tr>
<tr>
<td>portal</td>
</tr>
<tr>
<td>hepatic arterial</td>
</tr>
<tr>
<td>renal</td>
</tr>
<tr>
<td>other organs</td>
</tr>
<tr>
<td>Cardiac index</td>
</tr>
<tr>
<td>Albumin</td>
</tr>
<tr>
<td>α1-Acid glycoprotein</td>
</tr>
<tr>
<td>Haematocrit value</td>
</tr>
<tr>
<td>Functional liver mass</td>
</tr>
<tr>
<td>Hepatic enzymes</td>
</tr>
<tr>
<td>CYP3A4</td>
</tr>
<tr>
<td>CYP1A2</td>
</tr>
<tr>
<td>CYP2E1</td>
</tr>
<tr>
<td>GFR</td>
</tr>
</tbody>
</table>

Edginton, Clin Pharmacokinet, 2008

<table>
<thead>
<tr>
<th>Table III. Physiological and biochemical parameter changes associated with liver cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Liver volume fraction</td>
</tr>
<tr>
<td>CYP (μmol/mg)</td>
</tr>
<tr>
<td>1A2</td>
</tr>
<tr>
<td>2A6</td>
</tr>
<tr>
<td>2B6</td>
</tr>
<tr>
<td>2C8</td>
</tr>
<tr>
<td>2C9</td>
</tr>
<tr>
<td>2C18</td>
</tr>
<tr>
<td>2C19</td>
</tr>
<tr>
<td>2D6</td>
</tr>
<tr>
<td>2E1</td>
</tr>
<tr>
<td>3A4</td>
</tr>
<tr>
<td>Gut CYP3A4 (μmol per total gut)</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
</tr>
<tr>
<td>α1-Acid glycoprotein (g/L)</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
</tr>
<tr>
<td>Cardiac output (L/h)</td>
</tr>
<tr>
<td>Portal blood flow (L/h)</td>
</tr>
<tr>
<td>males</td>
</tr>
<tr>
<td>females</td>
</tr>
<tr>
<td>Hepatic arterial blood flow (L/h)</td>
</tr>
<tr>
<td>Q_vill (L/h)</td>
</tr>
<tr>
<td>GFR (mL/min)</td>
</tr>
</tbody>
</table>

CYP = cytochrome P450; GFR = glomerular filtration rate; Q_vill = villous blood flow.

Johnson, Clin Pharmacokinet, 2010
Organ Dysfunction: The Interplay

Effect of renal impairment on hepatic pathways

Table 1. Key physiological and biochemical parameter changes associated with differing degrees of renal impairment.

<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>F</td>
<td>41.8 [205]</td>
<td>38.8 [136,137,205]</td>
</tr>
<tr>
<td>Hematocrit (%) M</td>
<td>43.0 [43]</td>
<td>39.7 [43]</td>
</tr>
<tr>
<td>F</td>
<td>38.0 [43]</td>
<td>33.2 [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.  

PBPK Simulation: Renal Impairment + Moderate Enzyme Inhibitor in Elderly

<table>
<thead>
<tr>
<th>Rivaroxaban AUC Ratio</th>
<th>Renal functions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>No Erythromycin</td>
<td>1.0</td>
</tr>
<tr>
<td>With Erythromycin</td>
<td>1.6</td>
</tr>
</tbody>
</table>

- **a** Observed with in older subjects
- **b** Simulated using younger subjects with normal renal function as baseline

More than 2-fold AUC Ratio is considered clinically significant

Sponsor chose to study the combined effect (on-going)
PK Non-linearity

What is the drug-drug interaction potential of an investigational drug that demonstrates dose and time dependent PK?
**DDI Caused by Dose- and Time-dependent PK**

![Graphs showing DDI](image)

**Evaluation of sources of nonlinearity using PBPK**

- Absorption: Saturation of P-gp
- Metabolism: Saturation
- Excretion: Saturation
- Metabolism: Auto-inhibition (via time-dependent inhibition, TDI)

*Vieira et al, Clin Pharmacol Ther, In press*
Effect of telithromycin (p.o. 800 mg once daily)

<table>
<thead>
<tr>
<th></th>
<th>IV midazolam</th>
<th>PO midazolam</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed</td>
<td>PBPK Predicted</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; Ratio</td>
<td>1.05</td>
<td>1.13</td>
</tr>
<tr>
<td>AUC Ratio</td>
<td>2.20</td>
<td>3.26</td>
</tr>
<tr>
<td>Ratio of F&lt;sub&gt;G&lt;/sub&gt;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ratio of F&lt;sub&gt;H&lt;/sub&gt;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AUC ratio</td>
<td></td>
<td>&lt;1.25</td>
</tr>
<tr>
<td>(Model without TDI)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Study Design

Should inhibitor and substrate be given together?
How does drug-drug interaction or organ impairment affect metabolite exposure?
PBPK Provides Insights of Mechanism and Time-variation

QD400 achieved maximal inhibition but returned close to baseline before the next dose.

BID200 generally maintained >40% inhibition.

Zhao et al, J Clin Pharmacol, 2009

Should ketoconazole be administered 400 mg QD or 200 mg BID?
How metabolite exposure changes when multiple pathways are affected by multiple patient factors?

What if becomes ?

Distribution of metabolite?
PBPK model generates PK profiles of interested species with greater mechanistic insights
The Longitudinal Dimension

**Pediatrics**
- $f_p$
- $B/P$
- $V_{ss}$

**Geriatrics**
- $CL_r$

**Pregnancy**
- $F_h$
- $CL_h$

- $F_g$

**Parameters altered longitudinally**

**Substrate**
- ADME, PK, PD and MOA
  - Metabolism
  - Active transport
  - Passive diffusion
  - Protein binding
  - Drug-drug interactions
  - Receptor binding

**PBPK Model: Substrate**

- **System component (drug-independent)**
  - Lung
  - Rapidly perfused organs
  - Slowly perfused organs
  - Kidney
  - Liver
  - Intestines

**Dosing Elimination**
When is PBPK Needed in Pediatric Drug Development?

- Can we predict PK of an investigational drug in an age group that has NOT been exposed to the drug? (First in Pediatric PK Prediction)

- Can the effect of patient factor(s) on drug PK be assumed the same as that in adults?

  - *Diseases (including organ impairments)*
  - *Drug-drug interactions*
  - *Pharmacogenetics*
Clearance Prediction Needs To Be Tailored To Individual Drug

Modified from Johnson et al, Clin Pharmacokinet, 2006
### Pediatic submissions containing PBPK (2009-2011)

<table>
<thead>
<tr>
<th>Drug-specific data in adult PBPK model</th>
<th>Drug A</th>
<th>Drug B</th>
<th>Drug C</th>
<th>Drug D</th>
<th>Drug E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Integrate Physico-chemical data</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Integrate ADME data</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pediatric PBPK model development</th>
<th>Drug A</th>
<th>Drug B</th>
<th>Drug C</th>
<th>Drug D</th>
<th>Drug E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verify adult model using i.v. and p.o. data</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Demonstrate adequacy of adult model</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Justify age-dependent ADME processes</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Application of the pediatric PBPK model</th>
<th>Drug A</th>
<th>Drug B</th>
<th>Drug C</th>
<th>Drug D</th>
<th>Drug E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plan dedicated “first in pediatric” PK study</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Optimize study design</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Verify model of certain age groups</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recommend starting dose by targeting</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>appropriate steady-state exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inform enzyme ontogeny using bench-mark drug</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Facilitate covariate analysis</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

*Updated from Leong et al, Clin Pharmacol Ther, In Press*
PBPK model in adults

Develop, verify, and refine adult PBPK model

PBPK model in children

Develop, use, and refine PBPK model in pediatrics
- Simulate pediatric PK in all age groups
- Optimize design of “first in pediatric” PK study (dosage, formulation, sampling time)

Verify PBPK model with available pediatric data
- Data from conventional studies
- Data from small trial with intense PK sampling

Summary: Pediatric PBPK

- PBPK model building requires knowledge of physiology (system) and drug disposition
- Application of a pediatric PBPK model should use existing adult model and integrate/update with current knowledge in ontogeny of physiological processes
- PBPK model should be continuously updated for enhanced model confidence in predicting unknown clinical situations
Basic steps for PBPK analyses

0. **Determine Questions that may be addressed by PBPK**

1. Determine Clearance Pathways (e.g., $f_m$)

2. Build PBPK Model (Drug- and System- parameters)

3. Compare simulated profiles with in vivo data

4. Refine model

5. **Predict** (unlimited # of) unknown clinical settings

Conclusions

• PBPK models can be applied to quantitatively evaluate intrinsic and/or extrinsic factors
  - Provide full PK profiles of substrate and interacting drug - DDI
  - Assess effect of multiple factors
  - Optimize study design and data analysis
  - Identify knowledge gaps
  - Generate hypotheses (for further studies)

• It is important to integrate knowledge in mechanisms of DDI and drug disposition, and the effect of organ impairment

• It is important to understand the interplay of the intrinsic/extrinsic factors

• PBPK model can be continuously updated for enhanced model confidence in predicting unknown clinical situations
Acknowledgements

FDA Office of Clinical Pharmacology

Scientific Interest Group (PBPK-SIG)
- Formed March 2009
- Steering committee: Drs. Joe Grillo, Lei Zhang, Ping Zhao
- Dr. Manuela Vieira (University of Florida, FDA Critical Path Fellow)
- Mentors: Drs. Shiew-Mei Huang and Larry Lesko

External collaborators

Professors Sandy Pang (Toronto), Amin Rostami-Hodjegan (Manchester), Yuichi Sugiyama (Tokyo), and Malcolm Rowland (Manchester); Dr. Eva Gil Berglund (EMA-MPA); Drs. Karen Rowland-Yeo and Masoud Jamei (SimCYP)
Renal Impairment on Non-renally Eliminated Drugs

<table>
<thead>
<tr>
<th>Compound (% CL by kidney)</th>
<th>Observed AUCR Severe RI/Normal</th>
<th>PBPK&lt;sup&gt;a&lt;/sup&gt; Predicted AUCR Severe RI/Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil (&lt;1%)</td>
<td>2.0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>(Mild: 0.9; Moderate: 1.2)</td>
<td></td>
</tr>
<tr>
<td>Repaglinide (&lt;1%)</td>
<td>SD: 2.7; MD: 3.0&lt;sup&gt;c&lt;/sup&gt;</td>
<td>SD: 2.5; MD: 2.3</td>
</tr>
<tr>
<td></td>
<td>(Mild/Moderate: SD: 1.8; MD1.6 )</td>
<td></td>
</tr>
<tr>
<td>Telithromycin (~20%)</td>
<td>1.9&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>(Mild: 1.4; Moderate: 1.2)</td>
<td></td>
</tr>
</tbody>
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The Need to Consider Metabolites in RI or DDI

**A. Sildenafil Full PBPK Model**

- **Lung**
- **Rapidly perfused organs**
- **Slowly perfused organs**
- **Kidney**
- **Liver**
- **Intestine**

- \( f_p = 0.04; \ BP = 0.66 \)
- \( CL_{iv} = 30 \text{ L/h} \)
- \( V_{ss} = 1.5 \text{ L/kg} \)
- \( CL_R \approx 0 \)

\( CL_H = CL_{CYP3A} + CL_{CYP2C9} \)
- UK-103320: 15% \( CL_H \)
- (CYP3A:CYP2C9 80%:20%)
- Others: 85% \( CL_H \)
- (CYP3A 100%)

\( F_{oral} \approx 40\%

**B. UK-103320 Semi-PBPK Model**

- **Intestine**
- **Portal Vein**
- **Liver**
- **Apparent plasma compartment**

- Dosing
- Elimination

**Assuming UK103320 is solely metabolized by CYP3A4**

<table>
<thead>
<tr>
<th>AUCR of UK103320</th>
<th>Severe RI</th>
<th>Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obs.</td>
<td>3.0(^a)</td>
<td>1.4(^b)</td>
</tr>
<tr>
<td>Pred.</td>
<td>2.5</td>
<td>5.2</td>
</tr>
</tbody>
</table>


\*Over-predicted DDI: knowledge gap in metabolite disposition?\*