An integrated PBPK/PD feedback model to predict drug-drug interactions between gastric acid reducing agents and drugs with pH dependent solubility

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Background

Weakly basic drugs with low intrinsic solubility exhibit pH dependent solubility: solubility is high at low pH when the drug is predominantly ionised and low at high pH when the drug is predominantly un-ionised. Suppression of gastric acid by acid reducing agents (ARAs) such as proton pump inhibitors and H_2 receptor antagonists can result in reduced gastric solubility and reduced absorption of these compounds.

Clinically significant drug-drug interaction (DDI) via this mechanism has been observed for a number of drugs including a number of targeted anticancer agents and antifungal agents [1,2]. In some cases, this has resulted in labelling recommendations to avoid coadministration or to stagger the timing of administration of acid reducing agents [1].

We aimed to extend a PBPK/PD model to account for the change in gastric pH over time following administration of the H_2 receptor antagonist cimetidine and to predict the impact on the bioavailability of the weakly basic drug ketoconazole for different dosing regimens.

Methods

A function to enable feedback of gastric pH for each simulated individual and at each simulated time-step was implemented within the Simcyp Simulator Lua interface (V16.1).

The PK/PD of cimetidine was modelled using the default Cimetidine compound model [3] extended to include an indirect response model describing the change in gastric pH [4], with IC_{50} and hill slope fitted to data from [5] (Figure 1, *left*).

The Ketoconazole compound model was extended to include a mechanistic absorption model and pH dependent solubility [6] (Figure 1, *right*).

To investigate the impact of interaction between a single oral dose of 400 mg ketoconazole and 800 mg cimetidine, predictive simulation were run using the Sim-Healthy Volunteer population (10 trials of 10 individuals age 20-50 years, 50% female, fasted conditions). The impact of dose stagger was explored by running a series of simulation in which the timing of the ketoconazole dose relative to the cimetidine dose was modified in 1 h steps such that the dose was taken up to 1h before (-1h) to 13 h after ketoconazole.

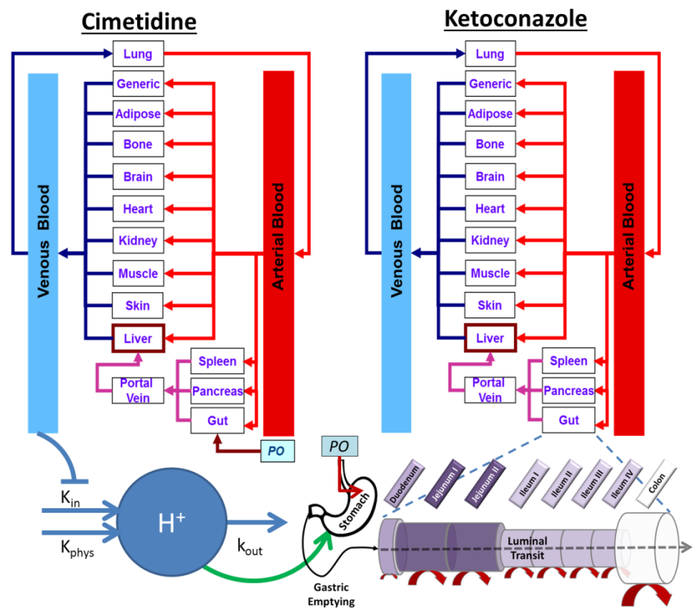

Figure 1. A schematic representation of the PBPK modelling approach to predict drug-drug interaction between cimetidine and ketoconazole. The inhibition of gastric acid secretion by cimetidine dynamically modifies the stomach pH in the mechanistic absorption model used for ketoconazole.

Results

The time-varying changes in the gastric acid pH following a single 800 mg oral dose of cimetidine was adequately captured (Figure 1).

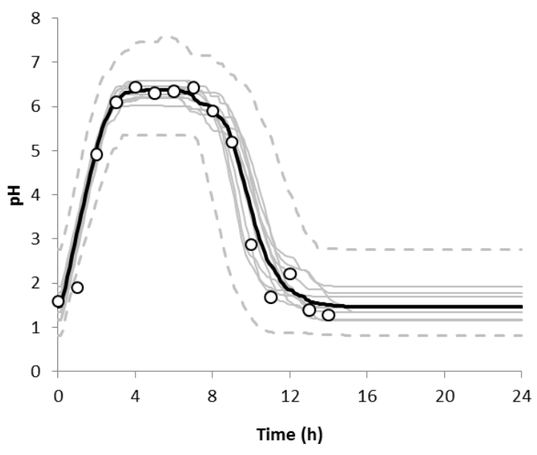

Figure 2. Predicted (lines) and observed (open circles, [5]) gastric pH profile following a single oral dose 800 mg cimetidine in healthy volunteers (12 individuals, age 20-31 years, 50% female). Black line is the median of the simulated population (10 trials of 12 individuals), grey lines are the median of each simulated trial and dashed lines are the 5th and 95th percentiles.

Results (Continued)

The population simulation predicts that the maximum extent of interaction is observed, when 400mg oral ketoconazole is administered between 3 and 6 hours after 800 mg cimetidine (Figure 3 and 4), when the geometric mean AUC and C_{max} ratios are 0.20 and 0.10. The maximal extent of interaction is consistent with the reduction in exposure to ketoconazole in clinical studies in which stomach pH is maintained above pH 6 [6,7]. No interaction is predicted for >95% of simulated individuals when ketoconazole is administered 13 hours after cimetidine (Figure 4). Simulations predict considerable interidividual variability in the extent of the interaction an the impact of dose stagger (Figure 4).

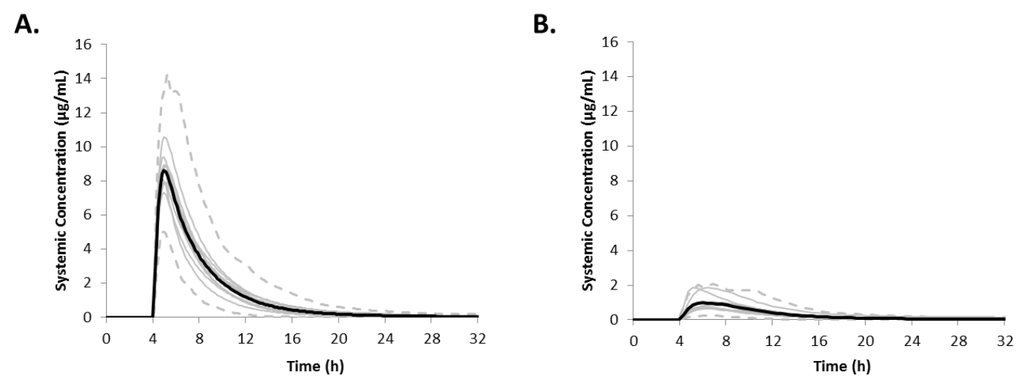

Figure 3. Predicted plasma concentration profile following a single oral dose 400 mg ketoconazole in the absence of (A) and dosed 4 h after cimetidine 800 mg (B). Solid black lines are the mean of 10 trials, solid grey lines represent the mean of an individual trial and dashed grey lines are the 5th and 95th percentiles.

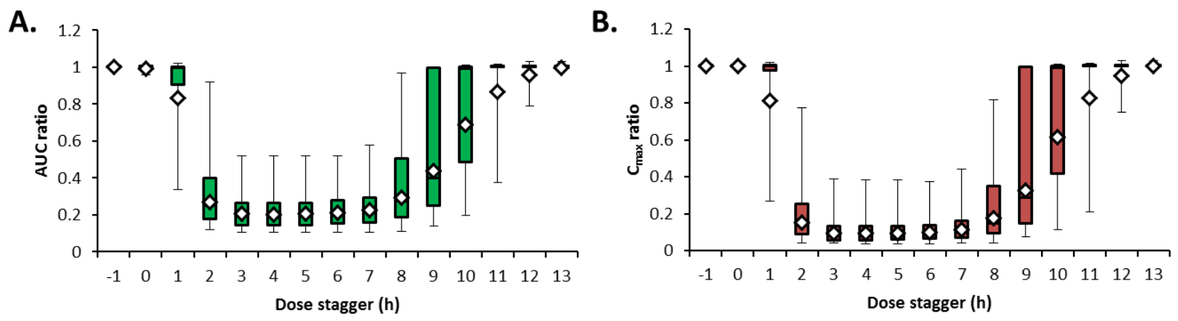

Figure 4. Box plot of the predicted AUC ratio (C) and C_{max} ratio (D) for 400 mg ketoconazole when administered with a single 800 mg dose of cimetidine. Dose stagger defines the time of the dose of ketoconazole relative to the dose of cimetidine. Bars show the 25th, 50th and 75th centiles, whiskers show the 5th and 95th centiles. Diamonds show the geometric mean.

Conclusions

An integrated PBPK/PD approach that accounts for the dynamics of the changes in gastric pH following an acid reducing agent enables prediction of the impact of dose staggering on the interaction with drugs with pH dependent solubility. The approach described can be extended to investigate the interaction between other acid reducing agents and drugs or formulations with pH dependent solubility.

A number of ARAs are known to be substrates or inhibitors of drug metabolising enzyme or transporters, thus may act as substrates or perpetrators of PK-DDI. A potential benefit of the PBPK/PD approach is the ability to simultaneously simulate the impact of multiple PK-DDI mechanisms in addition to increased gastric pH on drug concentrations.

The described approach can be of high interest in designing clinical studies for oncology drugs, which are often associated with pH dependent solubility.

References

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