PBPK-Based Prediction of Obesity-Mediated Changes in Small Molecule Pharmacokinetics.

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PURPOSE

- Obesity is associated with fat accumulation, combined with physiological alterations, (changes in organ sizes, blood flows, and metabolic enzyme activities).
- These pathophysiological modifications have profound effects on all phases of drugs' ADME.
- Dose selection, efficacy prediction, and safety assessment for obese patients are challenging.
- This applies to drugs designed to support weight loss as well as drugs intended to treat other diseases where obesity is a comorbidity.
- As part of MIDD, PBPK models are used to assess pharmacokinetic changes in special populations.
- This study aims to demonstrate the use of PBPK models in predicting obesity-induced changes in the PK of small molecules.

METHODS

- Clinical PK in lean and obese subjects following intravenous (IV) and oral (PO) administration of ten active pharmaceutical ingredients (API) were collected.
- API-specific PBPK models were built in GastroPlus® (Simulations Plus, Inc.) using literature parameters, in silico predictions from ADMET Predictor® (Simulation Plus Inc.), or fitted against in vivo PK data in lean subjects.
- The validated PBPK models were used to predict the APIs' PK in obese subjects.
- Observed and simulated Obese/Lean ratios for Cmax and AUC were calculated for each drug.
- The ability of the PBPK models to predict obesity-induced changes in the PK was deemed acceptable if the observed and predicted PK metrics ratios are within ± 25%.

PBPK models can predict the effect of OBESITY on small molecules PK

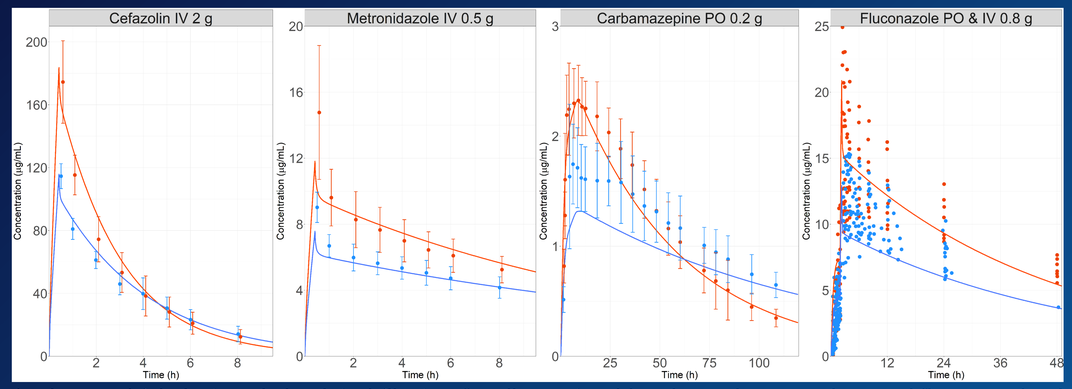

Figure 1: observed (circles) and simulated (line) cefazolin, metronidazole, carbamazepine, and fluconazole plasma concentration-time courses in lean (orange) and obese (blue) patients following a single IV infusion or PO administration. The fluconazole administration schedule was 0.4 g PO followed by 0.4g IV infusion 2 hours later.

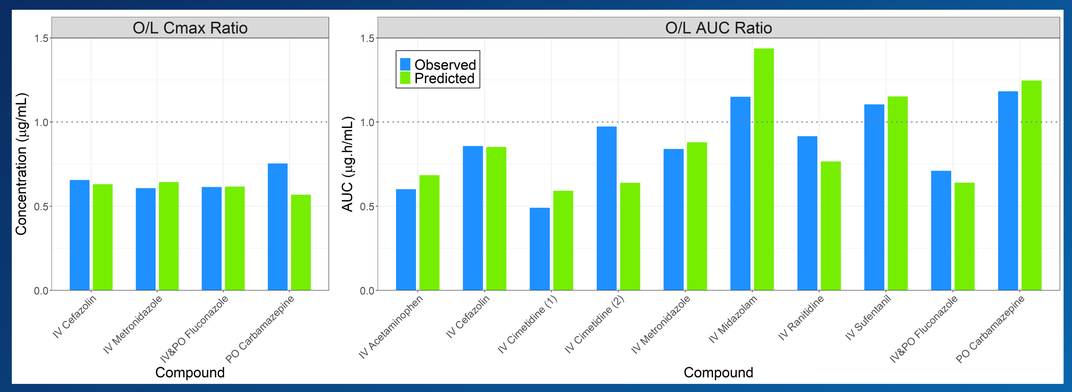

Figure 2: Observed (blue) and predicted (green) Obese/Lean Cmax and AUC ratios

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RESULTS

- The PBPK models accurately predicted the PK of all APIs in lean and obese patients (example profiles are shown in Figure 1 for cefazolin and metronidazole after IV administration, and carbamazepine and fluconazole after PO administration).
- The predicted Obese/Lean ratios for Cmax and AUC ratios are within 25% of the observed ratios for all compounds, except for one of the cimetidine studies.
- The trends for changes in Cmax and AUC in obese versus lean subjects are also captured correctly. Cmax values for carbamazepine, cefazolin, fluconazole, and metronidazole, are predicted to decrease in obese subjects, consistent with the observed changes. AUC for several test compounds (carbamazepine, midazolam, and sufentanil) was predicted and observed to increase in obese patients, whereas for the other APIs, a decrease in AUC for obese patients was observed and simulated (Figure 2).

CONCLUSIONS

- This study demonstrates the capability of the PBPK model integrated within the GastroPlus software to predict obesity-induced changes in the PK of small molecules.
- As a validated platform, it serves as a valuable tool for both the pharmaceutical industry and regulatory agencies in improving the efficacy and safety assessment of drugs in obese populations.

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