METHODS

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).

RESULTS

- 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, Vmax) 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).

CONCLUSION

- 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 Cmax 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).

REFERENCES