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Effect of Protease Inhibitors on Steady-State Pharmacokinetics of Oral Norethindrone Contraception in HIV-Infected Women

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Objective: Pharmacokinetic interactions exist between combined oral contraceptives and protease inhibitors (PI). However, such information is lacking for progestin-only oral contraception. We sought to define the steady-state pharmacokinetic interaction between norethindrone (NET) and PI in HIV-infected women.

Methods and Design: We conducted an open-label, prospective, nonrandomized trial to characterize the steady-state pharmacokinetics of serum NET in HIV-infected women receiving PI compared with a control group of HIV-infected women receiving other noninteracting drugs. After 21 days of 0.35 mg of NET ingestion once daily, serial serum samples were obtained at 0, 1, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours. The area under the curve between 0 and 72 hours after ingestion was calculated by trapezoidal approximation.

Results: Thirty-five women were enrolled, 2 withdrew. Sixteen women in the PI group and 17 controls completed the study. NET half-life and maximum concentration were not significantly different between the 2 groups. Minimum concentration of NET was significantly higher in the PI group ($P = 0.01$). The ratio of the geometric mean NET area under the curve in the PI group compared with controls was 1.5 (90% confidence interval: 1.21 to 1.86). NET serum concentrations were significantly higher in HIV-infected women taking a PI compared with controls ($P = 0.004$).

Conclusions: Coadministration of PI inhibits NET metabolism as shown by higher serum NET area under the curve levels, a surrogate marker for therapeutic contraceptive efficacy. This study supports the increased utilization of progestin-only pills in HIV-infected women receiving certain PI regimens.

Key Words: HIV, hormonal contraception, protease inhibitor, progestin only pills, norethindrone, pharmacokinetics, contraception, drug interactions, efficacy

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INTRODUCTION

Interactions between hormonal contraceptives and antiretroviral (ARV) medications to treat HIV are of great importance.[1] In 2009, approximately 1.2 million people in the United States were living with HIV.[2,3] Globally, the scope of the problem is more decimating, as HIV/AIDS is the leading cause of death among women aged 18–44 years.[4] ARV therapy is the standard of care and reduces morbidity and mortality in HIV-infected women.[5] ARV therapy typically consists of 2 or more medications from the various classes, including entry inhibitors, integrase inhibitors, CCR5 agonists, protease inhibitors (PI), nonnucleoside reverse transcriptase inhibitors, and nucleoside/nucleotide reverse transcriptase inhibitors.

Use of hormonal contraception is prevalent in HIV-prevalent regions of the world.[3] The Center for Disease Control (CDC) and World Health Organization (WHO) state that women living with HIV can safely use hormonal contraceptives.[6,7] The prevention of unintended pregnancy with safe and effective contraception to improve maternal health and to prevent mother-to-child transmission of HIV are strategies mentioned in the United Nation's Millennium Development Goals for 2010–2015.[8]

Multiple ARV drugs alter drug metabolizing enzyme activity, which may in turn alter the pharmacokinetics of concurrently administered medications.[9] Ritonavir, atazanavir, indinavir, nelfinavir, and saquinavir are all strong inhibitors of cytochrome P450 (CYP) 3A4.[10] Ritonavir acts via rapid, reversible, competitive binding.[10] This drug is used synergistically with other PIs to increase plasma drug concentrations and enhance ARV response in patients. Ritonavir is the preferred PI given in conjunction with atazanavir or darunavir to ARV-naive patients.[9] PIs also inhibit UDP-glucuronosyl transferase and decrease renal P-glycoprotein transport and excretion

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activity.[10] Based on these in vitro observations, it would be expected that plasma steroid levels would be increased after the coadministration of hormonal contraception and PI. However, in vitro models do not always correlate with in vivo drug interactions.[10,11] Complex alterations in pharmacokinetic processes, namely, absorption, distribution, metabolism, and excretion often make in vitro–in vivo correlations of drug–drug interactions difficult to predict.[10]

As evidence of this complexity, empiric trials with sample sizes of 5–10 HIV-negative women have demonstrated that administration of combined oral contraceptives and a PI or a nonnucleoside reverse transcriptase inhibitor produce decreased, and not increased, plasma ethinyl estradiol concentrations.[12] Decreased ethinyl estradiol concentrations may result in reduced efficacy, with an increased risk of unintended pregnancy. These combined oral contraceptive studies have demonstrated variable changes in serum progestins with ARV therapy.[5,12–14] Daily 0.35 mg of norethindrone (NET) is administered as a continuous oral contraceptive in US progestin-only pills. The half-life of NET is 8–12 hours, and its peak plasma concentration occurs within 2 hours of oral ingestion.[11] Hydroxylation of NET to its M1 metabolite is predominately due to CYP3A4 catalyzed reactions in the liver and to a lesser degree in the small intestine.[11,15] CYP2C19 enzymes may have a minor role.[15] Additionally, CYP3A4 is subject to a wide degree of interindividual variability, in the order of 11- to 20-fold, but no relevant genetic polymorphisms have been identified. Other CYP isoforms do contribute to intersubject variability in ARV metabolism, and they include 2D6, 2C9, and 2C19.[11,16,17]

Manufacturer product labels advise patients to use alternative methods of contraception when any PI is coadministered with combined oral contraceptives or progestin-only pills.[9,18] The WHO and CDC list the use of ritonavir-boosted PI and progestin-only pills as category 3 (risks outweigh benefit), thus limiting their use in HIV-infected women.[19,20] The WHO states, "as Category 3, use of that method is not usually recommended unless other more appropriate methods are not available or acceptable …. Where resources for clinical judgment are limited ….Category 3 indicates that a woman is not medically eligible."[20] No previous published pharmacokinetic trials have examined progestin-only pills in HIV-infected women taking any PI.[12] We studied HIV-infected women to determine if there was a significant interaction between PI and progestin-only pills.

MATERIALS AND METHODS

Study Design

This was a 2 arm, open-label, prospective, nonrandomized, steady-state pharmacokinetic trial of drug–drug interactions in HIV-infected women treated with oral NET and PI. Area under the time concentration curve of NET in these women was compared with HIV-infected controls taking NET and no ARV or an ARV regimen without a PI, which have demonstrated no significant interaction with NET in previous combined oral contraceptive trials.[12,14] Approval of the University of Southern California (USC) Institutional Review Board was obtained.

Study Population

Participants, aged 18–44 years, were HIV infected, and had no major lifestyle changes or changes in medications in the month before enrollment, no recent exposure to hormonal contraceptives (combined oral contraceptives >30 days, depot medroxyprogesterone acetate > 180 days), no evidence of immunocompromise, CD4 count of greater than 200 cells per cubic millimeter, no liver or renal disease, normal ovulatory function, body mass index of <40 kg/m^2, >30 days postpartum, abstained from grapefruit products (which contain furanocoumarin) or other CYP3A4-interacting substances, and agreed to use nonhormonal contraception. Women who were taking any PI as part of their anti-HIV therapy formed the study group, and those who were not taking a PI served as controls. Women were recruited from the Maternal Child Adolescent Clinic of Los Angeles County, University of Southern California.

Study Procedures

After screening and informed consent, women received a 28-day blister pack of NET (0.35-mg NET, Jolivette; Watson Pharmaceuticals Inc., Corona, CA) from the USC research pharmacy. Women took a single fixed dose of 0.35-mg NET daily for a minimum of 21 days and also adhered to dietary restrictions as per the protocol. On or after day 22, each woman was admitted to the Clinical Trials Unit at the University of Southern California, where a clinician observed her final ingestion of NET. Blood was collected by venous catheter and venipuncture before NET ingestion and at 1, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours after taking NET. After allowing the blood to stand for approximately 1 hour, the samples were centrifuged, and serum was removed and stored at −20°C until analyzed.

Treatment

For the treatment, 0.35-mg NET (Jolivette) was ordered, stocked, and monitored by the USC research pharmacy. All volunteers received prescriptions, and medication was dispensed at enrollment.

Assays

NET was measured in serum by radioimmunoassay, as described previously.[21,22] Before radioimmunoassay, NET was extracted with ethyl acetate:hexane (3:2) and then purified by Celite column partition chromatography. It was eluted off the column in 20% ethyl acetate in isooctane. Procedural losses were followed by adding small amounts of high specific activity–tritiated internal standard (^{3}H-NET) to the serum before the extraction step. A highly specific antiserum was used in conjunction with an iodinated radioligand in the radioimmunoassay. Separation of unbound from antiserum-bound NET was achieved by the use of second antibody. The sensitivity of the NET radioimmunoassay was 0.06 ng/mL. Intraassay and interassay coefficients of variation range from 4%–7% and 9%–12%, respectively.

Study End points

The primary study end point was the serum NET area under the time concentration curve from 0 to 72 hours,

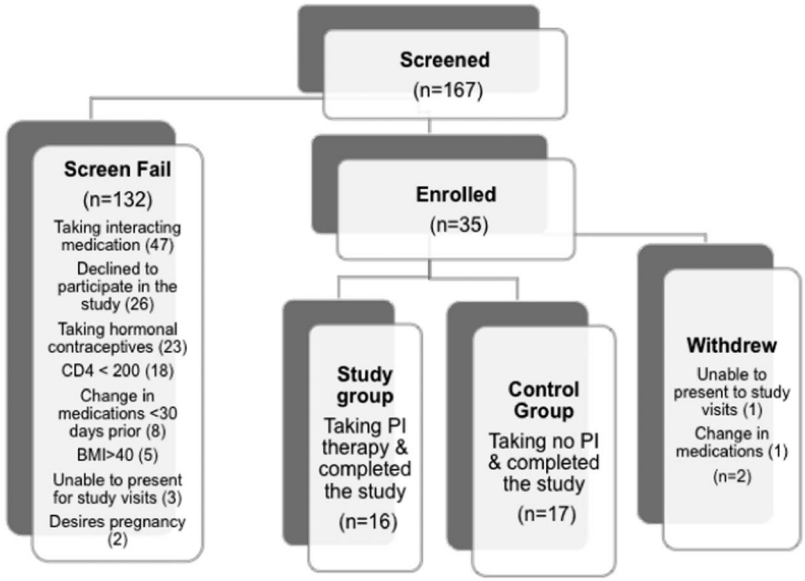

FIGURE 1. Screening, enrollment, and study completion. BMI, body mass index.

calculated using the linear trapezoidal approximation. Secondary end points were maximum NET concentration, minimum NET concentration, and the half-life that was estimated from the terminal elimination slope for each patient using concentrations sampled at 12 hours and beyond. For area under the curve and half-life, we used the Pmetrics package for R.[23]

Statistics and Sample Size

The null hypothesis used was that the 90% confidence interval for area under the curve geometric mean ratio would be within the range of 0.6–1.67, which is a clinically insignificant difference of ≤40%.[10] To reject the null hypothesis, we estimated that 16 women would be required in each arm to detect a >40% intergroup difference in area under the curve with a 2-tailed alpha of 0.05 and 80% power. Our assumptions for the sample size calculation were based on a previously reported mean (standard deviation) NET area under the curve of 22.1 (10.9) ng·hr/mL after an oral dose of 0.3-mg NET.[24] Peer-review literature does not specify minimum NET thresholds for contraceptive efficacy. We summarized normally distributed, continuous data with means and standard deviations and compared groups with Student *t* test. We summarized non–normally distributed, continuous data; we summarized them with medians and interquartile ranges and compared them with the Wilcoxon rank sum test. Categorical data were compared with Fisher exact test and displayed as numbers and percentiles. Log10 transformation was completed for all pharmacokinetic end points, which were compared with Student *t* test. We used SAS (version 9.3; SAS Institute, Cary, NC) and R (version 3.0.0; R Project for Statistical Computing, Vienna, Austria) for all analyses and plots.

RESULTS

Of 167 women who were screened, 132 were ineligible based on protocol restrictions or because they declined to participate, as shown in Figure 1. One of 17 women in the study group withdrew due to commitments that conflicted with her scheduled admission. One of 18 women enrolled in the control group withdrew due to medication change. Therefore, 16 women in the study group and 17 in the control group completed the trial. There were no significant differences between the 2 groups in terms of mean age, parity, CD4 count, history of opportunistic infections, body mass index, smoking status, ethnicity, or language, as shown in Table 1. In the control group, 4 women were not taking any ARV therapy. Other control participants were taking combinations of nucleoside reverse transcriptase inhibitors (n = 13), nonnucleoside reverse transcriptase inhibitors (n = 9), and integrase inhibitors (n = 4). Fifteen women in the study group took ritonavir, and 11 took atazanvir. Several women were taking a combination of ARV medications as listed in Table 2.

TABLE 1. Baseline Characteristics

	Study*	Control*	*P*
Age, median (IQR) (yr)	39.9 (35.9–42.3)	38 (33.4–41.3)	0.6
Nulliparous, n (%)	3 (9.1)	0 (0)	0.1
Parity, median (IQR)	3 (1–4)	3 (2–4)	0.3
CD4, median (IQR) (cells/mm^3)	618.5 (398–883.5)	669 (479–749)	0.65
OI, n (%)†	5 (31.3)	4 (23.5)	0.71
Body mass index, median (IQR)	26.8 (25.5–33.8)	29 (24.1–32.8)	0.9
Smoker, n (%)	3 (18.8)	2 (11.8)	0.66
Ethnicity and race, n (%)			
White	11 (69)	12 (71)	1.0
Black	4 (25)	4 (24)	—
Asian	1 (6)	1 (6)	—
Primary language, n (%)			
English	7 (44)	6 (36)	0.73
Spanish	9 (56)	11 (65)	—
Total	16	17	—

Body mass index = kg/m^2.
*Study group took PI therapy, control group took no PI.
†Opportunistic infections diagnosed in the past.
IQR, interquartile range.

TABLE 2. Antiretroviral Regimens*

	Study† (n = 16)	Control† (n = 17)	Total
PI†			
Atazanavir/ritonavir	10	0	10
Atazanavir	1	0	1
Darunavir/ritonavir	3	0	3
Lopinavir/ritonavir	2	0	2
NRTI			
Emtricitabine/tenofovir	11	6	17
Zidovudine/lamivudine	1	1	2
Abacavir/lamivudine	1	1	2
NNRTI			
Rilpivirine (with emtricitabine/tenofovir)	0	7	7
Etravirine	1	2	3
Integrase inhibitors			
Raltegravir	3	4	7
No HIV therapy	0	4	4

*Several participants took multiple medications.
†Study group took PI therapy, control group took no PI.
NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnuceloside reverse transcriptase inhibitor; PI, protease inhibitors.

The pharmacokinetic characteristics of NET in the study and control groups are shown in Table 3. The geometric mean NET area under the curve in the PI study group was 37.8 ng·h/mL, and in the control group, it was 25.2 ng·h/mL (Fig. 2). The geometric mean area under the curve ratio of the PI study group to the controls was 1.50, with a 90% confidence interval of 1.21 to 1.86 ($P = 0.004$). NET minimum concentration was higher among women taking a PI, whereas maximum concentration was not significantly different between the study groups ($P = 0.11$) and it tended to be higher in the PI group. The half-life was similar between the groups. Subset analysis was performed with the 11 women taking atazanavir and the 10 women taking atazanavir/norvir (excluding the participant on atazanavir without norvir); the results remained significant and were comparable.

DISCUSSION

It is recognized that there is a dearth of clinical data to guide contraceptive recommendations in HIV-infected women taking ARV therapy.[1] The WHO and CDC base their progestin-only pill recommendations on studies of ARV drugs and combined oral contraceptives.[19,20] Progestin-only pills are category 3 with ritonavir-boosted PI. As noted in the CDC Appendix M, "small mostly unpublished studies suggest that some antiretroviral therapies might alter the pharmacokinetics of combined oral contraceptives."[19] Progestin-only pills have fewer contraindications than estrogen-containing products, allowing greater use by more women. For example, women with hypertension, a history of venous thrombosis, smokers older than 35 years, and women in the postpartum period may all take progestin-only pills and would be discouraged from using ethinyl estradiol containing combined oral contraceptives. Furthermore, many HIV-positive women have comorbidities that would prevent them from using combined oral contraceptives. Additionally, they have a compelling need for dual contraception with condoms and an alternative method.

This present study showed that area under the curve of NET is significantly increased by 50% among HIV-infected women taking PI therapy as compared with controls. This ratio met our predefined criteria for a significant interaction, and we rejected the null hypothesis of no interaction. Because many PI, particularly ritonavir, are known to be sytsemic inhibitors of CYP3A4,[10] and NET is a substrate for CYP3A4[15], we presume that the mechanism of the interaction relates to the activity of this enzyme. In vivo the CYP3A4 inhibition typical of PI resulted in a significantly increased serum NET levels by decreasing systemic metabolism; this finding is supported by the increased area under the curve and increased minimum concentration of NET. The NET half-life is not significantly different between the 2 groups, which may be due to changes in steroid distribution. It is interesting that administration of combined oral contraceptives and PI have resulted in decreased serum ethinyl estradiol vis-à-vis alterations of microsomal enzymes.[12] As per the US Food and Drug Administration Product Insert, ritonavir is known to be an inducer and an inhibitor of CYP3A4, and drug-to-drug interactions are difficult to predict.[25]

The Hispanic and age demographic of our HIV-positive women at our single site in the United States may not reflect the same demographics of other regions. Our sample size was based on an a priori power analysis; however, it was still small. The variability of serum NET levels between different participants was extremely large, yet comparable to the range published in previous clinical research.[24] There is extremely limited or no published data to guide research on minimum serum levels of exogenous hormones for

TABLE 3. Pharmacokinetic Characteristics of Serum NET After 0.35 mg of Oral NET Ingestion With and Without PI

	Study (n = 16)* GM (Range)	Control (n = 17)* GM (Range)	GMR (95% CI)	*P*
AUC (ng·h/mL)†	37.81 (19.24–81.71)	25.21 (15.89–42.5)	1.5 (1.21 to 1.86)	0.004
Cmax (ng/mL)	2.76 (1.21–7.75)	2.09 (1.02–5.56)	1.33 (0.93 to 1.88)	0.11
Cmin (ng/mL)	0.17 (0.1–0.24)	0.13 (0.08–0.21)	1.26 (1.05 to 1.51)	0.01
Half-life (h)	22.5 (14.8–34.5)	24.3 (16.6–33.6)	0.92 (0.8 to 1.07)	0.28

*Study group took PI therapy, control group took no PI.
†Area under curve 0–72 hours after oral NET ingestion.
GM, geometric mean; GMR, geometric mean ratio; PI, protease inhibitor.

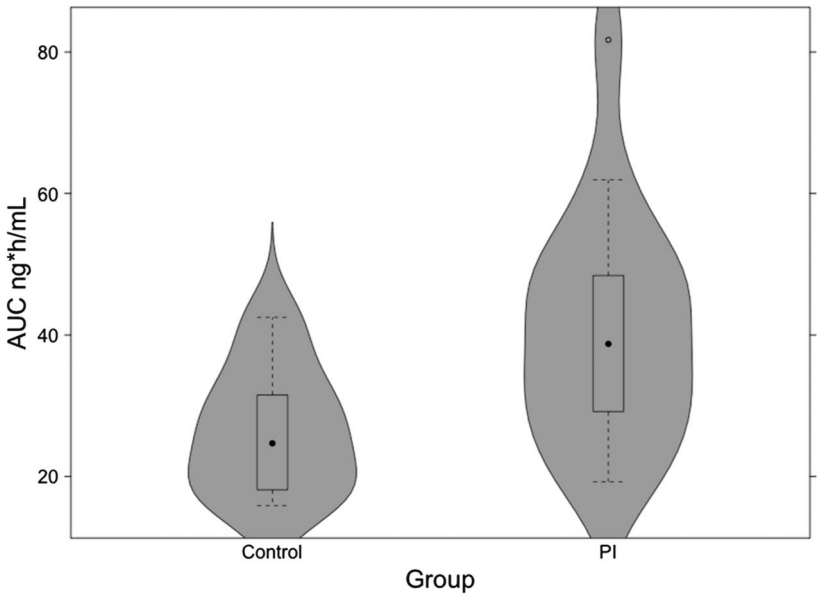

FIGURE 2. Violin plot of NET area under the curve by group. *The width of violin area corresponds to the mass of the data. A traditional box and whisker plot is centered within each violin, where the filled circle is the median, and the lower and upper bounds of the box are the 25th and 75th percentiles (ie, the interquartile range). The dashed "whiskers" indicate the range of the data within 1.5 interquartile range of the box boundaries, and the open circle is an outlier outside this range. Exclusion of this outlier did not change the results significantly (data not shown).

contraceptive efficacy. Other metabolic considerations, such as genetic differences or behaviors that deviated from protocol, may have also contributed to the significant findings. It may be difficult to generalize these results to women who are immunocompromised, who do not have access to clinicians, or who are unable to demonstrate strict adherence to their contraceptive and ARV therapy. The regimens of several participants, including the women who were not taking any ARV therapy, are not the standard recommendations for most ARV-naive HIV-positive women; they were specifically tailored to these women by their infectious disease clinician. Ten of the 16 in the PI group took atazanavir/ritonavir, and the results remained significant when this subset was analyzed. However, only 3 women took darunavir/ritonavir, and 2 took lopinavir/ritonavir. With these small numbers, it is difficult to know if NET is increased among all PI regimens. Additionally, none of the participants were taking other PI agents, such as fosamprenavir, indinavir, saquinavir, nelfinavir, or tipranavir. However, ritonavir is a potent inhibitor, and there remains biologic plausibility that it would increase NET in combination with other PIs.

The 50% increase in the area of NET noted among women taking PI in our study is not concerning for toxicity and does not warrant dose reduction. Many progestins are well tolerated, exhibit minimal side effects, and have excellent safety profiles.[26] The safety of this steroid and its metabolites has been demonstrated in clinical trials and postmarket surveillance.[26] Several current combined oral contraceptive products approved and marketed in the United States contain 1.5 mg of NET in addition to ethinyl estradiol, which is over 4 times as much progestin as the 0.35 mg of NET in the progestin-only pill.[26–29] The range of NET levels noted in the both groups of women were comparable with serum NET levels observed in previous clinical trials.[24,26] The dose determined for progestin-only pills contraception was a somewhat arbitrary historic assignment based on suspected bioequivalence of 0.5 mg of chlormadinone acetate.[30–34] In preliminary trials with the progestin NET, it was given in doses up to 20 mg, which demonstrates the wide therapeutic index, safety, and minimal toxicity of NET.[26]

CONCLUSIONS

Compared with combined oral contraceptives, progestin-only pills require less restrictive screening, have wider distribution potential, and can provide an additional safe contraception option for women with HIV. This is the first trial to describe NET progestin-only pill pharmacokinetics in HIV-infected women taking PI. NET area under the curve is increased by the coadministration of PI. Increased serum NET levels are a surrogate marker of continued therapeutic contraceptive efficacy. These findings should alter current progestin-only pill medical eligibility recommendations for women taking PI.

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