Predicting Pharmacokinetics in Humans: The Bottom-Up Approach

SOT RASS TELECON
February 11, 2009

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Agenda

- 3.00  Background – PK Modeling
- 3:10  The Bottom-Up Approach
- 4:00  Simcyp Rat
- 4:15  Discussion
- 4:30  End
Cost-Effectiveness of New Drug Development

Is it possible to optimise the clinical studies that are needed and eliminate the studies that are doomed to fail?

Description & Prediction
In Vitro – In Vivo Extrapolation (IVIVE)

PRE-CLINICAL

CLINICAL

Fu mic, fu, ED_{50}, Ki, LogP, V_{max}, K_{inact}, K_{m}
Simcyp: What We Do

Develop and update a user-friendly, comprehensive, mechanistic platform for integration of ADME models & databases

Regular worldwide workshops and seminars on PK & IVIVE for key players in drug development.

Provide consultancy services. Provide advice / help to reach consensus on IVIVE & ADME issues / Identify areas of further research - (defining common / specific projects in the form of focus groups)
Integration of demographic, physiological and genetic information with \textit{in vitro} drug absorption, metabolism and transport data to simulate and predict \textit{in vivo} drug absorption, disposition and drug-drug interactions in virtual patient \textit{populations}.

“The good physician treats the disease; the great physician treats the patient who has the disease.”

\textit{Teaching at the Bedside}

\textit{Sir William Osler, M.D.}\n\textit{1849 - 1919}
PK Modeling: Bottom-Up

Bioavailability = Release, Dissolution, Stability, Permeability, Efflux/ or Uptake Transporters, Gut Wall and Hepatic First pass Metabolism, ...

CL = Unbound Fraction, Efflux or Uptake Transporters, Enzymes, Blood Flow, Induction, Inhibition, ......

V = Unbound Fraction, Blood Flow, Efflux or Uptake Transporters, Organ Size, ......
Bioavailability = \( \frac{AUC_{po}}{AUC_{iv}} \)

\( CL = \frac{DOSE}{AUC} \)

\( V = \frac{D}{C_0} \)

Just Parameters in Equations:
Posterior Analysis of Their Covariation with Individual Characteristics
**Top-Down vs Bottom-Up**

**“TOP DOWN”**

- Plasma Data
- POPPK
- PBPK/IVIVE
- Confirming
- Learning

**“BOTTOM UP”**

Demography, Physiology, Genetics, *In Vitro* Data
Bottom-Up Approach in Risk Assessment


Systems Pharmacokinetics

POPULATION SPECIFIC FACTORS

Age
Weight
Height
Sex
Genetics
Race
Disease

SYSTEM SPECIFIC FACTORS

Organ size
Blood flow
Enzymes
Transporters
Plasma protein
Haematocrit
Transit time
pH

DRUG SPECIFIC FACTORS

MWt
pKa
Log D
H-bonding
Solubility
Permeability
Metabolism
fu, fu_B, fu_inc

CL,V,t½,DDI  PD

Jamei et al. EOMT 2009
Demographic features of ethnic groups and disease populations differ, and this should be considered when simulating drug behaviour:

- Addicts/AIDS
- CVD (general)
- Angina
- Arrhythmia
- Diabetes
- Heart Attack
- Schizophrenia
- Rheumatoid Arthritis
- Stroke
Factors Affecting Drug Absorption

**Physicochemical & Pharmaceutical issues**
- Disintegration
- De-aggregation
- Dissolution
- Solubility
- Precipitation
- Permeability
- Intra-gut degradation

**Physiological issues**
- Gastric emptying
- Intestinal mobility
- pH
- Intestinal metabolism
- Disease state
- P-gp and other transporters
- Intestinal blood flow
- Food effects
- GI-tract fluid secretion, re-absorption and motility
The Advanced Dissolution, Absorption & Metabolism (ADAM) Model

- Solid Dosage
- Fine Particles
- Dissolved Drug
- Enterocytes
- Dissolution / Precipitation / Super-Saturation
- Absorption / Efflux
- Metabolism

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

- Pgp

- Portal Vein
- Liver

- PBPK Distribution Model

- R distribution
- pH distribution
- Permeability distribution
- CYPs distribution
- Blood flow distribution
Intestinal Transit Time

Yu et al. (1998)
Variability in pH Profile in the GI Tract


Ven = stomach
Duo = duodenum
Pro = proximal small intestine
Mid = mid small intestine
Dis = distal small intestine
Cae = caecum
Asc = ascending colon
Tra = transverse colon
Des = descending colon
R/S = sigmoid colon or rectum
Fae = faeces
Effects of Food on Drug Absorption

Food can alter the absorption process by various means including interactions between the drug, its formulation, and the gastrointestinal (GI) tract.

- Delay gastric emptying
- Stimulate bile flow
- Change gastrointestinal (GI) pH
- Increase splanchnic blood flow
- Change luminal metabolism of a drug substance
- Physically or chemically interaction with a dosage form or a drug substance

Overall, the effects of food can vary depending on the composition and size of the meal.

Distribution

Venous Blood

Lung

Adipose

Bone

Brain

Heart

Kidney

Muscle

Skin

Liver

Portal Vein

Spleen

Gut

Arterial Blood

IV

PO
Covariates of Determining Tissue Volumes

- Age
- Sex
- Weight
- Height

Tissues:
- Adipose
- Brain
- Bone
- Gut
- Heart
- Kidney
- Liver
- Lung
- Muscle
- Skin
- Erythrocytes
- Plasma
- Spleen
Volume of Brain (L) for subjects aged 0-19 years

- Male = (-90.7 * BH(m) + 178.1) * BW(kg) / 1040;
- Female = (-97.5 * BH(m) + 181.2) * BW(kg) / 1040;

Volume of Heart (L) in Adults

- Male = 9.22 * BW(kg)^0.853 / 1040;
- Female = 9 * BW(kg)^0.855 / 1040;

Volume of Heart (L) for Pediatrics

- Male = (22.81 * BH(m) * BW^0.5 - 4.15) / 1040;
- Female = (19.99 * BH(m) * BW^0.5-1.53) / 1040;

Price et al., 2003
Drug Distribution in Tissues

EW: Extracellular Water
IW: Intracellular Water
NP: Neutral Phospholipids
NL: Neutral Lipids
AP: Acidic Phospholipids

Elimination
Predicting Drug Distribution

1. Tissue Volumes ($V_t$) + Compositions ($V_{nlt}$, $V_{phlt}$, $V_{wt}$) (generated in Simcyp)

2. In vitro drug dependent data on lipophilicity ($\log P$, $\log D$) + Tissue and plasma binding ($f_u$, $f_{u_t}$)

Predict $P_{t:p}$ and $V_{SS}$

One-compartment distribution model

Blood Flows ($Q_t$) (generated in Simcyp)

Physiologically-based distribution model

$C_{sys}$, $C_{pv}$, $C_{liv}$

Tissues and plasma concentrations
Prediction of Metabolism

**In vitro system**

**HLM**

\[
\frac{\mu L.min^{-1}}{mg \, mic \, protein}
\]

**HHEP**

\[
\frac{\mu L.min^{-1}}{10^6 \, cells}
\]

**rhCYP**

\[
\frac{\mu L.min^{-1}}{pmol \, P450 \, isoform}
\]

**Scaling Factor 1**

**Scaling Factor 2**

**CLu_{int} per g Liver**

**CLu_{int} per Liver**
Hepatic Clearance

- Hepatic blood flow
- Liver weight
- $\text{CL}_{\text{u,H,int}}/\text{G liver}$
- $f_{u_B}$

Factors affecting Hepatic Clearance:
- Age
- Sex
- Genetics
- Body Size
- Disease
- Environment
- Hepatocellularity ($10^6 \text{ cells/G liver}$)
- Microsomal protein (mg/G liver)
- CYP abundance (pmol/G liver)
- Plasma protein affinity
- Partition to Red cells
- Plasma protein concentration
- Haematocrit

Rostami-Hodjegan and Tucker, 2007
CYP Abundance Variability

P450 Relative Abundance
(average of 167 individuals with CYP3A5 *1 allele within a 1000 randomly selected Caucasian Population)

- Genetics (Ethnicity)
  
  PLUS

- Age (Ontogeny)
- Environment (Ethnicity)
- Sex / Co-medications
Rate per pmol of “Each Enzyme”

Knowing:

- the abundance of each CYP isoform per mg of microsomal protein
- the isoform(s) responsible for specific metabolic routes

\[
CL_h[L/h] = \left[ \sum_{j=1}^{n} \left( \frac{V_{max}(rhCYP_j) \times CYP_{abundance}}{K_m(rhCYP_j)} \right) \right] \times MPPGL \times Liver\ \text{Weight}
\]

Proctor et al. Xenobiotica 2004
CYP Abundances: Caucasian vs Japanese

CYP (pmol/mg)

<table>
<thead>
<tr>
<th>CYP Enzyme</th>
<th>Caucasian</th>
<th>Japanese</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A2</td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>2A6</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>2C8</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>2C9</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>2E1</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>3A5</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>3A4</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>2C18</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>2J2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2D6</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>2C19</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>2B6</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

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Ethnic Differences in Clearance

Caucasian (CC) vs Japanese (JP)

<table>
<thead>
<tr>
<th></th>
<th>CC&gt;JP*</th>
<th>CC≈JP</th>
<th>CC&lt;JP*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLpo</td>
<td>.1</td>
<td>1</td>
<td>10</td>
</tr>
</tbody>
</table>

Relative Difference (fold Mean(geo) in Caucasian)

- CC>JP*: Caucasian > Japanese
- CC<JP*: Caucasian < Japanese

(Geometric mean ± 90% confidence interval, *p<0.05)
Prediction of CLpo (Caucasian vs Japanese)

Caucasian

Observed CLpo (mL/min/kg) vs Predicted CLpo (mL/min/kg)

10/11

(Geometric mean ± 90% confidence interval)

Japanese

Liver Cirrhosis

Demographics

Incidence per 100,000

<table>
<thead>
<tr>
<th>Median age (y)</th>
<th>29.5</th>
<th>39.5</th>
<th>49.5</th>
<th>59.5</th>
<th>69.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP-A</td>
<td>55%</td>
<td>60%</td>
<td>65%</td>
<td>70%</td>
<td>75%</td>
</tr>
<tr>
<td>CP-B</td>
<td>50%</td>
<td>55%</td>
<td>60%</td>
<td>65%</td>
<td>70%</td>
</tr>
<tr>
<td>CP-C</td>
<td>45%</td>
<td>50%</td>
<td>55%</td>
<td>60%</td>
<td>65%</td>
</tr>
</tbody>
</table>

Liver volume

% of control

<table>
<thead>
<tr>
<th>CP-A</th>
<th>CP-B</th>
<th>CP-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>80%</td>
<td>70%</td>
<td>60%</td>
</tr>
</tbody>
</table>

Cardiac output & Blood Flow

CYPs e.g CYP3A4

% of control

<table>
<thead>
<tr>
<th>CP-A</th>
<th>CP-B</th>
<th>CP-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>80%</td>
<td>70%</td>
<td>60%</td>
</tr>
</tbody>
</table>

Albumin

Albumin (g/L)

<table>
<thead>
<tr>
<th>Control</th>
<th>CP-A (94)</th>
<th>CP-B (133)</th>
<th>CP-C (100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>60%</td>
<td>70%</td>
<td>80%</td>
</tr>
</tbody>
</table>

Gastric emptying

Gastric emptying T1/2 in cirrhosis

Shift in gastric emptying T1/2 in cirrhosis

Renal function

GFR (ml/min)

<table>
<thead>
<tr>
<th>Control</th>
<th>CP-A(112)</th>
<th>CP-B(110)</th>
<th>CP-C(120)</th>
</tr>
</thead>
<tbody>
<tr>
<td>120</td>
<td>110</td>
<td>100</td>
<td>90</td>
</tr>
</tbody>
</table>

CYPs e.g CYP3A4

% of control

<table>
<thead>
<tr>
<th>CP-A</th>
<th>CP-B</th>
<th>CP-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>80%</td>
<td>70%</td>
<td>60%</td>
</tr>
</tbody>
</table>

Liver

Stomach

Peritoneal effusion (ascites)

Peritoneal membranes

Bowel

Area containing small and large bowel

Rectum

Ascites

Lungs
Predicting the Effect of Liver Cirrhosis

- **CAFFEINE (oral)**
- **DICLOFENAC (oral)**
- **METOPROLOL (oral)**
- **MIDAZOLAM (oral)**

- Fold increase in exposure (CL ratio [controls:cirrhotics])

<table>
<thead>
<tr>
<th></th>
<th>observed</th>
<th>predicted</th>
<th>CP A</th>
<th>CP B</th>
<th>CP C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CAFFEINE (oral)</strong></td>
<td><img src="image1" alt="Graph" /></td>
<td><img src="image2" alt="Graph" /></td>
<td><img src="image3" alt="Graph" /></td>
<td><img src="image4" alt="Graph" /></td>
<td><img src="image5" alt="Graph" /></td>
</tr>
<tr>
<td><strong>DICLOFENAC (oral)</strong></td>
<td><img src="image6" alt="Graph" /></td>
<td><img src="image7" alt="Graph" /></td>
<td><img src="image8" alt="Graph" /></td>
<td><img src="image9" alt="Graph" /></td>
<td><img src="image10" alt="Graph" /></td>
</tr>
<tr>
<td><strong>METOPROLOL (oral)</strong></td>
<td><img src="image11" alt="Graph" /></td>
<td><img src="image12" alt="Graph" /></td>
<td><img src="image13" alt="Graph" /></td>
<td><img src="image14" alt="Graph" /></td>
<td><img src="image15" alt="Graph" /></td>
</tr>
<tr>
<td><strong>MIDAZOLAM (oral)</strong></td>
<td><img src="image16" alt="Graph" /></td>
<td><img src="image17" alt="Graph" /></td>
<td><img src="image18" alt="Graph" /></td>
<td><img src="image19" alt="Graph" /></td>
<td><img src="image20" alt="Graph" /></td>
</tr>
</tbody>
</table>
IVIVE & Allometric Scaling

In vitro human data → IVIVE → In vivo human PK

In vivo animal data → Allometric Scaling

Ward & Smith 2004
Why Simcyp Rat?

What shall I do with the *in vivo* animal data?

IVIVE in rat (Simcyp Rat)

- **Yes**
- **No**

Additional Data

IVIVE in human (Simcyp)
What Rat?

A random selection of rat studies were taken from DMD (2005-2008)

- 75% used Sprague-Dawley; 20% used Wistar
- 90% used males only; 10% used both males and females

Sprague-Dawley data used where available.

Male

250 g

No variability

Create your own rat
Predicted vs. observed (Igari et al. 1982) tissue distribution of diazepam in rat (1.25 mg/kg, iv)

- **Plasma**

- **Heart**

- **Lung**

- **Muscle**
“Everything should be made as simple as possible, but not simpler.”
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- Roche
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