PREDICTION OF THE IMPACT OF P-gp MEDIATED EFFLUX ON THE DOSE PROPORTIONALITY OF DIGOXIN BIOAVAILABILITY

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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 recent 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, we have developed a mechanistic PBPK model for digoxin, that accounts for differential permeability and P-gp-mediated efflux along the intestine.

METHODS

- *In vitro* information on the metabolism, permeability and P-gp efflux kinetics of digoxin were combined with physicochemical data in a PBPK model implemented in the Simcyp Population-based Simulator (V11) (Jamei *et al*., 2009).
- 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).

Relative P-gp distribution

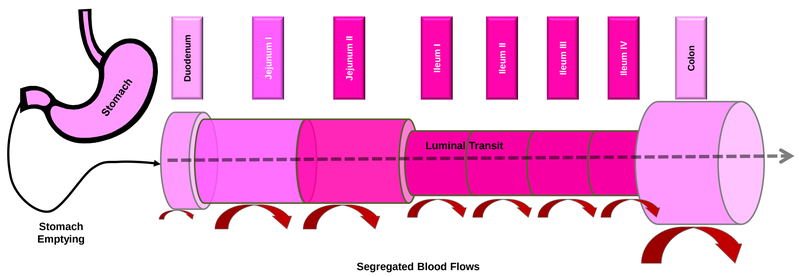

Figure 1 *– Schematic representation of the ADAM model, displaying the mechanistic segmentation of the GI tract into 9 sections with segregated blood flows to each section. The abundance of various enzymes and transporters in each segment varies non-monotonically along the intestine as depicted by the 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.*

- Physicochemical data were combined with parameters relating to villous morphology within the ADAM module to obtain estimates of segmental permeability using a Mechanistic Permeability Model (Turner *et al.,* in preparation).
- Transporter kinetic data (Km, J_{max}) and a relative expression factor [REF – the *in vivo* expression of P-gp in the jejunum relative to that of the *in vitro* Caco-2 cell system] were also incorporated into the model (Troutman & Thakker, 2003 a and b).
- 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 digoxin exposure and compared with observed data.
- As an additional validation exercise for the model, data relating to induction of intestinal P-gp by rifampicin were used to investigate the effects of this inducer on the systemic exposure of digoxin. Since concentration-dependent data relating rifampicin levels to P-gp induction were not available, the REF was increased *3.5-fold* to replicate the increase in expression observed *in vivo* (Greiner *et al*., 1999).

RESULTS

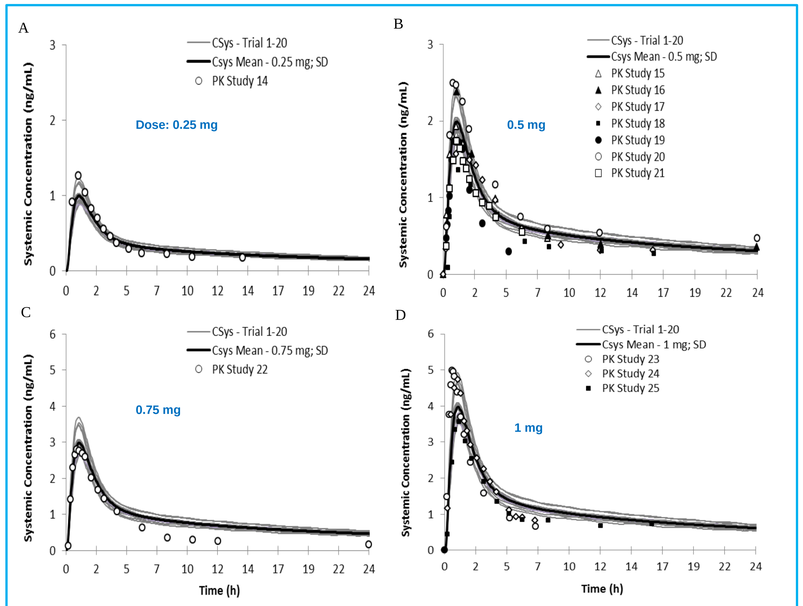

Figure 2*– Mean values and individual trials of simulated plasma concentration-time profiles of digoxin after an oral dose of (A) 0.25, (B) 0.5, (C) 0.75 or (D) 1 mg in a population of 200 individuals (20 trials of 10 healthy volunteers). The thin lines represent individual trials (n=20) and the solid black line is the mean of the population (n=200). The circles, triangles, diamonds and squares are mean observed values from 12 individual studies in Caucasians.*

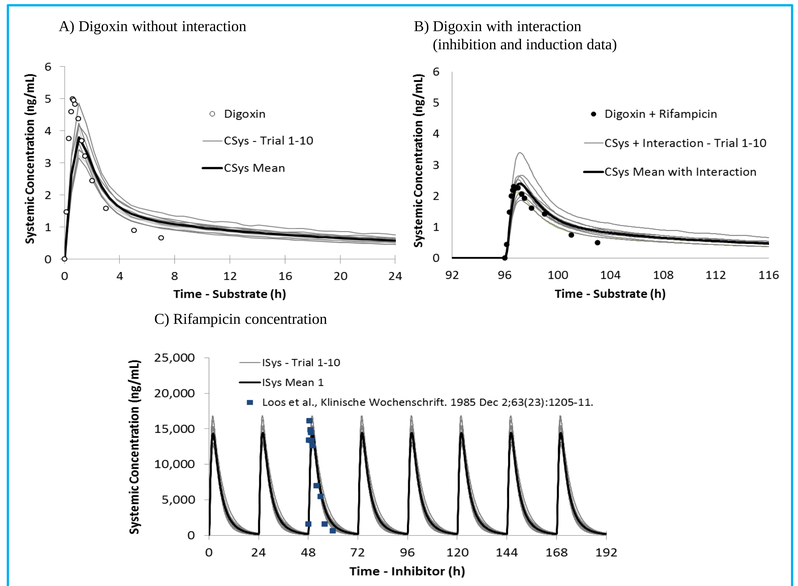

Figure 3 *– Simulated plasma concentration-time profiles of digoxin after an oral dose of 1 mg administered before (A) and after rifampicin therapy (600 mg QD for 10 days) (B). Each of the grey lines represents an individual trial of 8 males subjects based on the characteristics of the subjects (age, sex, etc.) recruited in the study reported by Greiner et al., 1999 and the solid black line is the mean of the simulated population (n=80). The circles are the mean observed values in the absence (open) and the presence (filled) of rifampicin (Greiner et al., 1999). (C) Corresponding simulated concentration-time profiles of the inhibitor concentration of Rifampicin.*

- The simulated concentration-time profiles of digoxin were consistent with observed data across 31 independent studies (13 SDiv, 12 SDpo and 6 MD). Simulated and observed profiles of digoxin following single oral doses of 0.25, 0.5. 0.75 and 1 mg digoxin are shown in Figure 2.
- The results confirmed that there was no indication of a departure from dose proportionality over the oral dose range studied (0.25 to 1.5 mg).
- Predicted decreases in AUC and C_{max} of digoxin following administration of rifampicin were 1.5- and 1.6-fold, which were reasonably consistent with observed values of 1.4- and 2.2-fold (Figure 3).

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.

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