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Investigation of the potential interactions of efavirenz with the GABAa receptor

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Background Efavirenz is a potent non-nucleoside reverse transcriptase inhibitor that is used as first line therapy in the treatment of HIV. Patients receiving efavirenz have reported central nervous system (CNS) disturbances such as depression, anxiety and hallucinations. CNS disturbances are reported in >50% of patients receiving efavirenz and are implicated as a cause of discontinuation. The mechanisms of the observed neuropsychiatric disturbances are currently unknown. Examination of the CNS side effects associated with efavirenz and drugs acting on the GABAa receptor, reveals many of the same adverse effects. Efavirenz is a 1,4-dihydro-2*H*-3,1-benzoxazin-2 which is structurally similar to benzodiazepines. Therefore, the aim of this work was to explore the putative involvement of GABAergic signalling in efavirenz-mediated CNS toxicity using a combination of homology modelling and genotyping techniques.

Methods A 3D model of the major isoform of the GABAa ($\alpha_1\beta_2\gamma_2$) receptor was generated, using MODELLER v9.8. The completed model was used in docking experiments (using Autodock v4.2) to investigate the potential interactions of efavirenz and its metabolites with the GABA and benzodiazepine binding sites. These docking positions were then compared with docking results of ligands of the GABA and benzodiazepine binding sites. The association of polymorphisms in various GABAa subunits with the frequency of CNS toxicity were also examined in a cohort of 522 patients receiving efavirenz containing therapy. In this cohort, early (<3 months) treatment discontinuation of efavirenz therapy was taken as a surrogate for CNS side effects. Genomic DNA was extracted from whole blood and patients were genotyped for polymorphisms in the α_1/α_2, β_2 and γ_2 subunits of the GABAa receptor (the major isoform present in the human CNS). Polymorphisms within genes previously shown to influence treatment discontinuation (*CYP2B6* and *CAR*) were also examined. Genotyping was conducted using real-time PCR based allelic discrimination. Univariate (Chi^2) and multivariate (backwards logistic regression) were performed using SPSS v20. Statistical significance was defined as $P<0.05$.

Results The docking results demonstrated that efavirenz and its metabolites did not share any common docking locations with ligands of the GABA binding site. However, models indicated that efavirenz may dock in a similar location to benzodiazepine ligands, showing the potential of efavirenz to interact with key amino acids involved in binding of ligands at this site. Previously identified associations with early discontinuation of efavirenz were confirmed in this analysis. Specifically, Black ethnicity (OR=0.29, P<0.01), smoking status (OR=0.38, P<0.01), *CYP2B6* 516TT (OR=1.37, P=0.05) and *CAR* rs2307424 CC (OR=0.692, P=0.04). Univariate and multivariate analysis failed to reveal an association with early treatment discontinuation and polymorphisms in the GABAa subunits.

Conclusions The data generated from the *in silico* models support the hypothesis that efavirenz associated CNS toxicity may be mediated by interactions with the GABAa receptor. However, the genotyping data revealed no association between polymorphisms in GABAa subunits and early treatment discontinuation. These data indicate efavirenz may interact with the benzodiazepine binding site but the polymorphisms investigated were not associated with efavirenz CNS toxicity. Further studies are required to delineate the interaction of efavirenz with receptors in the CNS.