Interplay of metabolism and transport in determining oral drug absorption and gut wall metabolism: a simulation assessment using the "advanced dissolution, absorption, metabolism (ADAM)" model

[1]Darwich, A.S., [2]Jamei, M., [2]Neuhoff, S. and [1,2]Rostami-Hodjegan, A.

Current Drug Metabolism 2010, 11, 716-729

Adam.Darwich@postgrad.manchester.ac.uk

[1]Centre of Applied Pharmacokinetic Research, University of Manchester, UK; [2]Simcyp Ltd, Sheffield, UK

Introduction

Active efflux by P-glycoprotein (P-gp) has been suggested to increase drug exposure to Cytochrome P450 3A (CYP3A) metabolising enzymes in the gastrointestinal tract, through cycling drug in and out of the enterocyte via absorption and active efflux, leading to a reduced fraction of drug escaping gut wall metabolism (F_G) (Benet & Cummins, 2001). However, when examining the transporter metabolism interplay using the Segmental Segregated Flow Model (SSFM) no evidence was found to support the above under linear kinetics (Pang 2003), attributing any interplay to the nonlinear aspects of gut wall metabolism.

The ADAM model, within the Simcyp® Simulator, is a comprehensive physiologically-based pharmacokinetic model, based on the Compartmental Absorption and Transit (ACAT) Model (Yu & Amidon, 1999) incorporating further features as compared to the SSFM (Pang 2003), as described in detail by Jamei *et al.,* (2009).

Objectives

To examine the impact of systemic variation in parameters relating to gut metabolism and transporter efflux interplay through studying the endpoints F_a (fraction absorbed into the enterocyte) and F_G, utilising the ADAM model.

Method

Simulations were carried out using the ADAM model (see Figure 1) within the Simcyp Simulator (v 9.1). The star map shown in Figure 2 indicates the allocation of compounds within the Simcyp library to the four subdivisions of the Biopharmaceutics Classification System (BCS), relating to their estimated fraction absorbed into the enterocyte (F_a estimated from measured or calculated human effective gut permeability), and dose number (Do), a measure of solubility (Amidon *et al*., 1995).

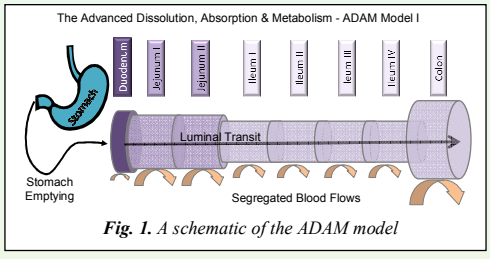

Fig. 1. *A schematic of the ADAM model*

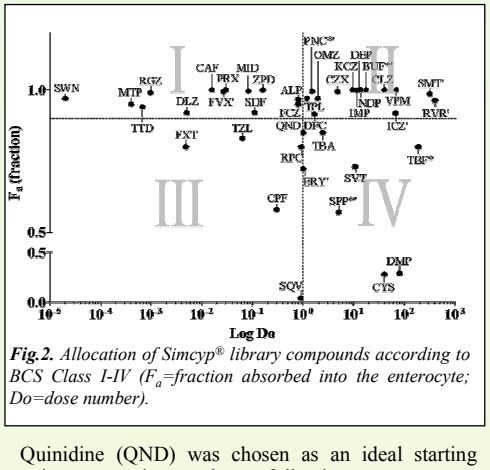

Fig.2. *Allocation of Simcyp® library compounds according to BCS Class I-IV (F_a=fraction absorbed into the enterocyte; Do=dose number).*

Quinidine (QND) was chosen as an ideal starting point, varying the following parameters systematically:

- Passive permeability (P_{app}) ($1_{1\text{-}7}$)
- CYP3A4 intrinsic clearance ($CL_{int\text{-}CYP3A4}$) ($2_{1\text{-}7}$)
- $K_{m\text{-}CYP3A4}$ ($3_{1\text{-}5}$)
- P-gp intrinsic clearance ($4_{1\text{-}7}$)
- $K_{m\text{-}Pgp}$ ($5_{1\text{-}5}$)

Resulting in a total of 8,575 simulations to be carried out (Figure 3).

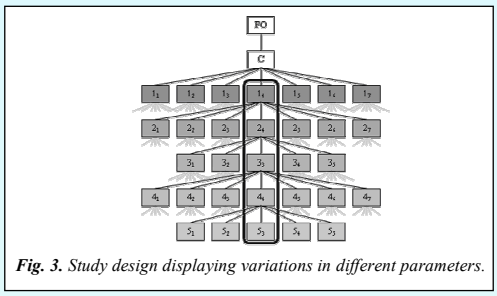

Fig. 3. *Study design displaying variations in different parameters.*

Results

$CL_{int\text{-}CYP3A4}$ and $K_{m\text{-}CYP3A4}$ showed no effect on F_a under the studied conditions. However, a significant effect on F_G was observed throughout the range ($CL_{int\text{-}CYP3A4}$=0.01 to 2000 µL/min/mg) (Figure 4).

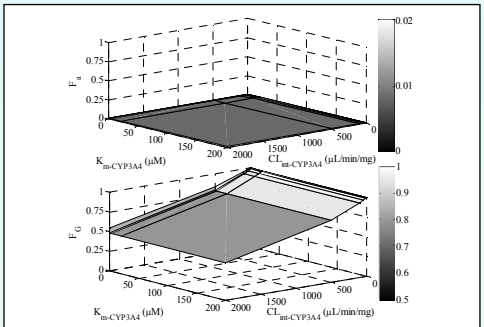

Fig. 4. *Variation of F_a and F_G in relation to $CL_{int\text{-}CYP3A4}$ and $K_{m\text{-}CYP3A4}$. Colour bar presents intensity corresponding to Y axis. Remaining compound conditions are midrange in accordance to study design: $CL_{int\text{-}P\text{-}gp}$=1 µL/min, $K_{m\text{-}P\text{-}gp}$=2 µM, P_{app}=4.12·10⁻⁶ cm/s, dose=100 mg, intrinsic solubility=0.05 mg/mL, compound acid base nature=neutral.*

P_{app} played a significant role in observing CYP3A4 saturation. P_{app} values greater than 0.35·10⁻⁶ cm/s at a dose of 100 mg were associated with saturation in some areas of $K_{m\text{-}CYP3A4}$ and $CL_{int\text{-}CYP3A4}$ parameter space studied (Figures 5 A, B and C).

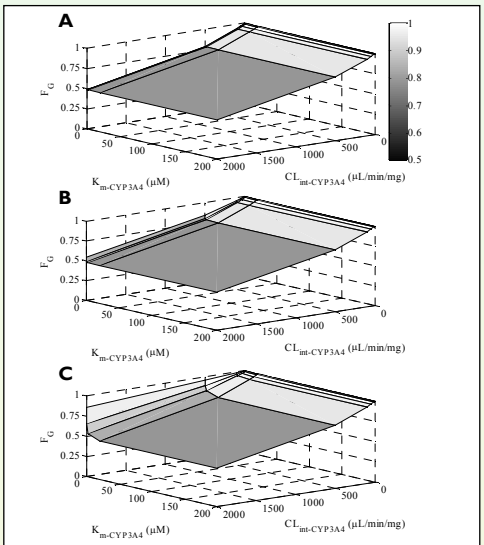

Fig. 5. *Variation of F_G in relation to $CL_{int\text{-}CYP3A4}$ and $K_{m\text{-}CYP3A4}$. Colour bar on right side presents intensity corresponding to a specific value of F_G according to axis value. **A:** P_{app}=0.06·10⁻⁶ cm/s. **B:** P_{app}=4.12·10⁻⁶ cm/s. **C:** P_{app}=100.17·10⁻⁶ cm/s. Remaining compound conditions are midrange.*

An increase in $CL_{int\text{-}P\text{-}gp}$ led to a significant decrease in F_a. An increase in $CL_{int\text{-}P\text{-}gp}$ was associated with a decrease in F_G, although at a practically insignificant level. The effect of $CL_{int\text{-}P\text{-}gp}$ on F_G became more apparent at a higher $CL_{int\text{-}CYP3A4}$ (Figures 6 A to D) $K_{m\text{-}CYP3A4}$ (data not shown).

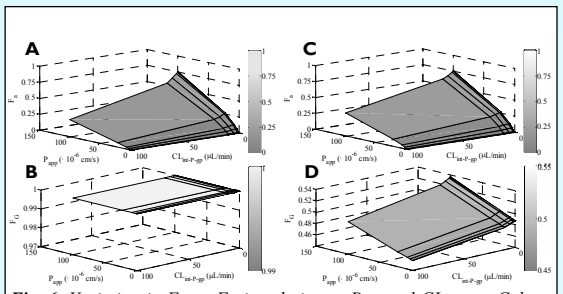

Fig. 6. *Variation in F_a an F_G in relation to P_{app} and $CL_{int\text{-}P\text{-}gp}$. Colour bars present intensities corresponding to Y axis. $CL_{int\text{-}CYP3A4}$=0.01µL/min/mg. **A:** Fa **B:** FG. $CL_{int\text{-}CYP3A4}$=2000 µL/min/mg. **C:** Fa **D:** F_G. Remaining compound conditions are midrange.*

For a majority of Simcyp library compounds the effect of P-gp efflux on metabolism was negligible. The effect was limited to compounds such as saquinavir (Class III) and simvastatin (Class IV) (Figure 7).

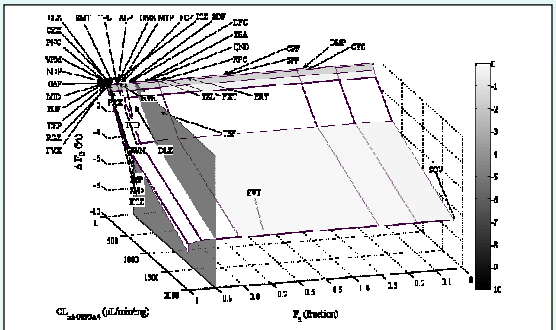

Fig. 7. *Variation of F_G (ΔF_G (%) in relation to changes to $CL_{int\text{-}P\text{-}gp}$ from 0.01 to 100 µL/min). The vertical planar surface illustrates the cut-off point between BCS between class I, III (F_a > 0.9) and II and IV (F_a < 0.9) at a F_a of 0.9. Colour bar on right side presents colour intensity corresponding to the Y axis. Not taking dose, solubility or compound acid base nature into account. Remaining compound conditions are assumed to be midrange.*

Discussion and Conclusions

Results suggest that P-gp efflux decreases enterocytic drug concentration for drugs given at a reasonably high dose, which possess adequate passive apparent permeability, by de-saturating CYP3A4 in the gut resulting in a lower F_G.

However, the P-gp / CYP3A4 interplay was observed in a very limited area of parameter space, matching very few therapeutic drugs expressing (Figure 7):

- High degree of CYP3A metabolism
- High affinity to P-gp efflux transporter
- Low permeability

The systematic approach enabled us to recognise the combination of parameter values where the potential interplay between metabolising enzymes and efflux transporters is expected to be highest, using a realistic range of parameter values taken from an intensive literature search.

Acknowledgments

Authors wish to thank Dr David Turner, Professors Margareta Hammarlund-Udenaes and Geoff Tucker for their fruitful discussions leading to conduct of the study, and Mr James Kay in preparing the manuscript.

References

Amidon, G.L., *et al. Pharm. Res.* 12(3): 413-420 (1995).

Benet, L.Z., Cummins, C.L. *Adv. Drug Deliv. Rev.* 50(S1): S3-S11 (2001).

Jamei, M., *et al. AAPS J.* 11(2): 225-237 (2009).

Pang, K.S. *Drug Metab. Dispos*. 31(12): 1507-1519 (2003).

Yu, L.X., Amidon, G.L. *Int J Pharm.* 186 (1999): 119-125 (1999).