# Accounting for CYP2C19 mechanism based inhibition and CYP1A2 induction in a PBPK model for omeprazole

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## Background

Omeprazole is a probe substrate for CYP2C19 but is also metabolised by CYP3A4. In individuals identified as poor metabolisers (PMs) of CYP2C19, the role of CYP3A4 in the elimination of the drug becomes more important. Omeprazole is also an *in vivo* inhibitor of these two enzymes. Although previously known to reversibly inhibit CYP2C19 and CYP3A4 *in vitro*, recent studies have shown mechanism based inhibition (MBI) of CYP2C19[1]. This is important, as omeprazole undergoes non-linear kinetics, with an increase in plasma concentration after multiple doses. In addition to this, omeprazole induces CYP1A2 *in vivo,* particularly in CYP2C19 PMs where the exposure concentration is much higher or when administered at higher doses[2]. The aim of this project was to account for CYP2C19 MBI and CYP1A2 induction in a physiologically based pharmacokinetic model of omeprazole to aid the prediction of drug-drug interactions (DDIs).

## Methods

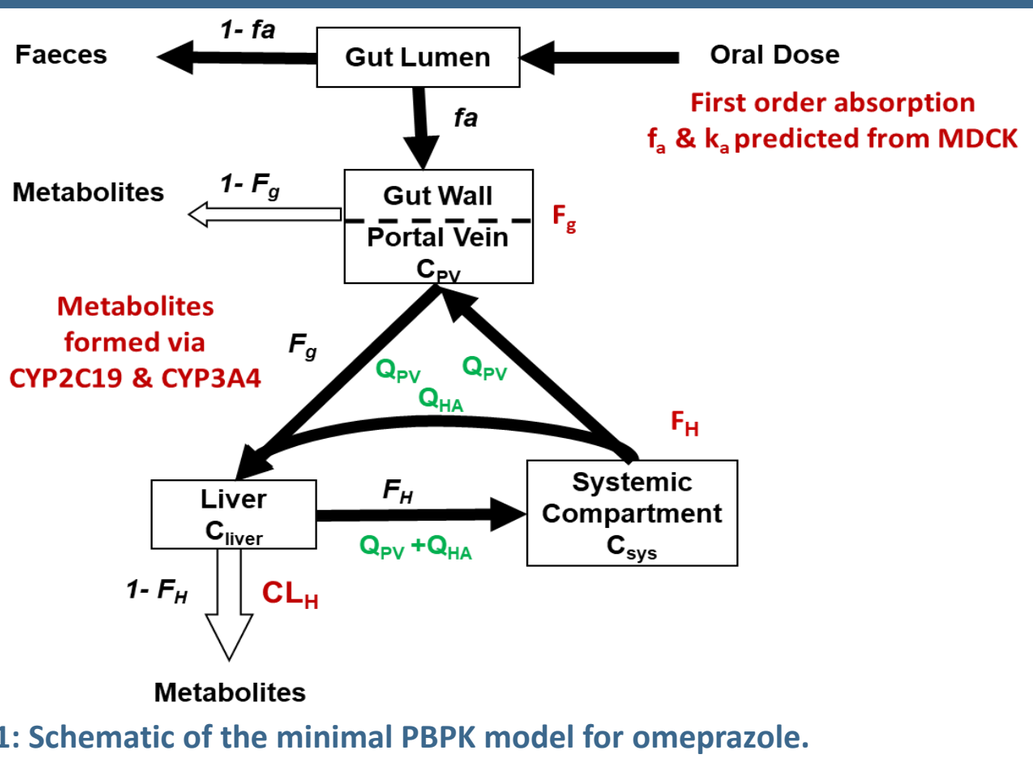


**Figure 1: Schematic of the minimal PBPK model for omeprazole.**

A minimal PBPK model was developed for omeprazole in Simcyp V18R1. First order absorption with fa and ka predicted from *in vitro* derived permeability data in MDCK cells is used in the file. A user-input lag time derived using manual sensitivity analysis is included in the model in order to recover the delayed Tmax characteristic of enteric-coated formulations. *In vitro* kinetic parameters for CYP2C19 and CYP3A4 was estimated by reverse translation using *in vivo* fm and $CL_{po}$ data from a single clinical study carried out in CYP2C19 EMs and PMs.[3] *In vitro* derived CYP2C19 MBI parameters did not recover the exposure of omeprazole after multiple doses (MD), so the $K_{app}$ was optimised against a single MD study[4], while retaining the highest derived *in vitro* $K_{inact}$[5]. Finally, an *in vivo* measured $Ind_{max}$[6] alongside an optimised $IndC_{50}$ derived using automated sensitivity analysis, to recover a clinical DDI between omeprazole and caffeine[6] was added to enable the modelling of CYP1A2 induction. The final input parameters used in the model are shown in Table 1 below.

## Results

**Table 1: Input parameters used in the SV-Omeprazole PBPK model.**

| Input Parameter | Value | Reference/Comment |
|---|---|---|
| Molecular weight | 345.4 g/mol | PubChem |
| Log P | 2.33 | Weighted mean from 3 studies |
| pKa | 9.33, 4.31 | Measured value at 37°C |
| fu | 0.053 | Average of measured value at 37°C |
| Absorption | Predicted fa and ka from MDCK<br>T-lag = 0.75 h<br>Fugut = fup | Manually optimised against Tmax of enteric coated formulations |
| Vss | Method 3 predicted 0.392 L/kg | In line with WX from observed data |
| $CL_{int}$ CYP2C9 | 62.593 µl/min/pmol | Estimated from $CL_{po}$ and in vivo fm from one study carried out in CYP2C19 EMs and PMs- Andersson et al., 1992. |
| $CL_{int}$ CYP3A4 | 0.201 µl/min/pmol | |
| CLr | 0 L/h | Regardh et al., 1990 |
| CYP1A2 Induction | Indmax = 2.4 CV = 33.4%<br>$IndC_{50}$ = 0.15 µM | Diaz et al., 1990<br>Optimised to recover clinical DDI |
| CYP2C19 MBI | Kapp = 0.65 µM, Kinact = 2.9 | Kapp: Optimised to recover Racc<br>Kinact: Zvyaga et al., 2012 |

## Results

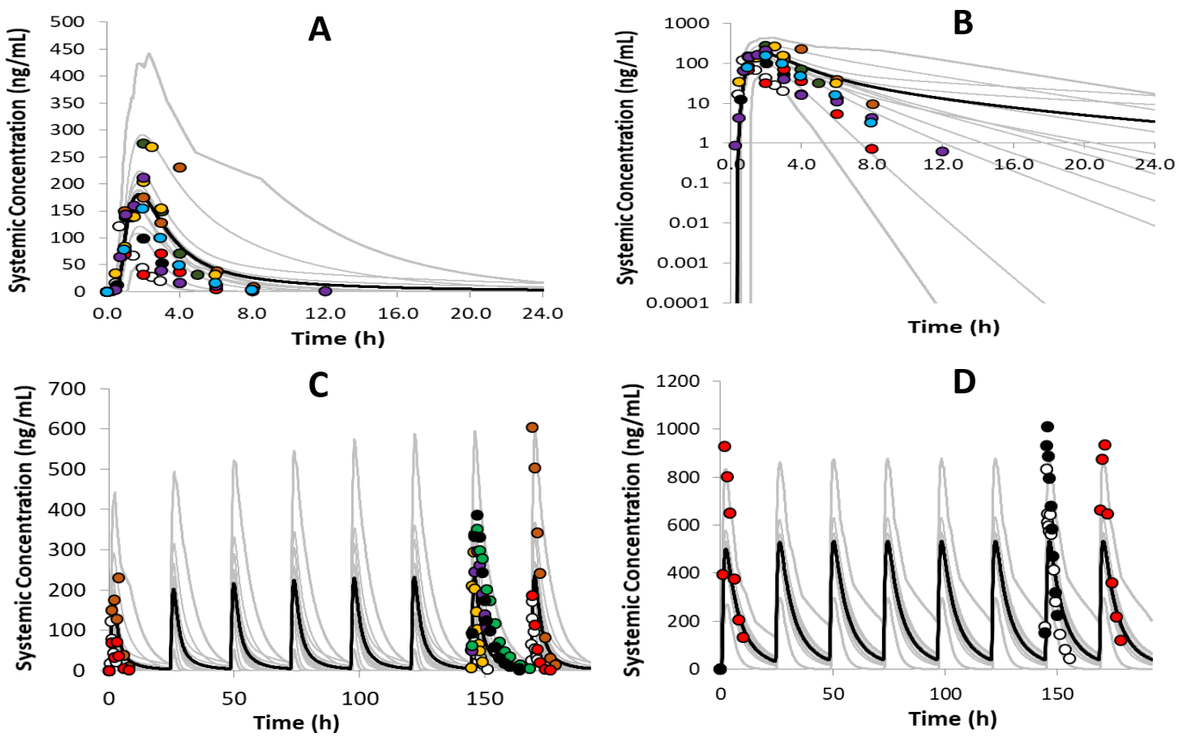


**Figure 2: Simulated (black line) & observed (data points) mean plasma concentration time profiles after a single oral dose of 20mg enteric coated omeprazole (A) & (B), and multiple doses (C) using the updated Healthy Volunteer CYP2C19 population frequency and abundance (59% CYP2C19 EMs, 32% UMs and 9% PMs); and administered to CYP2C19 PMs only (D). 10 trials of 10 HV, 50% females was used for all simulations.**

The performance verification of the new SV-Omeprazole model is shown by reasonable recovery of its exposure after single and multiple doses to both CYP2C19 EMs and PMs (Figure 1). In addition, the current model is able to predict clinical DDIs when omeprazole is co-administered with either CYP3A4 inhibitors, CYP2C19 substrates and/or inhibitors or CYP1A2 substrates.

**Table 2: Observed and predicted Cmax and AUC ratios when omeprazole is co-administered with CYP3A4 inhibitors (ketoconazole and clarithromycin), CYP2C19 inhibitor (fluvoxamine) and with a CYP1A2 substrate (caffeine).**

Omeprazole as a substrate

| Study | Substrate | Inhibitor | Observed | | Predicted | | Predicted/Observed | |
|---|---|---|---|---|---|---|---|---|
| | | | AUC ratio | $C_{max}$ ratio | AUC ratio | $C_{max}$ ratio | AUC ratio | $C_{max}$ ratio |
| Bottiger *et al.* 1997 (CYP2C19 EMs) | Omeprazole 20mg SD, Day 4 | Ketoconazole 200 mg QD x 4 Days | 1.36 | 1.37 | 1.11 (1.07 - 1.19) | 1.07 (1.05 - 1.12) | 0.82 | 0.78 |
| Bottiger *et al.* 1997 (CYP2C19 PMs) | Omeprazole 20mg SD, Day 4 | Ketoconazole 200 mg QD x 4 Days | 1.99 | 1.43 | 1.43 (1.25 - 1.82) | 1.34 (1.24 - 1.49) | 0.72 | 0.94 |
| Calabresi *et al.* 2004 (CYP2C19 EMs) | Omeprazole 20mg BID x 7 days | Clarithromycin 250mg BID x 7 days | 2.02 | 1.25 | 1.89 (1.46 - 2.15) | 1.42 (1.21 - 1.63) | 0.94 | 1.14 |
| Sager *et al.* 2014 (CYP2C19 & 2D6 EMs) | Omeprazole 20mg SD, Day 12, 1hr after fluoxetine | Fluoxetine 20mg SD, 60mg QD x 13 days | 7.1 (4.4-20) | NS | 6.52 (5.05 - 7.99) | 2.74 (2.26 - 3.04) | 0.92 | |

Omeprazole as a perpetrator

| Study | Substrate | Inhibitor | Observed | | Predicted | | Predicted/Observed | |
|---|---|---|---|---|---|---|---|---|
| | | | CL (Dose/AUC) CYP2C19 EMs | CL (Dose/AUC) CYP2C19 PMs | CL (Dose/AUC) CYP2C19 EMs | CL (Dose/AUC) CYP2C19 PMs | CYP2C19 EMs | CYP2C19 PMs |
| Sarich *et al.*, 1997 | Caffeine 100 mg SD on Day 8 | Omeprazole 40mg QD x 7 days | 1.04 (1.02 - 1.09) | 1.21 (1.13 - 1.35) | 1.15 | 1.5 | 0.9 | 0.81 |

## Conclusions

In addition to the performance verification of omeprazole as a CYP2C19 and CYP3A4 substrate, the incorporation of CYP2C19 MBI and CYP1A2 induction parameters in the SV-Omeprazole model enables the recovery of its multiple dose exposure, as well as clinical DDIs with other CYP2C19 and CYP1A2 substrates.

## References

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