Performance Verification of V17 Sim-Cancer Population in Simcyp

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Background

Oncology is an important area of pharmaceutical research. PBPK modelling can aid in oncology drug development when physiological and demographic differences in cancer patients compared to healthy volunteers are appropriately considered. For Simcyp V17 a Sim-Cancer population has been developed, taking into account differences in patient demographics and physiology. It has been debated in recent literature whether CYP abundance changes in cancer [1,2]. For the Sim-Cancer population no changes were made to CYP abundance. Performance verification of the population has been performed using a variety of probe CYP and transporter substrates.

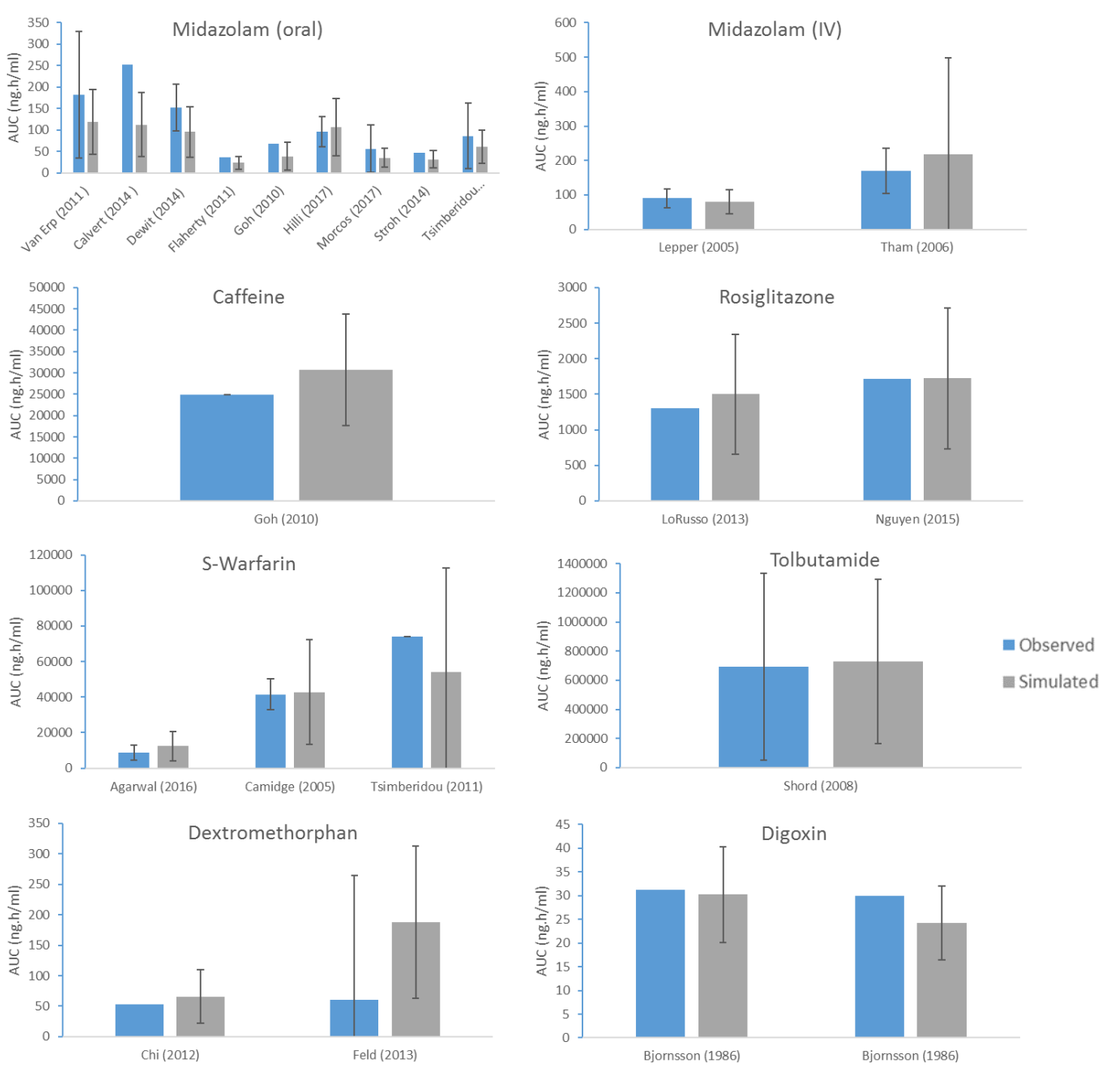
Methods

PK studies were collated from the literature for Simcyp Probe Substrates in cancer patients. Simulations were performed using matched trial designs with the Sim-Cancer population and the Simcyp compound files (without alteration) in Simcyp V17. Predicted PK parameters were compared to the reported values. Predicted AUCs are calculated for the same duration as the observed studies. PK studies in healthy volunteers using the same drugs and dosing regimens to the cancer studies were also collated where possible. Simulations were performed using 10 trials of matched trial designs with the Sim-NEurCaucasian population in Simcyp V17. The ratios of mean AUC and clearance (CL) in cancer patients compared to healthy volunteers were calculated from the reported clinical studies and the simulated studies. In addition, the range of AUC and CL ratios were calculated using the maximum and minimum values from the reported studies in cancer patients and healthy volunteers.

Results

26 PK studies were collated for 8 Simcyp compounds in cancer patients, including probes substrates for CYP1A2, 2C8, 2C9, 2D6, 3A4 and Pgp. Figures 1 and 2 show the mean (± SD) observed and predicted AUC or CL in cancer patients for each substrate.

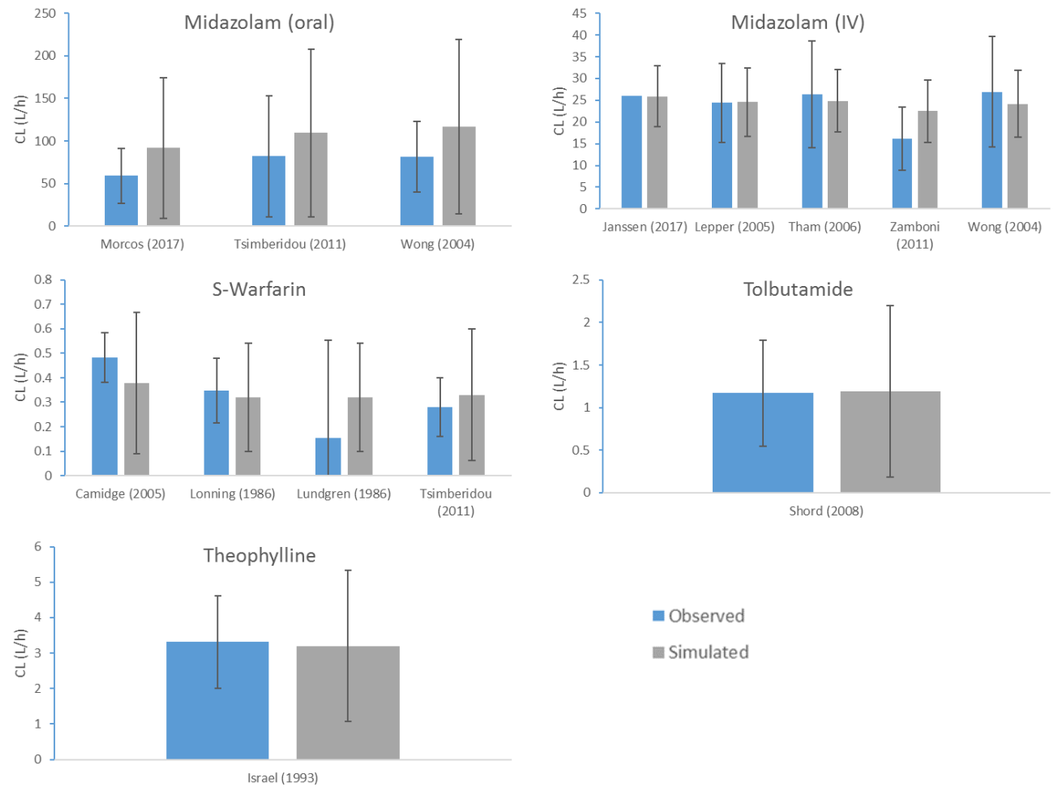
Figure 1: Observed and predicted mean (± SD) AUC for Simcyp compounds in cancer patients



Predicted parameters were generally within 50% of reported mean values and within the reported variability for cancer patients. A trend for over prediction of oral CL of midazolam was observed (1.3- to 1.6-fold) (Figure 2).

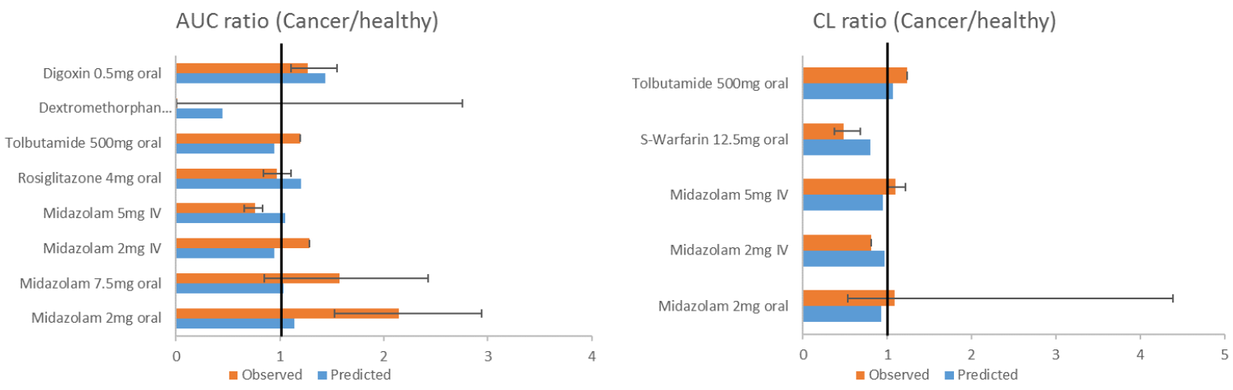
Figure 3 shows the observed and predicted ratios of AUC and CL between cancer patients and healthy subjects. Observed mean AUC and CL values in cancer patients were generally within 30% of those in healthy volunteers. Ratios from reported studies showed a significant difference for midazolam

Figure 2: Observed and predicted mean (± SD) CL for Simcyp compounds in cancer patients



AUC following oral dosing, however, the observed CL (IV and oral) was similar in cancer patients and healthy volunteers. A significant reduction in S-Warfarin CL in cancer patients was also observed from the reported studies, however, high variability was reported for this study.

Figure 3: Ratios of mean AUC and CL for Simcyp compounds in cancer patients compared to healthy volunteers



The predictions for AUC ratio were within 50% of the calculated values from reported studies, with the exception of dextromethorphan. However, there is very high variability in the reported AUCs for dextromethorphan in healthy volunteers (~500-fold). The predictions for CL ratio were within 0.8-1.25-fold of the calculated values from reported studies, with the exception of S-Warfarin (1.7-fold).

The minimum and maximum ratios calculated from the reported studies are shown as error bars in Figure 3. The healthy volunteer study chosen as the reference has a large impact on the calculated ratios and hence on prediction accuracy. This is particularly evident for midazolam AUC and CL following oral dosing and for dextromethorphan AUC and reflects the high variability in the observed PK data.

Conclusions

- The Sim-Cancer population for Simcyp V17 reasonably predicts the exposure and CL of probe substrates for CYP1A2, 2C8, 2C9, 2D6, 3A4 and Pgp in cancer patients (generally within 50% of observed values).
- The ratios of AUC and CL in cancer patients compared to healthy volunteers was generally predicted well (within 50% of observed values) when taking into account the different trial designs used for the studies in each population (e.g. ages).
- Based on these data CYP abundance appears to be similar in cancer patients to healthy volunteers and difference in PK are likely due to differences in the age of the trial subjects.
- High variability in the observed PK data has a large impact on the prediction accuracy of the difference in AUC and CL between cancer patients and healthy volunteers.

References

1. Cheeti *et al*., Biopharm Drug Dispos (2013) 34: 141-154; 2. Coutant *et al*., Clin Pharmacol Ther (2015) 98: 76-86.

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