Expert Opinion on human pharmacokinetic prediction

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The issue in prediction

I wonder what the PK profiles will be in me?

Often many compounds

Concerned with initial prediction

Why interested in predicting human PK?

- To help in preclinical candidate selection.
- To help predict the initial doses in ‘first-in-human’ (Phase I) studies.
- To minimize the need for animal testing of ‘undesirable’ compounds.
- To help predict the likely PK within the target patient population.
- Current comments deal primarily with small molecules
• Where have we been?
• Where are we now?
• Where are we going?
Allometry (body size scaling)

Assume: clearance (CL) and volume of distribution (V) scale to body weight (W).

\[ CL = a_1 W^{a_2} \]
\[ V = a_3 W^{a_4} \]

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\[ CL = a_1 W^{a_2} \quad a_2 = 0.75 \]
\[ V = a_3 W^{a_4} \quad a_4 = 1 \]
Allometric Scaling

Volume of Distribution

Clearance


Too often focus has been on parameters rather than shape

Same AUC (clearance)

Using predicted CL and Vss

Minimum Effective Concentration

True profile
Even though some of the early focus was on shape

Historical problem in defining ‘success’ when dealing with shape


Allometry: Comment

- Very widely used, based largely on historic data
- iv kinetics (clearance, volume of distribution, half-life)
  - Success generally taken as within a factor of 2
  - Generally have used a minimum of 3 species, sometimes more.
  - Prediction of clearance particularly poor for low clearance (stable), highly metabolized compounds
  - This is the most common category in modern drug development: error can be factor of 10.
**Allometry: Absorption**

- **Bioavailability:**
  - Not scalable allometrically
  - Generally, taken as average of 3+ animal species
  - Non-human primate often one, but not clear that it adds value.
  - **Challenging problem:** Formulations generally considerably different than administered during clinical development. Many compounds sparingly soluble (BCS Class 2 & 4).

**Common Problem**

- Generally, limited human intravenous data to check prediction of disposition kinetics owing to various hurdles, such as solubility, stability, safety, and perceived lack of need.
A more refined approach for prediction of human clearance

i. Partition clearance into hepatic and renal clearance

ii. Predict hepatic clearance from human in vitro metabolic data (e.g. microsomes, hepatocytes, or expression systems).

iii. No reliable accurate in vitro method to predict human renal (or biliary) clearance. Obtained through allometric scaling
Predicting Hepatic Clearance In Vivo from Human In Vitro Data - Strategy

**In vitro CL\textsubscript{int} (Vm/Km)**

Modeling and scaling of in vitro data to whole liver dimensions

**In vivo CL\textsubscript{int}**

Liver model (incorporate plasma protein binding and hepatic blood flow)

Hepatic Metabolic Clearance

+ biliary clearance (experimental)

**Hepatic clearance**

* CL\textsubscript{int}: Intrinsic clearance (within cell)

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Prediction of in vivo human metabolic clearance

![Graph showing predicted vs. observed in vivo CL\textsubscript{int} values](image)

**Predicted value** vs. **Observed in vivo CL\textsubscript{int}**

Observed in vivo CL\textsubscript{int} ml/min/SL/BW

Observed in vivo intrinsic clearance
Comment: in vitro methodology

- Most work with CYPs
- Not very good for metabolically stable compounds—little/no depletion seen.
- Tendency for underprediction
- More work needed to extend in vitro metabolic approaches to Phase II processes (eg glucuronidation, acetylation, hydrolysis..) and include transporters.

Where are we now?
Allometry

- Not much further progress, despite many publications.
- Most analysis has been retrospective (already have human data), rather than industrial setting of prospective prediction.
- Has been extended to compounds primarily eliminated unchanged, involving transporters.
- Continues to be only method for biologics (primate).
- Questions have been raised as to the value of including data from several species.

Whole body physiologically based (PBPK) model

Comprises a combination of
- **Physiological data** e.g.
  - Tissue weights/composition
  - Tissue blood flows
  - Enzymes, transporters etc
- **Drug data**
  - Tissue affinity
  - Tissue Permeability
  - Organ clearance
  - *In vitro* data
- **Whole Body Model**: Degree of complexity depends on intended application.

Tackling the problem of human prediction

Enzyme/transporter Activity
In vitro

Protein Binding
In vitro

Tissue Affinity
In vitro

Tissue Weights, Flow
Anatomic, physiologic

BLOOD

Rat
Human

ADIPOSE

Rat
Human

Prediction

Oral Bioavailability

**PBPK prediction of FIH PK**

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<th>cLog P</th>
<th>Dose (mg)</th>
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Gibson et al. Xenobiotica 2009

**Plasma Concentrations Predictions in Human**
(Experience of Roche)

**Allometry**

average fold error = 3.80

**PBPK**

average fold error = 1.91
Valsartan: Human PBPK prediction

Nonmetabolised, transport dependent

Intravenous

Oral


An industrial (Roche) PBPK decision tree for predicting human PK

PBPK: Comment

• Although more complex PBPK models highly mechanistic, with scope for integrating disparate knowledge and data.
• These models address the question: what determines an observed PK profile.
• Potential for predicting temporal events in tissues as well as plasma.
• Can readily be extended to clinical development: DDIs, age, genetics etc
• User-friendly software increasingly available.
• Increasingly being adopted by industry.

Simulation of individual profiles within the population using PBPK

Incorporates genetic variability in 2D6 and in vitro metabolic activity, as well as physiological parameters.

• Sometimes, little confidence in either allometry (e.g., large interspecies variability) or PBPK (e.g., little to no turnover in vitro)
**Microdosing: An empirical approach**

- Administer a minute dose (1/100th expected pharmacologic dose, ≤ 0.1 mg) to human. Requires minimal animal safety data.
- Very early human data before undertaking extensive animal studies.
- Concept: Characterizes human PK at pharmacologic doses, assuming linear (dose independent) PK.

**Midazolam oral microdose versus oral therapeutic dose (normalised for dose)**

![Graph showing plasma concentration over time for microdose and therapeutic dose of Midazolam with an example of LC-AMS and HPLC-AMS methods for measurement.]

*AMS — Accelerated mass spectrometry

Microdosing: Comment

- Total 30 (small) drugs reported in literature
- Approximately 80% successfully predicted PK at therapeutic doses, including shape of curve.*
- (Many more unpublished studies by companies)
- Generally, iv microdose predicts disposition kinetics following therapeutic doses

* Linearity defined as being within a factor of 2.

FEXOFENADINE

IV and oral microdoses, and IV tracer [14C]-fexofenadine (each 100 µg ~ 200 nCi). Mean ± SD dose normalised plasma profiles


Lappin et al Eur. J. Pharm. Sci. 40 125, 2010
**Microdosing: Comment**

- Some non-linearity, indicating saturation of one or more processes, *generally during oral absorption.*

![Graph showing non-linearity in microdosing data](image)

- Proposal that Oral PK linear if Dose/Km < 2.8 for CYP3A4 substrates and < 0.77 for PgP substrates (Tatsuhiko et al Pharm Res Online)

**Attempts to combine in vitro methods (to characterise saturable metabolism, transporters) with microdosing data to improve prediction of PK at therapeutic doses, is under consideration.**

- **A strategy:** evaluate backup compounds while taking lead candidate through Phase 1.
Where are we going?

- Various strategies exist for the prediction of human PK.
- Each has its strengths and weaknesses.
- There is general movement towards the development and use of more mechanistic approaches at the candidate selection stage and beyond.