BACKGROUND

- Ranitidine is a histamine H₂-receptor antagonist and a victim drug recommended by the FDA for assessment of transporter-mediated drug-drug interactions (tDDIs) involving the Organic Cation Transporter 2 (OCT2). [1]
- OCT2 is expressed in the basal membrane of the proximal tubule and the neurons of the brain.
- Ranitidine has also been suggested to be a weak inhibitor of the cytochrome P450 enzymes, CYP3A and CYP2D6.

AIM

To develop a mechanistic physiologically-based pharmacokinetic (PBPK) model in order to determine the impact of transporter-mediated uptake and efflux on the disposition of ranitidine.

METHODS

- In vitro information on the dissolution, permeability, metabolism and transporter kinetics (for Organic Anion Transporters, OAT2 and OAT3, the Multidrug And Toxin Extruders, MATEs and OCT2) of ranitidine were combined with physicochemical data in a PBPK model implemented in the Simcyp Population-based Simulator (V12r2).
- A whole body PBPK model including permeability-limited models for the gut (ADAM) the liver (PerL) and the kidney (Mech Km) were used (Figure 1).
- Concentration-time profiles of ranitidine following single (SD) and multiple (MD) intravenous (iv) or oral (po) administration were simulated over a range of doses (20 mg to 200 mg) to assess the potential effects of transporter saturation on dose proportionality of ranitidine exposure and compared with observed data.
- An additional validation exercise for the model, data relating to inhibition of renal OCT2, OAT3 and/or MATE by cimetidine were used to investigate the effects of this inhibitor on the systemic exposure of ranitidine.
- DDI simulations with metoprolol and midazolam were performed to investigate CYP3A and CYP2D6 inhibition potential of ranitidine.

RESULTS

PBPK model validation

Figures 2-4 show the observed versus simulated plasma concentration-time profiles for 4 SD iv, 10 SD po and 1 MD po, respectively.

Figure 2 – Simulated versus observed plasma concentration-time profiles of ranitidine in HV following the intravenous bolus administration of 20, 40, 50 and 80 mg. The grey thin lines represent simulated individual trials (10 of 10 male subjects (20-50 years), the dashed black thin lines are the upper (95th percentile) and lower (5th percentile) confidence intervals and the solid black line represents the simulated mean of the HV population (n=100). The circles denote observed mean values from the corresponding clinical study.[9]

Figure 3 – Simulated versus observed plasma concentration-time profiles of ranitidine in HV following the oral administration of a single dose ranging 20 to 400 mg. The grey thin lines represent simulated individual trials (10) in 10 male subjects age 20-50 years; the dashed black thin lines are the upper and lower confidence intervals and the solid black line represents the simulated mean of the HV population (n=100). The circles and squares denote mean values from the corresponding clinical study.[9-7]

Figure 4 – Simulated versus observed plasma concentration-time profiles of ranitidine in HV following the oral administration of 150 mg bid for 7 days. The grey thin lines represent simulated individual trials (10) of 10 male subjects (20-50 years), the dashed black thin lines the upper and lower confidence intervals and the solid black line represents the simulated mean of the HV population (n=100). The circles denote mean values from the corresponding clinical study.[9]

Interaction

- Using Ki values of 79, 0.37 and 0.47 µM for OAT3, OCT2 and MATEs respectively, the predicted increase in mean AUC and decrease in renal clearance of ranitidine following administration of cimetidine were 1.17 - range (1.14-1.2) and 0.8-fold (range: 0.75-0.86), which were reasonably consistent with observed values of 1.3- and 0.7-fold.[5]

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 transporter-mediated uptake and efflux and to elucidate the relative importance of hepatic and renal transporters to the bioavailability and drug interactions of ranitidine.

REFERENCES