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Acid Reduction With a Proton Pump Inhibitor Does Not Affect Pharmacokinetics of Lopinavir or Ritonavir in HIV-infected Subjects on Lopinavir/Ritonavir-based Therapy

Edgar T. Overton[1], Jean M. Tschampa[2], Michael Klebert[1], Mark Rodriguez[1], Teresa Spitz[1], GeYoul Kim[1], Kristin Mondy[1], Edward P. Acosta[3]
[1]Washington University School of Medicine, St. Louis, MO, U.S.A.; [2]Abbott, Abbott Park, IL, USA; [3]University of Alabama, Birmingham, AL, U.S.A.
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Abstract

Background: HIV-infected persons often use proton pump inhibitors (e.g., omeprazole) and H2 antagonists (e.g., ranitidine), to relieve GERD and other GI symptoms. These agents decrease the bioavailability of some ART agents. While the effect of acid-reducing agents on Kaletra (LPV/r) has been assessed in healthy volunteers, no formal assessment has been carried out with HIV-infected subjects on stable LPV/r-based therapy. We determined the effect of omeprazole on the pharmacokinetics of LPV/r tablet administered twice daily.

Methods: 15 HIV-infected subjects, aged 18 – 65, with a CD4 count >200c/mL and a plasma HIV viral load <1000 c/mL, on stable HAART including LPV/r 400/100 mg twice daily were eligible for participation. Persons on an acid-reducing agent were excluded from participation into this open-label, pharmacokinetic (PK) trial of orally administered LPV/r given with and without omeprazole. PK studies were completed at two time points: period 1, after reaching steady-state of LPV/r, and period 2, after reaching steady-state for the two drugs (LPV/r and omeprazole 40 mg daily). Pharmacokinetic parameters of LPV and RTV were determined using noncompartmental methods (WinNonlin version 4.0, Pharsight Corp., Mountain View, CA.). Comparison of period 1 vs. period 2 LPV and RTV pharmacokinetic parameters were completed using the paired, nonparametric Wilcoxon signed rank test.

Results: The 15 subjects ranged from 21 – 62 years of age; 8 white, 7 black; 5 female, 10 male. Median CD4 count was 505 cells/mm^3 (range 292 – 1329) with median HIV viral load <50 copies/mL (range <40 – 429). Median LPV and RTV C_{max} values were 9233.9 ng/mL and 759.3 ng/mL, respectively, in period 1 and 11273.50 ng/mL and 849.7 ng/mL respectively, in period 2. Median LPV and RTV C12 values were 4473.4 ng/mL and 180.0 ng/mL, respectively, in period 1 and 5111.2 ng/mL and 185.8 ng/mL respectively, in period 2. Median LPV and RTV AUC_{12} values were 89.1 hr•mg/L and 4.60 hr•mg/L, respectively, in period 1 and 98.5 hr•mg/L and 5.5 hr•mg/L respectively, in period 2. None of these differences were statistically significant (p<0.05).

Conclusions: In this crossover study of LPV/r with and without a proton pump inhibitor, no significant interactions were noted. These PK values are all consistent with previously published LPV/r pharmacokinetic data. Based on these results, co-administration of LPV/r and omeprazole can be given without concerns from a pharmacokinetic perspective.

Introduction

- Highly active antiretroviral therapy (HAART) has altered the paradigm of HIV care.[1]
- Clinicians must be aware of common side effects of antiretroviral therapy and complex drug interactions that may exist between antiretroviral agents and concomitant medications used for other co-morbid diseases.
- Reduced absorption of HIV protease inhibitors through the GI tract (by acid reducing agents) is one factor that may decrease the serum levels of protease inhbitors and thus limit the efficacy of viral suppression.
- Luber, et al., surveyed 200 HIV-infected patients to assess GI side effects of medicines and utilization of acid suppressive therapy since initiating HAART. He found that 77% of subjects had used an acid-suppressing agent since HAART initiation. Additionally, he found that 56% of patients who used an acid-suppressing agent obtained the agent over the counter without the knowledge of their HIV care provider.[2]
- Burger, et al., reported data on nine HIV-infected individuals who were receiving Indinavir in a study and were concomitantly receiving a proton pump inhibitor. Four of the nine patients had reduced plasma concentrations.[3]
- Atazanavir absorption has been shown to exhibit pH dependent solubility *in vitro*. This dependence on an acidic environment raises concerns for absorption with higher stomach pH as seen with the administration of proton pump inhibitors.[4] A study of 48 patients looked at the effects of omeprazole, a proton pump inhibitor, on plasma levels of atazanavir in healthy adults. They found a 76% reduction in the AUC and a 78% reduction in the C_{min} plasma levels of atazanavir when a proton pump inhibitor was co-administered.[4,5]
- Unlike the HIV protease inhibitors previously mentioned, lopinavir is a non-ionizable compound and therefore is not dependent on low gastric pH for optimal absorption. Ritonavir is a weak base with two ionizable sites that dissolve below a pH of 3. Because of their chemical nature, neither of these two compounds is expected to be affected by the coadministration of acid suppressing agents.
- Previous studies in HIV-uninfected persons found that neither proton pump inhibitors nor H2 blockers affected levels of lopinavir or ritonavir.[6]

Objective

- Primary: To compare the PK parameters of Kaletra (lopinavir/r) when taken under two conditions:
  1. Without gastrointrestinal acid suppression of Prilosec (omeprazole)
  2. With Prilosec (omeprazole) acid suppressing therapy
- Secondary: To examine the safety and tolerability of Kaletra (lopinavir/r) combined with Prilosec (omeprazole)

Study Design

Entry Criteria:

- HIV-infected subjects
- Age 18 – 65
- **CD4 > 200 cells/mm^3**
- **VL < 1000 copies/mL**
- Stable HAART including LPV/r 400/100 mg BID
- Not receiving acid reducing therapy

Blood samples collected for PK: Predose,1, 2, 3, 4, 6, 8, 10 and 12 hours post dose.

Methods

This was an open-label, pharmacokinetic (PK) trial of orally administered Kaletra (lopinavir/ritonavir) tablets as part of HAART given with and without omeprazole.

PK studies were completed at two time points

- After reaching steady-state using Kaletra alone
- After reaching steady-state for the two-drug (Kaletra and omeprazole) regimen

First PK Visit (day 1)

- Fasting samples for baseline testing were drawn prior to the Kaletra dose administration. A light meal was given half an hour before the PK dose. Subjects under direct observation were administered a dose of Kaletra 400/100 mg, followed by 12-hour PK sampling.

Days 1 – 7

- Subjects took Prilosec (omeprazole) 40 mg po QD. Subjects continued to take their Kaletra-based HAART regimen. Adherence was monitored.

Second PK Visit (day 8)

- A protocol-specified meal was given half an hour before the PK dose. Subjects were supervised taking their dose of Kaletra 400/100 mg plus omeprazole 40 mg, followed by a 12-hour PK sampling.

Bioanalysis of LPV and RTV

Bioanalysis of collected plasma samples was performed at the Antiviral Pharmacology Laboratory, University of Alabama at Birmingham. LPV and RTV plasma concentrations were quantitatively determined with sensitive and validated reverse-phase high-performance liquid chromatography (HPLC) with UV detection. This methodology has been approved by the ACTG QA/QC committee and undergoes twice yearly external proficiency testing.

Statistical Methods

- A paired nonparametric Wilcoxon signed rank test was used to compare the pharmacokinetic parameters. All tests were two-sided and alpha set to 0.05.
- Pharmacokinetic parameters measured included: Ke, $T_{1/2}$, T_{max}, C_{max}, C_{min}, AUC_t, AUC_{12}, V/F, CL/F.

Baseline Characteristics

- 15 subjects on stable LPV/r containing HAART
  - 10 males, 5 females
  - 8 Caucasian, 7 African American
  - Median age: 38 years (range 21 – 62)
  - Median CD4 count: 505 c/mm^3 (range 292 – 1329)
  - Median BMI: 25.9 kg/m^2 (range 19.5 – 41.8)
  - 14 subjects with baseline HIV VL <400 c/mL
    - 1 subject with VL = 429 c/mL
  - Other components of HAART
    - 11 FTC/3TC
    - 9 TDF
    - 6 AZT
    - 2 ABC
    - 2 DDI

Results

- A total of 15 subjects completed both intensive pharmacokinetic periods. A total of 540 patient plasma samples were analyzed for this study.
- There were no new or unexpected side effects from the medications.

Results (cont.)

- Tables 1 and 2 summarize the pharmacokinetic findings.

Table 1. Lopinavir (LPV) PK Parameters

Period 1	Drug	PID	Ke (1/hr)	$T_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/mL)	T_{last} (hr)	C_{last} (ng/mL)	AUC_T (hr•mg/L)	AUC_{12} (hr•mg/L)	V/F (L)	CL/F (L/hr)
LPV ONLY	LPV	N	14	14	15	15	15	15	15	15	14	14
		Mean	0.112	9.156	3.193	9244.713	12.061	5120.473	81.240	80.899	38.325	4.176
		SD	0.080	5.495	1.766	3324.780	0.125	2518.920	29.969	29.871	16.704	4.264
		Min	0.03	2.22	0.00	2243.20	11.97	1347.70	17.89	17.89	16.98	1.37
		Median	0.09	7.91	3.00	9233.90	12.00	4473.40	89.87	89.06	31.23	2.95
		Max	0.31	21.37	6.00	15429.60	12.42	10692.80	127.34	126.69	66.55	18.01
		CV%	71.5	60.0	55.3	36.0	1.0	49.2	36.9	36.9	43.6	102.1
		GM	0.091	7.634		8498.454	12.061	4498.907	73.896	73.603	35.199	3.196
Period 2	**Drug**	**PID**	**Ke (1/hr)**	**$T_{1/2}$ (hr)**	**T_{max} (hr)**	**C_{max} (ng/mL)**	**T_{last} (hr)**	**C_{last} (ng/mL)**	**AUC_T (hr•mg/L)**	**AUC_{12} (hr•mg/L)**	**V/F (L)**	**CL/F (L/hr)**
LPV+PPI	LPV	N	15	15	15	15	15	15	15	15	15	15
		Mean	0.136	6.850	3.081	11191.420	11.967	5494.333	95.908	95.928	28.722	3.305
		SD	0.076	3.868	1.830	3318.426	0.210	3512.220	33.083	32.993	20.122	1.781
		Min	0.05	2.15	0.00	6990.40	11.50	1080.10	40.96	40.96	11.81	0.85
		Median	0.11	6.41	3.00	11273.50	12.00	5111.20	98.45	98.45	22.21	2.83
		Max	0.32	14.91	8.00	16983.80	12.30	15510.10	157.40	157.40	93.71	7.29
		CV%	56.3	56.5	59.4	29.7	1.8	63.9	34.5	34.4	70.1	53.9
		GM	0.117	5.911		10724.860	11.965	4531.948	90.127	90.185	24.592	2.884

Table 2. Ritonavir (RTV) PK Parameters

Period 1	Drug	PID	Ke (1/hr)	$T_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/mL)	T_{last} (hr)	C_{last} (ng/mL)	AUC_T (hr•mg/L)	AUC_{12} (hr•mg/L)	V/F (L)	CL/F (L/hr)
LPV ONLY	RTV	N	14	14	15	15	15	15	15	15	14	14
		Mean	0.199	3.855	3.341	747.380	11.795	216.807	4.674	4.693	132.189	24.240
		SD	0.066	1.305	1.970	375.889	1.057	177.528	1.998	1.971	104.932	17.562
		Min	0.10	2.01	0.00	181.50	8.00	32.90	1.17	1.17	40.44	9.34
		Median	0.19	3.64	3.08	759.30	12.00	180.00	4.60	4.60	94.24	18.44
		Max	0.34	6.64	6.00	1534.80	12.42	742.90	8.63	8.63	406.74	75.75
		CV%	33.2	33.9	58.9	50.3	9.0	81.9	42.7	42.0	79.4	72.5
		GM	0.189	3.661		642.695	11.739	165.045	4.167	4.193	108.947	20.628
Period	**Drug**	**PID**	**Ke (1/hr)**	**$T_{1/2}$ (hr)**	**T_{max} (hr)**	**C_{max} (ng/mL)**	**T_{last} (hr)**	**C_{last} (ng/mL)**	**AUC_T (hr•mg/L)**	**AUC_{12} (hr•mg/L)**	**V/F (L)**	**CL/F (L/hr)**
LPV+PPI	RTV	N	15	15	15	15	15	15	15	15	15	15
		Mean	0.187	5.034	3.551	892.653	11.967	236.213	5.991	5.992	132.962	16.979
		SD	0.127	2.418	1.881	399.070	0.210	167.740	3.164	3.161	138.878	10.464
		Min	0.08	1.33	0.00	367.10	11.50	30.30	1.67	1.67	21.04	6.22
		Median	0.13	5.15	3.88	849.70	12.00	185.80	5.52	5.52	99.47	15.02
		Max	0.52	9.09	8.00	1833.90	12.30	701.30	14.61	14.65	584.48	47.98
		CV%	67.6	48.0	53.0	44.7	1.8	71.0	52.8	52.8	104.4	61.6
		GM	0.158	4.391		807.450	11.965	180.966	5.300	5.305	93.539	14.765

  - Lopinavir
    - There were no statistically significant differences in the PK parameters of lopinavir before and after the administration of omeprazole.
  - Ritonavir
    - There were no statistically significant differences in the PK parameters of ritonavir before and after the administration of omeprazole
    - The rate of clearance of ritonavir was faster after the administration of omeprazole.
- Figures 1 and 2 visually illustrate the AUC_{12} for both lopinavir and ritonavir, with and without omeprazole.

Figure 1. GMT Mean ± SD LPV Concentrations (n=15)

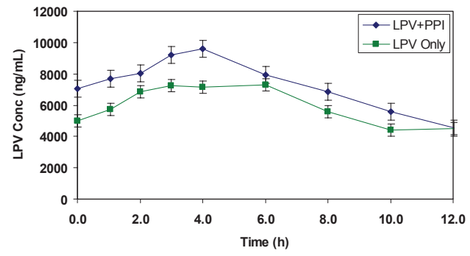
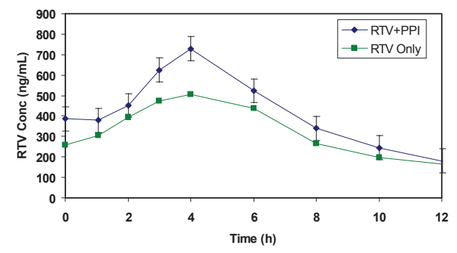


Figure 2. GMT Mean ± SD RTV Concentrations (n=15)



  - Although there was a trend for higher levels for both drugs with co-administration of omeprazole, the differences failed to reach statistical significance.
- The values determined in this study are all consistent with previous LPV/RTV pharmacokinetic data.

Conclusions

- There are no unexpected adverse events with the co-administration of Kaletra tablets and omeprazole.
- Co-administration of omeprazole with Kaletra tablets has no negative effects on the PK parameters of either lopinavir or ritonavir.
- No drug interaction concerns exist for persons taking Kaletra tablets and proton pump inhibitors.

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