Clinical Study

Pharmacokinetic Interactions between the Hormonal Emergency Contraception, Levonorgestrel (Plan B), and Efavirenz

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Objectives. Compare the Plan B levonorgestrel (LNG) area under the concentration-time curve (AUC12) prior to and with efavirenz (EFV).

Design. Prospective, open-label, single-arm, equivalence study.

Methods. Healthy HIV-negative subjects underwent 12 hr intensive pharmacokinetic (PK) sampling following single dose LNG alone and after 14 days of EFV. Geometric means, Geometric Mean Ratios, and 90% confidence intervals (CI) are reported for PK Parameters.

T-tests were utilized. Clinical parameters and liver function tests (LFTs) were assessed.

Results. 24 women enrolled and 21 completed the study. With EFV, LNG AUC12 was reduced 56% (95% CI: 49%, 62%) from 42.9 to 17.8 ng hr/mL, and maximum concentration (Cmax) was reduced 41% (95% CI: 33%, 50%) from 8.4 to 4.6 ng/mL. LNG was well tolerated with no grade 3 or 4 treatment-related toxicities.

Conclusions. EFV significantly reduced LNG exposures. Higher LNG doses may be required with EFV. These results reinforce the importance of effective contraception in women taking EFV.

1. Introduction

The majority of women with human immunodeficiency virus – 1 (HIV) are of reproductive age and may use an efavirenz- (EFV-) containing antiretroviral (ARV) regimen [1, 2]. EFV is a nonnucleoside reverse transcriptase inhibitor (NNRTI) indicated in combination with other antiretroviral agents for the treatment of HIV [3]. EFV is an FDA pregnancy category D drug based on animal studies and human case reports of fetal neural tube defects [3–6]. Thus, preventing pregnancy is critical in HIV-infected women receiving EFV.

Pregnancy rates for HIV-infected women range from 6.0 to 8.2 pregnancies per 100 person-years, and in 2001, 49% of all pregnancies in the United States were unintended [7–9]. Women with HIV not desiring pregnancy are advised to use dual methods of contraception to prevent pregnancy and HIV transmission to their partners. Some women use emergency hormonal contraception to prevent pregnancy after unprotected sex or contraceptive failure (condom breakage).

Plan B is a levonorgestrel- (LNG-) containing emergency contraceptive pill indicated for pregnancy prevention following unprotected intercourse or a known or suspected contraceptive failure [10]. It is taken as soon as possible within 72 hours after unprotected intercourse either as a single dose (LNG 1.5 mg) or as two doses (0.75 mg) taken twelve hours apart. LNG use for emergency hormonal contraception has been shown to reduce pregnancy rates by 85% [11]. The mechanism of action of Plan B is not fully elucidated. It may inhibit ovulation, fertilization, or implantation [10, 11]. The minimum effective LNG plasma concentration is unknown.

Few data are available on the pharmacokinetics (PK) of progestosterone-based contraceptives with NNRTIs. A study of depomedroxyprogesterone acetate (DMPA) depot injections in HIV-infected women on antiretroviral therapy revealed no significant change in plasma levels of MPA or EFV,
nevirapine, or nelfinavir [12]. However, in a study of EFV and the combination oral contraceptive pill OrthoTrisCyclen-Lo and OrthoCyclen (25 mg ethinyl estradiol plus 0.18–0.25 mg norgestimate), LNG area under the concentra-
tion time curve from 0 to 12 hours (AUC12), maximum
concentration (Cmax), and minimum concentration (Cmin)
were decreased by 80%, 83%, and 86%, respectively [13].
A case of contraceptive failure with ectopic pregnancy in
an HIV-infected woman occurred with the etonogestrel
contraceptive implant and EFV [14]. No PK interaction
studies of Plan B and concomitant efavirenz have been
performed [14].

2. Methods

2.1. Subjects. Subjects were HIV-seronegative women ages
18–45 years with normal body mass index and no recent
use of hormonal contraceptive agents (oral or vaginal
hormonal contraception use within 60 days or injectable
hormonal contraception use within 180 days of study
entry; subjects with Mirena IUD were excluded) or other
medications/therapies known to interact with EFV. Subjects
who had not undergone surgical sterilization used 2 nonhor-
monal types of contraception throughout the study period
and for 2 weeks following study completion.

The protocol was approved by the institutional review
board at participating sites, and informed consent was
obtained from each woman before participation.

2.1.1. Study Design. This was a prospective, open-label,
single-arm, two-period, PK equivalence study. The primary
objective was to compare Plan B LNG AUC12 prior to and
during steady-state EFV. Secondary objectives included (1)
characterization of other LNG plasma PK parameters, (2)
assessment of the safety and tolerability of coadministration
of Plan B and EFV, and (3) evaluation of potential effects
of LNG on EFV AUC24 with comparison to previous data
in HIV+ women. Study participants received LNG 0.75 mg
at time 0 and 12 hours at baseline (visit 1-day 0) and after
steady state EFV dosing (visit 2-day 17). Subjects were begun
on EFV 600 mg at bedtime on empty stomach 72 hours
after visit 1 for a total duration of 14 days. Participants
fasted at least 12 hours prior to the PK study visits and ate
a standardized breakfast with LNG dosing (600 kcal;
15% protein, 30% fat, and 55% carbohydrates). Serial blood
(plasma) sampling for LNG PK analysis was performed after
LNG dosing at 0 (predose), 2, 3, 4, 6, 8, 10, and 12 hours at
Visit 1 and 2. Blood (plasma) sampling for EFV PK analysis
was performed prior to LNG dose, 6 and 12 hours after LNG
dose at visit 2 only (corresponding to approximately 10, 16,
and 22 hours from EFV dosing). Relevant clinical adverse
events were assessed at study and 4 telephone visits (study
days 4, 11, 16, and 20–28). Safety and laboratory profiles and
pregnancy testing were performed at screening and visits 1,
2 (LFT’s only), and 3. EFV adherence was assessed by subject
self-report at telephone visits approximately 7 and 17 days
after EFV was initiated.

2.2. Bioanalyses. LNG plasma concentrations were deter-
mined with a liquid chromatographic assay with MS/MS
detection linear in the range of 50–25000 pg/mL. Accuracy
and precision were within ±11% using a 0.5 mL plasma
sample. EFV plasma concentrations were determined using
a validated HPLV/UC method linear in the range of 20–
20,000 ng/mL. Accuracy and precision were within ±15%
with 0.2 mL plasma. Samples were frozen and shipped to
PPD, Inc. for LNG analysis and University of Colorado
Pharmacology lab for EFV analysis.

2.3. Data Analyses. Sample size calculations assumed that
expected LNG AUC12 was 123.1 ng·hr/mL with a standard
deviation of 50.1 [15]. Assuming equal variances and a
modest correlation of 0.5, the standard deviation of the
difference is also 50.1. 18 subjects were required to detect a
difference of 49.2 (a 40% change) in LNG AUC12 using a two-
sided, paired t-test with a significance level of 0.05 and 97.5%
power. To account for drop-outs, we enrolled 24 participants.

LNG PK was determined by noncompartmental meth-
ods (WinNonLin V5.2.1, Pharsight Corporation, Mountain
View, CA). LNG AUC12 was calculated with the linear-
log trapezoidal rule and LNG Cmin, Cmax, and time to
Cmax (Tmax) determined visually. LNG half-lives (t1/2) were
calculated as 0.693 divided by λz, where λz was the terminal
elimination rate constant. LNG total apparent oral clearance
(CL/F) was determined as dose divided by AUC12. Apparent
volume of distribution (V/F) was determined by CL/F
divided by λz.

A post hoc Bayesian approach (NONMEM vVI) was used
to estimate each subject’s EFV AUC24 based on the three
measured EFV levels. The estimated AUC24 was compared
to data from a previous PK study of HIV+ women using a
2-sample t-test [16].

For the primary hypothesis, equivalence was defined as a
decrease of less than 40% LNG AUC12 after addition of EFV
based on previous studies utilizing a 40% difference in con-
traceptive steroid hormone AUC as that which is clinically
relevant [12]. Percent change was calculated from the raw
(untransformed) data. The null hypothesis of equivalence
was rejected if the corresponding 95% confidence interval
included values ≤40%.

PK data were log transformed. Point estimates and 90%
confidence intervals for geometric means of LNG AUC12,
Cmax, Cmin, V/F and CL/F, and t1/2 were determined for LNG
dosed alone and with EFV. Geometric mean ratios (GMR)
for LNG AUC12, Cmax, and Cmin with versus without EFV
were calculated. Relevant clinical adverse events and liver
function test elevations were summarized. Paired t-tests were
used.

3. Results

3.1. Demographics. Twenty-four women enrolled, and 23
subjects commenced study visits and treatments. Three sub-
jects discontinued; 2 for adverse events and 1 for personal
reasons. Evaluable PK data was generated for 21 women who
had a mean age of 31 years (range 21–45) and BMI of 27
pretreatment with efavirenz (blue).

Healthy volunteers administered alone (red) and after 14 days of stratified analysis.

The estimated percent decrease in LNG AUC$_{12}$ with EFV was 56% (Table 1), and the corresponding 95% confidence interval (49%, 62%) excluded a change of ≤40% ($P < 0.0001$), such that the equivalence hypothesis was rejected. A decrease in LNG AUC$_{12}$ of >40% was observed in 90.5% (95% CI: 0.70%, 0.99%) of women. LNG $C_{max}$ and $C_{min}$ GMR were 0.55 and 0.31, respectively. LNG concentration time curves are shown in Figure 1. The geometric mean EFV AUC$_{24}$ in combination with LNG was 69597 ng·hr/mL (90% CI 27629, 175316 ng·hr/mL). This value was compared to a previous study of EFV PK in HIV-infected females which demonstrated an EFV geometric mean AUC$_{24}$ of 61361 ng·hr/mL (90% CI 19076, 197379 ng·hr/mL) ($P$ value = 0.35) [15]. Study participants had a >95% adherence with EFV dosing, and all had detectable EFV levels.

**3.2. LNG and EFV Pharmacokinetics.** The estimated percent decrease in LNG AUC$_{12}$ with EFV was 56% (Table 1), and the corresponding 95% confidence interval (49%, 62%) excluded a change of ≤40% ($P < 0.0001$), such that the equivalence hypothesis was rejected. A decrease in LNG AUC$_{12}$ of >40% was observed in 90.5% (95% CI: 0.70%, 0.99%) of women. LNG $C_{max}$ and $C_{min}$ GMR were 0.55 and 0.31, respectively. LNG concentration time curves are shown in Figure 1. The geometric mean EFV AUC$_{24}$ in combination with LNG was 69597 ng·hr/mL (90% CI 27629, 175316 ng·hr/mL). This value was compared to a previous study of EFV PK in HIV-infected females which demonstrated an EFV geometric mean AUC$_{24}$ of 61361 ng·hr/mL (90% CI 19076, 197379 ng·hr/mL) ($P$ value = 0.35) [15]. Study participants had a >95% adherence with EFV dosing, and all had detectable EFV levels.

**3.3. Safety and Tolerability.** Headache, abdominal pain, diarrhea, and menstrual cycle changes were the most common adverse events occurring in >10% of subjects after Plan B dosing alone. The incidence of abdominal pain, diarrhea, and menstrual cycle changes was decreased, while incidence of fatigue was increased with EFV. The occurrence of rash, pruritus, abnormal dreams, and insomnia was similar to previous studies of EFV [3]. Changes in LFT’s were rare and resolved with discontinuation of EFV. Adverse events were mild (Grade 1) to moderate (Grade 2) in majority and were resolved at follow-up visits. Two subjects discontinued study secondary to adverse events. One subject had a grade 2 rash likely related to study treatment (EFV) and resolved at follow-up visits. One subject had grade 3 syncope not related to study treatment and attributed to a vasovagal reaction with phlebotomy.

**4. Discussion**

Data are limited regarding the use of hormonal contraception in HIV-infected women on antiretroviral therapy. Interactions have been described between steroid hormones and both protease inhibitors and NNRTIs which could lead to decreased protection from pregnancy or increased contraceptive side effects [17]. Previous studies have focused predominantly on combined oral contraceptive pills, injectable DMPA, and one small study evaluated PK with the transdermal contraceptive patch [12, 13, 18]. Women taking EFV are specifically advised to avoid pregnancy due to this agents’ potential role in fetal neural tube defects [3, 19]. Thus, emergency hormonal contraception, like Plan B, may be even more important for these women.

We sought to evaluate the effect of EFV on plasma concentration of LNG in Plan B in healthy HIV-negative women. We found that pretreatment with EFV for 14 days was associated with a 56%, 41%, and 67% decrease in LNG AUC$_{12}$, $C_{max}$, and $C_{min}$, respectively.

The mechanism for this interaction is likely EFV induction of LNG metabolism. EFV is an inducer of CYP3A and uridine-diphosphate glucuronosyl transferases (UGTs) in vivo [3]. LNG exposures are reduced approximately 40% with the anticonvulsants phenytoin and carbamazepine (inducers of CYP3A) and 19% with lamotrigine (an inducer of glucuronidation enzymes) [20, 21]. A study of rifampin and oral contraception demonstrated considerable reduction in contraceptive hormone levels; however, ovulation suppression persisted [22].

**Table 1: Estimated LNG PK parameters.**

| PK parameter | Percent change raw scale (95% CI) | LNG GM (90% CI) | LNG + EFV GM (90% CI) | $P$ value | GMR (90% CI) |
|--------------|----------------------------------|----------------|------------------------|-----------|-------------|
| AUC$_{12}$ (ng·hr/mL) | −56% (−49%, −62%) | 42.9 (38.0, 48.5) | 17.8 (15.5, 20.5) | <0.0001 | 0.42 (0.36, 0.48) |
| $C_{max}$ (ng/mL) | −41% (−33%, −50%) | 8.4 (7.6, 9.3) | 4.6 (4.0, 5.4) | <0.0001 | 0.55 (0.49, 0.63) |
| $C_{min}$ (ng/mL) | −67% (−59%, −74%) | 2.04 (1.7, 2.3) | 0.6 (0.5, 0.7) | <0.0001 | 0.31 (0.26, 0.36) |
| V/F (L) | 110% (−155%, 176%) | 144 (120, 173) | 256 (217, 301) | 0.0001 | — |
| CL/F (L/hr) | 260% (159%, 364%) | 9.7 (8.0, 11.6) | 32.1 (27.6, 37.3) | <0.0001 | — |
| $t_{1/2}$ (hr) | −34% (−17%, −55%) | 10.3 (8.1, 13.2) | 5.5 (4.6, 6.7) | 0.0001 | — |

**Figure 1: Mean plasma concentration versus time profile for LNG.** Mean (±SD) levonorgestrel concentration-time profile in 21 healthy volunteers administered alone (red) and after 14 days of pretreatment with efavirenz (blue).
These findings may have important ramifications with regard to the efficacy of Plan B when taken with this ARV. However, the clinical relevance of this finding is unclear as the minimal effective LNG plasma concentration is unknown. We did not monitor for ovulation which may signal failed contraception. It is possible the alternate Plan B single dosing of LNG 1.5 mg would mitigate this effect; however, this is unlikely given the magnitude of our observed difference. Further clinical studies of Plan B and EFV are thus needed to inform providers of potential need for Plan B dosing adjustments for these women. HIV providers’ role in providing family planning services including contraception and preconception counseling is significant given the inherent complexities with HIV and antiretroviral therapy.

**Conflict of Interests**

Drs. M. L. Carten, J. J. Kiser, A. Kwara, and S. Cu-Uvin have no conflict of interests to report.

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