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Effects of Valproic Acid Coadministration on Plasma Efavirenz and Lopinavir Concentrations in Human Immunodeficiency Virus-Infected Adults

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Valproic acid (VPA) has the potential to benefit patients suffering from human immunodeficiency virus (HIV)-associated cognitive impairment. The purpose of this study was to determine if VPA affects the plasma concentration of efavirenz (EFV) or lopinavir. HIV type 1 (HIV-1)-infected patients receiving EFV or lopinavir-ritonavir (LPV/r) had 9 or 10 blood samples drawn over 8 to 24 h of a dosing interval at steady state before and after receiving 250 mg of VPA twice daily for 7 days. VPA blood samples drawn before (C_0) and 8 h after the morning dose (8 h) were compared to blood samples from a group of HIV-1-infected subjects who were taking either combined nucleoside reverse transcriptase inhibitors alone or had discontinued antiretroviral therapy. Pharmacokinetic parameters were calculated by noncompartmental analysis, and tests of bioequivalence were based on 90% confidence intervals (CIs) for ratios or differences. The geometric mean ratio (GMR) (90% CI) of the areas under the concentration-time curve from 0 to 24 h ($AUC_{0\text{-}24}$s) of EFV ($n = 11$) with and without VPA was 1.00 (0.85, 1.17). The GMR (90% CI) of the $AUC_{0\text{-}8}$s of LPV ($n = 8$) with and without VPA was 1.38 (0.98, 1.94). The differences (90% CI) in mean C_0 and 8-h VPA concentrations versus the control ($n = 11$) were −1.0 (−9.4, 7.4) μg/ml and −2.1 (−11.1, 6.9) μg/ml for EFV ($n = 10$) and −5.0 (−13.2, 3.3) μg/ml and −6.7 (−17.6, 4.2) μg/ml for LPV/r ($n = 11$), respectively. EFV administration alone is bioequivalent to EFV and VPA coadministration. LPV concentrations tended to be higher when the drug was combined with VPA. Results of VPA comparisons fail to raise concern that coadministration with EFV or LPV/r will significantly influence trough concentrations of VPA.

Cognitive impairment is the most common complication of human immunodeficiency virus (HIV) infection affecting the central nervous system. Although the incidence of HIV-associated cognitive impairment has declined with the introduction of highly active antiretroviral therapy (30), the prevalence of this disorder is likely to increase given the increased life span of HIV-infected individuals. Despite numerous preclinical studies, the relationships between the neuropathogenesis of HIV-associated cognitive impairment and neurologic disease remain poorly understood. Extensive loss of neurons within certain regions of the brain (12, 19) and high levels of neuronal apoptosis (2, 16, 26, 32) have been reported in persons with HIV dementia. Neuronal apoptosis is believed to occur as a result of the production and release of a number of neurotoxic factors that include viral proteins and products of immune activation. Among the best characterized of these are the HIV type 1 (HIV-1) regulatory protein Tat and platelet-activating factor (PAF). PAF and recombinant Tat protein and peptides containing the basic Tat domain induce apoptosis in both human and rat neurons (15, 21, 24, 25, 27, 29, 35).

A number of studies have shown that phosphatidylinositol 3-kinase and Akt protein kinase may play a role in the regulation of cell fate, including neuronal survival (8, 11, 23, 36). Glycogen synthase kinase 3 beta (GSK-3β) has been identified as a major physiological target for Akt (7), and activation of GSK-3β can induce apoptosis. The finding that the HIV-1 neurotoxins Tat and PAF upregulate the activity of GSK-3β suggests that activity of this enzyme may play an important role in the pathogenesis of HIV-1-associated cognitive impairment (20). Furthermore, PAF-induced neurotoxicity can be reversed by GSK-3β inhibition, which is particularly important because PAF receptor activation has been implicated as the principal initiator of neuronal dysfunction and death by several candidate HIV-1 neurotoxins, including tumor necrosis factor alpha (25). Importantly, in a SCID murine model of HIV-1 encephalitis, we have recently shown that administration of the GSK-3β inhibitor valproic acid (VPA) ameliorates damage to the neuronal dendritic arbor induced by inoculation of HIV-1-infected mononuclear phagocytes into the basal ganglia (10). Taken together, our in vitro and in vivo data provide a compelling rationale for a trial of VPA as adjunctive therapy for neuroprotection in patients with HIV-1-associated cognitive impairment.

There is evidence of VPA interfering with the metabolism of concomitant medications. VPA has been shown to be an inhibitor of cytochrome P-450 (CYP) hepatic enzymes, including CYP 2C9, and to inhibit UDP glucuronosyltransferase (UGT) (3, 4, 31, 34, 37). Being highly bound to albumin, VPA also has the ability to interact with other drugs via protein displacement.

The primary purpose of this study was to determine whether VPA would reduce the plasma concentrations of protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibi-

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tors (NNRTIs), as this may preclude any further investigation of VPA for the treatment of HIV-associated cognitive impairment. Since VPA is also commonly used for headache and mood control in addition to its primary indication for epilepsy, we assessed whether PIs and NNRTIs affect trough levels of VPA. Lopinavir and efavirenz were chosen as representative of PIs and NNRTIs because of their frequent clinical use at the time the study was implemented.

MATERIALS AND METHODS

Study subjects. Subjects were recruited from the North East AIDS Dementia cohort and from the Rochester AIDS Clinical Trials Unit and sub-AIDS Clinical Trials Unit. Subjects who met the following criteria were eligible for enrollment in this trial: being seropositive for HIV on the basis of self-report confirmed by enzyme-linked immunosorbent assay and Western blot assay, having a viral load of <400 copies/ml (Roche Amplicor test), being on a stable antiretroviral regimen for 4 weeks, being on a regimen containing either lopinavir or efavirenz, being capable of giving informed consent, and being 18 years old or older.

Subjects with active opportunistic infections, neoplasms, or any other clinically significant condition or laboratory abnormality that in the investigator's opinion would interfere with the subject's ability to participate in the study; who were currently participating in other drug studies or had received other investigational drugs within the previous 30 days; and who were pregnant or nursing or taking medication known or suspected to interfere with drugs metabolized by the CYP isoenzyme system (including but not limited to ketoconazole, itraconazole, cimetidine, rifampin, and erythromycin) were excluded.

An additional HIV-infected control group was enrolled to assess the impact of lopinavir and efavirenz on the concentration of VPA in plasma. These subjects were not taking lopinavir and efavirenz and were not required to have a viral load of <400 copies/ml but met all of the other inclusion and exclusion criteria listed above.

Study design. This study consisted of three groups of HIV-infected subjects: a group receiving lopinavir-ritonavir, a group receiving efavirenz, and a VPA control group that received neither lopinavir-ritonavir nor efavirenz. The Research Subject Review Board at the University of Rochester approved this study, and all subjects were required to provide informed consent before any study procedures were initiated. Subjects arrived at the General Clinical Research Center in the morning, were required to fast for at least 8 h, and received a standardized light breakfast 1 h after observed study drug administration. Blood samples were drawn before and 0.5, 1, 1.5, 2, 3, 4, 6, and 8 h after administration of the morning dose of lopinavir-ritonavir. The sample strategy for efavirenz was the same except that subjects took their dose the evening prior to sampling and were required to return for 24-h postdose blood sample collection. Since subjects may have been less likely to agree to a 12-h stay at the General Clinical Research Center, an 8-h postdose sampling period was chosen. Trough and 8-h postdose concentrations of VPA were measured in all participants, including those in the control group. Each subject had blood samples drawn before and after receiving 250 mg of VPA by mouth twice daily for 7 days. Subjects who were taking didanosine were required to take didanosine 2 h after their morning dose of the study drug.

Drug assays. Efavirenz and lopinavir concentrations in plasma were measured by high-performance liquid chromatography in the Pharmacology Support Laboratory at the University at Buffalo with methods validated within the Adult AIDS Clinical Trials Group Quality Assurance Proficiency Testing program (18). The lower limits of quantitation were <100 and <200 ng/ml for efavirenz and lopinavir, respectively. VPA was measured with a standard cloned enzyme donor immune assay (Microgenic) with a limit of detection of 3 μg/ml.

Pharmacokinetic analyses. Standard noncompartmental techniques were used to assess pharmacokinetic parameters with WinNonlin Version 2.1 (Pharsight, Palo Alto, Calif.). The area under the concentration-time curve (AUC) was determined with the linear trapezoidal method, and the maximum observed concentration (C_{max}) and time to C_{max} (T_{max}) were determined by visual inspection. If the sample drawn at the end of the dosing interval was not available or had an increased drug concentration compared to that taken at the previous time point, the concentration reported was determined by extrapolation on the basis of the estimated terminal elimination rate. Efavirenz 24-h postdose samples were also used to estimate predose efavirenz concentrations in order to calculate the AUC during a 24-h dosing interval at steady state ($AUC_{0\text{-}24}$). Tests of bioequivalence were based on 90% confidence intervals (CIs) for ratios or differences, in accordance with Food and Drug Administration guidelines (90% CI of the geometric mean ratio [GMR] of the test AUC to the reference AUC within a range of 0.80 to 1.25). Pharmacokinetic parameters, or their log transforms, were compared between groups with the paired *t* test, the paired Wilcoxon tests, or the Kruskal-Wallis test when appropriate with SAS System v8 (SAS Institute, Cary, N.C.). Assuming a coefficient of variation of approximately 25% for the AUC of lopinavir or efavirenz when either drug is taken alone, a sample size of 10 HIV-1-infected subjects in each arm would be required for 90% power to detect a 30% decrease in the lopinavir or efavirenz AUC due to the administration of VPA with a two-sided paired *t* test with 0.05 type I error.

TABLE 1. Demographics and baseline clinical variables of the subject in this study

Analysis variable[a]	Efavirenz + NRTIs	Lopinavir-ritonavir + NRTIs	VPA without efavirenz or lopinavir
Mean age (yr), SD	41.0, 5.3	45.4, 6.7	43.0, 7.7
% of males	81.8	81.8	83.3
Ethnicity (%)			
Caucasian	45.4	63.6	66.7
Black	45.4	36.4	25.0
Hispanic	9.1		8.3
Karnofsky score of ≥80 (%)	100.0	81.8	91.7
History of HIV-related diagnoses (%)	27.3	36.4	16.7
Mean CD4 cell count/mm^3, SD	545.9, 214.0	416.7, 463.3	340.6, 232.9
Antiretroviral use (%)			
Abacavir	55	55	36
Didanosine	18	27	0
Lamivudine	72	55	45
Stavudine	18	45	0
Zalcitabine	0	0	9
Zidovudine	36	27	36
Indinavir	0	0	9
Amprenavir	0	0	9
Nevirapine	0	0	9
Nelfinavir	0	0	9

[a] The numbers of subjects included in the efavirenz plus NRTI, lopinavir-ritonavir plus NRTI, and VPA without efavirenz or lopinavir groups were 11, 11, and 12, respectively.

RESULTS

The genders, ages, ethnicities, Karnofsky performance statuses, antiretroviral drug use, and CD4 cell counts of subjects who received efavirenz, lopinavir-ritonavir, or neither efavirenz nor lopinavir-ritonavir (VPA control group) are listed in Table 1. Eleven subjects received 600 mg of efavirenz once daily with or without VPA. The pharmacokinetic parameters calculated for efavirenz are listed in Table 2. VPA does not appear to alter plasma efavirenz concentrations. Efavirenz administered with VPA is bioequivalent to efavirenz administered alone. The GMR (90% CI) of the $AUC_{0\text{-}24}$s was 1.00 (0.85, 1.17). None of the other pharmacokinetic parameters for efavirenz listed in Table 2 were found to be significantly different ($P > 0.10$).

Three subjects receiving lopinavir-ritonavir did not follow the protocol concerning the time of dose administration. The estimated lopinavir pharmacokinetic parameters for eight subjects who received 400 and 100 mg of lopinavir and ritonavir, respectively, twice daily with and without VPA are listed in Table 2. Administration of lopinavir-ritonavir alone does not appear to be equivalent to administration of lopinavir-ritonavir

TABLE 2. Pharmacokinetic parameters of efavirenz and lopinavir

Drug[b]	C_{last}[a] (μg/ml)	C_{max} (μg/ml)	AUC[c] (h · ng/ml)	$t_{1/2}$[d] (h)	T_{max} (h)
Efavirenz	1.44 (0.510–3.45)	2.43 (0.957–5.05)	39.86 (17.92–93.56)	30.1 (4.7–74)	10.5 (9.0–17.5)
Efavirenz with VPA	1.32 (0.598–3.81)	2.03 (1.12–5.73)	39.00 (18.30–104.09)	23.4 (5.9–266)	10.0 (8.5–13.5)
Lopinavir	6.81 (1.64–20.5)	12.4 (4.60–23.7)	61.02 (25.24–172.49)	7.0 (1.9–50.7)	2.0 (0.0–5.5)
Lopinavir with VPA	10.7 (2.07–17.0)	16.5 (5.56–22.3)	106.87 (30.51–142.25)	7.6 (2.9–32.5)	1.75 (0.0–7.8)

[a] C_{last} is the drug concentration drawn at the last time point. C_{last} is 24 h after dose administration for efavirenz and 8 h after dose administration for lopinavir.
[b] The numbers of subjects given 600 mg of efavirenz every 24 h and 400 and 100 mg of lopinavir and ritonavir twice daily were 11 and 8, respectively.
[c] Twenty-four-hour and 8-h AUCs at steady state are reported for efavirenz and lopinavir, respectively. The values reported are medians (ranges).
[d] $t_{1/2}$, estimated half-life.

with VPA. Our results suggest that plasma lopinavir concentrations may be higher during VPA coadministration. The GMR (90% CI) of the $AUC_{0\text{-}8}$s after administration of the dose of lopinavir with and without VPA coadministration was 1.38 (0.98, 1.94), and six of the eight subjects achieved higher plasma lopinavir concentrations during VPA coadministration. The lopinavir C_{max}, minimum observed concentration, T_{max}, and half-life were not significantly different during VPA administration ($P > 0.10$).

Eleven of the 12 subjects in the group who received VPA without efavirenz or lopinavir-ritonavir completed the study and were compared to those taking efavirenz or lopinavir-ritonavir. Neither administration of efavirenz nor that of lopinavir-ritonavir appeared to effect VPA concentrations measured just before (C_0) or 8 h after administration of the dose. The differences (90% CIs) in the mean C_0 and 8 h VPA concentrations versus the control concentrations ($n = 11$) were −1.0 (−9.4, 7.4) and −2.1 (−11.1, 6.9) μg/ml for efavirenz ($n = 10$) and −5.0 (−13.2, 3.3) and −6.7 (−17.6, 4.2) μg/ml for lopinavir-r ($n = 11$), respectively. Although 3 of the 11 control subjects received antiretroviral therapy consisting of zalcitabine-lamivudine-indinavir, nelfinavir-nevirapine, or trizivir-amprenavir; when comparing results to those obtained excluding these subjects, inclusion of these subjects did not appear to influence the C_0 ($P = 0.54$ versus $P = 0.49$) or 8-h ($P = 0.44$ versus $P = 0.30$) VPA results.

DISCUSSION

Before beginning a clinical trial to evaluate the use of VPA for HIV-associated cognitive impairment, we needed to determine if VPA would alter the disposition of NNRTIs or PIs and in particular whether VPA would lower the plasma concentrations of these antiretroviral drugs. We chose efavirenz and lopinavir-ritonavir to represent drugs from the NNRTI and PI inhibitor class of antiretrovirals because of their frequent use because part of the requirement for highly active antiretroviral therapy testing for bioequivalence is a comparison of achievable drug concentrations both with and without coadministration of the test drug. One of the Food and Drug Administration definitions of bioequivalence is that the 90% CI of the GMR of the test AUC to the reference AUC lie within a range of 0.8 to 1.25. Efavirenz is an NNRTI whose pharmacokinetic and dynamic properties include a long plasma half-life, a high level of plasma protein binding (99.5 to 99.75%) primarily to albumin, the ability to induce the hepatic metabolism of many drugs metabolized by the CYP enzyme system, and resistance to pharmacokinetic alterations when administered with other drugs (33). As expected on the basis of previous evidence that shows that efavirenz is recalcitrant to altered metabolism, we were able to show that administration of efavirenz alone is bioequivalent to administration with VPA (the GMR [90% CI] of the $AUC_{0\text{-}24}$s was 1.00 [0.85, 1.17]). Although the sampling strategy used may have limited the estimate of the efavirenz C_{max}, the C_{max} reported here is similar to previously reported values (median C_{max} [interquartile range], 2.83 μg/ml [1.82 to 3.71] μg/ml) (9).

With the exception of nelfinavir, a substrate for CYP 2C19, PIs are substrates for CYP 3A4, leading to many potential drug interactions (28). In light of the growing amount of evidence in support of a correlation between plasma PI concentrations and virologic response, avoidance of potential drug interactions, especially those that result in lower achievable plasma PI concentrations, is of increasing importance (1, 5, 13, 14; D. Burger et al., 12th World AIDS Conf., abstr. 42259, 1998). VPA has been shown to be an inhibitor of hepatic metabolism, including the CYP 2C9-dependent metabolism of certain drugs such as phenytoin and phenobarbital (3; S. I. Hurst et al., Int. Soc. Stud. Xenobiotics Proc., abstr. 12, 1997). VPA has also been shown to inhibit the UGT-mediated metabolism of drugs such as zidovudine, lamotrigine, and lorazepam (4, 31, 34, 37). VPA does not inhibit the metabolism of CYP 3A-dependent drugs such as cyclosporine and oral contraceptives, suggesting a lack of influence on CYP 3A-dependent metabolism (6, 17). Being highly bound to albumin, VPA also has the ability to interact with other drugs via protein displacement; however, PIs are thought to be primarily bound to alpha-1-acid glycoprotein, minimizing the potential for protein displacement by VPA (22, 31). Since lopinavir is primarily metabolized by CYP 3A4, the potential for VPA to influence blood lopinavir concentrations was minimal and expected to be one of inhibition, not induction (3; Si et al., Int. Soc. Stud. Xenobiotics Proc.). Given that blood lopinavir concentrations showed a statistically insignificant trend to increase in the presence of VPA, our results further support the potential for VPA to inhibit the metabolism of concomitant medications. Lopinavir concentrations may have been influenced indirectly by ritonavir inhibition. Failure to assay ritonavir concentrations limits the ability to determine if VPA could influence plasma lopinavir concentrations indirectly by influencing the metabolism of ritonavir.

At clinically achievable concentrations, lopinavir-ritonavir, primarily because of the actions of ritonavir, is an inhibitor of CYP 3A4 and to a lesser extent 2C9 whereas efavirenz has primarily been shown to induce CYP-mediated intestinal or hepatic metabolism (28; Kaletra package insert; Abbott Laboratories, North Chicago, Ill.). Ritonavir has also been shown to induce CYP metabolism, including its own, and to induce

UGT (Kaletra package insert). VPA is primarily hepatically metabolized by UGT enzymes and β-oxidation and to a much lesser extent by CYP 2C9 and 2C19; therefore, except for potential UGT induction by ritonavir, neither lopinavir-ritonavir nor efavirenz was expected to influence blood VPA concentrations (28). We were unable to detect a significant influence of either efavirenz or lopinavir-ritonavir on the trough (C_0) or 8-h postdose plasma VPA concentrations. It should be noted that the study was not able to determine VPA bioequivalence or designed to sample plasma VPA concentrations throughout an entire dosing interval. VPA concentrations appear to be on a downward trend in the presence of lopinavir-ritonavir, which could be due to ritonavir inducing UGT. However, our results, taken together with the reported wide therapeutic plasma concentration range of VPA (30 to 100 μg/ml), are reassuring for those HIV-infected individuals currently taking VPA for epilepsy, headache, or mood disorders (22).

In summary, coadministration of VPA with either efavirenz or lopinavir-ritonavir does not result in decreased plasma concentrations of efavirenz or lopinavir. Furthermore, since neither efavirenz nor lopinavir significantly altered the trough or 8-h postdose plasma concentrations of VPA, a clinically significant interaction is doubtful. These results encourage further investigation of VPA for the treatment of HIV-associated cognitive impairment.

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