Comparison of the "well-stirred" gut and the "Q_{Gut}" models for predicting intestinal first-pass metabolism

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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:

$$F_G = \frac{Q_G}{Q_G + fu_G \cdot CLu_{int,G}} \qquad (1)$$

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:

$$F_G = \frac{Q_{Gut}}{Q_{Gut} + fu_G \cdot CLu_{int,G}} \qquad (2)$$

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

$$Q_{Gut} = \frac{Q_{villi} \cdot CL_{perm}}{Q_{villi} + CL_{perm}} \qquad (3)$$

Substituting Eq. 3 into Eq. 2 gives the full "Q_{Gut}" model:

$$F_G = \frac{Q_{villi}}{Q_{villi} + fu_G \cdot CLu_{int,G} \cdot (1 + Q_{villi}/CL_{perm})} \qquad (4)$$

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_B) was assessed.

Results

The "well-stirred" model generally overpredicted F_G, particularly when fu_G was assumed to be equal to fu or fu_B, 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.

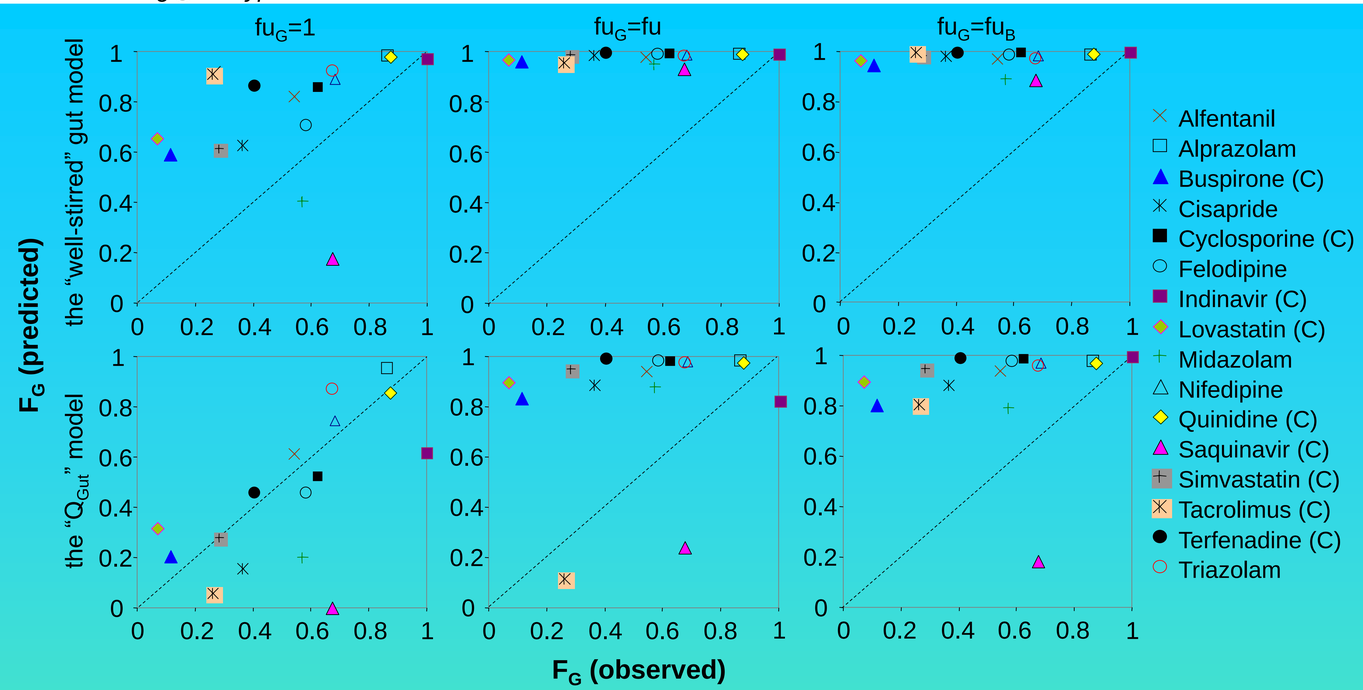

Fig. 1. Relationship between predicted F_G, based on the "well-stirred" and "Q_{Gut}" models of intestinal drug metabolism and F_G estimated from in vivo studies. (C indicates that there is evidence for a carrier-mediated transport component in drug absorption).

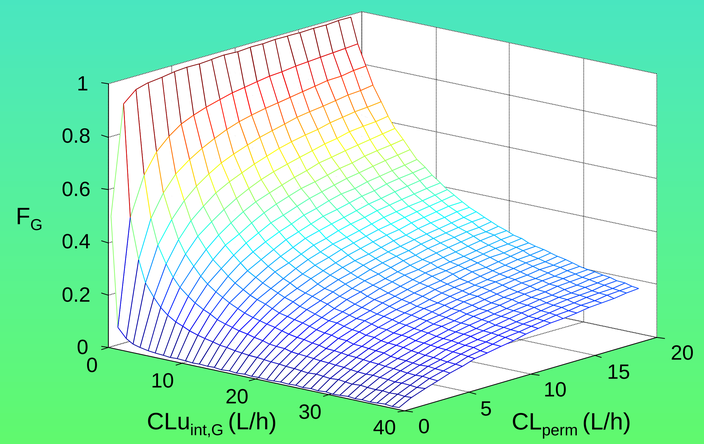

Fig. 2. The impact of changes in intestinal intrinsic metabolic clearance ($CLu_{int,G}$) and drug permeability clearance through the enterocyte (CL_{perm}) on the fraction of an oral dose avoiding first-pass intestinal metabolism (F_G), according to the "Q_{Gut}" model (Eq. 4, fu_G = 1).

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

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