Development of a Model of Omeprazole Pharmacokinetics in GastroPlus

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INTRODUCTION

- Proton pump inhibitors work by preventing proton secretion in the stomach, thus increasing gastric pH levels.
- Omeprazole is an orally bioavailable proton pump inhibitor drug.
- Omeprazole is administered as a racemic mixture of R-Omeprazole and S- Omeprazole
- Omeprazole is metabolized through CYP2C19 and CYP3A4 in the gut and liver.
- Omeprazole exhibits autoinhibition of CYP enzymes
- Omeprazole shows saturable pharmacokinetics with a single dose as the dose increases.
- With multiple dosing, omeprazole shows a slower rate of elimination
- ***Aim***: To investigate the pharmacokinetics of omeprazole by building a PBPK model that incorporates physicochemical data, human physiology, and CYP metabolism

METHODS

1. Collect data from the literature for pharmacokinetic studies of omeprazole[1-3]
2. Obtain baseline clearance (CL) and volume of distribution (Vd) using intravenous PK studies at doses 10mg and 40mg (Fig. 2A,D)
3. Reproduce plasma concentration-time curves for omeprazole oral solutions at doses 10mg and 40mg in a two compartmental model (Fig. 2B,E)[2]
4. Build a PBPK model for oral solutions at doses 10mg and 40mg (Fig. 2C,F)[2] with inclusion of CYP3A4 and CYP2C19 metabolism in the gut and liver
5. Build a PBPK model for a 90mg oral solutions that takes into account autoinhibition of CYP2C19 (Fig. 2G,H)
6. Extend PBPK model to an enteric coated oral tablet with inclusion of dissolution rate and adjustment of CYP enzymes to reproduce pharmacokinetics after multidosing (Fig 2I-K)[3]

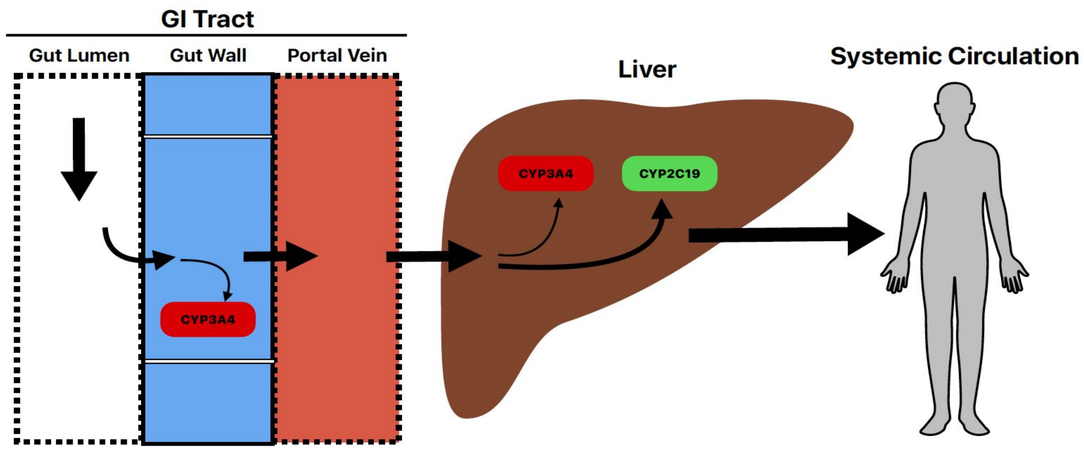

Fig 1. Pathway of omeprazole absorption into the systemic circulation

RESULTS

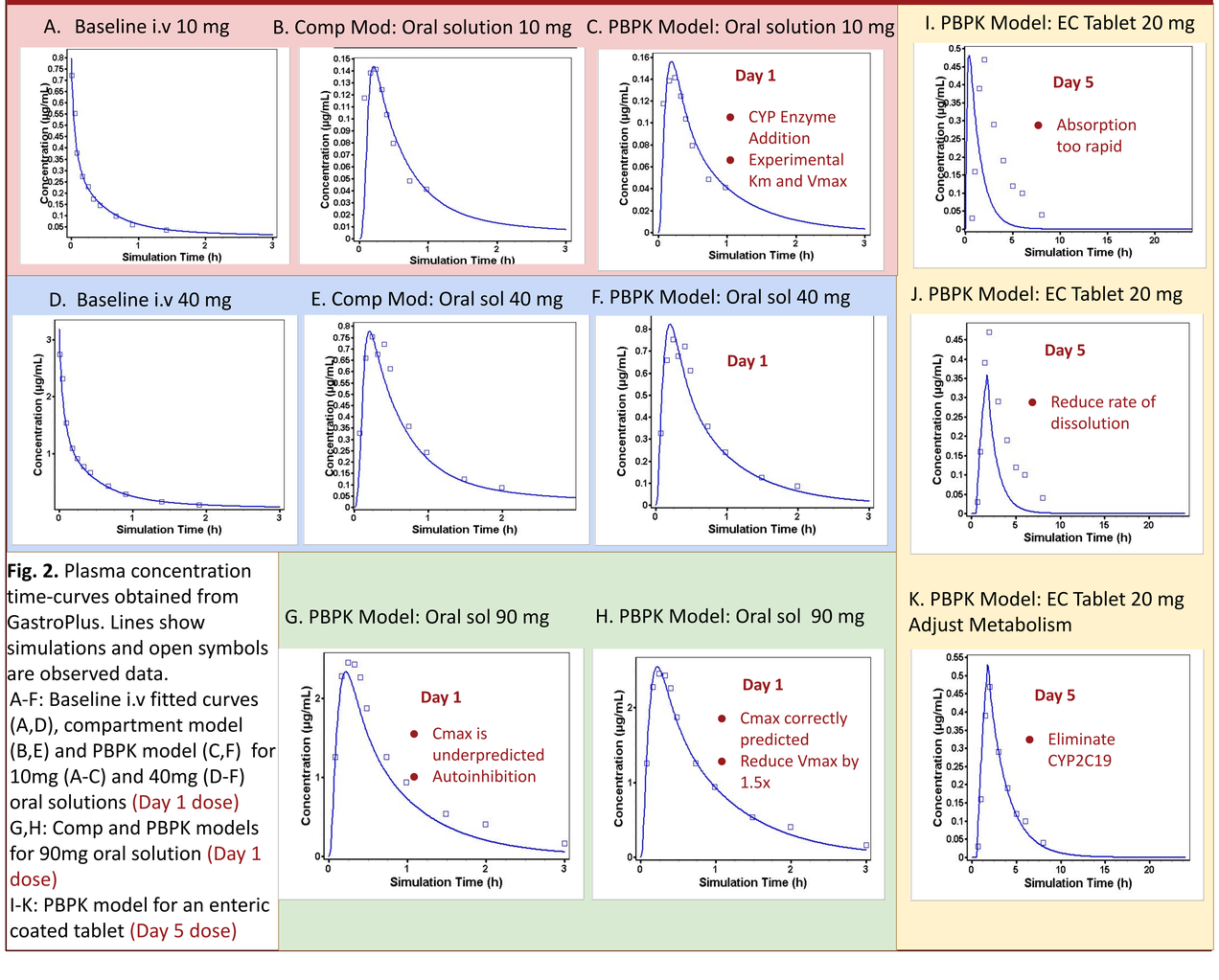

Fig. 2. Plasma concentration time-curves obtained from GastroPlus. Lines show simulations and open symbols are observed data.
A-F: Baseline i.v fitted curves (A,D), compartment model (B,E) and PBPK model (C,F) for 10mg (A-C) and 40mg (D-F) oral solutions (Day 1 dose)
G,H: Comp and PBPK models for 90mg oral solution (Day 1 dose)
I-K: PBPK model for an enteric coated tablet (Day 5 dose)

RESULTS

- The i.v data were used to obtain the clearance (CL) of 35.839 L/h and the volume of distribution (Vc) of 0.16066 L/kg. (Fig 2A, D)
- Using parameters from the i.v model and a numerical representation of gut metabolism, a two compartmental model reproduced PK for the 10mg and 40mg oral solutions (Fig.2B,E).
- The compartmental model was successfully "converted" to a PBPK model by inclusion of kinetics parameters for CYP3A4 and CYP2C19 to represent clearance (Fig.2C,F).
- This PBPK model only reproduced the 90mg oral solution PK by inclusion of saturation and autoinhibition of CYP enzymes. (Fig.2G,H)
- Application of this model for a 20mg enteric coated tablet (after multiple dosing) required modification of the dissolution rate (Fig.2I to 2J) and elimination of the CYP2C19 (Fig.2J to 2K).
- With these changes we were able to reproduce the PK of the 20mg tablet (Fig.2K)

DISCUSSION

- The nonlinear PK of omeprazole is due to the saturation of CYP3A4 in the gut and not to saturation of CYP2C19 even though this enzyme is the main CYP for omeprazole metabolism.
- Autoinhibition of CYP2C19 is important in single dose omeprazole PK
- With multiple doses, CYP2C19 is increasingly inhibited and our results suggest that this enzyme has limited involvement in omeprazole metabolism after several days of dosing.
- Our PBPK model is applicable to prediction of omeprazole PK in different populations, individuals, and dosing regimens with inclusion of variable pharmacogenetics.

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