Development of a Physiologically Based Pharmacokinetic Model of Buspirone and Its Active Metabolite 1-(2-Pyrimidinyl)-Piperazine to Estimate Drug-Drug Interaction and Food Effect

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Background

Buspirone is an antianxiety agent that undergoes extensive first-pass metabolism in gut and liver[1]. One of the metabolites, 1-(2-Pyrimidinyl)-Piperazine (1-PP), circulates at higher concentrations than buspirone and may play a significant role in the clinical effects after dosing buspirone[2]. Clinical pharmacology studies indicate that strong inhibitors and inducers of CYP3A4 significantly change the oral exposure to buspirone and 1-PP, while food increases the oral exposure of buspirone almost 2-fold[3].

The aim of this study was to develop a Physiologically Based Pharmacokinetic (PBPK) model to predict the changes in oral exposure to buspirone and its active metabolite 1-PP, following concomitant CYP3A4 perpetrator use or food intake.

Methods

The PBPK model of buspirone was developed with the Simcyp Simulator V17R1. The Advanced Dissolution, Absorption, Metabolism (ADAM) model and a full PBPK model were applied to describe the absorption and distribution of buspirone, while a minimal PBPK model was adopted to describe the distribution of 1-PP. The models were parameterised based on physicochemical, in-vitro and clinical data that are available in the public domain[3-6].

Results

The model predictions successfully recovered the plasma concentration-time profiles of buspirone and 1-PP after oral administration of single and multiple doses of buspirone (**Fig. 1**).

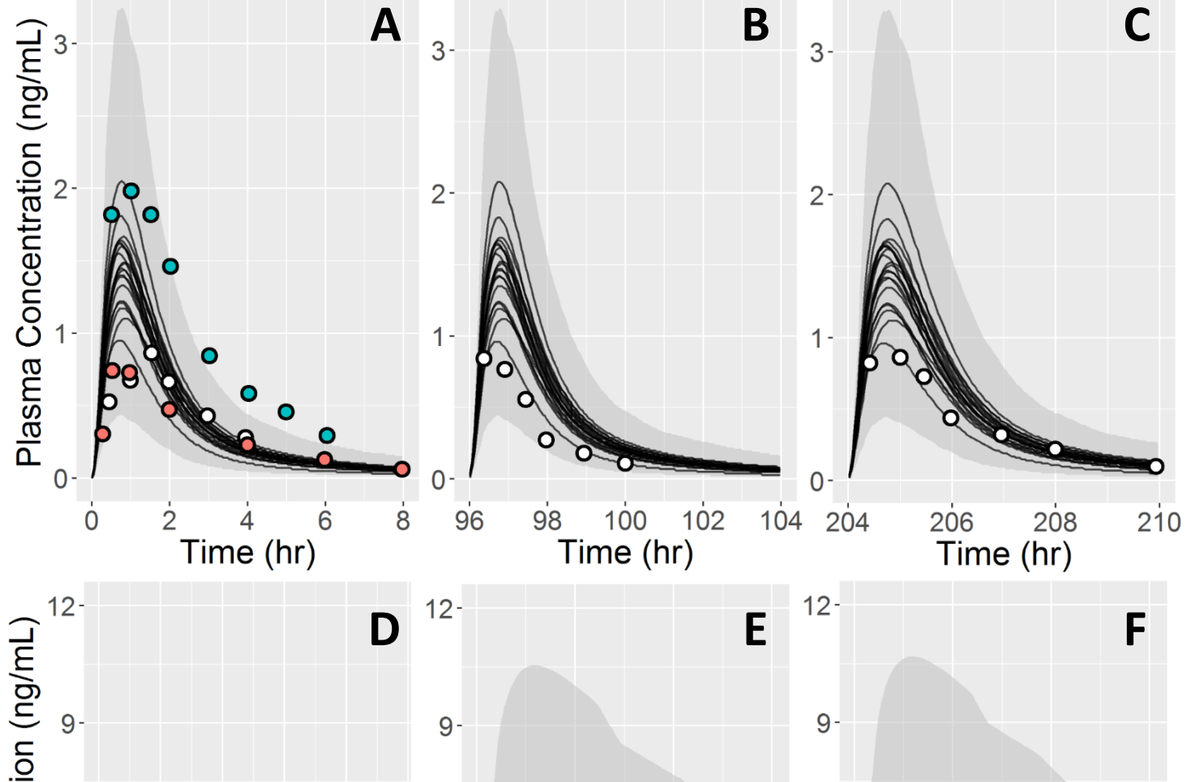

Figure 1. *Simulated and observed (data points[7-9]) plasma concentration-time profiles of buspirone **(A-C)** and 1-PP **(D-F)** after single and multiple oral administrations of 10 mg buspirone hydrochloride tablets. The black lines represent the predictions from individual trials. The grey-shaded area represents the 5th to 95th percentile of the total virtual population.*

Results

The model reasonably captured the plasma concentration-time profiles of buspirone and 1-PP under the interaction of CYP3A4 perpetrators (**Fig. 2**). The predicted mean AUC and C_{max} ratios of buspirone in the absence and presence of perpetrators or food intake were within 1.5-fold of the observed values, while the predicted mean ratios of 1-PP were within 2-fold of the observed values (**Fig. 3**).

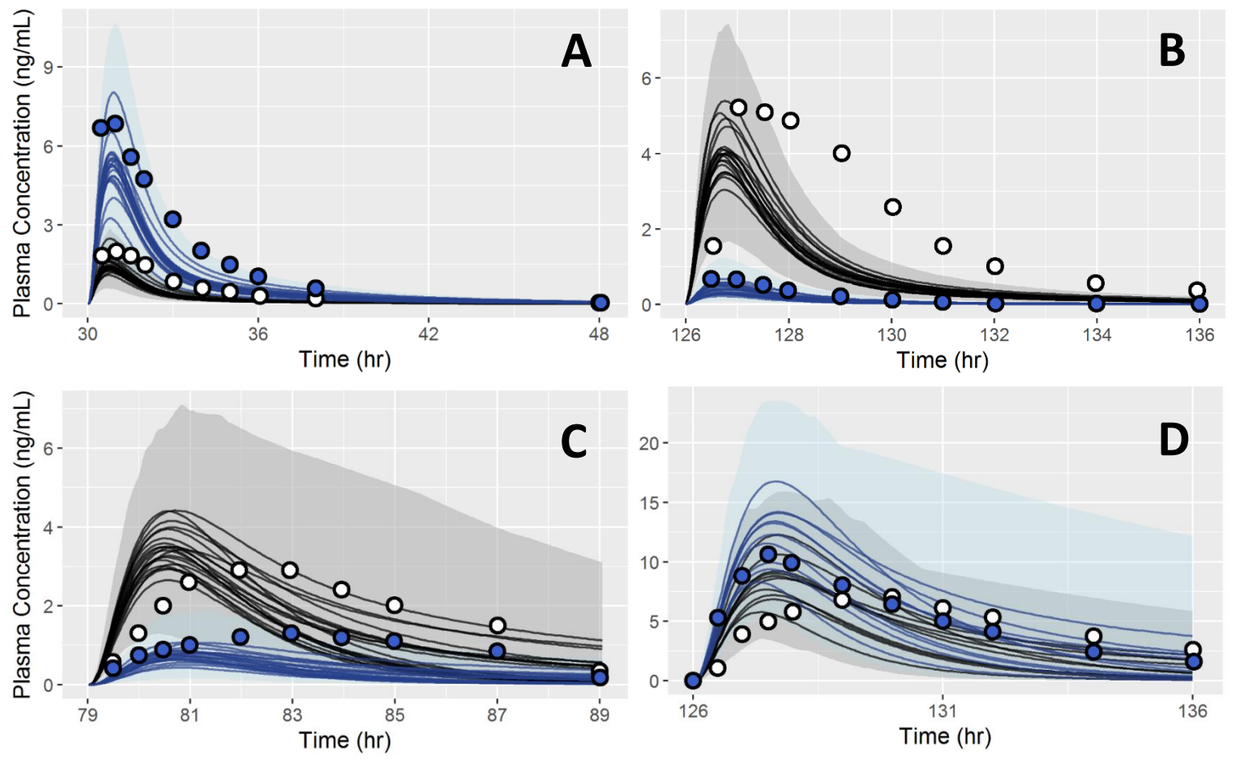

Figure 2. *Simulated (solid lines) and observed (data points[9,10,14]) plasma concentration-time (C-T) profiles of buspirone **(A, B)** and 1-PP **(C, D)** in the absence (black lines and white points) or presence (blue lines and points) of CYP3A4 perpetrators including **(A)** Verapamil (80 mg×5 in 29 hours), **(B,D)** Rifampicin (600 mg once daily for 5 days), **(C)** Itraconazole (100 mg twice daily for 4 days). The solid lines represent the predictions from individual trials. The grey and blue-shaded areas represent the 5th to 95th percentile of the total virtual population in the absence and presence of CYP3A4 perpetrator, respectively.*

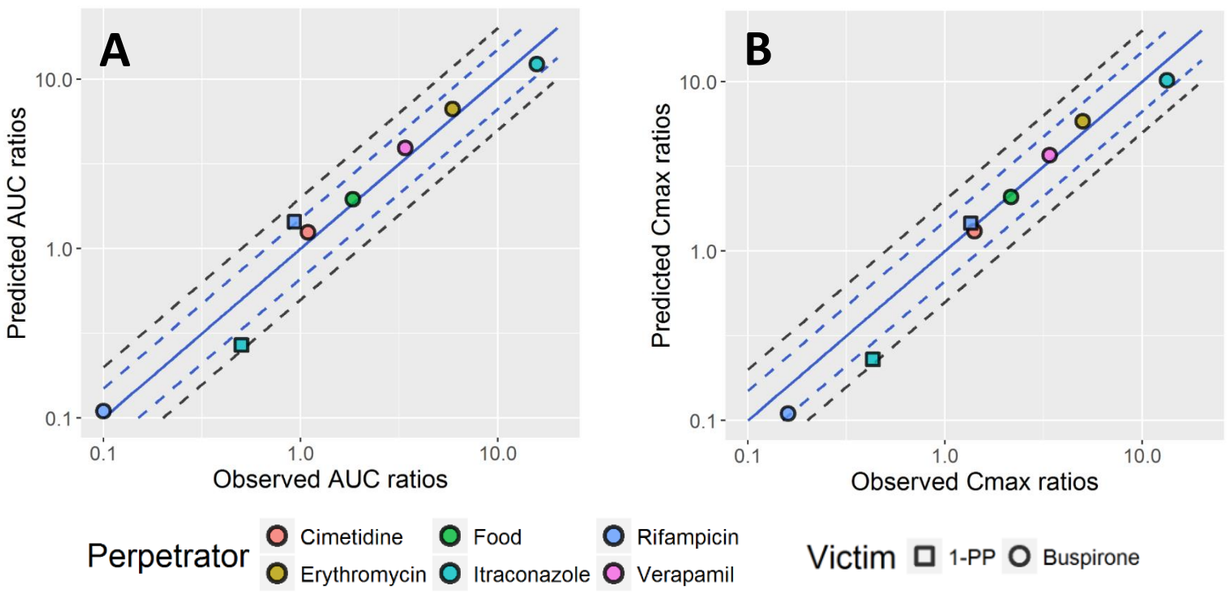

Figure 3. *Simulated and observed AUC **(A)** and C_{max} **(B)** ratios of buspirone and 1-PP in the absence and presence of various CYP3A4 perpetrators and concomitant food intake[9,11-14]. The blue solid line represents unity. The blue and black dashed lines indicate 1.5 and 2-fold deviation from unity.*

Conclusions

Collectively, the present study demonstrated the usefulness of PBPK in predicting oral exposure to buspirone under the interaction of a CYP3A4 inhibitor, inducer and food, supporting its further application in prospective prediction of DDIs between buspirone and other CYP3A4 perpetrators on the market or in the development pipelines.

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