Simulation of the Effect of P-glycoprotein on Drug Absorption in the Human Gastrointestinal Tract

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Objectives

(1) To investigate the dose-dependency of drug efflux by P-glycoprotein (P-gp) and the relative roles of P-gp-mediated efflux and passive diffusion in drug absorption.

(2) To use the ADAM model to predict fraction absorbed (fa) and its *inter-individual variability* in humans.

(3) To assess the sensitivity of predictions to the distribution of P-gp in the gut (Mouly and Paine, 2003; Troutman and Thakker, 2003).

The new P-gp algorithm in the ADAM Model

Intestinal P-gp is considered to play a significant role in the oral bioavailability of some drugs by limiting their uptake from the gut.

A new algorithm considering nonlinear (saturable) drug efflux by intestinal P-gp was developed and integrated into the Advanced Dissolution, Absorption and Metabolism (ADAM) model (Simcyp®, Simcyp Limited, Sheffield, UK), which has been used to predict the rate and extent of intestinal drug absorption and metabolism and their associated inter-individual variability based on physiochemical and *in vitro* data. In addition to the existing physiological parameters in the ADAM model, including:

- gastric emptying time,
- intestinal transit time,
- regional pH values, and
- fluid dynamics,

the new module also considers regional expression of P-gp in the human gastrointestinal tract (Mouly and Paine, 2003; Troutman and Thakker, 2003).

Methods

Three commonly used P-gp substrates, digoxin, quinidine and talinolol were used to assess the model. Physiochemical and *in vitro* parameters of the compounds were collated from the literature and entered into Simcyp Simulator V7.20 to predict the fraction absorbed (fa) in virtual populations (10 trials with 10 Caucasians in each trial).

The simulations were performed with the drug in solution as well as in solid form (instant release formulation) in the fasted state.

Results

The predicted fa values for digoxin (1 mg, p.o., Figure 1a), quinidine (500 mg, p.o., Figure 1b) and talinolol (50 mg, p.o., Figure 1c) were 0.54 ± 0.15 [Mean ± SD], 0.92 ± 0.07 and 0.45 ± 0.11, respectively.

These values were in agreement with reported *in vivo* values for corresponding doses: 0.63 ± 0.11 for digoxin (Greiner et al., 1999), 0.76 ± 0.17 for quinidine (Darbar et al., 1997) and 0.55 ± 0.15 for talinolol (Trausch et al., 1995).

When digoxin, quinidine and talinolol were given at low doses (*e.g.* 0.1 mg), P-gp was not saturated and the predicted fa values were 0.54 ± 0.15, 0.74 ± 0.10, and 0.45 ± 0.11, respectively.

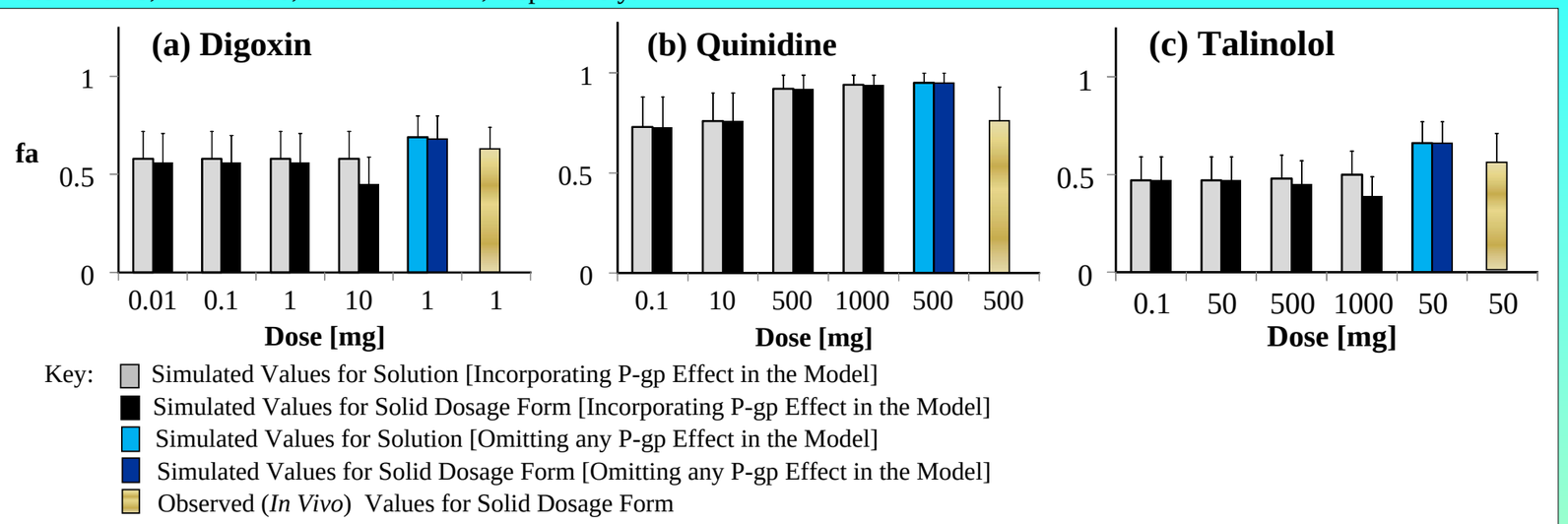

Figure 1: Effects of Dose and Dosage Form on Predicted Fraction Absorbed

(a) Digoxin: No dose dependency in absorptive direction was observed (as expected from *in vivo* data). At a hypothetical dose of 10 mg the absorption is predicted to be limited by solubility. However, the *in vivo* maintenance dose for digoxin is only 0.1 mg/day!
(b) **Quinidine:** Dose dependency in absorptive direction was found (as expected from *in vivo* data). Solubility is not a limiting factor for quinidine. The passive permeability is high and, thus, the effect of P-gp is limited.
(c) **Talinolol:** A limited dose dependency in absorptive direction was found. Solubility might be a limiting factor for talinolol absorption.

Conclusions

It was shown that an increased dose can lead to increased absorption due to the saturation of P-gp. However, P-gp saturation is unlikely to occur with compounds of poor solubility (*e.g.*, intrinsic solubility of 0.001 mg/mL), especially those with low affinity for P-gp (high Km values).

In addition, P-gp-mediated drug efflux can play a significant role for compounds with low passive permeability like talinolol, but not for compounds with high passive permeability such as quinidine.

Thus, the ADAM model is capable of predicting spatial and inter-individual variability in intestinal drug absorption, metabolism and P-gp efflux along the gut. Its use exemplifies the value of physiologically-based mechanistic models, with incorporation of realistic population variability, in the drug development process.

References

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