What is the contribution of CYP2B6 to bupropion metabolic clearance? Implications for the prediction of CYP2B6 mediated drug-drug interactions.

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Background

- Bupropion, an anti smoking and antidepressant drug, undergoes extensive hepatic metabolism *via* oxidative and reductive pathways to three principal metabolites; hydroxybupropion, threohydrobupropion and erythrohydrobupropion (Figure 1).

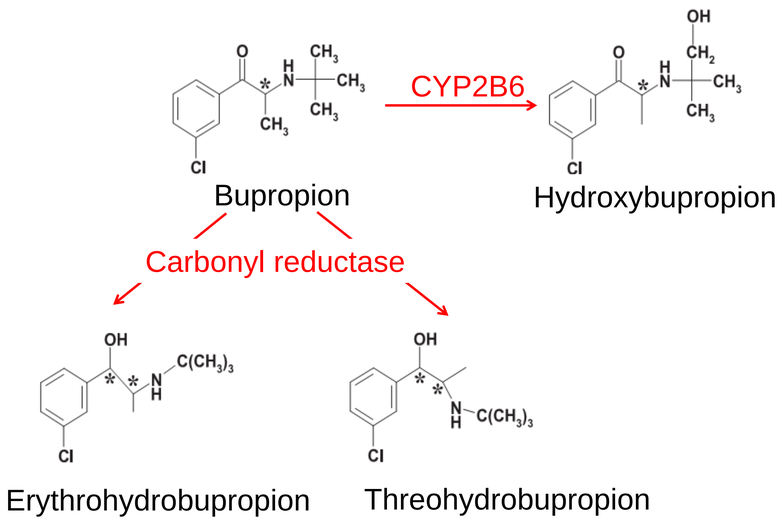

Figure 1. Major metabolic routes of bupropion in humans.

- The hydroxylation pathway appears to be the major metabolic route since peak plasma concentrations of hydroxybupropion are about 5- and 3-fold greater than those of parent drug and threohydrobupropion, respectively[1] (Figure 2).

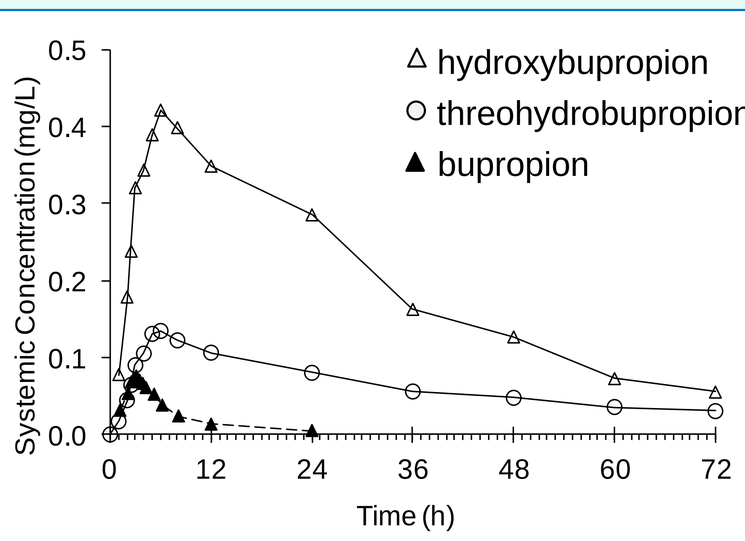

Figure 2. Observed plasma concentration-time profiles of bupropion, hydroxybupropion and threohydroxybupropion after a single oral dose of 150 mg bupropion to healthy subjects (adapted from [1]).

- Studies with human liver microsomes have shown CYP2B6 to be the primary enzyme involved in bupropion hydroxylation (minor contributions from CYP2E1 and CYP2C19)[2,3].
- Hence, bupropion hydroxylation is recommended for use in CYP2B6 phenotyping and drug-drug interaction (DDI) studies[4].
- However, the results of a recent *in vitro* study appear to contradict the *in vivo* finding that the fractional contribution (fm) of hydroxylation to the overall bupropion metabolic clearance is significant. The data indicate that reductive and oxidative pathways contribute 99% and 1% to the metabolism of bupropion, respectively[5].

Objectives

- The aim of this study was to use a modelling and simulation approach to obtain an estimate of fm_{CYP2B6} that could then be applied for 'a priori' assessment of the CYP2B6 DDI potential of bupropion.

Methods

- Relevant *in vitro* and *in vivo* data were incorporated into a mechanistic physiologically based pharmacokinetic (PBPK) model within Simcyp (Version 11.1) to simulate the plasma concentration time profiles of bupropion and hydroxybupropion (Figure 3).
- For assessment of DDI, a model for the CYP2B6 mechanism based inhibitor ticlopidine was also developed (Figure 3). Ticlopidine was assumed only to inhibit bupropion hydroxylation.
- As there was uncertainty regarding the fm of the hydroxylation pathway (fm_{CYP2B6}), a sensitivity analysis was performed using a range of fm_{CYP2B6} values (0.01 to 1) to assess the impact of this variable on the plasma exposure to both bupropion and hydroxybupropion.

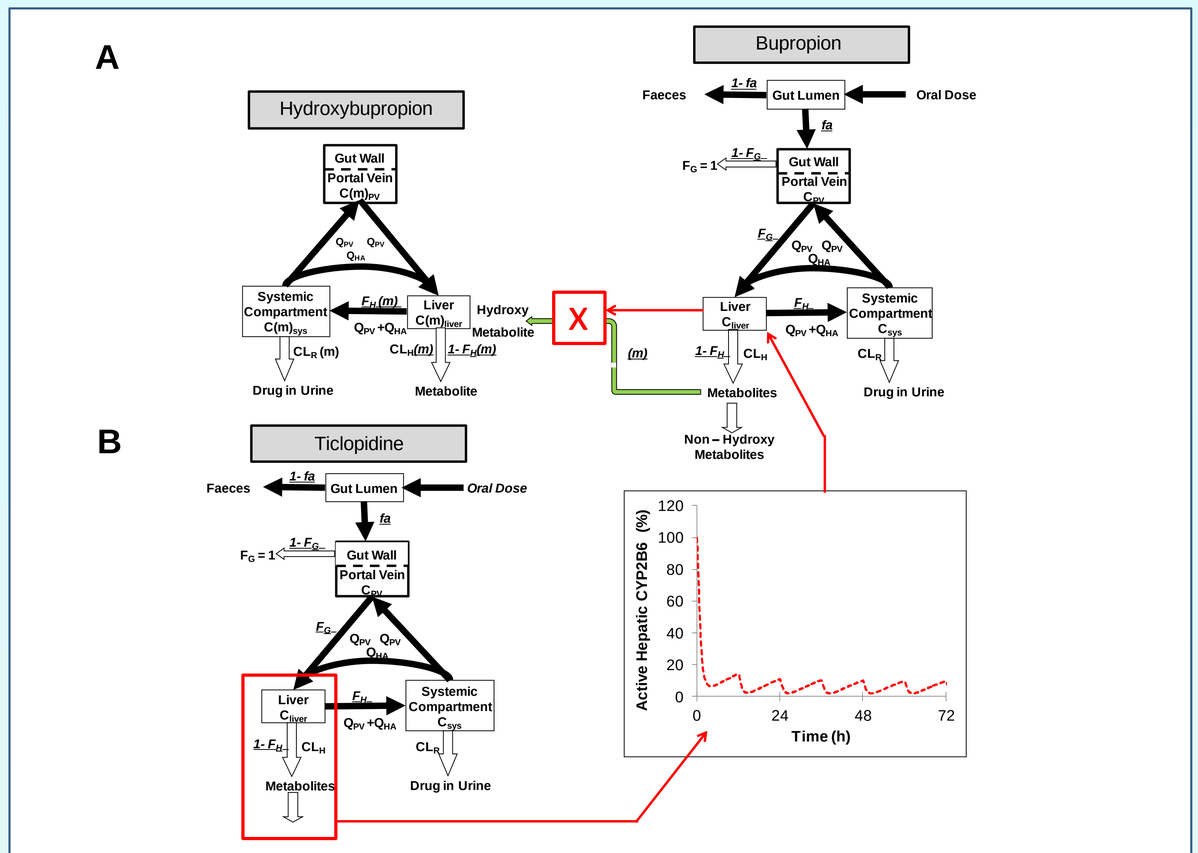

Figure 3. Mechanistic physiologically based models describing the kinetics of A) bupropion and its metabolite hydroxybupropion and B) ticlopidine and its inhibitory effect on hepatic CYP2B6 levels and formation of hydroxybupropion (indicated by X) after oral administration.

- The fm_{CYP2B6} value that allowed recovery of observed bupropion and hydroxybupropion plasma concentration time profiles was then used for prediction of the DDI between bupropion and the CYP2B6 mechanism based inhibitor ticlopidine[6].

Results

- Assuming a bupropion fm_{CYP2B6} of 0.6, plasma concentrations of hydroxybupropion were well predicted (Figure 4)
- Geometric mean AUC ratios of bupropion and hydroxybupropion (± ticlopidine) were 1.89 and 0.11 respectively, which were consistent with observed values of 1.78 and 0.13, respectively[6].
- Use of an fm_{CYP2B6} of 0.01 (as reported[5]), resulted in a predicted lack of interaction between ticlopidine and bupropion and a 54-fold underprediction in plasma concentrations of hydroxybupropion (Figure 4).
- The relationship between fm_{CYP2B6} and the simulated bupropion AUC ratio (± ticlopidine) is shown in Figure 5.

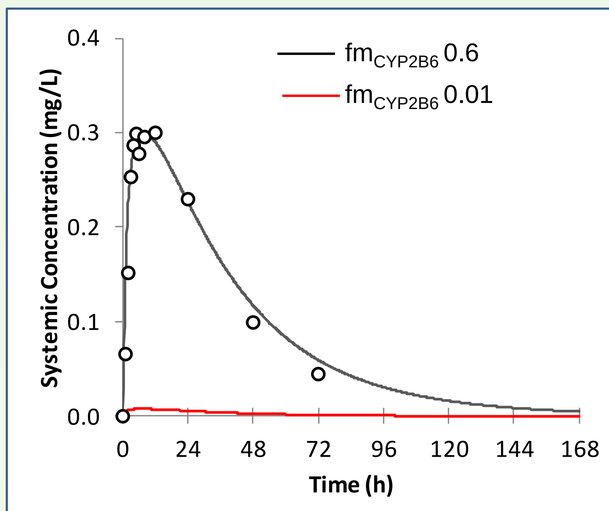

Figure 4. Simulated (line) and observed (data point[6]) plasma concentration-time profiles of hydroxybupropion after a single oral dose of 150 mg bupropion to healthy subjects.

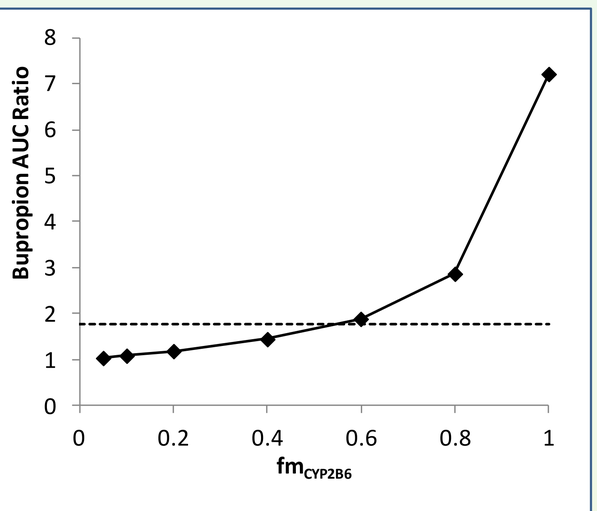

Figure 5. Relationship between fm_{CYP2B6} and simulated bupropion AUC ratio (± ticlopidine). The dotted line indicates the observed bupropion AUC ratio[6].

Conclusions

- The results of this study demonstrate the utility of performing sensitivity analysis in conjunction with PBPK modelling to provide reasonable estimates of parameters with substantial uncertainty – in this case fm_{CYP2B6}. This allowed prospective assessment of metabolic DDI potential.
- Further *in vitro* studies are indicated to confirm the fm_{CYP2B6} of bupropion.

References

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