DEVELOPMENT OF A PBPK MODEL FOR EFAVIRENZ THAT ACCOUNTS FOR AUTO-INDUCTION AND ITS EFFECT ON THE CYP2B6 SUBSTRATE BUPROPION

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Introduction

- Being both a substrate and an inducer of CYP2B6 the antiretroviral efavirenz undergoes auto-induction of its own clearance.
- The aims of this work was to develop a model that describes the auto-induction of CYP2B6 by efavirenz and its resultant steady state concentrations and to simulate the effect of multiple dose efavirenz on exposure of the CYP2B6 substrate bupropion, and its metabolite, hydroxybupropion.
- Key parameters include the fractional contribution of CYP2B6 to the systemic clearance (fmCYP2B6) of efavirenz and its potency and efficacy to induce CYP2B6.

Methods

- The PBPK model included prior *in vitro* and *in vivo* data describing the disposition of efavirenz.
- The metabolic intrinsic clearance was derived from an observed CL_{po} (single dose) using a retrograde approach in conjunction with *in vitro* data [1] describing the relative contribution of elimination routes (Figure 1). A final fm_{CYP2B6} of 0.62 was applied.
- Induction parameters (Ind_{max} and $IndC_{50}$) were assessed in human hepatocytes *in vitro* (activity; hydroxybupropion formation) as previously described [2].
- Multiple dose (600mg QD) concentrations were simulated in a virtual matched healthy volunteer population and verified against observed data before the model was used to simulate the interaction between bupropion and its metabolite, hydroxybupropion, reported by Robertson *et al*. (2008) [3], using previously presented PBPK models for parent and metabolite [4].

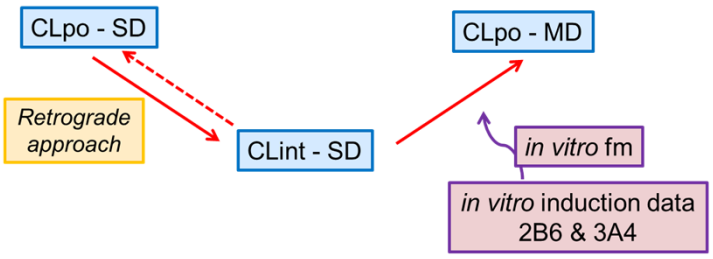

Figure 1 A schematic representation of the retrograde approach used in model development where the oral clearances following single dose was used to back calculate an intrinsic clearance. This was apportioned to different enzymes using fm derived from *in vitro* data. This was then used in the model, in conjunction with *in vitro* induction data for CYP2B6 and CYP3A4, and the multiple dose oral clearance simulated.

Results

- Simulated multiple dose concentrations were in reasonable agreement with observed data (Figure 2; $AUC_{0\text{-last}}$ 46.2 *vs.* 65.4mg/L.h; C_{max} 3.2 *vs.* 4.4mg/L).
- The mean simulated ratio of accumulation (single dose $AUC_{0\text{-}\infty}$ /steady-state $AUC_{0\text{-tau}}$) was 0.60, indicative of auto-induction.
- The simulated magnitude of interaction with bupropion was also in reasonably good agreement with the observed data (Figure 3a & b; predicted 0.44 and 0.50-fold vs. observed 0.45 and 0.66-fold change in AUC and C_{max} , respectively.

Results Cont.

- The predicted fold change in hydroxybupropion C_{max} was in good agreement with the observed, whereas fold change in AUC was over predicted (Figure 3c & d; 1.5 and 1.6-fold change vs. observed 1.0 and 1.5-fold in AUC and C_{max} respectively). This may be because the metabolic routes of the metabolite itself are unknown and so any induction of the metabolism of the metabolite could not be included in the model.

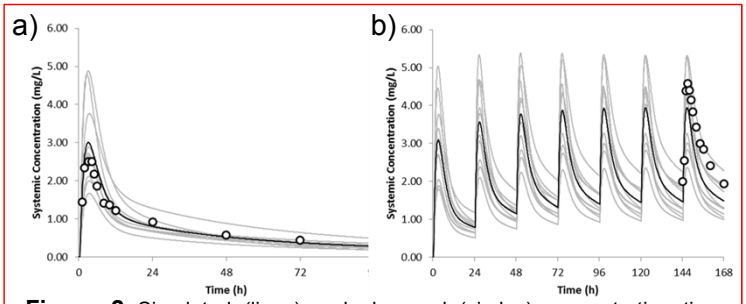

Figure 2 Simulated (lines) and observed (circles) concentration time profiles of efavirenz following a) a 600mg single dose [1] and b) multiple 600 mg doses (QD;[5]). Mean (black line) and individual (grey lines) virtual trials are shown.

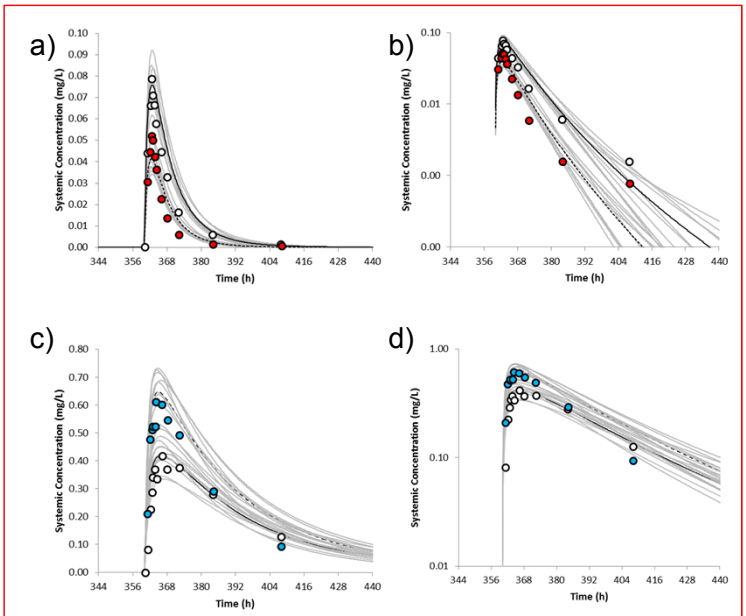

Figure 3 Simulated (lines) and observed (circles) concentration time profiles of bupropion (a & b) and hydroxybupropion (c & d) following a 150mg single dose [3]). Data are shown on linear (a & c) and log (b & d) scales. Mean (black line) and individual (grey lines) virtual trials are shown.

Conclusions

- The PBPK model for efavirenz described here was able to recover a complex DDI scenario, accounting for CYP2B6-mediated auto-induction and its effect on the disposition of the CYP2B6 substrate bupropion.

References

1. Ogburn et al., 2010 DMD 38:1218–1229. Efavirenz primary and secondary metabolism in vitro and in vivo: identification of novel metabolic pathways and Cytochrome P450 2A6 as the Principal Catalyst of Efavirenz 7-Hydroxylation

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4. Barter, Z.E. et al., 2012. What is the contribution of CYP2B6 to bupropion metabolic clearance? Implications for the prediction of CYP2B6 mediated drug-drug interactions. *The 19th International Symposium on Microsomes and Drug Oxidations and 12th European ISSX Meeting, Noordwijk, Netherlands, June 17 - 21, 2012.*.

5. Provided by BMS