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 (Vi1). 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).

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 1 – Schematic representation of the ADAM model, displaying the mechanistic segmentation of the GI tract into 9 sections with segregated blood flows in 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.

Figure 2 – Using Automatic Sensitivity Analysis, the change in Cmax 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 vivo 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 ‘loss’ 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, Vmax) and a scaling factor for the in vitro Caco-2 cell system (REF - a relative expression factor that links the in vitro 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 Thakkher, 2003 a and b). In Figure 2 the impact of the intestinal REF for P-gp on Cmax is illustrated.

Therefore, assuming concentration-time profiles of digoxin following single (SD) and multiple (MD), intravenous (iv) or oral (po) doses were simulated using 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).

The fact that predicted Cmax and Cmax 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 Cmax 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).

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

Turner et al., in preparation.