Use of PBPK in Clinical Pharmacology Reviews

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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
- Verification of PBPK models through predict-learn-confirm processes
Physiologically-based Pharmacokinetic models (PBPK)

The model

Effect of absorption kinetics

History: One of the Earliest PK Models “Was a PBPK Model”

Teorell, Arch Intern Pharmacody., 1937
Can Model Provide Desired Insights?

1-Compartmental PK

Oral Dose

\[ \text{V}^* \frac{d\text{C}}{d\text{t}} = \text{K}_a \text{V}_a \text{C}_a (\text{CL}_h + \text{CL}_r) \text{C} \]

\[ \text{V}_a \frac{d\text{C}_a}{d\text{t}} = - \text{K}_a \text{V}_a \text{C}_a \]

\[ \text{C} = \frac{\text{K}_a \text{Dose}}{\text{V} \left( \text{Ka} - \frac{\text{CL}_h + \text{CL}_r}{\text{V}} \right)} \left( e^{-\frac{(\text{CL}_h + \text{CL}_r)}{\text{V}} \text{t}} - e^{-\text{K}_a \text{t}} \right) \]

System component (drug-independent)

- Lung
- Rapidly perfused organs
- Slowly perfused organs
- Kidney
- Liver
- Intestines

Drug-dependent component

ADME, PK, PD and MOA

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

PBPK Model

Blood

- Elimination

Dosing

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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?
PBPK: Predict, Learn, and Confirm

A. Patient Factors

Intrinsic factors
Extrinsic factors

Huang and Temple, 2008

B. PBPK Model components

System component (drug-independent)

Physiology
Anatomy
Biology

Drug-dependent component

Drug disposition
Drug action

PBPK Model

Predict, Learn, Confirm

Adapted from Zhao P, et al Clin Pharmacol Ther 2011
Increased Interest in Using PBPK

Rowland M, Peck C, Tucker G,
Physiologically-based pharmacokinetics in Drug Development and
Regulatory Science
Annu Rev Pharmcol Toxicol, 2011
Supplementary Figure 1: Distribution of clinical pharmacology questions addressed by PBPK among submissions over the period between Jun 2008 and December 2011.
Recently published PBPK work by OCP


Renal impairment, metabolite PK, transporter-enzyme


Nonlinear PK and time-dependent inhibition


Pediatrics and pregnancy


Outline

- Why PBPK
- Application of PBPK in clinical pharmacology review
- Verification of PBPK models through predict-learn-confirm processes
Multiple Factors
Situations requiring mechanistic models

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
Blood
Lung
Rapidly perfused organs
Slowly perfused organs
Kidney
Liver
Intestines

Blood

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

ADME, PK, PD and MOA
Metabolism
Active transport
Passive diffusion
Protein binding
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Receptor binding

PBPK Model: Interacting Drug

Dosing
Elimination

Parameters can be altered by DDI

PBPK Model: Substrate
Extrapolating effect of CYP2D6 PM + CYP3A4 moderate inhibitor when data on PGx with strong inhibitor are available

<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>

Or, can we PREDICT DDI BEFORE any DDI/PG study is conducted? Which one to do first? Which one can be waived?

Observed

<table>
<thead>
<tr>
<th>Condition</th>
<th>AUCR</th>
<th>CmaxR</th>
</tr>
</thead>
<tbody>
<tr>
<td>EM +/- Ketoconazole</td>
<td>1.9</td>
<td>1.8</td>
</tr>
<tr>
<td>PM +/- Ketoconazole</td>
<td>3.3</td>
<td>2.4</td>
</tr>
<tr>
<td>PM / EM</td>
<td>1.6</td>
<td>1.5</td>
</tr>
<tr>
<td>PM + Keto / EM</td>
<td>5.4</td>
<td>3.6</td>
</tr>
<tr>
<td>EM +/- Fluconazole</td>
<td>1.3</td>
<td>1.2</td>
</tr>
<tr>
<td>PM + Fluconazole / EM</td>
<td>2.57</td>
<td>2.09</td>
</tr>
</tbody>
</table>

Predicted

- **Oral Fesoterodine**
  - Absorption Hydrolysis
  - CYP2D6
  - CYP3A4
  - Renal CL

**Graph:**
- 5-HMT (ng/mL): EM (n=11)
- Clin Pharm Review: drugs@FDA

**References:**
- Vieira et al, ASCPT Annual Meeting, National Harbor, MD, March 2012
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A. Patient Factors

Intrinsic factors

Extrinsic factors

Huang and Temple, 2008

B. PBPK Model components

System component (drug-independent)

Drug-dependent component

Physiology

Anatomy

Biology

Drug disposition

Drug action

PBPK Model

Predict, Learn, Confirm

Adapted from Zhao P, et al Clin Pharmacol Ther 2011
How “valid” is a PBPK model?

- Multiple solutions due to numerous system- and drug-dependent parameters

- It is equally important to demonstrate
  - Model plausibility with regard to physiology and drug ADME sources, justifications, assumptions
  - Visual inspection of the simulation results against observed data
    curve shape, match of profiles from multiple studies with population simulations
Verification of PBPK Models through Predict-learn-confirm: An Ongoing Process for Both Drug and System Components

- Like any model, PBPK is built for purpose
- Comparing plasma PK profiles is not sufficient to validate a drug PBPK model
PK Non-linearity

What can we **LEARN** from nonlinear PK?

Can PBPK model integrating nonlinear PK **PREDICT** DDI?
LEARNING Nonlinear PK through PBPK

Evaluation of sources of nonlinearity using PBPK

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

PBPK Model Integrating Nonlinear PK
PREDICTED DDI Without Using Known DDI Data

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>$C_{\text{max}}$ 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 $F_G$</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ratio of $F_H$</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$AUC$ ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Model without TDI)</td>
<td></td>
<td></td>
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</tbody>
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Organ Impairments

Parameters altered by Organ impairment: importance of “INTERPLAY”
# 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>
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<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)</td>
<td></td>
<td></td>
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<tr>
<td>M</td>
<td>44.9 [205]</td>
<td>41.6 [136,137,205]</td>
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<tr>
<td>F</td>
<td>41.8 [205]</td>
<td>38.8 [136,137,205]</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td></td>
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<tr>
<td>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>
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F: Female; GFR: Glomerular filtration rate; M: Male.

**CONFIRMING the Effect of Renal Impairment on Hepatic Pathways via PBPK**

<table>
<thead>
<tr>
<th>Compound (% CL by kidney)</th>
<th>Observed AUCR Severe RI/Normal</th>
<th>PBPK(^a) Predicted AUCR Severe RI/Normal</th>
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<tbody>
<tr>
<td>Sildenafil (&lt;1%)</td>
<td>2.0(^b) (Mild: 0.9; Moderate: 1.2)</td>
<td>2.2</td>
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<tr>
<td>Repaglinide (&lt;1%)</td>
<td>SD: 2.7; MD: 3.0(^c) (Mild/Moderate: SD: 1.8; MD1.6 )</td>
<td>SD: 2.5; MD: 2.3</td>
</tr>
<tr>
<td>Telithromycin (~20%)</td>
<td>1.9(^d) (Mild: 1.4; Moderate: 1.2)</td>
<td>1.6</td>
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### PREDICTING Effect of Renal Impairment And DDI in The Elderly

<table>
<thead>
<tr>
<th>Rivaroxaban AUC Ratio</th>
<th>Renal functions</th>
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<tr>
<td></td>
<td>Normal</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
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<tr>
<td>No Erythromycin</td>
<td>1.0⁹</td>
<td>1.4⁹</td>
<td>1.5⁹</td>
<td>1.6⁹</td>
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<tr>
<td>With Erythromycin</td>
<td>1.6⁹</td>
<td>2.5⁹</td>
<td>2.9⁹</td>
<td>3.0⁹</td>
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⁹ Observed with in older subjects

Simulated using younger subjects with normal renal function as baseline

More than 2-fold AUC Ratio is considered clinically significant

Grillo et al, Biopharm Drug Dispo, 2012
LEARNING time-dependency through PBPK

Parameters altered longitudinally

Pediatrics
- $f_p$
- B/P
- Vss

Geriatrics
- $CL_r$

Pregnancy
- $F_h$, $CL_h$
- $F_g$

Blood
- Rapidly perfused organs
- Slowly perfused organs
- Kidney
- Liver
- Intestines

System component (drug-independent)
- Lung

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

Dosing
- Elimination

PBPK Model: Substrate

Parameters altered longitudinally
Clearance Prediction Needs To Be Tailored To Individual Drug

* Post-conceptional age

Modified from Johnson et al, Clin Pharmacokinet, 2006
Conclusions

- PBPK model integrates knowledge in drug disposition, DDI mechanisms, and the effect of patient factors (disease, age, genetics), and can be applied to quantitatively evaluate intrinsic and/or extrinsic factors.

- For PBPK of each drug, “predict-learn-confirm” verifies the approach in general, and improves our understanding of the interaction between the drug molecule and the system.

- PBPK model should 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

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