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STEADY-STATE PHARMACOKINETICS OF LOPINAVIR/RITONAVIR IN COMBINATION WITH EFAVIRENZ IN HUMAN IMMUNODEFICIENCY VIRUS-INFECTED PEDIATRIC PATIENTS

Jennifer R. King, PharmD[*], **Edward P. Acosta, PharmD**[*], **Ram Yogev, MD**[†], **Andrew Wiznia, MD**[‡], **Joyce Kraimer, MS**[§], **Bobbie Graham, MS**[¶], **Vincent Carey, PhD**[‖], **Paula Britto, MS**[‖], **Patrick Jean-Philippe, MD**[**], **John Moye, MD**[††], and **Douglas Watson, MD**[‡‡]

[*] The University of Alabama at Birmingham, Birmingham, AL

[†] Children's Memorial Hospital, Northwestern University Feinberg School of Medicine, Chicago, IL

[‡] Jacobi Medical Center, Brooklyn, NY

[§] Social and Scientific Systems Inc, Silver Spring, MD

[¶] Frontier Science and Technology Research Foundation, Buffalo, NY

[‖] Harvard School of Public Health, Boston, MA

[**] Henry Jackson Foundation, Therapeutic Research Program, DAIDS/NIAID/NIH, Bethesda, MD

[††] The Pediatric Adolescent and Maternal AIDS Branch, NICHD, Bethesda, MD

[‡‡] University of Maryland, Baltimore, MD

Abstract

The pharmacokinetics of lopinavir/ritonavir (LPV/RTV) 300 mg/m^2 twice daily and efavirenz (EFV) 350 mg/m^2 once daily were evaluated in HIV-infected children. The minimum concentrations for LPV contained values above the target range, and the estimated minimum concentrations for EFV contained values below the range. Our data support the current LPV/RTV dose, but EFV 350 mg/m^2 may not be sufficient.

Keywords

HIV; pharmacokinetics; lopinavir/ritonavir; efavirenz

An antiretroviral regimen containing efavirenz (EFV) plus lopinavir (LPV) boosted with ritonavir (RTV) in addition to nucleoside reverse transcriptase inhibitors (NRTI) is commonly administered throughout the world as second-line therapy for treatment of the human immunodeficiency virus because it has demonstrated efficacy in NRTI- and protease inhibitor-experienced adults.1 Although the EFV dose remains unchanged, LPV and RTV doses require adjustments when used in combination with EFV, because EFV induces their metabolism.2 Body weight adjusted doses are recommended for this combination in pediatric patients. However, controversy remains as to whether this approach is optimal because body surface area (BSA), which takes into account weight and height, is a better

Address for correspondence: Jennifer R. King, PharmD, Division of Clinical Pharmacology, University of Alabama at Birmingham, 1530 3rd Avenue South, VH 101A, Birmingham, Alabama 35294-0019. jennifer.king@ccc.uab.edu.

predictor of the physiological changes occurring with age.3 Thus, the objective of protocol P1058 conducted through the International Maternal Pediatric Adolescent AIDS Clinical Trials group was to examine the pharmacokinetics of interacting antiretroviral combinations, specifically EFV, LPV, and RTV, when dosed on a mg/m^2 basis in HIV-infected children and adolescents.

METHODS

Study Design

The International Maternal Pediatric Adolescent AIDS Clinical Trial P1058 was an observational pharmacokinetic study of LPV/RTV 300 mg/m^2 twice daily (b.i.d.) and EFV 350 mg/m^2 once daily (q.d.) in combination with any nucleoside or nucleotide reverse transcriptase inhibitor or fusion inhibitor. Eligible subjects included HIV-infected children, 2–18 years of age receiving at least 2 weeks of antiretroviral therapy. No other non-nucleoside reverse transcriptase inhibitor or protease inhibitor was allowed. Antiretroviral drugs were administered in an open-label fashion. Subjects were excluded if they had hepatic disease likely to affect the metabolism of the studied drugs, bilirubin ≥5.0 × the upper limit of normal, hemoglobin <7.0 g/dL or receiving a drug that might interact with the antiretroviral drugs of interest. A negative pregnancy test was also required at the time of enrollment for females of childbearing capacity. The study was approved by the institutional review board at each site and informed consent or assent when appropriate was obtained from each subject's parent or legal guardian.

Pharmacokinetic Sampling and Analyses

All subjects underwent a formal pharmacokinetic evaluation in a General Clinical Research Center or clinic setting. Blood samples were collected at 0, 1, 2, 3, 4, 6, 8, and 12 hours post dose. Samples could be collected in the morning or evening; however, the EFV evening dose had to be changed to the morning for at least 1 week before the pharmacokinetic study visit if samples were collected in the morning. LPV, RTV, and EFV plasma concentrations were determined by a modification of a fully validated method using high performance liquid chromatography with ultraviolet detection.4 The assay is linear over a concentration range of 25 to 20,000 ng/mL.

Pharmacokinetic parameters of LPV, RTV, and EFV were determined using noncompartmental methods (WinNonlin version 4.01, Pharsight Corp., Mountain View, CA). The area under the plasma concentration time curve [estimated (Est) AUC_{24} for EFV and AUC_{12} for LPV and RTV] was calculated using the linear-up/log-down trapezoidal rule. Maximum plasma concentration (C_{max}) and time to maximum concentration (T_{max}) were taken directly from the observed concentration-time data. Oral clearance (CL/F) was calculated as dose/AUC_{τ}. Terminal apparent distribution volume (V_z/F) was calculated as dose divided by the product of the elimination rate constant (λ_z) and AUC_{τ}. The elimination rate constant was determined by linear regression of the terminal elimination phase concentration-time points; elimination half-life ($t_{1/2}$) was calculated as ln(2)/λ_z. Regression analysis of the terminal phase was used to estimate the 24-hour concentration of EFV ($EstC_{24\ hours}$).

Statistical Analyses

For each subject, statistical comparisons examined whether the 90% confidence intervals (CIs)of the LPV and EFV geometric mean (GM) AUC and C_{min} overlapped with the interval covering 0.5- to 2.0-fold of the target value defined on the basis of studies establishing safety and efficacy of LPV and EFV administered separately.5,6 The target GM (range) for LPV AUC_{12} was 80 (40 –160) mg × h/L, LPV C_{min} was 3.5 (1.75–7) mg/L, EFV

AUC_{24} was 64 (32–124) mg × h/L and EFV $C_{24\ hours}$ was 1.8 (0.9 –3.6) mg/L. The 90% CI for LPV and EFV pharmacokinetic parameters when coadministered were compared with the predefined target values for each antiretroviral drug and a substantial overlap between the 2 was indicative of acceptable pharmacokinetics for the combination.

RESULTS

Twenty HIV-infected children between 10 and 16 years of age were enrolled into the study. Intensive pharmacokinetic data were available from 15 patients. Pharmacokinetic parameters could not be determined for 5 patients who received the EFV dose on the evening before the pharmacokinetic visit. Median (range) age, weight, and BSA for the 15 patients were 13 (10 –16) years, 44.5 (26.9 – 63.9) kg, and 1.4 (1.0 –1.7) m^2, respectively. The median (range) LPV dose was 289 (132– 407.4) mg/m^2 or 9.0 (3.4 –14.9) mg/kg and median (range) EFV dose was 354.2 (132.1– 401.9) mg/m^2 or 10.7 (3.4 –13.7) mg/kg.

Pharmacokinetic results for LPV, EFV, and RTV are listed in Table 1. The LPV GM (90% CI) AUC and C_{min} were 91.3 (68.5–121.6) mg × h/L and 5.8 (4.2– 8.0) mg/mL, respectively. The LPV C_{min} was within the predefined target range for 60% (n = 9) of patients, below the target range for 7% (n = 1) and above the target range for 33% (n = 5). LPV AUC_{12} was within the predefined target range for 86% (n = 13) of patients, below the target range for 7% (n = 1), and above the target range for 7% (n = 1). The EFV GM (90% CI) AUC_{24} and $EstC_{24\ hours}$ were 44.1 (36.3–53.5) mg × h/L and 0.8 (0.5–1.1) mg/L, respectively. EFV $EstC_{24}$ was within the predefined target range for 47% (n = 7) of subjects and below the predefined target range for 53% (n = 8) of patients. Except for 1 patient, all of those with an $EstC_{24\ hours}$ below the target range (n = 7) had a predose concentration that was also below the target range. EFV AUC_{24} was within the target range for 86% (n = 13) of patients and below the target range for 14% (n = 2).

DISCUSSION

P1058 was an intensive pharmacokinetic study of LPV/RTV 300 mg/m^2 b.i.d. in combination with EFV 350 mg/m^2 q.d. in HIV-infected children receiving a NRTI-based regimen. The GM (90% CI) for both LPV and EFV AUC were within the target range for all the 15 patients enrolled. In contrast, although the LPV C_{min} (GM 90% CI) contained values above the target upper limit of 7 mg/L, the EFV EstC24 hours GM (90% CI) contained values below the target lower limit of 0.9 mg/L.

LPV C_{max}, C_{min}, and AUC_{12} observed in our patients in the presence of EFV were 20%, 54%, and 10% higher, respectively, than those observed in adults receiving LPV/RTV 533/133 mg b.i.d. and EFV 600 mg q.d.7 Yet, our results were similar to those observed in HIV-infected children receiving LPV/RTV 300 mg/m^2 b.i.d. in combination with EFV 14 mg/kg once daily.8 Of interest, 5 patients (33%) in this study had significantly lower LPV exposure, which is different from our findings where only 1 patient (6.6%) had LPV exposure below the target range of 0.9 mg/L. In the current study, patients received an EFV dose of 350 mg/m^2, which approximates 11 mg/kg; the recommended dose is 15 mg/kg. The lower EFV dose in our study may have had a smaller inhibitory effect on LPV metabolism resulting in a smaller number of patients with low LPV exposure. Furthermore, 5 patients in our study had LPV C_{min} above the target range of 7 mg/L. Each patient received LPV 400 mg, which was below the recommended 300 mg/m^2 dose for 3 patients and approximately 35% higher in 2 patients. Again, higher LPV exposure in these patients is likely the result of the decreased inhibitory effect of the lower EFV dose.

The EFV C_{min} and AUC in our patients were 60% and 30% lower, respectively, compared with pediatric and adult patients.9 This difference is also likely due to the lower mg/kg equivalent EFV dose used in our study. However, an evaluation of EFV exposure in 15 South African children receiving a median dose of 352 mg/m^2, which was equivalent to 14 mg/kg, revealed that 40% of patients had an estimated C_{min} <1 mg/L.10 Another study evaluating EFV exposure in children dosed according to body weight-adjusted dose recommendations observed that 64% of patients had plasma concentrations below the targeted range.11 Taken together, these data suggest that the current weight-based dosing recommendations and the BSA-based dosing of 350 mg/m^2 will often result in insufficient EFV exposure.

In conclusion, data from our study support the current strategy of increasing the LPV/RTV dose to 300 mg/m^2 in the presence of EFV. However, EFV dosed at 350 mg/m^2 may not be adequate in HIV-infected children. This conclusion is supported by several other studies evaluating EFV exposure in HIV-infected children, which also found plasma concentrations lower than expected relative to adult exposures, even when the recommended weight-based dosing was used. Because suboptimal EFV plasma concentrations can increase the development of viral resistance, additional studies are needed to further evaluate BSA-based and the current weight-based dosing of EFV.

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TABLE 1

Median (Range) Lopinavir, Ritonavir, and Efavirenz Pharmacokinetics

	C_{max} (mg/L)	T_{max} (hr)	$t_{1/2}$ (hr)	C_{min} (mg/L)	AUC_{τ} (mg × hr/L)	V (L)	CL (L/h)
LPV	12.0 (1.5–36.6)	3.0 (2.0–11.8)	9.3 (4.6–19.1)	6.3 (0.7–25.1)	100.2 (13.4–318.5)	26.8 (8.7–177.9)	2.4 (0.57–20.25)
RTV	1.0 (0.04–3.7)	3.0 (1.0–8.1)	4.5 (3.1–8.2)	0.3 (0.01–1.2)	6.6 (0.3–28.9)	69.1 (16.2–1708)	11.8 (2.0–264.8)
EFV	3.57 (1.4–7.6)	3.0 (2.0–11.9)	9.94 (4.9–27.8)	0.77 (0.2–2.5)	40.87 (13.7–86.2)	104.76 (64.0–343.0)	8.5 (2.3–22.9)

AUC_{τ} was AUC_{12} for LPV and AUC_{24} for EFV.

C_{min} was $C_{12\ h}$ for LPV and estimated $C_{24\ h}$ ($EstC_{24\ h}$) for EFV.