Effect of CYP2B6 Metabolizer Status on Levonorgestrel Pharmacokinetics When Combined with Efavirenz-based Antiretroviral Therapy

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M. Pham has no financial relationships with commercial entities to disclose.
Background

• Progestin-releasing implants are an important contraceptive option
• Significant drug-drug interactions (DDIs) exist between levonorgestrel (LNG) and efavirenz (EFV)-containing antiretroviral therapy (ART):
  • LNG subdermal implant (150mg) plus EFV-based ART resulted in 45-57% lower LNG concentrations\(^1\)
  • Doubling the LNG implant dose (300mg) still resulted in 34% lower LNG concentrations\(^2\)
  • The mechanism of this interaction is proposed to be CYP3A4 mediated
• EFV metabolism is influenced by \textit{CYP2B6} single nucleotide polymorphisms (SNPs)
  • \textit{CYP2B6} SNPs associated with slow metabolism and high EFV concentrations resulted in lower LNG exposure\(^3\)

Objective

To evaluate the impact of CYP2B6 genotype on double dose (300 mg) levonorgestrel pharmacokinetics (PK) when combined with EFV-based ART.
Methods

• Participants
  • EFV-based ART ≥ 30 days with HIV-1 RNA ≤400 copies/mL
  • EFV 600mg daily + 2 NRTIs
  • Copper IUD as a second form of contraception

• Pharmacokinetic (PK) Sample Collection
  • LNG implants were inserted, one in each arm, on Day 0
  • Plasma samples were collected on Day 0 and Weeks 1, 4, 12, and 24 for LNG PK analysis
  • Validated LC-MS/MS method; assay calibration 50-1500 pg/mL
  • Area under the concentration time curve from entry to 24 weeks (AUC_{0-24weeks}) was calculated using the trapezoidal rule
Methods

• Genotyping
  • Real-time PCR based allelic discrimination assays for selected candidate SNPs
  • 3 CYP2B6 SNPs defined EFV normal, intermediate, and slow metabolizer phenotype

• Statistical Analysis
  • SNPs tested for Hardy-Weinberg equilibrium
  • Univariate and multivariate linear regression (P < 0.05) used to assess impact of genotype on LNG PK
  • Univariate linear regression (P < 0.05) to investigate correlations between EFV and LNG PK

| Normal                  | 516GG – 983TT – 15582CC |
|                        | 516GG – 983TT – 15582CT |
| Intermediate           | 516GG – 983TT – 15582TT |
|                        | 516GG – 983CT – 15582CC |
|                        | 516GG – 983CT – 15582CT |
|                        | 516GT – 983TT – 15582CC |
|                        | 516GT – 983TT – 15582CT |
| Slow                   | 516TT – 983TT – 15582CC |
|                        | 516GT – 983CT – 15582CC |
|                        | 516GG – 983CC – 15582CC |

1 Haas et al. CROI 2019
## Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, median (IQR)</td>
<td>33.0 (28.0 – 40.5)</td>
</tr>
<tr>
<td>Weight in kg, median (IQR)</td>
<td>58.0 (48.5 – 66.0)</td>
</tr>
<tr>
<td>SHBG* in nmol/L, median (IQR)</td>
<td>148.9 (98.4 – 185.5)</td>
</tr>
<tr>
<td><strong>CYP2B6 Metabolizer Status</strong></td>
<td></td>
</tr>
<tr>
<td>Normal, n (%)</td>
<td>8 (29%)</td>
</tr>
<tr>
<td>Intermediate, n (%)</td>
<td>15 (54%)</td>
</tr>
<tr>
<td>Slow, n (%)</td>
<td>5 (18%)</td>
</tr>
</tbody>
</table>

*CYP2B6 rs4803419 15582C→T was not in Hardy-Weinberg equilibrium ($\chi^2=11.75$), which may compromise its interpretation.

*Sex Hormone Binding Globulin
LNG Week 24 Concentrations and CYP2B6 Metabolizer Status

- Compared to normal CYP2B6 metabolizers at week 24:
  - Intermediate metabolizers: LNG ↓ 42%
  - Slow metabolizers: LNG ↓ 69%

<table>
<thead>
<tr>
<th>Status</th>
<th>Median pg/mL (IQR)</th>
<th>β-coefficient</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>534 (507 – 577)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>310 (279 – 346)</td>
<td>-0.21</td>
<td>5.16 x 10⁻⁵</td>
</tr>
<tr>
<td>Slow</td>
<td>167 (103 – 301)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Multivariate adjusted model with Age, Weight, and SHBG
LNG AUC\(_{(0-24\text{ weeks})}\) and CYP2B6 Metabolizer Status

- Compared to normal CYP2B6 metabolizers
  LNG AUC\(_{(0-24\text{ weeks})}\):
  - Intermediate metabolizers: LNG ↓ 34%
  - Slow metabolizers: LNG ↓ 46%

<table>
<thead>
<tr>
<th>Status</th>
<th>Median pm*week/mL (IQR)</th>
<th>β-coefficient</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>13989 (12470 - 15432)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>9221 (8466-10617)</td>
<td>-0.15</td>
<td>2.26 x 10(^{-4})</td>
</tr>
<tr>
<td>Slow</td>
<td>7576 (3963-8474)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Multivariate adjusted model with Age, Weight, and SHBG
For every 3.6 µg/mL ↑ in EFV, LNG ↓ 1 pg/mL at Week 24
Comparing LNG Standard and Double dose regimens
LNG PK Results with and without EFV-based ART

**Historical Control Group:**
LNG 150mg implant + ART-Naïve

**Historical LNG 150mg Group:**
LNG 150mg implant + EFV-based ART

- In women receiving EFV-based ART compared to the Control Group at week 48:
  - Double dose LNG ↓ 34%
  - Standard dose LNG ↓ 57%

Comparing CYP2B6 genotypes to a control group

- Normal metabolizers receiving double dose had similar LNG exposure to historical controls
  - Less than 5% decrease in LNG exposure
- Intermediate and slow metabolizers had statistically lower LNG than historical controls

Comparison | P-value*
---|---
Normal to ART-Naïve | 0.474
Intermediate to ART-Naïve | 0.014
Slow to ART-Naïve | 0.003

*Wilcoxon Rank Sum
Comparison of LNG Doses by Metabolizer Status

<table>
<thead>
<tr>
<th>Parameter</th>
<th>β-coefficient</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\log_{10} \text{AUC}_{(0-24 \text{ weeks})}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard Dose</td>
<td>-0.18</td>
<td>$1.65 \times 10^{-3}$</td>
</tr>
<tr>
<td>Doubled Dose</td>
<td>-0.16</td>
<td>$1.04 \times 10^{-3}$</td>
</tr>
<tr>
<td>Comparison</td>
<td>GMR* (300mg:150mg)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1.27</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>1.29</td>
<td></td>
</tr>
<tr>
<td>Slow</td>
<td>1.52</td>
<td></td>
</tr>
</tbody>
</table>

*Geometric Mean Ratio
Conclusions

• In women receiving 600mg EFV-based ART plus LNG implants:
  • Double dose (300mg) of LNG in participants with normal *CYP2B6* metabolizer status result in comparable LNG exposure to standard dose LNG (150mg) in mixed-genotype ART-naïve controls
  • Intermediate and slow *CYP2B6* metabolizer status is associated with lower LNG concentrations, irrespective of LNG dose

• We propose that higher EFV exposure results in increased induction of *CYP3A4*¹,²

• The potential for stratified LNG dosing based on *CYP2B6* genotype and EFV dose is worthy of further investigation

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