Incorporation of the time-dependent postprandial increase in splanchnic 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 splanchnic 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 splanchnic blood flow as a fixed, fed/fasted ratio applied to all the splanchnic organs.
- However, it has been postulated that accounting for the time-dependent changes in splanchnic 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]

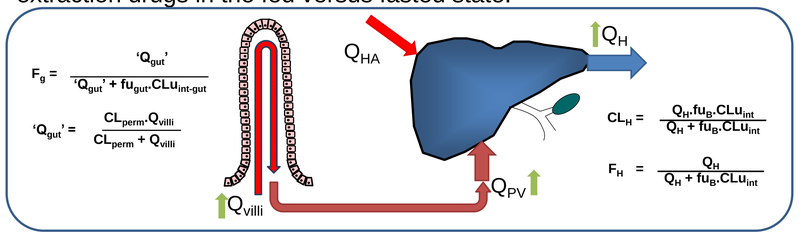

Figure 1. Postprandial increase in blood flow to the liver (Q_H) and villi of the small intestine (Q_{villi}) can impact on first pass clearance by the gut and liver (F_G and F_H) and systemic clearance by the liver (CL_H). $CLu_{int\text{-}gut}$, unbound intrinsic clearance in the gut; fu_{gut}, free fraction in enterocytes; CL_{perm}, permeability clearance; fu_B, free fraction in the blood; CLu_{int}, unbound hepatic intrinsic clearance; The 'Q_{gut}' model is used for a first order absorption model.

Objective

To extend a PBPK model to incorporate the time-dependent change in splanchnic blood flow (TD-$Q_{Splanch}$) 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-$Q_{Splanch}$. 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-$Q_{Splanch}$ 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).

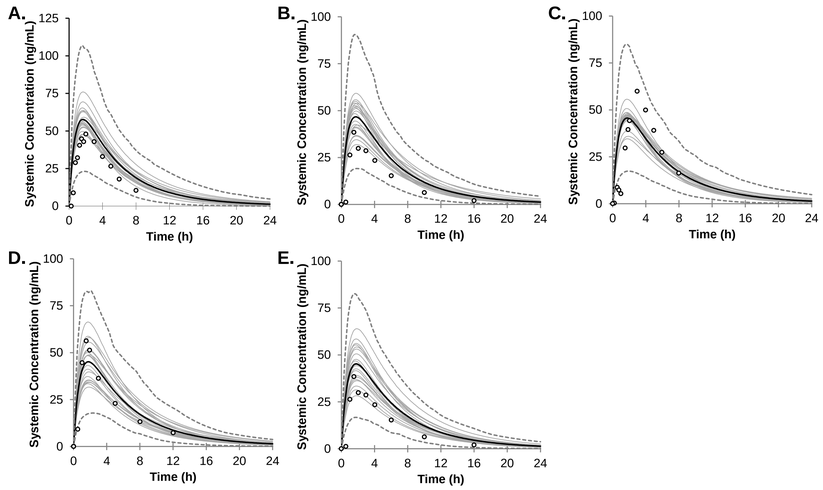

Figure 2. Simulated and observed propranolol plasma concentration time profile in the fasted state following a single oral dose of 80 mg propranolol. Observed data (open circles) are from (A) Liedholm *et al*. 1990[3], (B) McLean *et al.* 1981[4], (C) Meleander *et al.* 1977[5], (D) Olanoff *et al*. 1986[6] and (E) Walle *et al.* 1981[7]. 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 splanchnic blood flow, the simulated fed/fasted AUC and C_{max} 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-$Q_{Splanch}$ model, the simulated fed/fasted AUC and C_{max} 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.

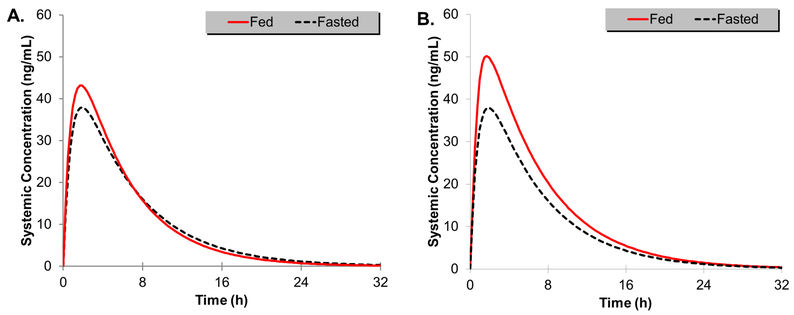

Figure 3. Comparison of the propranolol plasma concentration profile in the fed and the fasted state following 80 mg oral propranolol (A) assuming a fed state fixed ratio increase in splanchnic blood flow of 1.3 (Simcyp V13.2) or (B) using the TD-$Q_{Splanch}$ model (Simulink / Simcyp V14.1). Simulations were run for a population representative individual.

- The geometric mean of the simulated fed/fasted AUC and C_{max} ratios for 200 individuals using the TD-$Q_{Splanch}$ model were in reasonable agreement with geometric mean ratios from 5 clinical studies (Figure 3, Table 1).
- However, the range in values of fed/fasted AUC and C_{max} ratios were underpredicted (Figure 3, Table 1).

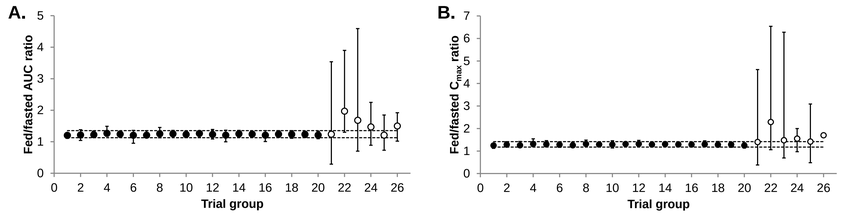

Figure 3. Predicted fed/fasted (A) AUC and (B) C_{max} ratios for propranolol using the TD-$Q_{Splanch}$ model. Circles represent the geometric mean, error bars the range of values and dashed lines are the 5th and 95th percentiles. Closed circles are simulated trials while open circles are observed data,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

Table 1. Summary of the predicted fed/fasted (A) AUC and (B) C_{max} ratios for propranolol using the TD-$Q_{Splanch}$ model.

Study	Trial group	Fed/fasted ratio: AUC Geomean	AUC Min	AUC Max	C_{max} Geomean	C_{max} Min	C_{max} Max
Simulated		1.23	0.95	1.49	1.29	1.12	1.54
Liedholm *et al.* 1990[3]	11	1.24	0.29	3.54	1.4	0.38	4.62
McLean *et al.* 1981[a,4]	12	1.97	1.30	3.9	2.29	1.06	6.54
McLean *et al.* 1981[b,4]	13	1.68	0.70	4.59	1.48	0.69	6.28
Meleander *et al.* 1977[5]	14	1.47	0.89	2.25	1.55	0.97	2.00
Olanoff *et al.* 1986[6]	15	1.21	0.73	1.85	1.42	0.48	3.09
Walle *et al.* 1981[7]	16	1.5	1.02	1.92	1.7	NA	NA

NA, not available. [a] Protein-lipid rich meal; [b] carbohydrate-rich meal.

Conclusion

- Extension of the PBPK model to include post-prandial TD-$Q_{Splanch}$ 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.
  - Interoccasion variability.[3]
  - Differences in meal composition[8] and the precise timing drug dose and meal.
  - Pharmacodynamic effect of propranolol on hepatic blood flow.[9]

References

1. McLean (1978) *Clin Pharmacol Ther*, 24:5-10; 2. Rose *et al.*, Development of a model of the time-dependent postprandial change in splanchnic blood flow. *9th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology*, Lisbon, Portugal, 31 March – 4 April, 2014 (Poster presentation); 3. Liedholm (1990) *Eur J Clin Pharmacol* 38:469-475; 4. McLean (1981) *Clin Pharmacol Ther* 30:31-34; 5. Meleander (1977) *Clin Pharmacol Ther* 22:108-112; 6. Olanoff (1986) *Clin Pharmacol Ther* 40:408-414; 7. Walle (1981) *Clin Pharmacol Ther* 30:790-795; 8. Moneta (1998) *Gastroenterology 95: 1294-301;* 9. Daneshmend (1981) *Br J Clin Pharmacol* 11: 491-496