Evaluation of CYP2B6 Induction and Prediction of Clinical DDI using PBPK Modeling

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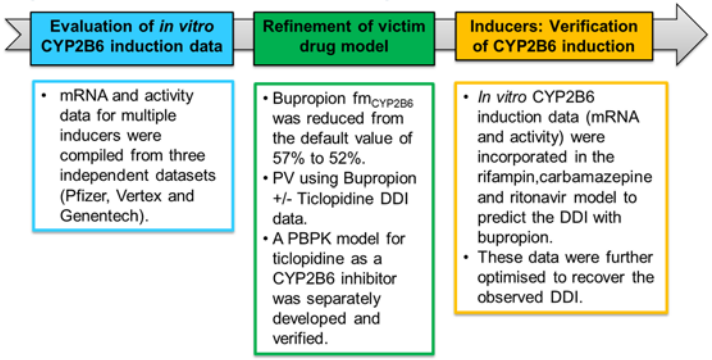
Background

CYP2B6 represents one of the highly-inducible and polymorphic CYP isoforms. Clinical risk assessment of CYP2B6-mediated induction is recommended by the regulatory agencies to assess the necessity of dose adjustment in patients. Here we assessed the predictability of CYP2B6 induction using a CYP2B6 marker substrate (e.g. bupropion).

Methods

Figure 1. General workflow of evaluating CYP2B6 induction



- The bupropion and OH-bupropion models[1] were refined based on literature data[2]. Specifically, the contribution of CYP enzymes to the formation of OH-bupropion was split between CYP2B6 (90%), CYP3A4 (4%) and CYP2C19 (6%).
- Default files (Simcyp Simulator V15) for rifampin, carbamazepine and ritonavir were used to assess the prediction accuracy of the files as CYP2B6 inducers using available *in vitro* CYP2B6 induction data and relevant clinical studies. The respective E_{max} and EC_{50} values for rifampin, carbamazepine and ritonavir are 5.04-fold and 0.67µM, 9.95-fold and 8.74µM, 5.73-fold and 0.87µM, respectively.
- All simulations used reduced CYP2B6 abundance CV% from the default value of 122% to 60%, to ensure the simulated bupropion fmCYP2B6 using virtual healthy volunteers is close to the derived fm_{CYP2B6} from *in vitro* data.

Results

- A correlation analysis of E_{max}:EC_{50} ratios obtained from mRNA and activity endpoints for seven dual CYP2B6/CYP3A4 inducers showed that the two endpoints were linearly correlated for CYP2B6 (R^2=0.587) and CYP3A4 (R^2=0.944).

Figure 2. A comparison of the mean ratios of E_{max}:EC_{50} derived from mRNA and activity data in 3-4 human hepatocyte donors after incubation with seven dual inducers of CYP2B6/CYP3A4. The lines of unity (unbroken line), 0.8- to 1.25-fold (dotted line) and 0.5 to 2-fold (dashed line) are shown.

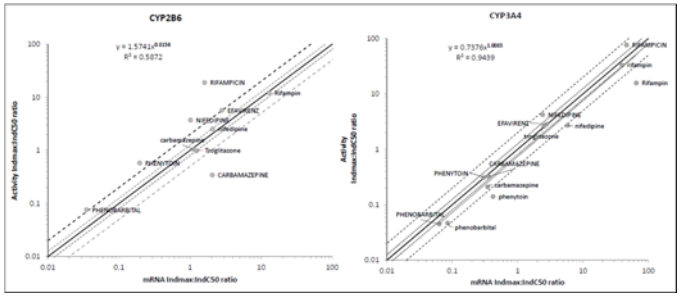
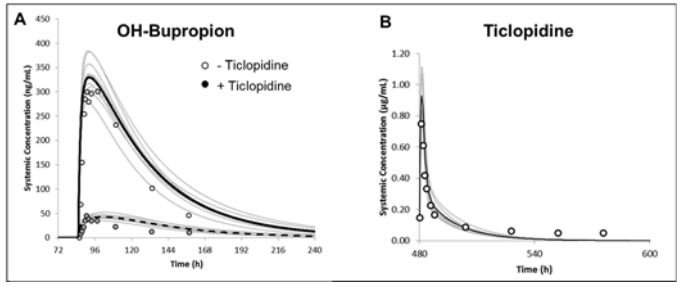
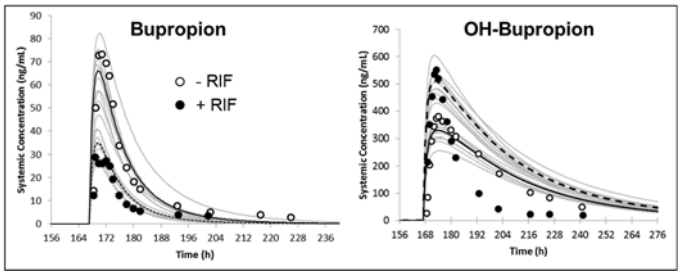


Figure 3. A) Mean simulated and observed[3] (symbols) plasma concentration-time profiles of OH-bupropion following dosing of 150mg SR bupropion either before (solid line) or following 4 days of oral dosing (250 mg b.i.d) of ticlopidine (dotted line) to healthy subjects. B) Simulated and observed[4] plasma concentration-time profiles of ticlopidine during 21 days of oral dosing (250 mg b.i.d) to healthy subjects.



- The predicted fold-reduction in AUC and C_{max} for OH-bupropion were 5.4 and 6.7, respectively, compared to the observed ratios[3] of 6.25 and 4.55, respectively.
- Simulations to investigate the induction effects of rifampin (600 mg q.d. for 10 days), carbamazepine (314 mg t.i.d. for 3 weeks) and ritonavir (100 mg b.i.d. for 23 days) treatment on bupropion (150 mg SD) and OH-bupropion using either mRNA or activity data resulted in under-prediction of the effects on the systemic exposures of bupropion, but not OH-bupropion.
- Sensitivity analysis showed that a 10- and 5-fold reduction in the rifampin and ritonavir EC_{50} values, respectively, were required to recover the observed bupropion data. For carbamazepine, reduction in EC_{50} value alone was not enough.

Figure 4. Mean simulated and observed[5] (symbols) plasma concentration-time profiles of bupropion and OH-bupropion following dosing of 150mg SR bupropion either before (solid line) or following 600 mg q.d. rifampin for 10 days (dotted line) to healthy subjects.



Conclusions

- Under-prediction of CYP2B6 induction from *in vitro* data is evident using bupropion as the victim drug, which may reflect 1) insufficient characterization of IVIVE of CYP2B6 induction; 2) Bupropion and OH-bupropion not being an ideal probe for CYP2B6.

References

1. Ke et al. , *CPT Pharmacometrics Syst Pharmacol. 2016 Jul; 5(7): 367–376.*
2. Sager et al., *Drug Metab and Dispos.* 2016 Oct;44(10):1709-19.
3. Turpeinen et al., *Clin Pharmacol Ther.* 2005 Jun;77(6):553-9
4. Shah et al., *Br J Clin Pharmacol* **32:**761-764.
5. Loboz et al., *Clin Pharmacol Ther* **80:**75-84.

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