Development of a model of the time-dependent postprandial change in splanchnic blood flow

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INTRODUCTION

- Following a meal, physiological changes occur that can impact upon drug absorption and elimination.
- 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).
- 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, 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.[5]

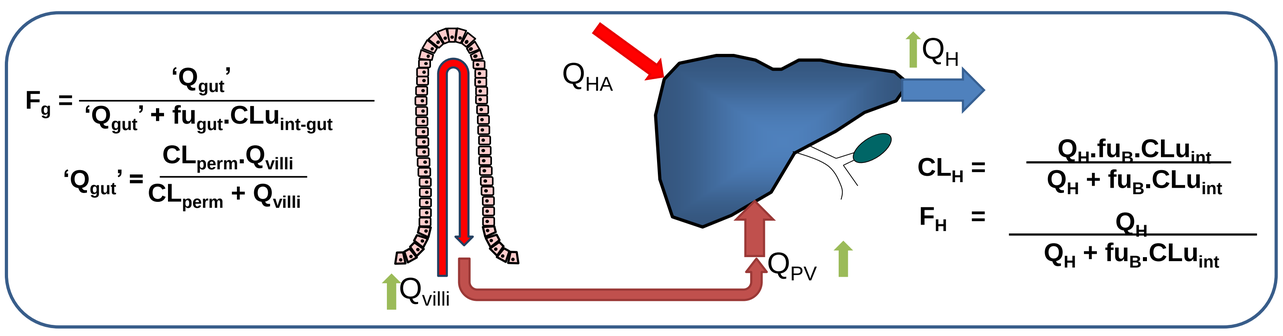

Figure 1. Postprandial increase in blood flow to the liver (Q_H) and villi of the small intestine (Q_{villi}) can impact on first pass clearance by the gut and liver (F_G and F_H) and systemic clearance by the liver (CL_H). $CLu_{int\text{-}gut}$, unbound intrinsic clearance in the gut; fu_{gut}, free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

AIM

- To review the literature to identify data describing the dynamic (time-dependent) change in the splanchnic blood flow following a meal and to build a model of the postprandial splanchnic blood flow profile that takes into account inter-individual variability (IIV).

METHOD

Data Collection and Analysis

Data on the postprandial change in blood flow of the splanchnic circulation in healthy adults were extracted from the literature using the US National Library of Medicine's online bibliographic database (PubMed). Any additional references in the recovered papers not found in the initial search were identified. Splanchnic blood flow profiles were extracted and used in the model development.

Model Description

- Equations describing the time-dependent increase in small intestine blood flow fed/fasted ratio ($\mathrm{Fe{:}\,Fa}_{Q_{SI}}(t)$) were based upon published data for the change in superior mesenteric artery (SMA) blood flow following a moderately high fat / high calorie meal.
- A linear equation was used to describe the increase in blood flow to the peak blood flow response (R_{max}) at time T_{max} where $t \leq T_{max}$.

$$\mathrm{Fe{:}\,Fa}_{Q_{SI}}(t) = 1 + \frac{(R_{max} - 1)}{T_{max}} \cdot t$$

- An exponential equation was used to describe the decrease in blood flow R_{max} to the fasted state for $t > T_{max}$, using the first order rate constant k_Q.

$$\mathrm{Fe{:}\,Fa}_{Q_{SI}}(t) = 1 + (R_{max} - 1) \cdot \exp^{-k_Q \cdot (t - T_{max})}$$

- Gastric emptying (GE) rate in part determines intestinal exposure to nutrients and was assumed to be a determinant of the IIV in $\mathrm{Fe{:}\,Fa}_{Q_{SI}}(t)$; the latter was assumed to return to the fasted state after 5 GE half-lives.
- Based upon published data[3,6] and the mean first order GE rate constant (k_s) for 100 healthy volunteers simulated using the default fed state settings in the Simcyp Simulator v13 R1, T_{max} was set to one gastric emptying half-life and k_Q was set to 5/4*k_s. R_{max} (mean 4.0, CV 20%) was fitted to recover published data for the SMA blood flow profiles following a meal.
- Portal vein and hepatic blood flow fed/fasted ratios ($\mathrm{Fe{:}\,Fa}_{Q_{PV}}(t)$ and $\mathrm{Fe{:}\,Fa}_{Q_H}(t)$) were calculated assuming that the small intestine, portal vein and hepatic artery fasted state blood flow rates were 10, 19 and 6.5% of cardiac output (*CO*) , respectively, for males and 11, 21.5 and 6.5% of CO for females (Simcyp healthy volunteer values) as follows:

$$\mathrm{Fe{:}\,Fa}_{Q_x}(t) = 1 + \frac{Q_{SI}(\%CO)}{Q_x(\%CO)} \cdot \left(\mathrm{Fe{:}\,Fa}_{Q_{SI}}(t) - 1\right)$$

where Q_x represents blood flow rate to the portal vein or liver.

- Fe:Fa blood flow profiles were calculated for 100 simulated individuals using individualized fed state k_s values generated by the Simcyp Simulator.

RESULTS

Data Collection and Analysis

- 20 publications were identified that reported the change in blood flow to the small intestine, portal vein or liver at multiple time points following a meal. Considerable between-study and within-study variability in the extent of postprandial blood flow change was observed.
- Six studies were identified with reasonably high fat and high calorie meal composition in reasonable agreement with the high fat breakfast recommended by the FDA (Table 1).
- Studies covered measurement of SMA, portal vein and hepatic blood flow changes and were used in the development and validation of the splanchnic blood flow profile.
- Data that were presented as absolute blood flow profiles were converted to the relative increase from the fasted (baseline) measurements.

Table 1. Composition of study meals and the standard FDA high fat breakfast.

	Energy (kCal)	Fat (% energy)	Meal Type	n
Jager 1986[3]	1000	35	Solid	20
Sieber 1992[6]	547	41	Solid	6
Cooper 1991[2]	778	35	Solid	11
Burkart 1995[1]	720	53	Liquid	10
Madsen 2006[4]	860	38	NA	18
Svensson 1983[7]	760-1140	30	Solid	6
FDA breakfast	*800-1000*	*50*	*Solid*	-

NA: information not available.

Model of the Postprandial Splanchnic Blood Flow Profile

Figure 2 shows the mean predicted fed/fasted blood flow ratio for the small intestine, portal vein and liver for 100 individuals. The time profile of the change in small intestine fed state blood flow is well predicted. The postprandial increase in blood flow rate for the portal vein and liver was over-predicted for three out of four studies, while for one study the relative increase in hepatic blood flow from the fasted state was well predicted.

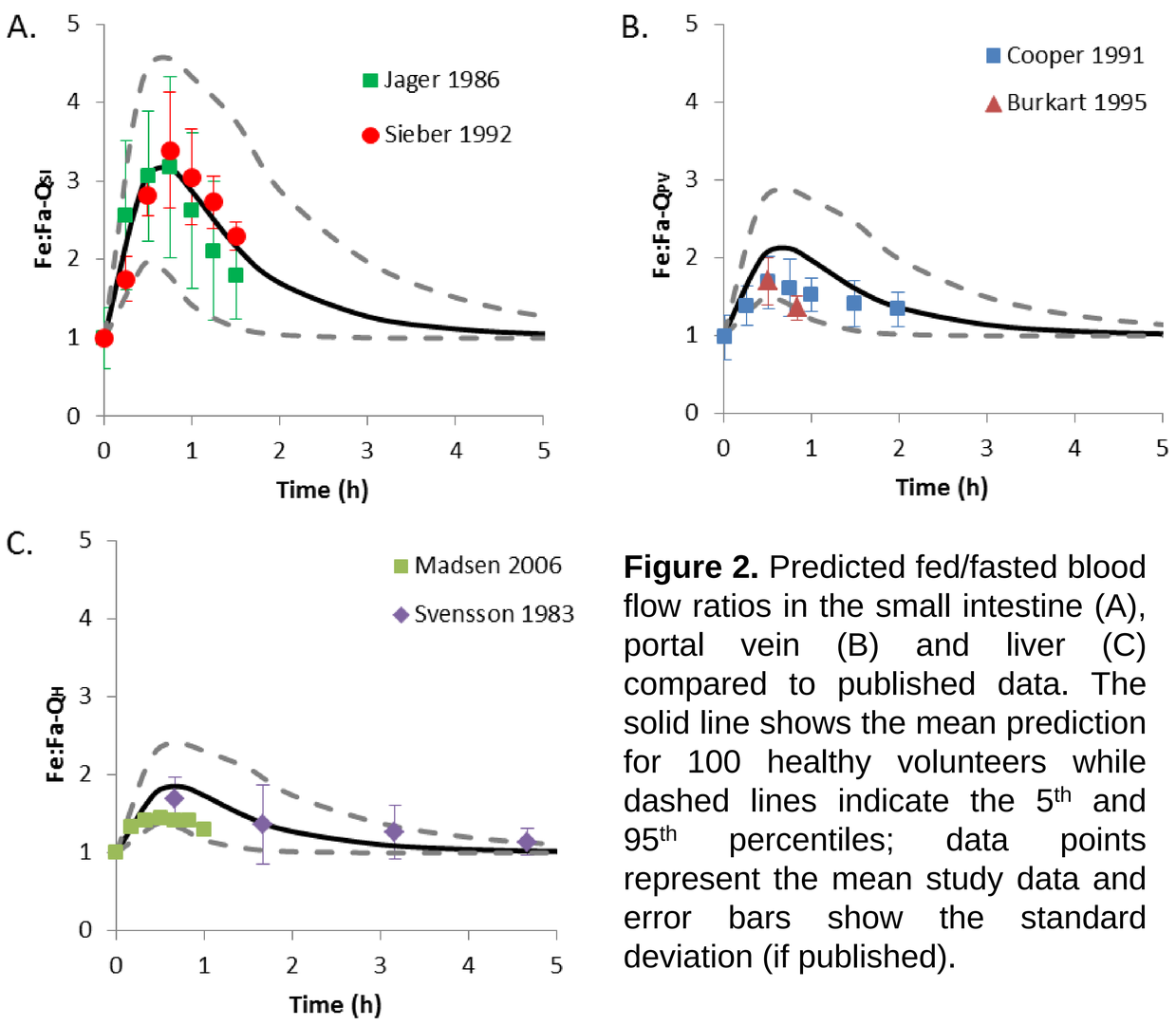

Figure 2. Predicted fed/fasted blood flow ratios in the small intestine (A), portal vein (B) and liver (C) compared to published data. The solid line shows the mean prediction for 100 healthy volunteers while dashed lines indicate the 5th and 95th percentiles; data points represent the mean study data and error bars show the standard deviation (if published).

CONCLUSION

- The developed model for time-dependent change in splanchnic blood flow following a high calorie meal was able to reasonably well recover clinical data for the change in blood flow to the small intestine, portal vein and liver.
- Future work will include incorporation of the developed model into the Simcyp Simulator. Simulations will then be performed to validate the model for predicting the effect of food on clearance of orally and intravenously administered high extraction drugs.

References: 1. Burkart *et al.* Radiology, 194, 801-806 (1995); 2. Cooper *et al.* Clin Sci (Lond), 81, 169-175 (1991); 3. Jäger *et al.* J Vasc Surg, 3, 462-469 (1986); 4. Madsen *et al.* Scand J Gastroenterol, 41, 87-92 (2006); 5. McLean *et al*. Clin Pharmacol Ther, 24, 5-10 (1978); 6. Sieber *et al.* Gut, 33, 497-501 (1992); 7. Svensson *et al.* Clin Pharmacol Ther, 34, 316-323 (1983).