Higher relative bioavailability following extended release oral formulations: Exploring the potential mechanisms and associated parameter space using a physiologically-based pharmacokinetic approach

Yoshiteru Kamiyama1,2, Andrés Olivares-Morales3, Adam S. Darwich1, Amin Rostami-Hodjegan1,3
1- Centre of Applied Pharmacokinetic Research, University of Manchester, UK
2- Analysis & Pharmacokinetics Labs, Astellas Pharma Inc., Japan
3- Simcyp Ltd, Sheffield, UK

Introduction and Purpose

- Gastrointestinal (GI) absorption and metabolism are important for determining the disposition of orally administered drugs.
- Extended-release (ER) formulations are used to prolong the duration of drug delivery to the systemic circulation and to reduce the frequency of dose administration.
- However, ER formulations may display an altered extent of oral drug bioavailability as compared to immediate-release (IR) formulations, this may vary based on the interplay between the physicochemical characteristics of the drug and GI disposition such as: metabolic enzyme and efflux transporter affinity [1].
- The Advanced Dissolution, Absorption and Metabolism (ADAM) model (Figure 1), incorporated into the physiologically-based pharmacokinetic (PBPK) simulator Simcyp® v12.2 was used to assess pharmacokinetic parameters associated with an altered bioavailability for ER formulations relative to that of IR.

Method

- Information on relative bioavailability of ER and IR was collated from published literature. Weighted mean (Wj), ER/IR, AUC ratio and variances (s2) were calculated based on number of subjects (w) and mean AUC ratio (x) in the ith study (Eq. 1 and 2).

\[
W_j = \sum w_i, \quad s^2 = \frac{\sum w_i (x_i - \bar{x})^2}{\sum w_i - 1} \quad (1) \quad \text{Eq. 1} \text{ and } 2
\]

- Hypothetical compounds were simulated based on oxycodin (molecular weight: 357.45 g/mol and LogP: 2.6) by varying drug and formulation specific parameters including: pKa, solubility, permeability, Km for CYP3A4 (Km(CYP3A4)), maximum metabolic rate (Vmax(CYP3A4)), Km and Vmax for P-gp (Vmax(Fp) and Km(Fp), respectively) (Table 1).

- Simulated AUC, fraction of drug absorbed into the gut wall (Fp), and fraction that escapes gut wall extraction (Fr) were examined for differences between IR and ER three formulations (ERj) where first order rate of release from formulation (Km(Fl)) were 3.79 (IR), 0.32 (ER1), 0.16 (ER2), and 0.03 (ER3) (Figure 2).

Results

- A large variation of ER/IR AUC ratios was observed among the 21 identified drugs (Figure 3).

Table 1. Pharmacokinetic parameters of simulated hypothetical compounds.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solubility (Sol)</td>
<td>mg/mL</td>
<td>0.04</td>
<td>0.06</td>
<td>0.12</td>
</tr>
<tr>
<td>Permeability in Caco-2 cell (Papp)</td>
<td>× 10^8 cm/s</td>
<td>0.019</td>
<td>0.759</td>
<td>74.5</td>
</tr>
<tr>
<td>Vmax for CYP3A4 (Vmax(CYP3A4))</td>
<td>pmol/min/mg MS protein</td>
<td>0.001</td>
<td>100</td>
<td>40000</td>
</tr>
<tr>
<td>Km for CYP3A4 (Km(CYP3A4))</td>
<td>μM</td>
<td>0.1</td>
<td>2</td>
<td>200</td>
</tr>
<tr>
<td>Vmax for P-gp (Vmax(Fp))</td>
<td>pmol/min</td>
<td>0.01</td>
<td>2</td>
<td>20000</td>
</tr>
<tr>
<td>Km for P-gp (Km(Fp))</td>
<td>μM</td>
<td>0.1</td>
<td>2</td>
<td>200</td>
</tr>
<tr>
<td>pKa</td>
<td>-</td>
<td>4.5</td>
<td>Neutral</td>
<td>8</td>
</tr>
</tbody>
</table>

- An increase in Vmax(CYP3A4) from 0.001 to 40,000 pmol/min/mg microsomal protein resulted in an increase in Fp of up to 2.2-fold for the ER formulations as compared to IR for all ionic classes (Figure 4-6).
- Alternation of Km(Fp) from 0.1 to 200 μM caused a minor increase in Fp when comparing between ER and IR formulations (Figure 4-6).
- The ER/IR ratios of Fp and AUC displayed up to a 1.6-fold increase for basic compounds at a low Km(Fp) (Figure 4).

Conclusions

Analysis of the simulation study identified a higher affinity for CYP3A4 and P-gp to be associated with a larger relative bioavailability for ER as compared to IR formulations. These findings may have implications for study design and pharmacotherapy as well as the relative exposure of metabolite versus the parent compound.

References