CYP2B6 Activity in HIV-infected Children and Adolescents: Pharmacokinetic Evaluation of Efavirenz and its 8-hydroxymetabolite

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INTRODUCTION

- Efavirenz (EFV) is widely used in pediatric and adolescent populations worldwide
- Superior efficacy when compared to Nevirapine in large (716 children) African pediatric cohort (Lowenthal E. et al, Abstract 965, CROI 2012)
- Substrate of CYP2B6 with some involvement of CYP3A, CYP1A2, and CYP2A6
- CYP2B6 (G516T) polymorphisms result in large variability in EFV exposure among infants (Bolton C. et al, IMPAACT P1070, Abstract 981, CROI 2012), children and adolescents (Viljoen M. et al., Eur J Clin Pharmacol 2012; Rakhmanina et al., Ther Drug Monit 2010)
INTRODUCTION

- High variability in EFV concentrations with pediatric EFV dosing (Fillekes Q. et al, J Acquir Immune Defic Syndr 2011)
  - Steady-state $C_{(24)} < 1.0$ mg/L in 38% of children (3-12 years old) (median [IR range] 1.1 (0.7-2.9) [0.3-18.4])


- Developmental changes in the CYP2B6 metabolism may have a potential role in sub-therapeutic or high pediatric EFV exposure
METABOLISM of EFV

Desta Z. et al., Pharmacogenomics 2007;8(6):547-58
This study was aimed to evaluate EFV metabolism and CYP2B6 and UGT activity in HIV-infected children and adolescents at different stages of their development.
PATIENTS AND METHODS

• Cross-sectional sub-study of pediatric and adolescent patients (8-18yo) with HIV infection receiving EFV as part of ART

• CYP2B6 genotyping (G419A, A415G, G516T, A785G, T983C, C1459T) - ABI TaqMan assay

• PK samples - at steady-state at 0, 1, 2, 4, 6, 8, 12 and 24 hours after an observed standard EFV dose taken on empty stomach
PATIENTS AND METHODS

- EFV, total (E8T) and free (E8F) 8-hydroxy-EFV measured by solid phase extraction of plasma followed by HPLC-MS/MS method using the Sciex APT-2000
- 8-hydroxy-EFV glucuronide (E8G) estimated after overnight hydrolysis using β-glucuronidase
- Non-compartmental PK analyses
- Non-parametric analysis of the association between the different CYP2B6 516 genotypes and EFV, E8F and E8F+E8G exposures
RESULTS

• 13 patients = 7 girls + 6 boys
• 12 Black + 1 Hispanic
• Median age = 12.8 yrs (8.2-17.4 yrs)
• Median BMI = 20.8 (16.8-26.3)
• CYP2B6 516 genotype (HWE p-value=0.207):
  – GG=6, GT=4, TT=3
• Median weight = 46.8 kg (26.5-69.7 kg)
• EFV dose=600 mg x 8 patients
• EFV dose=300-400 mg x 5 patients
RESULTS

- EFV AUC=62.3 mcg*hr/mL (21.6-271.6)
- EFV CL/F=0.21 L/h/kg (0.047-0.460)
- High EFV AUC (96.3-271.6) + low CL/F (0.047-0.113) in 3 subjects with TT
- Sub-therapeutic $C_{24}(<1.0 \text{ mg/L})$ in 2 subjects with GG
EFFECT of CYP2B6 GENOTYPE and AGE on EFV CL

![Graph showing the effect of CYP2B6 genotype and age on EFV CL](image-url)
RESULTS

• E8G>E8F in all but one subject

• Trend to decreasing E8G/EFV (p=0.075):
  - **GG** - 3.43 (0.00-9.45)
  - **GT** - 2.83 (1.48-6.04)
  - **TT** - 1.03 (0.61-1.38)

• E8G/EFV and E8T/EFV correlated with EFV CL/F (r=0.79 and r=0.74, respectively) while the E8F/EFV ratio did not (r=0.27)
EFFECT of CYP2B6 on EFV METABOLITES/EFV RATIO

![Graph showing the effect of CYP2B6 on EFV metabolites](image-url)
RESULTS

• Highest E8T/EFV in GG genotype 8.97 (2.68-14.41) and lowest in TT genotype 1.04 (0.93-1.60), (p=0.013)

• With GG and GT genotypes combined, significant difference for both E8F/EFV and E8T/EFV was observed with the GG genotype having a greater median than the GT and TT genotype, p=0.046 and p=0.046, respectively
CONCLUSIONS

• EFV PK were highly variable among children and adolescents in our study cohort
• CYP2B6 G516T genotype was directly related to the AUC and CL/F of EFV
• Extensive conversion of E8F $\rightarrow$ E8G limited the usefulness of E8F as a phenotypic probe for CYP2B6 activity
• Ongoing study with repeat within-subject sampling will allow further investigate the full impact of developmental changes on the metabolism of EFV in children and adolescents
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