P-gp EFFLUX HAS NO IMPACT ON DOSE PROPORTIONALITY OF DIGOXIN BIOAVAILABILITY OVER A DOSE RANGE OF 0.125 TO 1.5 mg: THE OUTCOME OF A NEW PBPK MODEL, THAT INCLUDES THE *IN VITRO* TRANSPORTER INFORMATION, IS CONSISTENT WITH THE CLINICAL OBSERVATIONS

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Background

Predicting the magnitude of *in vivo* drug-drug interactions (DDIs) involving P-glycoprotein (P-gp) transport from *in vitro* data requires accurate knowledge of the kinetics describing transport of the substrate in the gut and liver, inhibition constants for transport, and reliable estimates of the inhibitor concentrations at the transporters active site. The anticipated update of regulatory guidance relating to transporters has led to an increased level of interest in physiologically-based pharmacokinetic (PBPK) models used for prediction of transporter-mediated DDIs. Digoxin has been proposed as a model *in vivo* test compound for clinical P-gp-mediated DDI investigations (Zhang *et al.*, 2010; Giacomini *et al.*, 2010). Therefore, , using available *in vitro* data, a mechanistic PBPK model is developed for digoxin that accounts for differential permeability and P-gp-mediated efflux along the intestine.

Purpose

Application of a PBPK model that addresses the relative importance of intestinal and hepatic P-gp for digoxin.

Method

Prior *in vitro* information on the metabolism, permeability and P-gp efflux kinetics of digoxin were combined with physicochemical data within the Simcyp Population-based Simulator (V11). The PBPK model included the "Advanced Dissolution, Absorption and Metabolism" (ADAM) model and incorporated the variability of different parameters (Jamei *et al.*, 2009) (Figure 1).

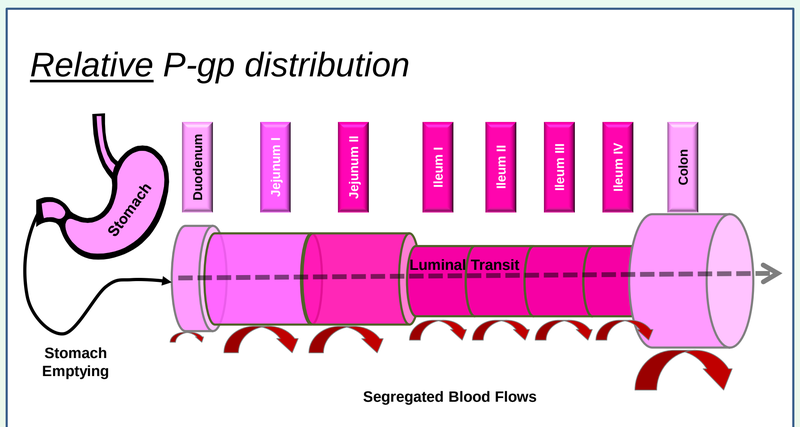

Figure 1 *– Schematic representation of the ADAM model, displaying the mechanistic segmentation of the GI tract into 9 sections with segregated blood flows to each section. The abundance of various enzymes and transporters in each segment varies non-monotonically along the intestine as depicted by the varying intensity of the colour for each section, representing P-glycoprotein in this case. The small intestine consists of 7 segments where drug can dissolve, re-precipitate or be exposed to chemical degradation. Fluid dynamics (secretion and re-absorption), varying pH and bile salt concentrations in each section are considered.*

The permeability across each of the segments in the ADAM model was estimated using a Mechanistic Permeability Model (Turner *et al.*, in preparation), which accounts for the free fraction in the unstirred boundary layer and the intrinsic transcellular and paracellular permeation. Physicochemical data were combined with parameters relating to villous morphology within the model to obtain estimates of segmental permeability.

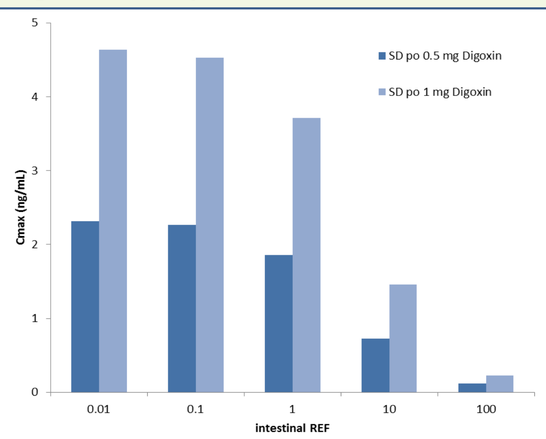

Figure 2 *– Using Automatic Sensitivity Analysis, the change in C_{max} values due to the change in REF was simulated. Assuming the same activity per unit of protein in vitro and in vivo, a REF value of 1 represents an in vitro system that has the same expression of the transporter as the in vivo situation, i.e. the jejunum. If the activity per unit of protein is different a Relative Activity Value should be used. A REF higher than 1 represents a 'lazy' in vitro system and a REF lower than 1 is obtained for an overexpressed system that is more efficient or abundant than the transporter in vivo.*

Transporter kinetic data (Km, J_{max}) and a scaling factor for the *in vitro* Caco-2 cell system [REF - a relative expression factor that links the *in vivo* expression of P-gp in the jejunum to the expression of P-gp in the *in vitro* system] were also incorporated into the model (Troutman and Thakker, 2003 a and b). In Figure 2 the impact of the intestinal REF for P-gp on C_{max} is illustrated.

Then, concentration-time profiles of digoxin following single (SD) and multiple (MD), intravenous (iv) or oral (po) doses were simulated over a range of doses (0.125 to 1.5 mg) to assess the potential effects of P-gp efflux on dose proportionality of exposure of digoxin.

Where possible (SD iv: 0.5, 0.75, 1 and 1.5 mg; SD po: 0.25, 0.5, 0.75 and 1 mg; MD: 0.125, 0.25 qd and 0.25 mg bid), simulations were compared with corresponding observed data.

As an additional validation exercise for the model, *in vitro* data relating to inhibition and induction of intestinal P-gp efflux by rifampicin were used to investigate the effects of this modulator on the systemic exposure of digoxin. Since concentration-dependent data relating rifampicin levels to P-gp expression were not available, the REF value was increased *3.5-fold* to replicate the increase in expression observed *in vivo* (Greiner et al., 1999).

Results

The simulated concentration-time profiles of digoxin were consistent with observed data across 31 independent studies (13 SD iv, 12 SD po and 6 MD (Figures 3-5).

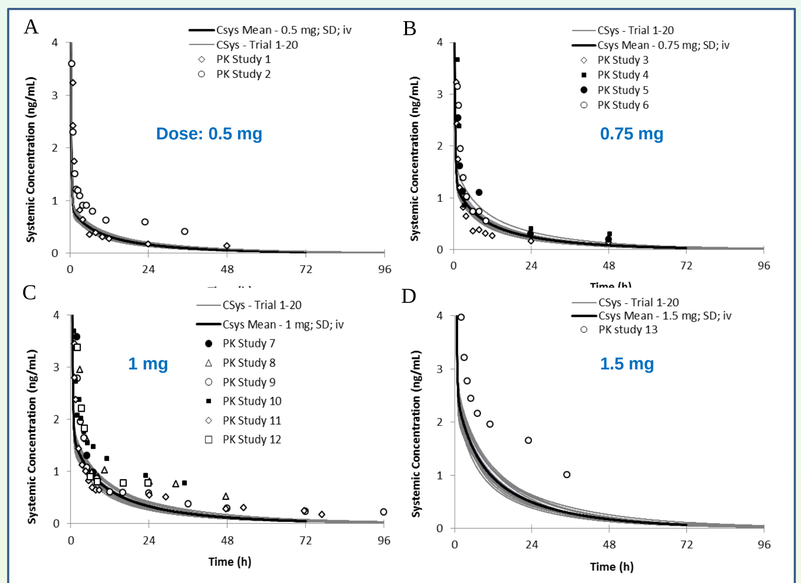

Figure 3 *- Mean values and individual trials of simulated plasma concentration-time profiles of digoxin after an intravenous bolus dose of (A) 0.5, (B) 0.75, (C) 1, (D) or 1.5 mg in a population of 200 individuals (20 trials of 10 healthy volunteers). The thin lines represent individual trials (n=20) and the solid black line is the mean of the population (n=200). The circles, triangles, diamonds and squares are mean observed values from individual 13 studies in HV.*

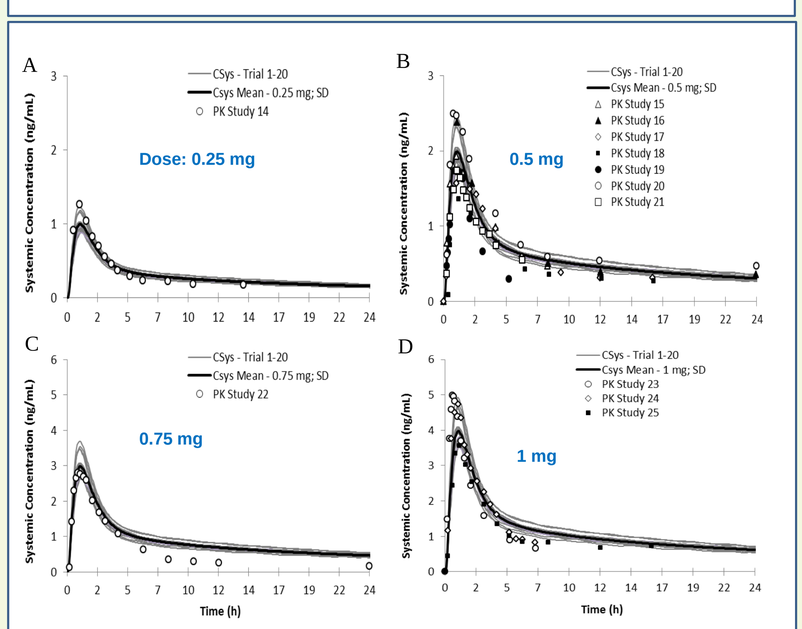

Figure 4 *– Mean values and individual trials of simulated plasma concentration-time profiles of digoxin after an oral dose of (A) 0.25, (B) 0.5, (C) 0.75 or (D) 1 mg in a population of 200 individuals (20 trials of 10 healthy volunteers). The thin lines represent individual trials (n=20) and the solid black line is the mean of the population (n=200). The circles, triangles, diamonds and squares are mean observed values from individual 12 studies in Caucasians.*

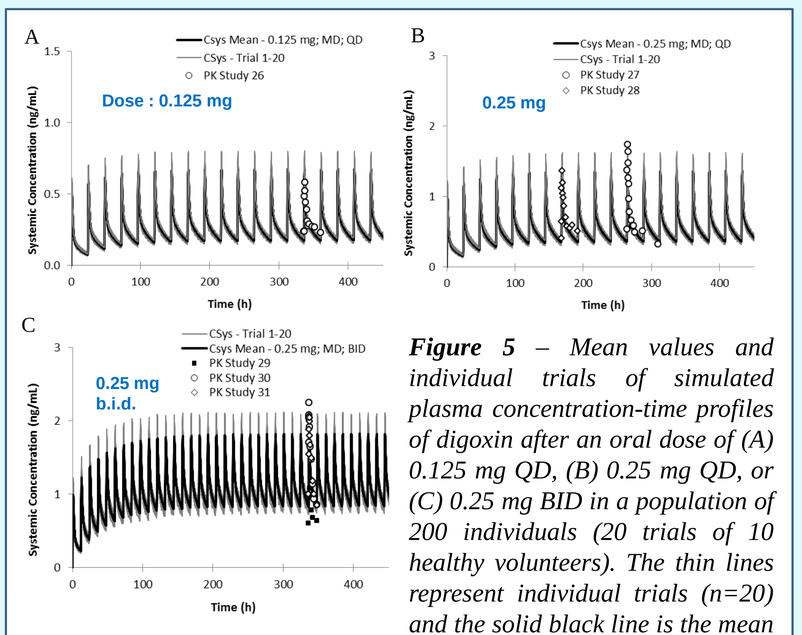

Figure 5 *– Mean values and individual trials of simulated plasma concentration-time profiles of digoxin after an oral dose of (A) 0.125 mg QD, (B) 0.25 mg QD, or (C) 0.25 mg BID in a population of 200 individuals (20 trials of 10 healthy volunteers). The thin lines represent individual trials (n=20) and the solid black line is the mean of the population (n=200). The circles, diamonds and squares are mean observed values from individual 6 studies in HV.*

The fact that predicted t_{max} and C_{max} values of oral digoxin were similar to observed data indicates that the relative contributions of permeation and P-gp mediated efflux are appropriate.

There was no indication of a departure from dose proportionality over the dose range studied (0.25 to 1.5 mg). All dose normalised AUCs for 0.25, 0.5, 0.75 and 1 mg doses resembled each other.

The predicted decreases in AUC and C_{max} of digoxin following administration of rifampicin were 1.5 (range: 1.4–1.7) and 1.6-fold (range: 1.3-1.6), which were reasonably consistent with observed values of 1.4- and 2.2-fold (Figure 6).

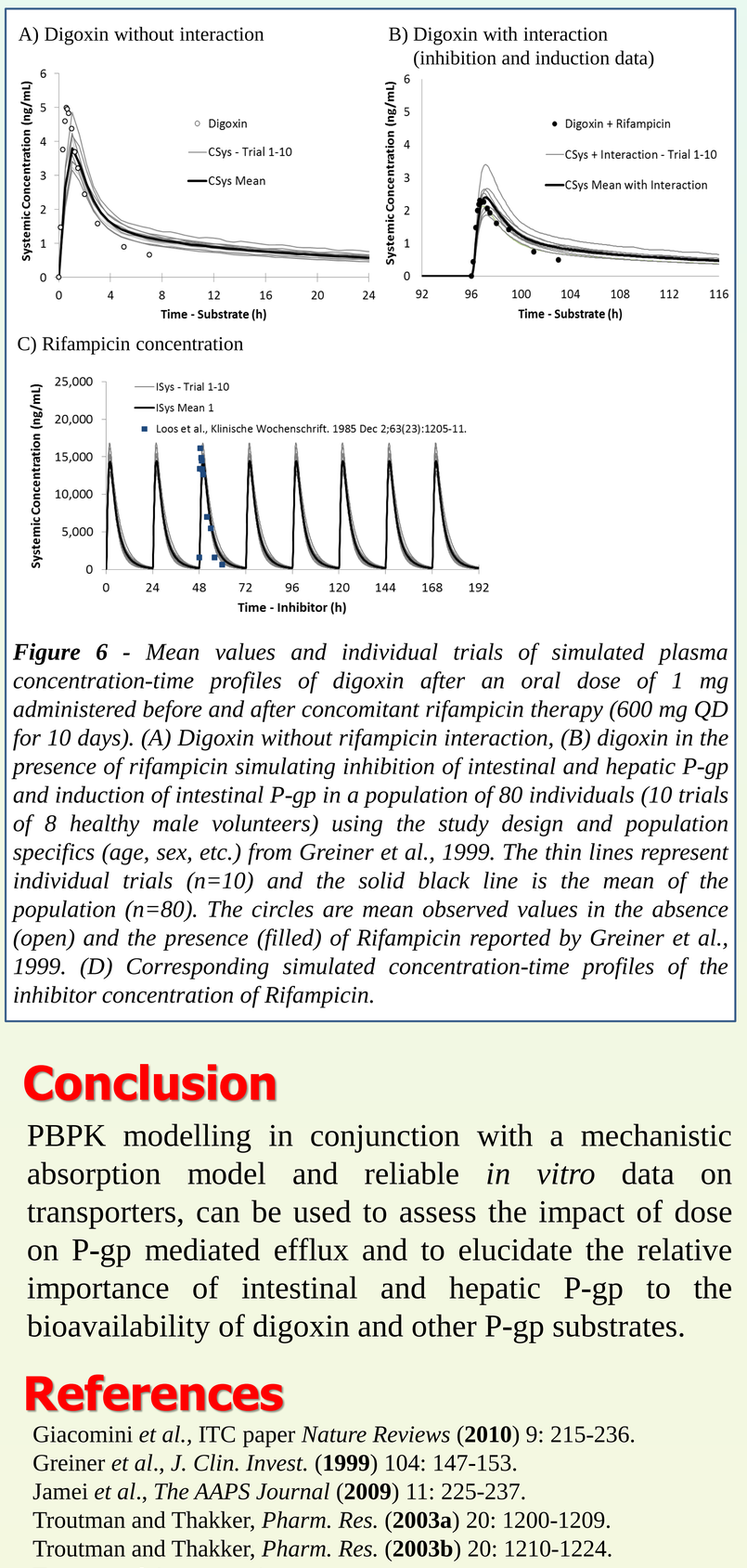

Figure 6 *- Mean values and individual trials of simulated plasma concentration-time profiles of digoxin after an oral dose of 1 mg administered before and after concomitant rifampicin therapy (600 mg QD for 10 days). (A) Digoxin without rifampicin interaction, (B) digoxin in the presence of rifampicin simulating inhibition of intestinal and hepatic P-gp and induction of intestinal P-gp in a population of 80 individuals (10 trials of 8 healthy male volunteers) using the study design and population specifics (age, sex, etc.) from Greiner et al., 1999. The thin lines represent individual trials (n=10) and the solid black line is the mean of the population (n=80). The circles are mean observed values in the absence (open) and the presence (filled) of Rifampicin reported by Greiner et al., 1999. (D) Corresponding simulated concentration-time profiles of the inhibitor concentration of Rifampicin.*

Conclusion

PBPK modelling in conjunction with a mechanistic absorption model and reliable *in vitro* data on transporters, can be used to assess the impact of dose on P-gp mediated efflux and to elucidate the relative importance of intestinal and hepatic P-gp to the bioavailability of digoxin and other P-gp substrates.

References

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