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Steady-State Pharmacokinetics, Cord Blood Concentrations, and Safety of Ritonavir-Boosted Fosamprenavir in Pregnancy

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Abstract

Steady-state pharmacokinetics in pregnant women prescribed ritonavir boosted fosamprenavir (FPV/RTV) to prevent HIV transmission were assessed in the second trimester, third trimester, and postpartum. Compared to postpartum, geometric mean amprenavir (APV, FPVs active metabolite) area under the plasma concentration-time curves (AUC) were 35% lower in the second trimester and 25% lower in the third trimester. Maternal APV concentrations were 9 – 15-fold above the mean APV protein-adjusted 50% inhibitory concentration for wild-type HIV. Median ratio of cord blood/maternal APV levels was 0.27 and all infants were HIV negative. FPV/RTV during pregnancy was well tolerated and led to virologic suppression.

Keywords

Fosamprenavir; pharmacokinetics; pregnancy; HIV

INTRODUCTION

The number of women of reproductive age living with HIV infection is increasing in worldwide and many of these women desire to have children.^{1–3} As guidelines evolve to initiate treatment at higher CD4 T-cell levels, the number of pregnant HIV-infected women receiving antiretroviral therapy can be expected to increase.⁴ The use of combination antiretroviral therapy during pregnancy has reduced the HIV transmission rate from approximately 20–30% to <2% in developed countries.^{5,6} However, physiologic changes occurring during pregnancy can greatly alter the pharmacokinetics of antiretroviral drugs.⁷ Plasma concentrations of most protease inhibitors (PI) have been reported to decrease during

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pregnancy.^{8–19} Increased doses are sometimes needed to ensure maintenance of virologic suppression in pregnancy with atazanavir, lopinavir/ritonavir, and saquinavir. This underscores the importance of optimizing treatment choices during pregnancy so as to prevent mother-to-child HIV transmission (p-MTCT) while minimizing the risks to both the mother and fetus.

The primary objective of this study was to assess the pharmacokinetics of fosamprenavir boosted by ritonavir (FPV/RTV) in pregnancy in the second and third trimesters compared to postpartum and to determine the transplacental transfer via cord blood/maternal APV ratios.

METHODS

Study Population

Eligible participants were women age 18 years or older, HIV-infected as confirmed by western blot or HIV-1 viral load, who had an intrauterine pregnancy and had received FPV/RTV for at least 14 days prior to study entry. Individuals were excluded if they were intolerant or allergic to FPV; had a history of non-adherence; received concomitant drugs known to significantly interact with FPV or RTV; or had severe hepatic impairment. The FPV/RTV regimen could include any nucleos(t)ide reverse transcriptase inhibitor (NRTI) backbone.

Study Design

This was a prospective, single-center, open-label, non-randomized, single-arm study of on FPV/RTV 700/100mg twice daily for p-MTCT. Participants meeting inclusion criteria who consented for enrollment were followed from their second or third trimester (depending on week of gestation at study entry) through week 12 postpartum. The protocol and informed consent were approved by the New York University School of Medicine Institutional Review Board and approved by the Office of Clinical & Health Services Research at New York City Health and Hospital Corporation Central Office.

Demographic, clinical, immunologic, virologic parameters, and self reported adherence were documented at enrollment and at each visit. Pharmacokinetic evaluations were performed at the clinical research center of the NYU-HHC Clinical and Translational Science Institute. Participants were assessed for adverse events, anemia, renal function via glomerular filtration rate (GFR), and hepatic function every 2 months and again at least 4 weeks postpartum.²⁵ The delivery mode and any complications relating to delivery were documented. Virologic and serologic testing of infants was performed at delivery, 3, 6 and 12 months.

Pharmacokinetic Sampling

Intensive 12-hour pharmacokinetic sampling for analysis of APV and RTV concentrations was performed during the second and third trimesters of pregnancy and again at least 4 weeks postpartum. Blood samples were collected at time 0, 1, 2, 3, 4, 5, 6, 8, 10, and 12 hours post-dose. All plasma samples, including maternal and umbilical cord plasma collected at delivery to assess APV transplacental transfer, were stored at -70°C pending bioanalysis for APV and RTV.

Assay Analyses

The bioanalytical method used for the determination of APV and RTV in human plasma was validated using a high-performance liquid chromatography assay with tandem mass spectrometric (HPLC-MS/MS) detection. Bioanalyses were performed at the

GlaxoSmithKline reference laboratory. The accuracy (% bias) values calculated from the quality control samples ranged from -1.8% to 2.8% for APV, and from -3.1% to 1.4% for RTV. The overall precision (% coefficient of variation [CV]) calculated from the quality control (QC) samples was 4.2% for both APV and RTV.

Pharmacokinetic and Statistical Analysis

Plasma APV and RTV PK parameters were estimated by non-compartmental analysis of concentration-time data using WinNonlin Professional (version 5.2). The geometric mean and 95% confidence intervals (CIs) were computed for area under the plasma concentration versus time curve over 12 hours post-dose (AUC), maximum plasma concentration ($C_{\max}$) and concentration at 12 hours post-dose (C_{12}). A within-subject analysis was conducted using plasma pharmacokinetic PK parameter values for AUC, $C_{\max}$ and C_{12} . Estimated means were log transformed and expressed as geometric least square (GLS) mean ratios and the associated 90% CI on the original scale to compare APV and RTV parameters from the second and third trimester to postpartum values. Within-subject GLS mean ratios were computed using SAS PROC MIXED (version.9.2).

RESULTS

Subject Characteristics and Outcomes

Between February 2009 and May 2010, ten women were screened, enrolled, and followed from their second or third trimester through week 12 postpartum. Five of the women were Black / African American, and the remaining five were of Hispanic ethnicity. The median age at the time of pregnancy was 29 years (range 19 – 38 years), and median CD4 T-cell count at the start of the p-MTCT regimen was 354 cells/mm³. There was one dizygotomous twin pregnancy included in this study.

All ten women received FPV/RTV as prescribed by their primary care providers for p-MTCT. The most common NRTI backbone co-administered with FPV/RTV was the fixed-dose combination of tenofovir/emtricitabine, used by 7 of the 10 subjects. Two subjects used zidovudine/lamivudine and one received abacavir/lamivudine as a dual NRTI backbone. Subjects initiated FPV/RTV during pregnancy at a median of 19 weeks gestation (range, 6 – 31 weeks), including two women who initiated therapy in the third-trimester after presenting to care relatively late in pregnancy. Nine women were treatment-experienced, six of whom had previously discontinued antiretroviral therapy postpartum in accordance with historical treatment guidelines. Four had undetectable HIV-1 RNA viral loads (<50 copies/mL) at the time of initiation of the FPV/RTV regimen for p-MTCT, including one woman who was an elite controller having an undetectable viral load in the absence of antiretroviral treatment. One subject conceived while on a fully suppressive FPV-containing regimen. Of the six genotypes sent for resistance testing, three women had documented minor PI mutations. All three women with resistance mutations had a L63P and two had an A71 V/T mutation.

Pharmacokinetic Analysis

Six subjects completed the second trimester 12-hour pharmacokinetic study and nine completed both the third-trimester and postpartum pharmacokinetic analysis, respectively. The geometric mean APV AUC₀₋₁₂ was 26.0, 30.1, and 39.9 mcg•h/mL, respectively for each progressive phase of pregnancy, consistent with those observed in other non-pregnant individuals receiving FPV/RTV 700/100 mg twice daily.²⁰ (Table 1). APV PK parameters were significantly lower in both the second trimester and third trimester when compared to postpartum. Compared to postpartum, geometric mean APV AUC₀₋₁₂, $C_{\max}$, and C_{12} were 35%, 37%, and 36% lower in the second trimester, respectively, and 25%, 19%, and 38% lower in the third trimester. Geometric mean C_{12} for all pregnancy phases were 9–15-fold

above the mean APV protein-adjusted IC_{50} of 0.146 mcg/mL for wild-type HIV strains (Fig. 1). Second trimester RTV AUC_{0-12} was approximately one-third that observed postpartum and less than half that seen during the third trimester.

In seven infant cord blood samples, the mean (SD) umbilical cord APV blood concentration was 0.11 (0.07) mcg/mL. The maternal plasma concentration at delivery was 0.43 (0.29) mcg/mL. APV GLS mean ratio (95% CI) of fetal cord to maternal peripheral plasma concentration was 0.267 (0.241, 0.297).

Safety

One woman with a history of nephrolithiasis prior to pregnancy developed pyelonephritis during week 34 of gestation. Another woman developed a transient asymptomatic grade 3 transaminitis after receiving nitrofurantoin for a urinary tract infection. Her liver function tests rapidly returned to her normal baseline upon nitrofurantoin discontinuation while maintaining FPV/RTV as part her p-MTCT regimen. No changes in baseline hemoglobin or renal function based on GFR were noted in any subject. No subject met criteria for delivery via C-section for p-MTCT. At delivery, nine subjects had HIV-1 viral loads <50 copies/mL and one subject had a viral load of 111 copies/mL. All 11 infants born were HIV-1 RNA PCR-negative at birth and remained so at 3, 6, and 12 months. Three infants (two from the dizygotous twin gestation) had low-birth weight (<2500 g). All infants met the WHO infant growth standards for height and weight at 3, 6, and 12 months postpartum.

DISCUSSION

Fosamprenavir (FPV), the phosphoester prodrug of the PI amprenavir (APV), is approved for use in treatment-naïve and treatment experienced HIV-infected individuals. APV is predominantly eliminated by the hepatic microsomal enzyme CYP3A4 and a substrate for an inducer of the efflux transporter P-glycoprotein.^{20,21} To date, little data have been published about the pharmacokinetics or safety of FPV during pregnancy.²²⁻²⁴ Second-trimester pharmacokinetics of APV following FPV administration have never been investigated.

The pharmacokinetics of FPV and magnitude of reduction in third-trimester APV plasma concentrations that we observed in pregnant HIV-infected women in our study were comparable to those reported by Capparelli et al.²² APV exposure appeared lower during the second trimester than during the third trimester, although wide confidence intervals that included 1 limited conclusion of statistical difference between the two stages of pregnancy. Lower RTV exposures and, hence, less boosting of APV concentrations in the second trimester relative to third trimester may have produced the trend for reduced APV PK parameters observed in the second semester.

Despite lower APV PK parameters during pregnancy relative to postpartum values, HIV-1 RNA was <200 copies/mL in all mothers at delivery and CD4 counts were stable throughout the study, suggesting that APV exposures were sufficient to maintain viral suppression, particularly given the fact that nine mothers were treatment experienced at enrollment.

The mean ratio of cord blood/maternal APV concentration was 0.27, suggesting that transplacental transfer of APV is higher than that reported for other PI.^{8,12,13,19,27} The mean umbilical cord blood concentration of 0.11 mcg/mL seen in our study is within the range of the mean protein binding-adjusted IC_{50} for wild-type HIV (0.146 mcg/mL), suggesting that APV cord concentrations may contribute to the prevention of HIV transmission to the fetus.

The FPV/RTV was well tolerated by both mother and infant consistent with the results of a previous study.²⁴ There has been no association with fosamprenavir use in pregnancy and an increased risk of birth defects.²⁸ The rate of birth defects for infants exposed to fosamprenavir in utero is 2.42 %, similar to that of the general population of 2.72% reported by the CDC.²⁹

Our limited study demonstrated that the standard twice-daily FPV/RTV 700/100mg regimen provided adequate APV exposure during the second and third trimesters of pregnancy. The observed reduction in APV concentrations appeared not to be clinically significant because all women remained virologically suppressed during the study and no cases of vertical HIV transmission occurred. Transplacental passage of APV with the FPV/RTV regimen was relatively high compared to that reported for most other PIs. The regimen was well tolerated in both mothers and infants, with no reports of drug-related adverse events. The pharmacokinetics, safety, and efficacy results we observed suggest that dose adjustment is not required for FPV/RTV twice-daily administration during pregnancy. Close virologic monitoring is suggested with the use of fosamprenavir, as with the use of any PI, for p-MTCT in women with significant PI mutations.

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FIGURE 1.
Median steady-state amprenavir (APV) plasma concentration-time profile during fosamprenavir/ritonavir therapy.

Steady-State¹ and Trimester Comparison Ratios² for Amprenavir and Ritonavir Pharmacokinetic Parameters during Fosamprenavir/Ritonavir Treatment in Pregnancy

Table 1

Pregnancy Phase	Amprenavir		Ritonavir	
	AUC ₀₋₁₂	C _{max}	AUC ₀₋₁₂	C _{max}
Second Trimester (n=6)	26.0 (19.5, 34.6)	4.19 (3.19, 5.51)	1.31 (0.97, 1.77)	1.22 (0.73, 2.04)
Third Trimester (n=9)	30.1 (21.6, 41.9)	5.36 (3.98, 7.22)	1.34 (0.95, 1.89)	2.93 (2.01, 4.29)
Postpartum (n=9)	39.9 (31.9, 50.1)	6.65 (5.24, 8.44)	2.03 (1.46, 2.83)	3.27 (1.84, 5.84)
Second vs. Third trimester ³	0.86 (0.63, 1.19)	0.78 (0.58, 1.06)	0.97 (0.67, 1.41)	0.32 (0.17, 0.60)
Second Trimester vs. Postpartum	0.65 (0.47, 0.89)	0.63 (0.47, 0.85)	0.64 (0.45, 0.93)	0.32 (0.17, 0.60)
Third Trimester vs. Postpartum	0.75 (0.57, 1.00)	0.81 (0.62, 1.06)	0.62 (0.48, 0.92)	1.00 (0.58, 1.71)
Second and Third Trimester vs. Postpartum	0.70 (0.54, 0.90)	0.71 (0.56, 0.91)	0.65 (0.49, 0.88)	0.59 (0.39, 0.88)

¹Geometric mean (95% CI)

²Geometric least squares mean ratio (90% CI) used for PK comparisons by phase of pregnancy

³Mean gestational age in weeks (±SD) by stage of pregnancy : 2nd trimester 24 ± 3.6, 3rd trimester = 35 ± 1.7, Weeks post partum at final PK = 10 ± 6