Incorporation of the time-dependent postprandial increase in splanchic blood flow into a PBPK model to predict the effect of food on oral propranolol pharmacokinetics.

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Introduction

Following a meal, increased blood flow to the splanchic circulation, which includes the liver (via the portal vein) and the small intestine, can result in altered clearance and bioavailability of high-extraction drugs (e.g., propranolol) (Figure 1).

- Commercially available physiologically based pharmacokinetic (PBPK) models often incorporate the postprandial increase in splanchic blood flow as a fixed, fed/fasted ratio applied to all the splanchic organs.
- However, it has been postulated that accounting for the time-dependent changes in splanchic blood flow is necessary to model the increase in exposure of orally or even intravenously administered high extraction drugs in the fed versus fasted state.¹

Objective

To extend a PBPK model to incorporate the time-dependent change in splanchic blood flow (TD-Qsplanch) and to use the model to predict the food-effect on exposure to orally administered propranolol.

Methods

- Relevant physicochemical, in vitro and in vivo (fasted state only) data were incorporated into a PBPK model (first order absorption and minimal PBPK model) within Simcyp (Version 13.2) to simulate the propranolol plasma concentration time profile.
- For preliminary simulations, a PBPK model in Simulink (V2013a) that uses similar structure to the Simcyp minimal PBPK model was extended to incorporate a model describing the post-prandial TD-Qsplanch. The model included changes in small intestine and liver blood flows and maintained mass balance in blood flow rates.² The fed and fasted state plasma concentration profile was predicted for a population representative healthy volunteer subject.
- To investigate interindividual variability in the fed/fasted state propranolol exposure, the post-prandial TD-Qsplanch model was incorporated into the Simcyp Simulator (Version 14.1). Predictive simulations were run using the Sim-Healthy Volunteer population (20 trials of 10 individuals, age 20-50 years, 50% female).

Results

- The PBPK model for propranolol adequately recovered the plasma concentration time profile for fasted state studies (Figure 2).


Figure 2. Simulated and observed propranolol plasma concentration time profile in the fasted state following a single oral dose of 80 mg propranolol. Observed data (open circles) are from (A) Liedholm et al. 1990, (B) McLean et al. 1981, (C) Meleander et al. 1977, (D) Olanoff et al. 1986, and (E) Walle et al. 1981. Solid black lines represent the mean of 20 trials, solid grey lines represent the mean of an individual trial and dashed grey lines are the 5th and 95th percentiles. Simulated trial design was matched to the clinical study in terms of study size, subject age and proportion of females.

- Assuming a fixed ratio increase in splanchic blood flow, the simulated fed/fasted AUC and Cmax ratios were 1.01 and 1.14, respectively (Figure 3a). The increase in hepatic clearance balances the increase in bioavailability so there is little change in AUC in the fed state.
- Using the TD-Qsplanch model, the simulated fed/fasted AUC and Cmax ratios were 1.28 and 1.32, respectively (Figure 3b). The larger increase in blood flow at earlier time points has a greater effect on bioavailability with only a transient effect on hepatic clearance.


Figure 3. Predicted fed/fasted (A) AUC and (B) Cmax ratios for propranolol using the TD-Qsplanch model. Circles represent the geometric mean, error bars the range of values and dashed lines are the 5th and 95th percentiles. Closed circles are simulated trials while open circles are observed data, as indicated in Table 1.

Table 1. Summary of the predicted fed/fasted (A) AUC and (B) Cmax ratios for propranolol using the TD-Qsplanch model.

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial group</th>
<th>AUC</th>
<th>Cmax</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Geomean</td>
<td>Min</td>
</tr>
<tr>
<td>Liedholm et al. 1990</td>
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<td>0.39</td>
</tr>
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<td>Alunoff et al. 1986</td>
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<td>1.97</td>
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<tr>
<td>Meleander et al. 1977</td>
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<td>0.50</td>
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<tr>
<td>Walle et al. 1981</td>
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<td>1.97</td>
<td>0.87</td>
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</table>

Conclusion

- Extension of the PBPK model to include post-prandial TD-Qsplanch model improved the ability to capture the increased exposure to oral propranolol in the fed state.
- However, interindividual variability in the effect of food on propranolol was underestimated. A number of factors not included in the current model may contribute to interindividual variability, including:
  Food effects on gastrointestinal physiology that may affect the rate and extent of propranolol absorption and are not accounted for in the first order absorption model used in this study.
  Intercocassion variability.³
  Differences in meal composition⁴ and the precise timing drug dose and meal.
  Pharmacodynamic effect of propranolol on hepatic blood flow.⁵

References