Application of physiologically based pharmacokinetic (PBPK) modelling for prediction of complex drug-drug interactions (DDIs) involving inhibition of OATP1B1-mediated uptake and CYP2C8 metabolism by gemfibrozil and its major metabolite gemfibrozil 1-*O*-β glucuronide

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BACKGROUND

Gemfibrozil (GFZ) and its metabolite **Gemfibrozil 1-*O*-β Glucuronide (GFZglu)** are both inhibitors of metabolism (CYP2C8) and hepatic uptake (OATP1B1). Unbound plasma concentration of the metabolite is higher than for the parent and GFZglu is the more potent inhibitor.

AIM

To use PBPK modelling to predict complex DDIs involving **both GFZ and GFZglu** as inhibitors of the metabolism and transport of **Rosiglitazone (RSG), Rosuvastatin (RSV) and Repaglinide (RPG)**

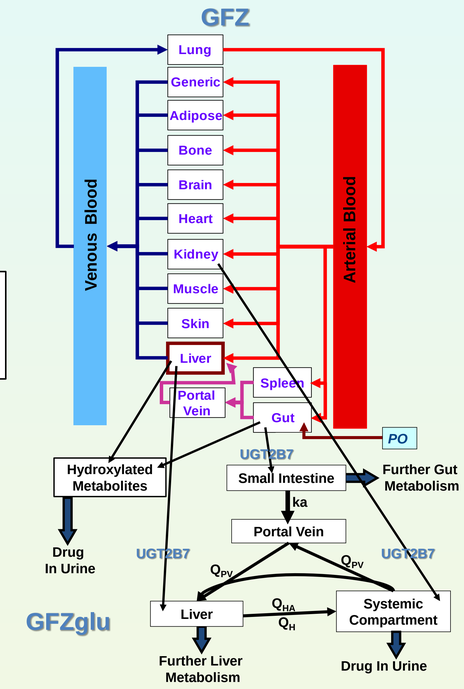
METHODS AND RESULTS

Prior metabolic, protein binding and physicochemical data for GFZ, GFZglu, RSG, RSV and RPG were obtained from the literature and incorporated into a PBPK model within the Simcyp Simulator Version 12.

1. Model Construction - GFZ and GFZglu

Stage 1 of Recommended PBPK Modelling 'Best Practice' (1):

- Model Construction
- Model Verification/Modification (Refinement)
- Model Application



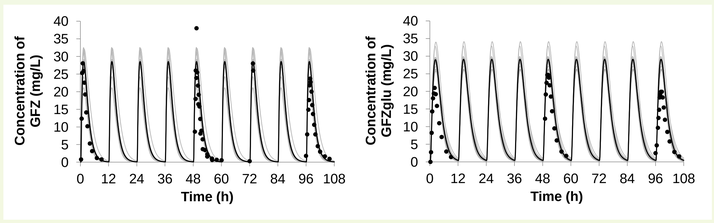


Figure 1. PBPK model (top) used to simulate the concentration-time profiles of GFZ and GFZglu (bottom) following dosing of 600 mg GFZ (bid) for 3 days. Mean observed data (circles) from 6 clinical studies are overlaid.

2. Model Verification - DDI with RSG (CYP2C8 only, (2))

Using CYP2C8 $K_{i,u}$ 9 µM (GFZ), $K_{i,u}$ 0.8 µM (GFZglu) and k_{inact} 13 /h, $K_{app,u}$ 19 µM (GFZglu: $k_{inact}/K_{app,u}$ 0.7), the predicted increase in plasma $AUC_{(0-\infty)}$ of RSG was 2.0-fold (range for 10 trials: 1.8-2.6), which was consistent with the observed value of 2.3-fold (3).

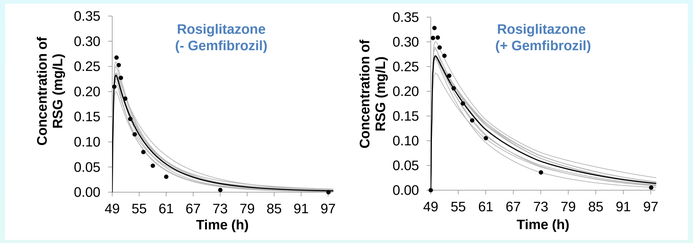


Figure 2. Comparison of simulated (10 trials) and observed (circles; mean data for n=10) change in exposure of RSG after a 4 mg oral dose in the absence and presence of GFZ and GFZglu (GFZ 600 mg bid for 3 days).

3. Model Modification – DDI with RSV (OATP1B1 only)

In vitro OATP1B1 $K_{i,u}$ values for GFZ and GFZglu ranging from 12-65 µM and 8-22 µM, respectively, did not allow recovery of the observed DDI with RSV. Thus, sensitivity analysis was performed to assess the impact of OATP1B1 $K_{i,u}$ values of both moieties on the predicted DDI.

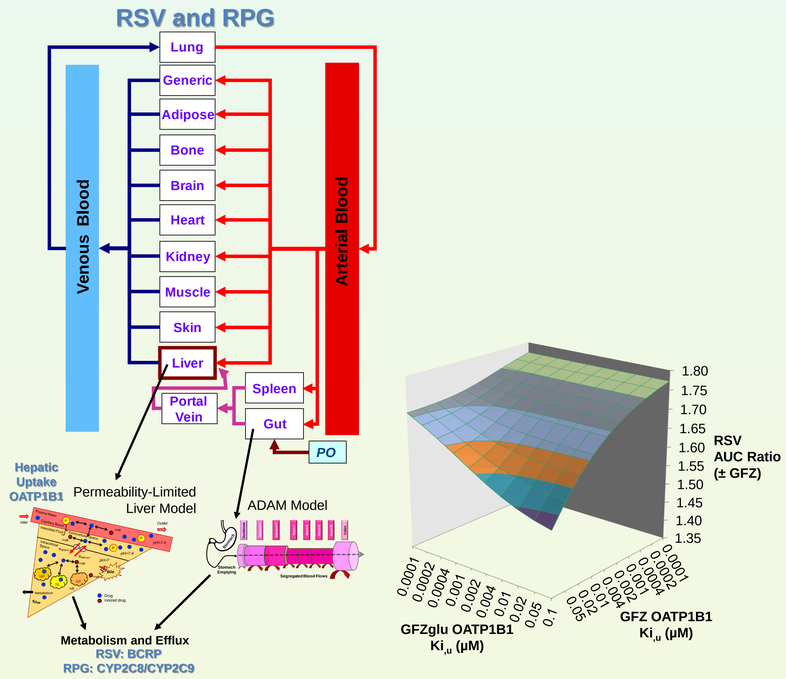


Figure 3. PBPK model (left) used to assess the impact of OATP1B1 Ki values for GFZ and GFZglu on RSV exposure during co-administration of GFZ (right). ADAM – advanced dissolution absorption and metabolism model.

DDI with RSV (OATP1B1 only)

Using an OATP1B1 $K_{i,u}$ of 0.01µM for both GFZ and GFZglu allowed recovery of the observed DDI with RSV (1.7-fold *versus* 2.0-fold (4))

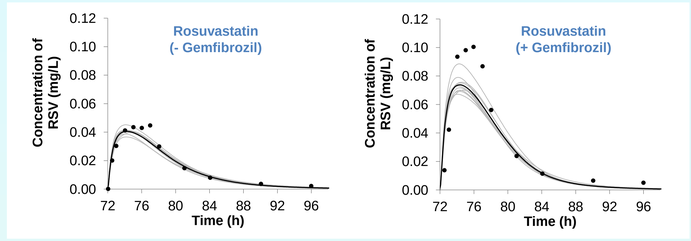


Figure 4. Comparison of simulated (10 trials: lines) and observed (circles; mean data for n=20) change in exposure of RSV after an oral dose of 80 mg RSV in the absence and presence of GFZ and GFZglu (GFZ 600 mg bid for 3 days).

4. Model Application - DDI with RPG (CYP2C8 and OATP1B1)

Using the "*in vivo*" OATP1B1 $K_{i,u}$ of 0.01 µM for both GFZ and GFZglu, the predicted increase in plasma $AUC_{(0-\infty)}$ of RPG was 4.1-fold (range of values for 10 simulated trials of virtual subjects: 3.5–5.1), compared to 5.0-fold (5), observed.

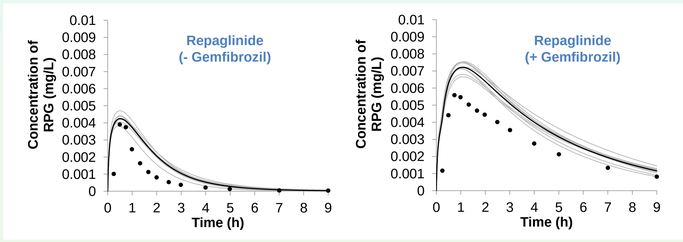


Figure 5. Comparison of simulated (10 trials: lines) and observed (circles: mean data for n=10) change in exposure of RPG after an oral dose of 0.25 mg RPG in the absence and presence of GFZ and GFZglu (GFZ 600 mg single dose).

CONCLUSIONS

The study demonstrates the utility of PBPK modelling to accurately predict complex DDIs involving inhibition of OATP1B1- and CYP2C8-mediated interactions by both the parent and metabolite moieties GFZ and GFZglu.

The validated GFZ and GFZglu model can be used to predict DDIs *"a priori"* for other CYP2C8 and OATP1B1 substrates, for which the *in vivo* interaction is unknown.

REFERENCES

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