Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study.

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OBJECTIVES: Efavirenz is an effective antiretroviral agent, but central nervous system side effects occur commonly, and population (racial) differences in pharmacokinetics and response have been reported. Efavirenz is metabolized by cytochrome P4502B6 (CYP2B6). We investigated whether polymorphisms in CYP2B6, CYP3A4, CYP3A5, and MDR1 were associated with efavirenz central nervous system side effects and pharmacokinetics.

DESIGN: Twenty-four week cohort from a randomized study.

METHODS: Adult AIDS Clinical Trials Group study A5097s examined relationships between central nervous system side effects and efavirenz plasma concentration-time profiles in HIV-infected subjects. Efavirenz plasma pharmacokinetics were estimated by a population-based method. Central nervous system symptoms were assessed by questionnaires and neuropsychological testing.

RESULTS: Study subjects included 89 (57%) European-Americans, 50 (32%) African-Americans, and 15 (10%) Hispanics. The CYP2B6 T/T genotype at position 516 (GlnHis) was more common in African-Americans (20%) than in European-Americans (3%), and was associated with greater efavirenz plasma exposure (P < 0.0001). The median efavirenz [area-under-the-curve] (0-24 h) according to G/G, G/T, and T/T genotype was 44 (n = 78), 60 (n = 60), and 130 (n = 14) mug.h/ml, respectively (P < 0.0001). The CYP2B6 G516T genotype was also associated with central nervous system symptoms at week 1 (P = 0.036). Analysis of DNA from other subjects confirmed population differences in frequency of the G516T variant. No associations were apparent with the other polymorphisms studied.

CONCLUSIONS: A CYP2B6 allelic variant that is more common in African-Americans than in Europeans-Americans was associated with significantly greater efavirenz plasma exposure during HIV therapy. Inter-individual differences in metabolism may, in part, explain susceptibility to efavirenz central nervous system side effects.

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