Abstract

The aim of this study was to assess the relationship between mRNA and activity data for known inducers of CYP2C9 in human hepatocytes in vitro and to apply these data for prediction of the magnitude of CYP2C9-mediated drug-drug interactions (DDIs) in vivo.

There was a strong correlation ($r^2 = 0.96$) between in vitro induction markers for CYP2C9 (mRNA and activity).

Utilising a combination of IVIVE and physiologically based pharmacokinetic (PBPK) modelling (Simcyp, V16, UK), the induction potential of rifampicin (RIF), phenobarbital (PBT) and ritonavir (RTV) was evaluated using C9 substrates [tolbutamide (TBT), S-warfarin (WFN), phenolphthalein (PHN), glibenclamide (GMP)].

Using the measured in vitro C9 induction parameters (weighted mean; activity data), with the exception of PBT [6], both RIF and RTV models markedly under-predicted the induction magnitude (up to 3-fold) compared to observed and predicted mean ratio (GMR) for AUC or CL for C9 substrates [1-4, 7].

For RIF, the optimised induction parameters for C9 (IndmRNA = 6; IndC = 0.01 µM) using the clinical data [1] predicted the clinical outcome reasonably well (2.5-3 GMR within 2-fold for AUC and CL). For RTV (IndmRNA = 3.33; IndC = 0.07 µM) or PBT (IndmRNA = 6.25; IndC = 43.9 µM), the calibrated induction parameters using the RIF induction data was able to capture the induction interaction well (GMR within 2-fold for AUC or CL).

These results warrant further investigation of the in vitro data, and verification of the C9 induction model with additional clinical DDI studies.

Results (Contd.)

Fig 1: The fold difference in IndmRNA (blue) and IndC (red) values determined from mRNA and activity data (A), and the fold difference in the induction factor (IndmRNA; IndC) between mRNA and activity (B) for CYP2C9. The line of unity and +/- 2-fold are shown as reference data. Data are plotted as means +/- SD for RIF and PBT. N=1 data for RTV.

The overall IndmRNA and IndC values (derived from mRNA or activity) for CYP2C9 ranged from 3.6-5.6 fold and 0.1-1.5 µM, respectively, for RIF, 3.2-4.2 fold and 68-849 µM, respectively, for PBT, 2.4-3.9 fold and 1.9-7.5 µM, respectively, for RTV [1, 3-11].

For C9 induction, mRNA data showed broadly similar level of induction efficacy and potency relative to activity data for RIF and PBT (Fig 1A). For RTV, mRNA data exhibited higher efficacy (1.6-fold higher IndmRNA and lower potency (mean 3.95-fold higher IndC) (Fig 1A).

When the ratio of IndmRNA/IndC for CYP2C9 (mean ± SD) across three inducers was compared between mRNA and activity, it was variable, but broadly similar for RIF (0.93 ± 0.33) and PBT (1.64 ± 1.58) (Fig 1B), and lower for RTV (0.41) (data is based on n=1 study only).

Also, a comparison of the ratios (IndmRNA/IndC) for these inducers based on mRNA versus activity data indicated that there was a strong correlation ($r^2 = 0.96$) between these markers (Fig 2).

In the in vitro C9 induction data (weighted mean; activity data), contrasts between the clinical data (1, 9-11) for RIF (IndmRNA = 4.01; IndC = 0.93 µM), PBT (IndmRNA = 5.27; IndC = 320 µM), and RTV (IndmRNA = 2.4; IndC = 1.9 µM) were used in the model for predicting C9 induction mediated DDIs in vivo.

Utilising the measured in vitro C9 induction data (weighted mean; activity data), with the exception of PBT [6], both RIF and RTV models significantly under-predicted the magnitude of interaction for C9 substrates (ratio of predicted and observed GMR of AUC ranged from 1.3-3 fold) compared to clinical outcome [1-4, 7].

The IVIVE of induction potential using the in vitro C9 mRNA data [1, 9-11] was also investigated in this study and the predicted magnitude interaction was comparable with that of activity data (data not shown).

Conclusions

There was a strong correlation ($r^2 = 0.96$) between in vitro induction markers for CYP2C9 (mRNA vs. Activity).

Using the measured in vitro induction data as inputs, with the exception of PBT, both RIF and RTV models significantly under-predicted the induction potential for C9 substrates.

Optimisation of induction parameters using the clinical DDI data was needed for RIF to predict the C9 induction potential in vivo, and for RTV and PBT models, the calibration of induction data improved DDI predictions.

While these results are encouraging, considering the high inter-donor/inter-labiability in the in vitro induction data, future investigation with robust in vitro data and verification of the model with additional clinical DDI studies would be beneficial for better understanding of IVIVE of induction potential for CYP2C9.

References

6. Simcyp (a Certara company), Sheffield, UK.