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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Objectives: Absorption of weakly basic drugs with pH dependent solubility can be reduced in the presence of gastric acid reducing agents such as proton pump inhibitors and H₂ receptor antagonists. We aimed to extend a PBPK/PD model to account for the change in gastric pH over time following administration of cimetidine to predict the impact on the bioavailability of 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 and indirect response model describing the change in gastric pH [1], with IC₅₀ and hill slope fitted to data from [2]. The Ketoconazole compound model was extended to include a mechanistic absorption model and pH dependent solubility [3].

Results: The time-varying changes in the gastric acid pH following a single 800 mg oral dose of cimetidine was adequately captured (Figure 1a). Preliminary simulations for a population representative individual under fasted conditions predict a maximal reduction in AUC of 85% when 400 mg oral ketoconazole is administered between 2 and 7 hours after 800 mg cimetidine (Figure 1b) and no interaction when administered 10 hours after or simultaneously with cimetidine.

Conclusion: 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. This can be of high interest in designing clinical study of oncology drugs.