**PBPK Modelling and its Applications to Predict Transporter-Mediated Drug-Drug Interactions**

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**Different PK models**

- **Empirical**
- **Compartmental**
- **Physiological**

GT Tucker (Basic PK Course)

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**PBPK Modelling – Not a New Idea!**

**Teorell 1937**

A mathematical expression of processes involved.  
Understanding of different influencing factors on time and concentration in target tissue(s).  
Using this knowledge to achieve a desired therapeutic response.
Dealing with ADME Properties

Bioavailability: release, dissolution, stability, permeability, efflux and/or uptake transport, gut wall and hepatic first pass metabolism, ...

Distribution: unbound fraction, blood flow, efflux and/or uptake transport, organ size, HSA, ...

Metabolism: unbound fraction, efflux and or uptake transport, enzyme abundance, blood flow, HSA, Hematocrit, induction, inhibition, ...

Excretion: renal clearance, re-absorption, pH effects, active transport, biliary secretion, ...

The Need for Systems Pharmacology Approach

Systems pharmacology can be defined as the quantitative analysis of the dynamic interactions between several components of a biological system with the goal of understanding the behaviour of the system as a whole, as opposed to the behaviour of its separate components.

Inherent in the development of systems clinical pharmacology is a need for models that are physiologically realistic enough to provide accurate systems information yet retain sufficient simplicity to be computationally feasible - in other words, what Vicini [9] describes as 'fit-for purpose' models. However, encouraging progress has been made in predicting individual and even population pharmacokinetics from models that combine biological systems information with physicochemical drug characteristics [10].

Clinical Pharmacology & Therapeutics 2010
Systems Approach: Inter-Individual Variability in PK

Reference to Success Story!

A Framework for Assessing Inter-Individual Variability in Pharmacokinetics Using Virtual Human Populations and Integrating Genomic Knowledge and Physical Chemistry, Biodrug, Anatomy, Physiology, and Genomics: A Tale of Intevo-Up vs a Top-Down Recognition of Covariates

Mechanistic IVIVE & PBPK

Population PK (PD) Covariates & Study Design

In Vitro - In Vivo Extrapolation (IVIVE)

Mechanistic Models
Scaling factors

Hepatic Clearance

In vitro CLu\text{int}\text{per g Liver}

Scaling Factor 1

Scaling Factor 2

CLu\text{int}\text{per Liver}

Scaling Factors in Human IVIVE

HHEP \mu L.min^{-1} 10^6 cells x HPGL

HLS9\mu L.min^{-1} SPPGL

HLM mg protein x MPPGL

HLC x Liver Weight CPPGL
The Segmental-Segregated Flow Model

(Tam et al. 2003)

The Advanced Dissolution, Absorption & Metabolism (ADAM) Model

Jamei et al. 2009 and Darwich et al. 2010

One Segment in the ADAM Model

Jamei et al. 2009 and Darwich et al. 2010
Inter-individual Variability & fa

M Jamei et al, LogP 2004, Switzerland

Yu et al. (1998)

Example of Co-Morbid Obesity & Surgery

BPD-DS: Bilio-Pancreatic Diversion with Duodenal Switch

GBP: Gastric By-Pass (GBP)

ADAM with BPD-DS or GBP

Enterocytes

PBPK Distribution Model

Detail features .....
Predicting $V_{ss}$ knowing distribution into individual tissues is (Sawada et al., 1984):

$$V_{ss} = V_p + \sum_{t} V_t 	imes E : P + \sum_{t} V_t 	imes P_{tp}$$

$V_p$ = volume of plasma; $V_t$ = tissue (t) volume

Erythrocyte : Plasma partition coefficient

$$E : P = \frac{C_{Ep}}{C_{Ep}}$$

Tissue : Plasma partition coefficient

$$K_t = P_{tp} = \frac{C_{Ep}}{C_{Ep}}$$

Determining Tissue Volumes

System data and their inter-correlations

Disease | Age | Gender | Weight | Height

Adipose | Brain | Bone | Gut | Heart | Kidney | Liver | Lung | Muscle | Skin | Plasma | Spleen | Erythrocytes

Organs/Tissue Distributions

Lungs | Liver | Stomach | GI Tract | Heart
Monte Carlo (MC) vs Correlated Monte Carlo (CMC) Sampling

A randomly generated subject using MC sampling

Randomly generated subjects using CMC sampling

The Complexity of Covariate Effects

Genotypes (Distribution in Population)

Renal Function

Serum Creatinine

Age (Distribution in Population)

Enzyme Abundance

Brain Volume

Liver Weight

Cardiac Output

Intrinsic Clearance

Heart Volume

Liver Volume

Cardiac Index

Body Fat

Height

Body Surface Area

Sex (Distribution in Population)

Ethnicity

Disease

Age

Body Fat

Body Surface Area

Sex

Ethnicity

Disease

Age

The Complexity of Covariate Effects

Jamei et al. (DMPK, 2009)

Prediction of Tissue:Plasma Partition Coefficients (Kp)

One of the most challenging aspects of PBPK modelling is prediction of Kp.

Two commonly used mechanistic approaches are:

1. Poulin and Theil* (Berezhkovskiy** correction)
2. Rodgers and Rowland***

Similarities:
 Passive diffusion and perfusion-limited tissues models

Main differences:
 Separate models according to compound type (pKa)
 Considering ionisation
 Acidic phospholipid binding (Kap)
 Extracellular compartment protein binding (Kap)

Summary of PBPK-IVIVE M&S in submissions

From July 2008 to June 2010, the FDA reviewed 7 investigational new drug (IND) and 6 new drug applications (NDA) submissions containing PBPK modeling and simulations conducted by sponsors.

In addition, FDA reviewers conducted PBPK modeling and simulations to support clinical pharmacology reviews of another 4 NDA submissions for which the sponsors did not use PBPK.

As a comparison, in the 3 years before 2008, FDA received only 2 submissions containing PBPK modeling and simulations. Many of the PBPK modeling and simulation evaluations addressed questions relating to DDIs; others addressed pediatric dosing, the impact of hepatic impairment on drug exposure, and the impact of multiple factors on drug exposure.

(Zhao et al., 2011)

0.66 per year → 8.5 per year

>12 FOLD INCREASE

An Essential Read on PBPK

Physiologically-Based Pharmacokinetics in Drug Development and Regulatory Science

Adams, David J. "CP201C and CB201C: An Essential Read on PBPK." Ann Rev Pharmacol Toxicol 2011; 51: 45-73
Questionnaire Results: Transporters Focus Group (2006)

Relative Expression Factor (REF): Gut

Fig. 5: Western blot analysis of P-gp expression in human intestine and Caco-2, MDCK, and MDR-MDCK monolayers. For human intestine, duodenum, jejunum, and ileum samples were taken at 26, 11, and 13 feet along the jejunum duodenum, respectively. For each lane, 15 μg total protein was loaded. The expression of P-gp was quantified as described in Materials and Methods section. P-gp expression was quantified by integrated optical density (IOD) analysis as 1.15.

REF = 2064/1014 = 2.04
Troutman & Thakker, Pharm Res 2003
Bias in Estimation of Transporter Kinetic Parameters

The reanalysis of the experimental data using the new model revealed that the $K_m$ values defined for the intracellular concentration were almost the same among the cells expressing various levels of P-gp for each substrate.

Shirasaka et al. (2008), J Pharm Sci
Tachibana et al. (2010), Pharm Res

See also Kakwas and Pollack (2007), Pharm Res and Lumen et al. (2010), DMD

The changes in the experimental conditions caused 1 order of magnitude variation in $K_{m,app}$ and a 5-fold difference in $V_{max,app}$. However, fitting the concentration data into a compartmental model which accounted for the aqueous boundary layers, cell membranes and cellular retention suggested that the P-gp function per se was not altered.

It was the differences in the passive transfer of quinidine which changed the apparent transport kinetics.

Permeability-Limited Model (Liver)

EW: Extracellular Water
NL: Neutral Lipids
AP: Acidic Phospholipids
IV: Intracellular Water
NP: Neutral Phospholipids
**Scaling Approach for Liver Transporters**

Liver: Scaling to and of Hepatocyte Data

<table>
<thead>
<tr>
<th>HEK-293 HepG2, Oocytes etc.</th>
<th>HEP</th>
<th>HEPEF</th>
<th>CLint/k per g Liver</th>
<th>Scaling Factor 1</th>
<th>Scaling Factor 2</th>
<th>Scaling Factor 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>OATP1B3</td>
<td>HPGL</td>
<td></td>
<td>Expression per 10⁶ Hepatocyte cells</td>
<td>Expression per 10⁶ cells in vitro system</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OATP1B1 2000 1000 1000/2000 = 0.5

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Application of Kinetic Models in In Vitro Assays

Different processes have an effect on the distribution of a compound:
- Passive diffusion
- Active uptake or efflux
- Protein binding

Kinetic studies in combination with in vitro assays have highlighted the importance of assessment of these processes.

Baker 2007; Poirer 2008; Paine 2008

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Decision Tree for P-gp Mediated Interaction

Bi-directional transport assay with a probe P-gp substrate in Caco-2 or MDRI-overexpressed polarized epithelial cell lines

Net flux ratio of the probe substrate decreases with increased concentrations of the investigational drug

Likely a P-gp inhibitor

Determine Ki or IC₅₀ of the inhibitor

[RI/IC₅₀ (or Kᵢ) > 0.1 or (3)IC₅₀ (or Kᵢ) = 10]

An in vitro drug interaction study with a P-gp substrate such as digoxin is recommended.


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10/06/2011
Inhibitor Concentrations - Verapamil

Dose = 120 mg, MW = 454.6, fu= 0.1, multiple dose, in a 5x5 simulation:

$[I]_1 = 1.1 \mu M$

$[I]_2 = 120mg/250mL = 1056 \mu M$

Bias in Estimation of Transporter Kinetic Parameters

Effect of not considering aqueous boundary layer resistance on $K$ estimates.

Results indicate that aqueous boundary layer resistance can bias $K_i$ and $K$ estimates from over-expression systems, where the extent of bias is determined by transporter expression level and substrate affinity.

Balakrishnan et al. (2007), J Pharmacol Exp Ther

Transports Inhibition

% inhibition transport of a substrate

$IC_{50} = \frac{\text{max} \text{ CL}_{0,\text{int}}}{K_{\text{int}}} \left[ \frac{([H]_0 - C_i)}{K_i} \right]$

Keogh and Kunta, 2006

Eberl et al., 2007

$IC_{50}$ determination for clarithromycin varied more than 20-fold:

Keogh and Kunta, 2006: > 100 \mu M

Eberl et al., 2007: 4.1 \mu M
Jmax (pmol/min/million cells) = 50
Km (uM) = 1
Ki (uM) = 0.1
Brain 4-Compartmental Model

- CSF: circulation, proteins, pH, volume, ...
- Brain: anatomy, physiology, proteins, enzymes, ...
- BBB and BCSFB permeability values
- Active transport in any of the barriers

System parameters

Drug-related parameters

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