Genetic variants of CYP2B6 and CYP2A6 explain variations in efavirenz plasma levels of children

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Conclusion

Genetic polymorphisms in CYP2B6 and CYP2A6 drug metabolizing enzymes explained a significant part of variability in efavirenz (EFV) plasma levels. Asian origin gave lower plasma concentration in HIV-infected children in a multi-ethnic outpatient clinic.

Knowledge about individual variants in key drug metabolizing enzymes could improve clinical safety and help to achieve more predictable EFV plasma concentrations in HIV-infected children.

Background

EFV is one of the most commonly used antiretroviral agents in HIV positive children. There are concerns about the appropriateness of current EFV dosing in children, which is based on body weight and age.

Aim

To investigate if pediatric EFV dosing should be guided by genetic variation in drug metabolizing enzymes rather than by body weight and age.

Method

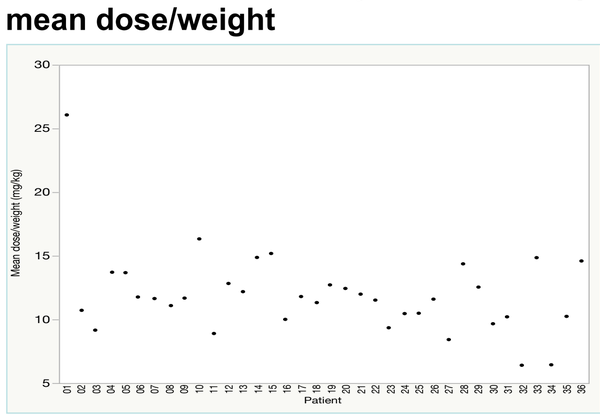
EFV plasma levels, measured for clinical purposes in all children treated with EFV at Karolinska University Hospital, Sweden were collected retrospectively.
EFV levels divided by (dose/weight) was the main outcome measure and was $\log_e$ transformed.
EFV was correlated with 11 polymorphisms in genes coding for enzymes of potential importance for EFV disposition as well as origin, sex, age, weight. Virological, immunological and clinical data were collected.

Results

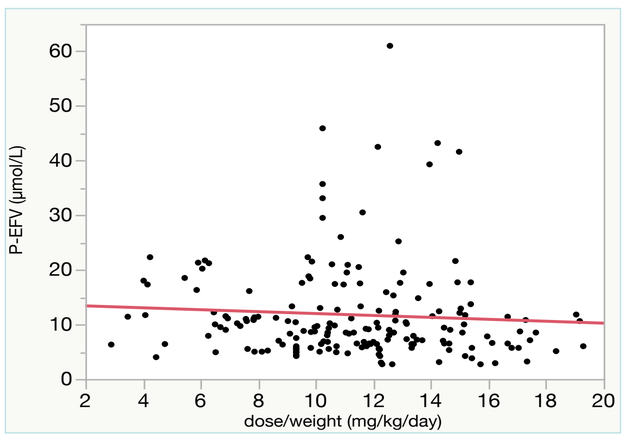
36 patients and 182 (mean 5 samples/patient) EFV plasma levels were included. Individual mean EFV plasma concentration varied 9-fold (4.9 - 42.4 µmol/L) and EFV plasma concentration varied 21-fold (2.7 - 61 µmol/L) across the subject.

CYP2B6*6 T/T, CYP2B6*11 G/G, CYP2A6*9 A/C genotypes, age at treatment initiation and time from treatment initiation was identified as independent factors significantly related to $\log_e$ concentration/(dose/weight). Asian origin was significantly related to lower $\log_e$ mean concentration/(dose/weight) compared to African ($p = 0.0085$) and Hispanic origin ($p = 0.038$).

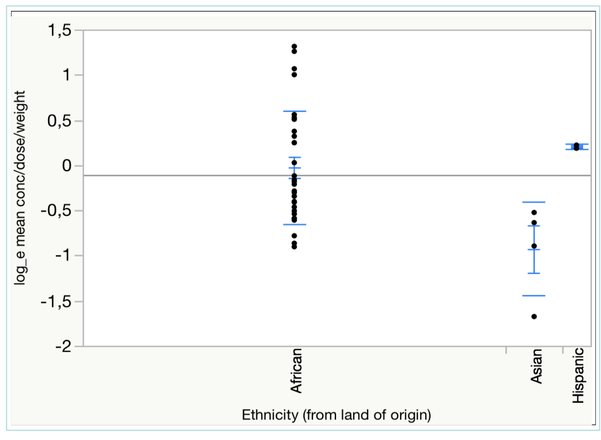
Interindividual variability in mean EFV plasma concentrations and mean dose/weight



Correlation between dose/weight and efavirenz plasma concentration



Distribution of $\log_e$ mean efavirenz plasma concentration/(dose/weight) by ethnicity.



Relation between genetic variants, age at treatment initiation, time from treatment initiation, sex and $\log_e$ EFV plasma concentration /(dose/weight)

	Coefficient	P > |z|	[95% Confidence Interval]	
CYP2B6*6 G/T genotype	0.053	0.74	-0.26	0.36
CYP2B6*6 T/T genotype	1.10	< 0.0005	0.67	1.54
CYP2B6*11 A/G genotype	0.54	0.17	-0.24	1.32
CYP2B6*11 G/G genotype	1.60	< 0.0005	0.86	2.33
CYP2B6 g.18492 C/T genotype	-0.084	0.61	-0.41	0.24
CYP2A6*9 A/C genotype	0.50	0.001	0.20	0.80
CYP2A6*9 C/C genotype	-0.66	0.12	-1.49	0.16
Time from treatment initiation	0.00014	< 0.0005	0.000074	0.00021
Age at treatment initiation	0.064	0.002	0.023	0.10
Sex	0.084	0.54	-0.19	0.36
Ethnicity	-0.31	0.20	-0.79	0.17

Multivariate mixed-effects REML regression model

Together with Makerere University and Baylor Uganda, we now investigate the importance of pharmacogenetics for EFV plasma levels in Ugandan children, in a prospective study.

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