PBPK modelling of the DDI between a Drug X and gemfibrozil

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INTRODUCTION AND OBJECTIVES

A PBPK model for drug X and its active metabolite was built in Simcyp V20. The parent drug was an orally administered compound (immediate release tablet) with a high extraction ratio, high plasma protein binding, and mainly eliminated through CYP3A4 and CYP2C8. Part of the CYP2C8 metabolism leads to the formation of a pharmacologically active metabolite. This metabolite is mainly eliminated through CYP2D6 and CYP3A4 metabolism (See Fig. 1). The parent and metabolite were found not to be transporters substrates. CYP-specific fraction metabolized (fm) of the parent and metabolite, originally based on in vitro data, were refined using clinical data from itraconazole and gemfibrozil DDI studies and human mass balance data. Regarding enzyme inhibition, itraconazole and its metabolite OH-itraconazole are potent CYP3A inhibitors, while gemfibrozil and its glucuronide metabolite both inhibit CYP2C8 with high potency. Gemfibrozil also inhibit CYP2C9.

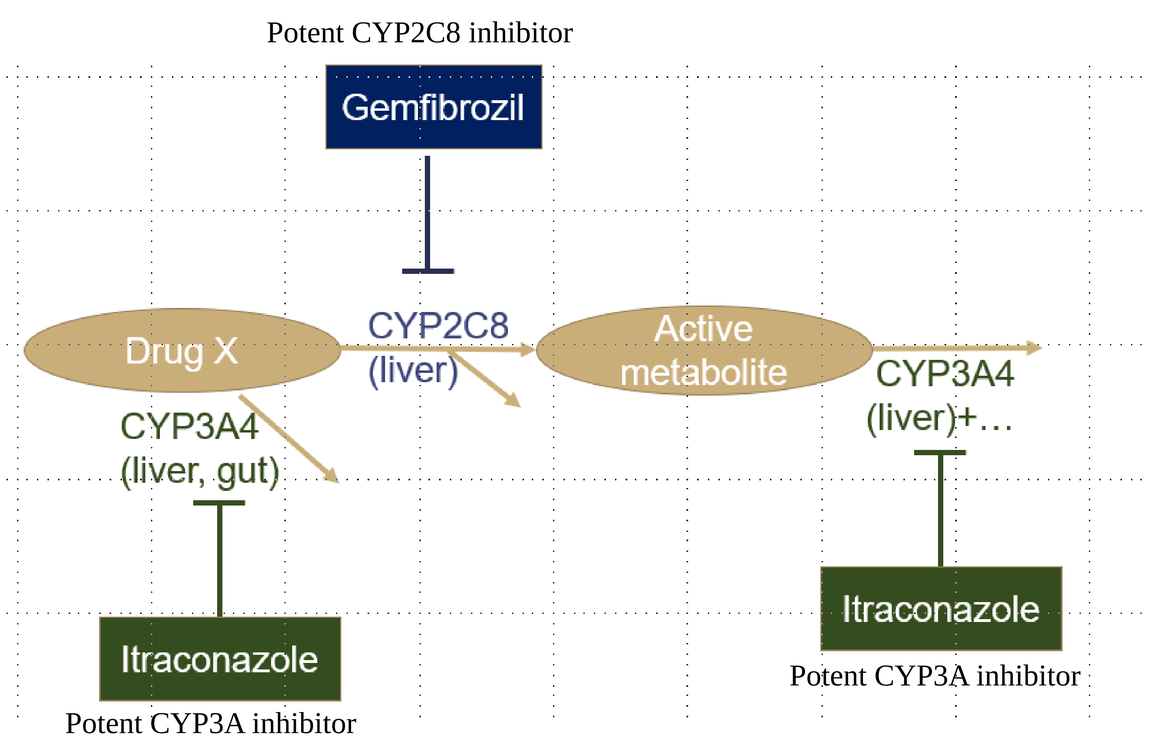

Figure 1. Metabolic pathway of drug X and its active metabolite and their drug-drug interactions with gemfibrozil and itraconazole.

The developed PBPK model reasonably predicted the exposure and observed DDI for the parent drug as well as the exposure of the metabolite but led to a 10-fold and 2-fold overprediction of the metabolite AUC ratios (AUCr) for gemfibrozil and itraconazole DDI studies respectively. It was not possible to explain the observed DDI data by changing the PBPK parameters of the parent and metabolite. Therefore, it was hypothesized that the CYP2C8 inhibitory constants from the gemfibrozil Simcyp V20 model (includes both gemfibrozil and one of its glucuronides) might not be suitable given their substrate dependency. **The objective of this work was to update and qualify these constants using our parent and metabolite PBPK model and DDI data.**

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Iain Gardner from Simcyp designed and performed the sensitivity analysis with each CYP2C8 substrates.

CONCLUSIONS

The gemfibrozil PBPK model as inhibitor on CYP2C8 was refined using drug X / metabolite model as substrate and was qualified using 5 available CYP2C8 sensitive substrates of reference from literature. Gemfibrozil compound file optimization could benefit from in vitro CYP2C8 Ki calibration [13]. This case is a good example of collaboration between Sanofi and Simcyp consortium to improve scientific knowledge of PBPK modelling.

RESULTS

The median P/O AUCr and Cmaxr for the five CYPC8 substrates increased as the gemfibrozil and glucuronide inhibitory constants were decreased for both scenario 2 and 3 as compared to scenario 1. For scenario 3, this increase was higher but small, with the maximum changes being noted between scenario 1 and 3 for P/O_AUCr of 37.3% corresponding to dasabuvir and of P/O_Cmaxr of 10.9% corresponding to repaglinide. For scenario 3, maximum P/O_Cmaxr was 1.52 and maximum P/O_AUCr was 1.28, for repaglinide and montelukast respectively. A 200-fold change in gemfibrozil CYP2C8 Ki did not significantly impact Montelukast AUC and Cmax ratios (See Fig. 2). Decreasing the gemfibrozil and metabolite Ki and Kinact values (15 and 5-fold respectively) together with fm refinement of drug X and its metabolite, led to accurate AUC and Cmax ratios predictions and concentration time curve predictions for both the parent compound and its active metabolite. Allocation of decrease in CYP2C8 inhibition across the three inhibitory constants was arbitrary due to identifiability issues.

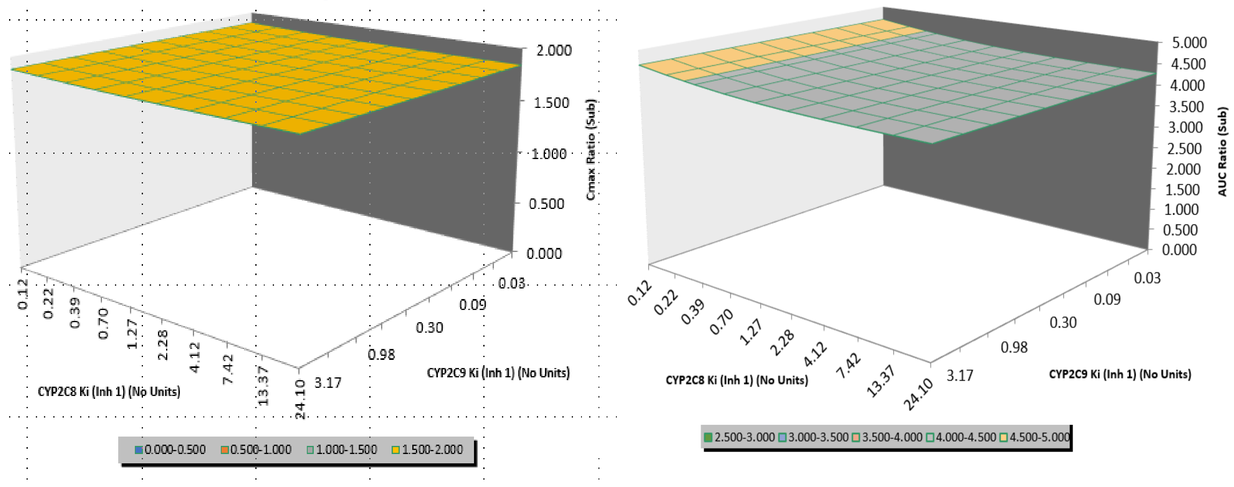

Figure 2. Sensitivity of Cmax (left) and AUC (right) ratios to changes in CYP2C8 and CYP2C9 Ki for Montelukast

METHODS

Rosiglitazone, repaglinide, dasabuvir, pioglitazone and montelukast were selected as the five CYP2C8 substrates, which CYP2C8 is responsible for 55, 60, 61, 63 and 79% of drug metabolism. Sensitivity of the predicted AUCr and Cmax ratio (Cmaxr) of these five drugs to the decrease in gemfibrozil Ki was explored in three simulated scenarios:

1) default Ki values
2) competitive Ki's 15-fold decrease for gemfibrozil and its glucuronide (1.61µM and 0.325 µM respectively)
3) 5-fold decrease in competitive Ki for gemfibrozil and its glucuronide (4.82 µM and 0.976µM respectively) and in mechanism-based inhibition parameter Kapp for gemfibrozil glucuronide (5.42µM).

For montelukast, a 200-fold change in Ki was investigated.

AUCr and Cmaxr were compared to observation from publishes clinical DDI data [1-12] by computing predicted/observed ratios (P/O_AUCr and P/O_Cmaxr). Further refinement of the PBPK model using DDI data of drug X and its active metabolite were performed.