APPLICATION OF PHYSIOLOGICALLY-BASED PHARMACOKINETIC (PBPK) MODELLING FOR PREDICTION OF CYP-MEDIATED DRUG-DRUG INTERACTIONS (DDIs) INVOLVING ETHINYLESTRADIOL (EE)

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Background

Current formulations of combined oral contraceptives (COC) containing ethinylestradiol (EE) have doses of ≤ 35µg due to increased risks of cardiovascular diseases (CVD). Low dose formulations have however resulted in increased incidences of breakthrough bleeding and contraceptive failure particularly when co-administered with inducers of cytochrome P450 (CYP450). The aim of this study was to develop a PBPK model for EE as a victim drug, to predict CYP3A4 mediated drug-drug interactions (DDIs) and hence understand its limits of safety and toxicity.

Methods

Prior metabolic, protein binding and physicochemical data for EE were collated from the literature and incorporated into a minimal PBPK model with a single adjusting compartment within the Simcyp Simulator (Version 17R1) assuming first order absorption. Scaled up *in vitro* enzyme kinetic parameters[1,2] resulted in a fraction metabolised by CYP3A4 (fm_{CYP3A4}) of ≈ 10%, which under-predicted the DDI with ketoconazole by more than 2-fold. Refinement of the model using the clinical DDI study with ketoconazole resulted in an increased fm_{CYP3A4} of ≈ 22%.

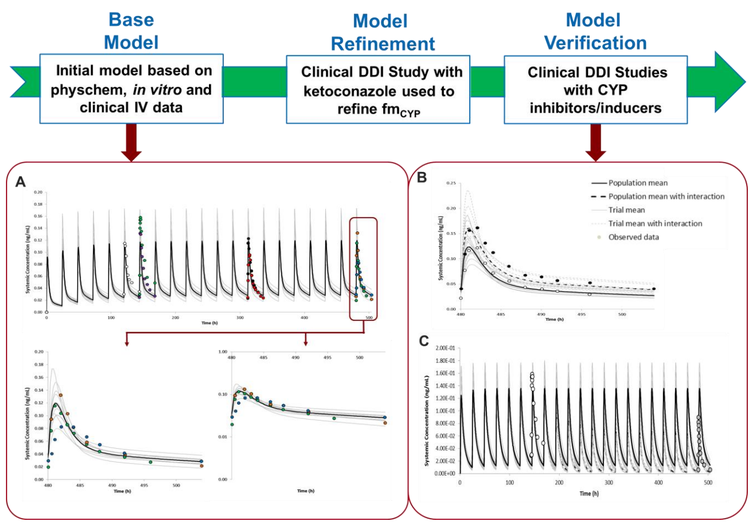

Figure 1: Workflow of EE model development combining a bottom-up (*in vitro* data) and top-down (clinical data) approach. The final model showed reasonable recovery of observed data after multiple doses of 35µg EE (A); and the refined fm_{CYP3A4} was further verified in clinical DDI studies with fluconazole (CYP3A4 inhibitor, B) and rifampicin (CYP3A4 inducer, C)

Results

To verify the refined fm_{CYP3A4}, simulations of multiple doses of 35 µg EE in the presence of other CYP3A4 inhibitors (voriconazole and fluconazole) and CYP3A4 inducers (rifampicin and carbamazepine) were carried out. The observed AUC and C_{max} ratios for all the studies were all reasonably recovered by the model as shown in Figure 2.

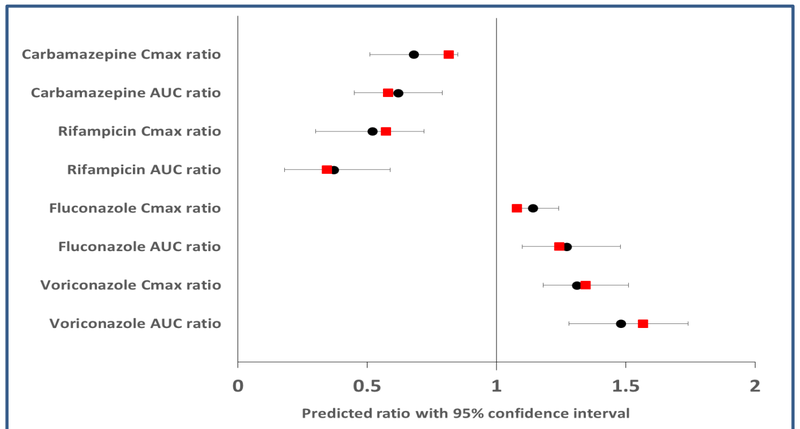

Figure 2: Forest plot of the predicted C_{max} and AUC ratios of the developed EE victim model when co-administered with various CYP3A4 perpetrators. Observed ratios of the mean are denoted by red squares.[3]

- The steady state AUC (AUC_{ss}) of EE for most of the clinical DDI studies with reported breakthrough bleeding or contraceptive inefficacy published in the University of Washington database was ≤ 1000 pg/ml.hr.[3]
- The safety and non-CVD risk of COCs is assured for doses of EE < 50 µg in non-smoking women, including those > 35 years.[4,5]
- We therefore determined how frequently within a simulated population of 100 female healthy volunteers (20-50 years), the AUC_{ss} for formulations containing 20 & 35 µg EE was below 1000 pg/ml.hr or above 1675 pg/ml.hr (the simulated population mean AUC_{ss} for a 50 µg dose), when taken alone or alongside CYP inhibitors or inducers.
- As shown in Figure 3, the AUC_{ss} for the 20 µg dose in almost 90% of the simulated individuals was below 1000 pg/ml.hr. Adequate concentrations were only attained in ≈ 50% of the individuals when taken alongside CYP inhibitors. On the other hand, although the 35 µg dose provided adequate dosing in ≈ 50% of the population, co-administration with CYP inducers could result in a loss in efficacy, while CYP inhibitors resulted in higher EE AUC_{ss} > 1675 pg/ml.hr .

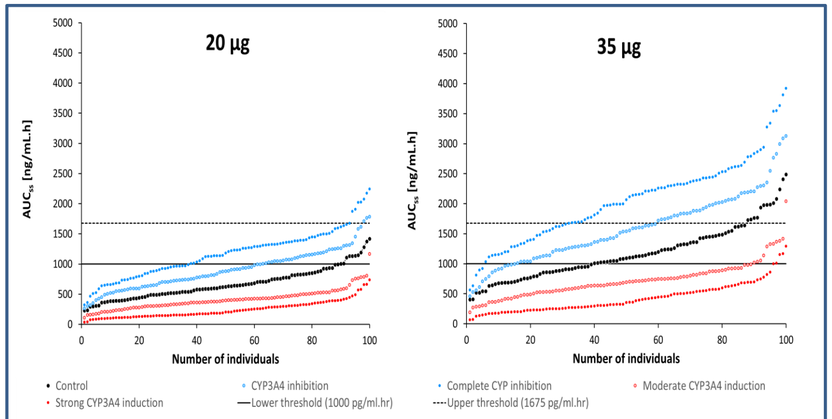

Figure 3: Simulated mean AUC_{ss} for 100 females (20-50 years) of 20 and 35 µg EE alone and when co-administered with a moderate CYP3A4 inducer (efavirenz), strong CYP3A4 inducer (rifampicin), strong CYP3A4 inhibitor (ketoconazole) and a hypothetical drug with complete inhibition against all CYP enzymes.

Conclusions

A recent article based on data from the British Pregnancy Advisory Service indicated that more than 50% of over 60000 women who visited their clinics in 2016 for an abortion reported using at least one form of contraception when they got pregnant.[6] This study not only corroborates this finding, but also highlights the relatively narrow therapeutic index of COCs containing EE; particularly when prescribed alongside inhibitors and inducers of CYP3A4.

References

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