Introduction

Despite a much lower content of many drug metabolising enzymes in the intestinal epithelium compared to the liver (e.g. intestinal CYP3A abundance in the intestine is 1% that of the liver [1,2]), intestinal metabolic extraction may be similar to or even exceed hepatic extraction. The purpose of this study was to evaluate the performance of two ‘minimal’ models, the “well-stirred” gut model and the “Q_{Gut}” model, in predicting intestinal first-pass metabolism from *in vitro* metabolism data.

Methods

This “well-stirred” gut model adapts the form of the well-known “well-stirred” liver model [3] of hepatic drug clearance to describe intestinal first-pass metabolism:

$$F_G = \frac{Q_G}{Q_G + fu_G \cdot CLu_{int,G}}$$

Where $F_G$ is the fraction of dose that escapes intestinal first-pass metabolism in the enterocyte, Q$_G$ is ‘gut’ blood flow, fu$_G$ is the fraction of drug unbound in the enterocyte, and CLu$_{int,G}$ is the net intrinsic metabolic clearance in the gut based on unbound drug concentration.

The Q$_{Gut}$ model [4, 5] retains the form of the “well-stirred” model but the flow term (Q$_{Gut}$) is a hybrid of both permeability through the enterocyte membrane and villous blood flow:

$$F_G = \frac{Q_{Gut}}{Q_{Gut} + fu_G \cdot CLu_{int,G}}$$

Q$_{Gut}$ can be expanded further into two more fundamental parameters: CL$_{perm}$, a clearance term defining permeability through the enterocyte, and Q$_{vill}$, the villous blood flow (18 L/h):

$$Q_{Gut} = \frac{Q_{vill} \cdot CL_{perm}}{Q_{vill} + CL_{perm}}$$

Substituting Eq. 3 into Eq. 2 gives the full “Q$_{Gut}$” model:

$$F_G = \frac{Q_{vill}}{Q_{vill} + fu_G \cdot CLu_{int,G} \cdot (1 + Q_{vill}/CL_{perm})}$$

The performance of the “well-stirred” and “Q$_{Gut}$” models in predicting $F_G$ was compared based on data for 16 drugs. All of the compounds are metabolised predominantly (>80%) by CYP3A, and information was available from the literature on their in vitro metabolism, plasma binding (fu), and permeability. Seven of the compounds appear to be passively absorbed, and there is evidence for the involvement of carrier-mediated transport in the absorption of the other nine. The impact of different assumptions about fu$_G$ (fu$_G$ = 1, or fu, or fu$_G$) was assessed.

Results

The “well-stirred” model generally overpredicted $F_G$, particularly when fu$_G$ was assumed to be equal to fu or fu$_G$, when virtually no first-pass intestinal metabolism was indicated for any of the compounds (Fig. 1). Inclusion of the interplay between permeability and metabolism in the “Q$_{Gut}$” model improved the predictions, but this was substantial only when fu$_G$ was assumed to be 1. Under this condition, the impact of relative changes in metabolic clearance and cell permeability on the value of $F_G$ is illustrated in Fig. 2.

Conclusion

In summary, modelling of intestinal first-pass metabolism requires attention to the complex interplay between passive permeability, active transport, binding, relevant blood flows, and the intrinsic activity and capacity of enzyme systems.

References