Quantitative drug interaction prediction system as support system for drug metabolism interactions

P. Bonnabry
J. Sievering, T. Leemann, P. Dayer
University hospitals, Geneva, Switzerland

Verona
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Drug interactions are a major source of clinical problems. Pharmacodynamic interactions can generally be anticipated on the basis of the pharmacologic effects of drugs. Pharmacokinetic interactions are difficult to predict for the clinician, both qualitatively and quantitatively. Cytochrome P450 metabolism constitutes the major site of pharmacokinetic interactions.
Cytochrome P450 is a family of multiple isozymes made up of at least 500 genes.

Only 12 human drug-metabolizing P450s have been characterized to varying degrees.

6 isozymes account for most of the identified cytochrome P450 mediated metabolism.
Figure 2. (a) Relative proportion of pharmaceuticals metabolized by the major human cytochrome P450 isoforms, (b) relative concentrations of these isoforms in human liver. Data for (a) have been obtained by survey of the major drug metabolism journals over the past 6 years and represent over 100 different drugs. Data for (b) are reported by Shimada et al. (1994).
**IN VITRO STUDIES**

**Pros**
- Accurate determination of the isozymes involved
- Determination of inhibition parameters
- Determination of inhibition mechanism

**Cons**
- Partial information
- PK not taken into account
- Interpretation?

In vitro results must be integrated in a global approach (extrapolation techniques, in vivo studies)

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### Interpretation of in vitro data

<table>
<thead>
<tr>
<th></th>
<th>CYP1A2</th>
<th>CYP2C19</th>
<th>CYP2D6</th>
<th>CYP3A4</th>
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</thead>
<tbody>
<tr>
<td>theophylline</td>
<td>&gt;100</td>
<td>87</td>
<td>5.1</td>
<td>&gt;100</td>
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<tr>
<td>S-mephenytoïn</td>
<td>56</td>
<td>7.7</td>
<td>0.60</td>
<td>24</td>
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<tr>
<td>sparteine</td>
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<td>0.43</td>
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<tr>
<td>testosterone</td>
<td>&gt;100</td>
<td>0.15</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

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<th>CYP2D6</th>
<th>CYP3A4</th>
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<tbody>
<tr>
<td>Citalopram</td>
<td>&gt;100</td>
<td>87</td>
<td>5.1</td>
<td>&gt;100</td>
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<tr>
<td>Demethyl-</td>
<td>&gt;100</td>
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<td>&gt;100</td>
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<tr>
<td>Didemethyl-</td>
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<tr>
<td>Fluoxetine</td>
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<td>5.2</td>
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<td>Norfluoxetine</td>
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<tr>
<td>Fluvoxamine</td>
<td>0.1</td>
<td>8.2</td>
<td>19</td>
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<tr>
<td>Paroxetine</td>
<td>50</td>
<td>7.5</td>
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<td>&gt;100</td>
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<tr>
<td>Sertraline</td>
<td>&gt;100</td>
<td>2.0</td>
<td>0.70</td>
<td>&gt;100</td>
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</table>

\( K_i \) [\( \mu M \)]
QUALITATIVE DEDUCTIONS

3 tables:
- substrates
- inhibitors
- inducers

based on:
- in vitro studies
- in vivo studies
- logic deductions

Part of inhibitor’s table

IN VITRO/IN VIVO LINK

- Ki = concentration at which the in vitro rate of metabolism is diminished by 50%
- When the in vivo unbound concentration of the drug equals Ki, then the activity of the inhibited isozyme will be reduced by 50%
- The metabolic clearance of all substrates metabolized by the inhibited enzyme will be reduced
IN VITRO-IN VIVO EXTRAPOLATION (Q-DIPS)

- Method based on several prediction models, corresponding to several specific situations.
- In the absence of knowledge of these specificities, strategy consist to predict with the simplest case model.
- As the number of hypotheses increases, the confidence level in the results decreases!
IN VITRO-IN VIVO EXTRAPOLATION (Q-DIPS)

**Hypotheses for the simplest case model**

- Unbound inhibitor concentrations in plasma and effective concentrations at the enzyme site are equal
- Metabolites are not themselves inhibitors
- Substrate elimination is controlled by a single enzyme
- The substrate has a low extraction ratio
- There is a single reversible inhibition mechanism
IN VITRO-IN VIVO EXTRAPOLATION (Q-DIPS)

The **in vivo** effect of an inhibitor can be modeled by defining an *Inhibition Index* ($I_I$):

**Simplest case model**

$$I_I = 1 + \frac{f_u \cdot I_{pl}}{K_i}$$

$I_{pl}$: inhibitor total concentration in plasma

$f_u$: fraction unbound in plasma

**More complex models** can be used to simulate more complex situations (intrahepatocyte accumulation, multi-drug inhibition...)

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IN VITRO-IN VIVO EXTRAPOLATION (Q-DIPS)

The **Inhibition Index** presents interesting features:

- it is characteristic of a given **enzyme/inhibitor pair**
- the **kinetics** of a drug's Inhibition Index can be simulated
Inhibition of metabolism is described both in vitro and in vivo for several selective serotonin reuptake inhibitors (SSRI) antidepressants. Profile and intensity of inhibitions vary between the different drugs of the class. Predictions were done with a model including intrahepatocyte accumulation (and role of metabolite for fluoxetine)

\[
I_I = 1 + \frac{\alpha \cdot f_u \cdot I_{pl}}{K_i}
\]

\(\alpha = \text{ratio hepatocyte/plasma}\)
SSRI: CYP2D6 INHIBITION

Intrahepatocyte accumulation model ($\alpha=20$)

Time [h]

Inhibition Index

- Citalopram (40mg/d)
- Fluoxetine (20mg/d)
- Fluvoxamine (100mg/d)
- Paroxetine (20mg/d)
- Sertraline (50 mg/d)
SSRI: CYP1A2 INHIBITION

Intrahepatocyte accumulation model ($\alpha=20$)

Inhibition Index

Time [h]

Citalopram (40mg/d)
Fluoxetine (20mg/d)
Fluvoxamine (100mg/d)
Paroxetine (20mg/d)
Sertraline (50 mg/d)

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SSRI: CYP3A4 INHIBITION

Intrahepatocyte accumulation model ($\alpha=20$)

**Inhibition Index**

- Citalopram (40mg/d)
- Fluoxetine (20mg/d)
- Fluvoxamine (100mg/d)
- Paroxetine (20mg/d)
- Sertraline (50 mg/d)
**SSRI: IN VIVO VALIDATION**

- **CYP2D6**: strong inhibition by fluoxetine and paroxetine
- **CYP1A2**: selective and very strong inhibition by fluvoxamine
- **CYP3A4**: very moderate inhibition by fluvoxamine

- **Citalopram** and **sertraline** seem to be the safer drugs on the basis of their interaction profiles, but few in vivo data exist to confirm these predictions.
Q-DIPS: DRUGS STUDIED

- SSRI antidepressants
- Azoles antifungals
- NSAID’s
- HIV protease inhibitors
- HMG-CoA reductase inhibitors
- Mibefradil

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## QUANTITATIVE VALIDATION

<table>
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<tr>
<th></th>
<th>Number</th>
<th>% total</th>
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<td>64%</td>
<td>79%</td>
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<td>Wrong prediction</td>
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<tr>
<td>Validation impossible</td>
<td>8</td>
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</tr>
<tr>
<td></td>
<td>Total</td>
<td>42</td>
<td>100%</td>
</tr>
</tbody>
</table>
Concentrations at the active enzymatic site are difficult to estimate and this factor is not investigated in classic experimental procedures.

Main parameters (in vitro, PK) are generally poorly characterized for metabolites.

Possible saturation of enzymes during first pass is not taken into account by the simplest case model.

Impact of irreversible inhibition is not predictable with the simplest case model.
UNCERTAINTY (IN VIVO STUDIES)

- Choice of selective prototypes
- First-pass metabolism
- Half-life
- Inhibitor dose
- Single dose vs chronic administration
- Interindividual variability
«GOOD INTERACTIONS PRACTICE (1)»

- **In vitro** characterization and quantification of isozymes responsible for **metabolism**
- **In vitro** evaluation of potential to **inhibit** specific P450s isozymes and determination of the mechanism
- **Extrapolation** of inhibition data to the in vivo situation
- **Evaluation** of in vivo studies that would be useful to perform
In vivo potential of selective inhibitors to reduce the elimination of the drug

In vivo potential of the drug to inhibit the metabolism of known prototype substrates during chronic administration

Impact of specific conditions (poor metabolizers, renal insufficiency,...) on the interaction profile
CONCLUSIONS

- In vitro/in vivo extrapolation techniques are useful to help predict in vivo impact a priori, but their reliability directly depends on the exhaustivity and the accuracy of in vitro and pharmacokinetic data.
- The investigation of drug interactions during drug development should sequentially include in vitro studies, extrapolation techniques and well-designed clinical studies.