Prediction of human intestinal metabolism of CYP3A substrates using the Advanced, Dissolution, Absorption and Metabolism (ADAM) Model

H.Mishra[1#], M. Jamei[1], K. Rowland-Yeo[1], A. Rostami-Hodjegan[1,2]

[#]h.mishra@simcyp.com

1- Simcyp Ltd, Blades Enterprise Centre, John St, Sheffield, S2 4SU, UK

2- School of Pharmacy and Pharmaceutical Sciences, Manchester University, Manchester, UK

Objectives

To predict the fraction of dose escaping the gut first-pass metabolism (F_G) and its inter-individual variability using the ADAM model.

Introduction

Oral bioavailability (F) is defined as $F = F_a \times F_G \times F_H$; where F_a is the fraction of the dose absorbed, F_G is the fraction escaping the intestinal first-pass metabolism; F_H is the fraction that escapes hepatic first-pass metabolism. For orally administered drugs, first-pass metabolism can be a limiting factor to get the desired bioavailability. As cytochrome P450 3A (CYP3A) comprise of a large percentage of intestinal CYP enzymes[1], CYP3A substrates are most affected by gut metabolism. However, at discovery stage, where metabolism of drug is not fully characterised & in absence of clinical data, F_G has to be predicted using pragmatic approaches such as the 'Q_{Gut}' model[2], which combines the drug permeability (CL_{perm}) and unbound gut intrinsic clearance ($CLu_{int\ gut}$) which are estimated from appropriate *in vitro* systems.

$$F_G = \frac{Q_{Gut}}{Q_{Gut} + fu_{gut} \times CLu_{int\ gut}}$$

$$Q_{Gut} = \frac{CL_{perm} \times Q_{villi}}{CL_{perm} + Q_{villi}}$$

Where, fu_{gut} is the fraction unbound in the enterocytes and Q_{villi} is the villous blood flow. The 'Q_{gut}' model is suitable for early drug discovery; however, its application in late development may have some limitations. For e.g., it assumes the gut as a single homogenous compartment with a uniform permeability throughout the intestine & uniform distribution of enzymes, blood flow & transporters. However, the latter assumption is not true, because of the known variable distribution for different segments from proximal to distal part of the gastrointestinal tract (GIT) and therefore, more mechanistic models are required to account for such physiological, biological and anatomical changes along the GIT.

Methods

The Advanced, Dissolution, Absorption and Metabolism (ADAM) model as implemented in Simcyp® Population-based Simulator[3] (v10) is used to predict the F_G values. The model divides the gut into nine anatomically defined segments from the stomach through the intestine to the colon (Fig. 1). Drug absorption from each segment is described as a function of release from the formulation, dissolution, precipitation, luminal degradation, permeability, metabolism, gut-wall transport and transit from one segment to another.

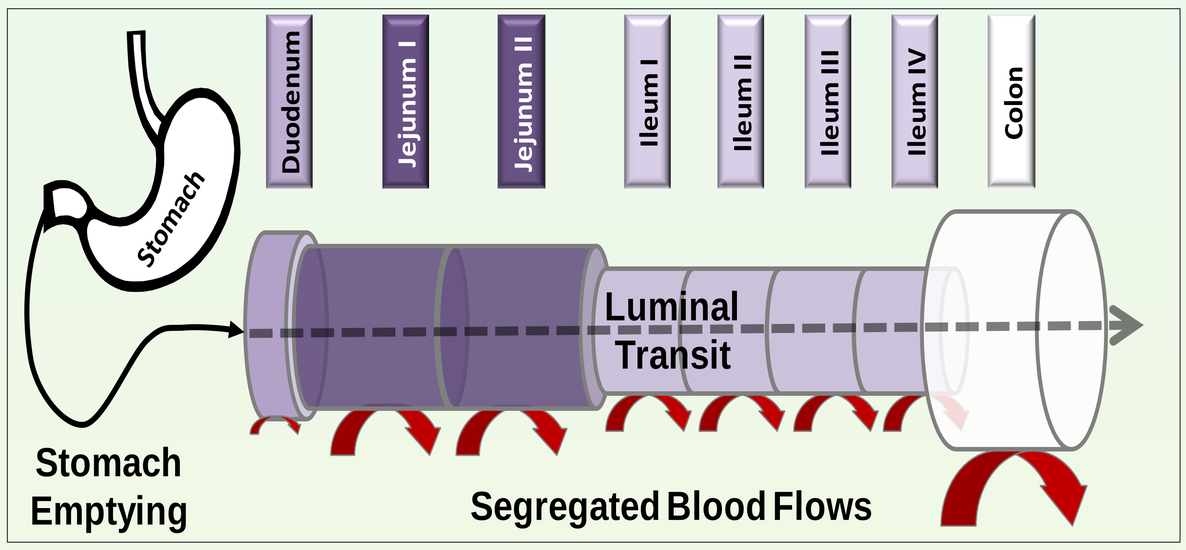

Figure 1. *Schematic diagram of the ADAM model, displaying the mechanistic segmentation of the GIT into 9 sections with segregated blood flows to each section. The varying intensity of the colour for each section represents the enzyme abundance gradient along the gut (representing CYP3A in this case, with the darkest showing maximum concentration and white showing absence of the enzyme).*

In vivo, F_G can be estimated by conducting clinical studies involving concomitant administration of grapefruit juice with drug. It is known that furanocoumarins in grapefruit specifically inhibit intestinal CYP3A and not hepatic CYP3A[4]. So, a comparison of Area under the curve (AUC_{oral}) values after administration of the drug with and without grapefruit juice can provide F_G[2].

Reported F_G values for 25 compounds (Table 1) along with their $CL_{int\ gut}$ values (measured in human intestinal microsomes system, prepared by elution method (HIM_{el}), not reported here) were obtained from the review by Gertz *et al*.[5]. *In vivo* variability for F_G values for 15 out of the 25 compounds was calculated by meta-analysis & scrutinising the references of Gertz *et al.*[5]. These observed F_G values were compared against those predicted from ADAM model (with variability). Additional simulations were conducted using data from Simcyp compound library, for 11 out of the above mentioned 25 compounds, and F_G predictions (Table 1) for these were compared against the reported values[5].

Results

The predictions of ~55% of the studied compounds fall within 1.5 fold (and ~75% fall within two-fold, Fig. 2). The deviations are seen mostly (~80%) in compounds, with observed F_G values < 0.5. Using Simcyp data, the predictions for ~80% of the 11 compounds were within 1.5 fold. F_G for saquinavir and cyclosporine was over-predicted (Fig. 3).

Table 1: *Observed[5] and predicted data for 25 compounds*

Compound Id	Observed	SD	ADAM	SD	Simcyp data	SD
Alfentanil (Alf)	0.60	0.15	0.94	0.03		
Alprazolam (Alp)	0.94	0.03	1.00	0.00	0.96	0.01
Atorvastatin (Ato)	0.24	0.02	0.98	0.01		
Buspirone (Bus)	0.21	0.15	0.87	0.05		
Cisapride (Cis)	0.55	0.17	0.84	0.06		
Cyclosporine (Cyc)	0.44	0.06	0.98	0.01	0.90	0.03
Felodipine (Fel)	0.45	0.11	0.44	0.10		
Indinavir (Ind)	0.93	0.00	0.75	0.08		
Lovastatin (Lov)	0.07	0.00	0.27	0.08		
Methadone (Met)	0.78		1.00	0.00		
Midazolam (Mid)	0.51	0.09	0.69	0.09	0.50	0.13
Nifedipine (Nef)	0.74		0.87	0.05	0.76	0.11
Nisoldipine (Nis)	0.11		0.19	0.07		
Quinidine (Qui)	0.90		1.00	0.00	0.93	0.02
Repaglinide (Rep)	0.89		0.97	0.01		
Rifabutin (Rif)	0.21		0.97	0.01		
Saquinavir (Saq)	0.18	0.05	0.26	0.08	0.82	0.05
Sildenafil (Sil)	0.54	0.00	0.93	0.03	0.55	0.11
Simvastatin (Sim)	0.14		0.22	0.07	0.12	0.11
Tacrolimus (Tac)	0.14		0.56	0.10		
Terfenadine (Ter)	0.40		0.36	0.10		
Trazodone (Tra)	0.83		0.98	0.01		
Triazolam (Tri)	0.75	0.04	0.99	0.00	0.85	0.04
Verapamil (Ver)	0.65	0.09	0.87	0.05	0.61	0.11
Zolpidem (Zol)	0.79	0.00	1.00	0.00	0.93	0.02

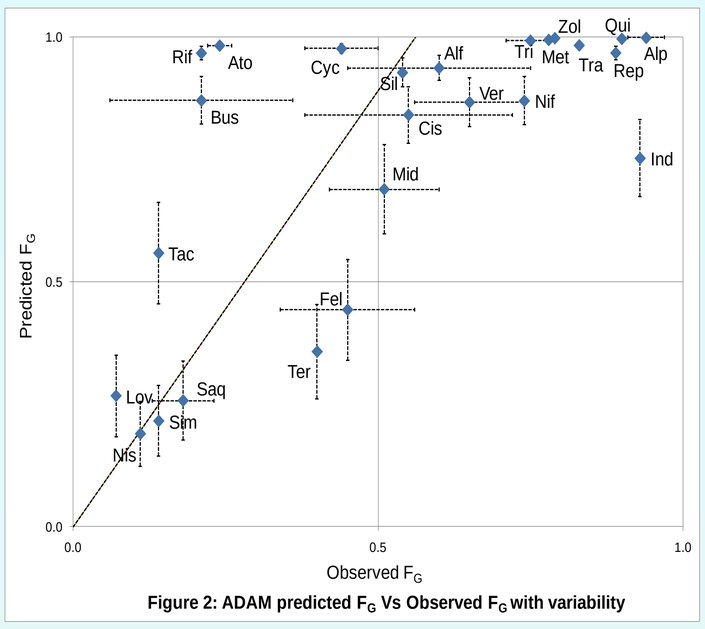

Figure 2: ADAM predicted F_G Vs Observed F_G with variability

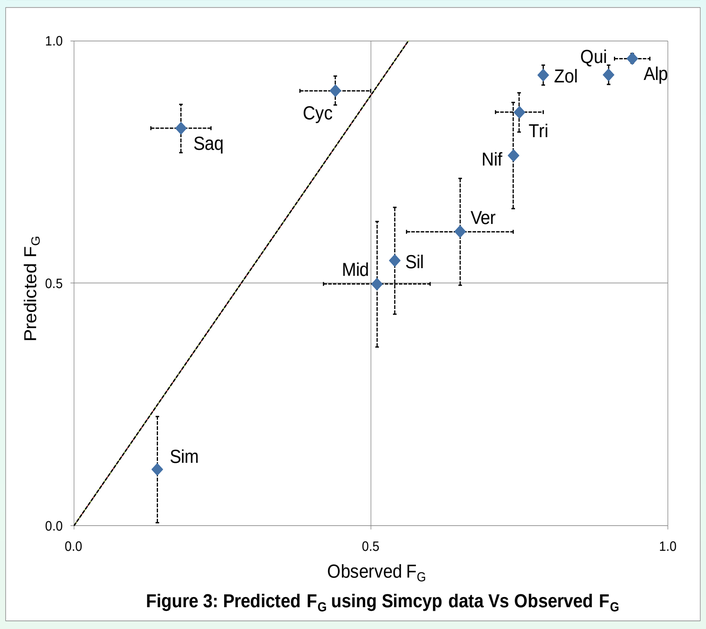

Figure 3: Predicted F_G using Simcyp data Vs Observed F_G

Discussion

The Mean Fold Error (MFE) in predictions by the ADAM model was 1.68, slightly better than 1.84, for predictions by 'Q_{gut}' model (F_G reported by Gertz *et al.*[5]). The Root Mean Square Error (RMSE) for both prediction sets was ~0.3. The predictions for the 11 compounds using Simcyp compound library data were better (MFE=1.3), when compared to same 11 compounds from the dataset generated by using ADAM model (MFE=1.38) and from reported data in Gertz *et al.*[5] (MFE=1.64), using HIM_{el} $CL_{int\ gut}$ data, RMSE for all three datasets was ~0.2. The deviations (~25 % compounds, Fig. 2) in the predicted values of F_G might be due to **a)** the system used to determine the $CL_{int\ gut}$ data i.e. the HIM_{el} system. As, although the clearance values were corrected for the CYP3A enzyme activity[6] in the ADAM model, the HIM_{el} system itself is not enzyme specific nor does it account for effect of transporters.

b) Missing data for induction/inhibition effect of compounds such as, indinavir (CYP3A4 inhibitor[7]), rifabutin (CYP3A4 inducer[7]) or transporter data for compounds such as cyclosporine & saquinavir (both substrates for P-gP[8,9]). So, improvement in the prediction of the intestinal metabolism can be made by incorporation of such data in the model. A better prediction (MFE=1.3; ~80% compounds, Fig.3) is seen when using Simcyp data, but still predictions for saquinavir and cyclosporine are not satisfactory due to limited and/or poor data in the literature sources. The large variability seen in *in vivo* data (Fig. 2; e.g. cisapride) maybe due to the effect of variable solubility of the drug and/or chemical stability (luminal degradation) *in vivo* and such additional data needs to be incorporated in the model.

Conclusion

Both 'Q_{Gut}' and the ADAM model can be used satisfactorily for the prediction of F_G at the early drug discovery stage. However, a more physiologically relevant and mechanistic model is needed to predict special cases, such as the effect of transporters, inhibition and/or induction of enzymes, formulation effects (e.g. sustained/delayed release), gastric by-pass (i.e. surgical removal of sections of GIT in case of obese patients), effect of pH gradient and/or bile acid secretion on absorption and also for the incorporation of the population variability around the physiological or drug specific parameters.

References

(1) Paine *et al*. 1997, JPET; 283:1552-62

(2) Yang *et al.* 2007, CDT; 8:676-84

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(4) Greenbatt *et al.* 2003, CPT; 74:121-9

(5) Gertz *et al.* 2010, DMD; 38: 1147-58

(6) Galetin & Houston 2006, JPET; 318:1220-29

(7) Kraft *et al.* 2004, JCP; 44: 305-13

(8) Lee *et al.* 2001, JCP; 41: 317-23

(9) Eagling *et al.* 1999, BJCP; 48: 543-52