Systems Pharmacology Approach to Modelling Pharmacokinetics in Pregnancy

Amin Rostami-Hodjegan, PharmD, PhD, FCP

Professor of Systems Pharmacology
University of Manchester, Manchester, UK
&
Vice President R&D
SimpCyp, Sheffield, UK

amin.rostami@manchester.ac.uk
Physiologically-Based Pharmacokinetics Joined with In Vitro-In Vivo Extrapolation of ADME: A Marriage under the Arch of Systems Pharmacology

Amin Rostami-Hodjegan

**Schematic Representation of Workflow**

- **Systems Data**
- **Trial Design**
- **Drug Data**

**PBPK-IVIVE Linked Models**

**Associated IT Elements**

- **Input Data:**
  - Population Library
  - Compound File
  - Project (Workspace)

- **Integrated Models:**
  - Simulation Tool
  - Simulation Environment

- **Output:**
  - Raw Output Data
  - Output Environment
  - Data Analysis

**Assessment of Covariates & Study Design using PK (PD)**

Simulated the Target Population

**July Issue of CPT – Online now**
... proposes that new technologies will enable the adoption of virtual R&D; and by operating in a more connected world, the industry in collaboration with researchers, governments, healthcare payers and providers, can address the changing needs of society more effectively.

(1) Requires More Data not Less!

(2) Requires Different Type of Data

(3) Requires Huge Integration Task

(4) Appropriate Tools Are Essential

Kate Moss June 2008
Systems Approach: e.g. Inter-Individual Variability in PK

A Framework for Assessing Inter-individual Variability in Pharmacokinetics Using Virtual Human Populations and Integrating General Knowledge of Physical Chemistry, Biology, Anatomy, Physiology and Genetics: A Tale of ‘Bottom-Up’ vs ‘Top-Down’ Recognition of Covariates

Masoud JAMEI¹, Gemma L DICKINSON² and Amin ROSTAMI-HODJEGAN¹,3,*

Age / Genetics / Environment / Disease
Well Recognised by Leading Regulatory Agencies

A. Intrinsic/extrinsic Factors

- EXTRINSIC
  - Smoking
  - Environment

- INTRINSIC
  - Pregnancy
  - Race
  - Organ Dysfunction
  - Lactation
  - Gender
  - Disease
  - Age
  - Genetics

- DDI
- Regulatory
- Medical Practice

Huang and Temple, 2008

Individual or combined effects on human physiology

B. PBPK Model components

- System component (drug-independent)
  - 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

Drug-dependent component

Predict, Learn, Confirm

Summary of PBPK-IVIVE M&S in Submissions

From July 2008 to June 2010, the FDA reviewed seven investigational new drug (IND) and six new drug applications (NDA) submissions containing PBPK modeling and simulations conducted by the sponsors. In addition, FDA reviewers conducted PBPK modeling and simulations to support clinical pharmacology reviews of another four NDA submissions for which the sponsors did not use PBPK. As a comparison, in the 3 years before 2008, FDA received only two submissions containing PBPK modeling and simulations. Many of the PBPK modeling and simulation evaluations addressed questions relating to drug–drug interactions; others addressed pediatric dosing, the impact of hepatic impairment on drug exposure, and the impact of multiple factors on drug exposure (Table 1).

0.66 per year  8.5 per year

>12 FOLD INCREASE

(Zhao et al., 2011)
Today’s Headline: Application of PBPK Modeling to Pediatric Drugs Cautiously Favored

The latest developments from US FDA drug and biologic advisory committee meetings.

March 14, 2012
Meeting Begin Time: 7:30 a.m. | End Time: 1:47 p.m.

IN THIS ISSUE

Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (IDRAC 137880) Meeting

AdComm Profiles and AdComm Voting (IDRAC 40094)

Subject: The clinical pharmacology aspects of pediatric clinical trial design and dosing to optimize pediatric drug development. Input is sought on how to strategically inform pediatric clinical trial design and dosing by utilizing existing knowledge, including available adult and non-clinical data.

Announced in the Federal Register
January 11, 2012 (IDRAC 137218) (Volume 77, Number 7)

Should the routine use of PBPK in pediatric drug development, when possible, be recommended at the present time?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
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<td>7</td>
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Physiologically-based Pharmacokinetic (PBPK) Models for Assessing the Kinetics of Xenobiotics during Pregnancy: Achievements and Shortcomings

G. Lu¹*, K. Abduljalil¹, M. Jamei¹, T.N. Johnson¹, H. Soltani² and A. Rostami-Hodjegan¹,³

Time –varying component to account for changes to the system (anatomical, physiological and biological; CYPs abundance, etc.)
**In Vitro Drug Metabolism Tools**

- Homogenisation
- Centrifugation @ 9,000g
  - S9: Nuclear / Mitochondrial pellet
  - S9

- CYP450
- FMO
- MAO
- Aldehyde oxidase
- Aldehyde dehydrogenase
- Epoxide hydrolase
- Xanthine oxidase
- Esterases
- UGT

- rhUGT
- HLM
- HIM
- HKM
- rhCYP

- Hepatocytes

- Cytosol
- Glutathione S transferase
- Alcohol dehydrogenase
- Xanthine oxidase

- SULT

- Centrifugation @ 100,000g
  - Cytosol
  - Microsomes
SIMCYP Pregnancy PBPK Model

Venous blood:
- Lung
- Adipose
- Bone
- Brain
- Heart
- Kidney
- Muscle
- Skin
- Liver
- Spleen
- Gut

Arterial blood

Pregnancy
Foetal volume (ml) = 0.01 \cdot \exp \left[\frac{(0.955 / 0.0702) \cdot (1 - \exp (-0.0702 \cdot \text{GA}))}{\text{GA}=\text{gestational age (week)}}\right]

Placenta volume (ml) = -0.716 \text{GA} + 0.9149 \text{GA}^2 - 0.0122 \text{GA}^3

Amniotic Fluid (ml) = 1.9648 \text{GA} - 1.2056 \text{GA}^2 + 0.2064 \text{GA}^3 - 0.0061 \text{GA}^4 + 0.00005 \text{GA}^5
Results

Simulated versus mean observed (Brazier et al 1983) PK parameters for 150 mg caffeine
CYP2D6 activity was detectable and concordant with genotype by 2 weeks of age, showed no relationship with gestational age, and did not change with postnatal age up to 1 year.

However: we know that:

\[
\frac{\text{DM/DX}}{\text{CLu}_R} \approx \frac{\text{CLu}_R}{\text{CLu}_{\text{int.DX}}}
\]

Thus, the development of renal function from birth may change in parallel with the development of the enzyme such that the drug/metabolite ratio may be relatively constant !!!!

Figure 3  Effect of post-natal age on CYP2D6 activity. Boxplot of the logarithm of DM/DX as a function of post-natal age. Boxes are interquartile range; bars are medians. Whiskers represent the 10th to 90th percentile. ○ Outlying values between 1.5 and 3 box lengths from the interquartile range.
Figure 1. Changes in CYP2D6 (a) and CYP3A4 (b) activity relative to adult values. The data of Blake et al, corrected for the development of renal function, are indicated by the diamonds. The simulated change in the activity of each enzyme (solid line) was derived from in vitro data on hepatic enzyme expression and increase in liver weight with age.
Temporal changes in drug metabolism (CYP1A2, CYP2D6 and CYP3A Activity) during pregnancy

Timothy S. Tracy, PhD, a,* Raman Venkataramanan, PhD, b Douglas D. Glover, MD, c Steve N. Caritis, MD, d for the National Institute for Child Health and Human Development Network of Maternal-Fetal-Medicine Units

A

Caffeine Clearance (mL/min)

<table>
<thead>
<tr>
<th>Weeks Gestation</th>
<th>14-18 Wks</th>
<th>24-28 Wks</th>
<th>36-40 Wks</th>
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<td></td>
<td></td>
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</tr>
<tr>
<td>p</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td></td>
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B

% Change in CYP1A2 Activity within Subjects Compared to Postpartum

<table>
<thead>
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<th>Weeks Gestation</th>
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<tr>
<td>p</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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</tbody>
</table>
Systems Approach: Absorption

- Duodenum
- Jejunum I
- Jejunum II
- Ileum I
- Ileum II
- Ileum III
- Ileum IV
- Colon

Stomach

Stomach Emptying

Luminal Transit

Segregated Blood Flows

Enzymes (CYP3A4) vs Transporters (Pgp)
Systems Approach: Brain

- CSF: circulation, pH, volume, …
- Brain: anatomy, physiology, …

- Passive permeability at three interfaces
- Active transporters at BBB/BCSFB

(Eyal et al., 2009)
Transporters are available in all three proximal tubule cell compartments on the apical and basal membrane.

The model can handle:

- regional distribution/activity of transporters
- nephrotoxicity as well as changes in systemic exposure
- interplay between uptake, efflux and passive permeation
- metabolism and transport interplay
A PBPK Model to Predict Disposition of CYP3A-metabolized Drugs in Pregnant Women: Verification and Discerning the Site of CYP3A Induction

A.B. Ke\textsuperscript{1,2}, S.C. Nallani\textsuperscript{2}, P. Zhao\textsuperscript{2}, A. Rostami-Hodjegan\textsuperscript{3,4}, J. D. Unadkat\textsuperscript{1}

**Midazolam, Nifedipine, Indinavir**

Pharmacometric & Systems Pharmacology \textit{(to appear soon)}

**Introduction**

The American Society for Clinical Pharmacology and Therapeutics (ASCPT) and Nature Publishing Group are pleased to announce the upcoming launch of a brand new publication: \textit{CPT: Pharmacometrics & Systems Pharmacology}.

\textit{CPT: Pharmacometrics & Systems Pharmacology} is a sibling journal to the well-established high impact journal, \textit{Clinical Pharmacology & Therapeutics} (2010 Impact Factor, 6.378, Journal Citation Reports, Thomson Reuters, 2011). The journal will provide a unique international forum for scientists in the pharmacometrics and systems pharmacology space. \textit{CPT:}
WE ALL KNOW that:

(1) All Models Are Wrong, but Some Models Are Useful!

George EP Box 1987

WE SHOULD ALSO KNOW that:

(2) Science is built of facts as a house is built of stones; but an accumulation of facts is no more science than a pile of stones is a house.

Henri Poincare, 1902