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

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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 an 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 >200 cells/mm3 and a plasma HIV viral load <1000 c/mL, in stable HAART including LPV/r 400/100 mg twice daily were eligible for participation. Informed consent was obtained from all subjects. Subjects were excluded from participation into this open-label, pharmacokinetic (PK) trial of orally administered LPV/r given with and without omeprazole. PK studies were conducted 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. Comparison of period 1 vs. period 2 of 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/mm3 (range 292 – 1329) with median HIV viral load <50 copies/mL (range <40 – 429). Median LPV and RTV Cmax values were 9233.9 ng/mL and 759.3 ng/mL, respectively, in period 1 and 11273.9 ng/mL and 849.7 ng/mL, respectively, in period 2. Median LPV and RTV C12 values were 4473.4 ng/mL and 180.6 ng/mL, respectively, in period 1 and 5111.2 ng/mL and 185.6 ng/mL, respectively, in period 2. Median LPV and RTV AUC0 values were 89.1 h*ng/mL and 4.6 h*ng/mL, respectively, in period 1 and 98.5 h*ng/mL and 5.5 h*ng/mL, respectively, in period 2. None of these differences were statistically significant (p>0.05). Conclusions: In this cross-over 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. 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 suppressing agents is one factor that may decrease the serum levels of protease inhibitors and thus limit the efficacy of viral suppression. Lubero et. al. surveyed 250 HIV-infected patients to assess GI side effects of medications 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 continued the agent over the counter without the knowledge of their care provider. The stomach pH is required for the solubility of many drugs in the GI tract. The pH-dependent solubility of LPV is 7.6% at pH 1.2 and 80% at pH 6.8. The pH-dependent solubility of RTV is 0.3% at pH 1.2 and 12% at pH 6.8. Thus, the stomach pH is required for pharmacokinetics and pharmacodynamics of all three drugs.

The effect of omeprazole on the pharmacokinetics of LPV/r tablet administered twice daily is uncertain. We determined the effect of omeprazole on the pharmacokinetics of LPV/r tablet administered twice daily.

Materials & Methods
HIV-infected subjects, aged 18 – 65, with a CD4 count >200 cells/mm3 and a plasma HIV viral load <1000 c/mL, in stable HAART including LPV/r 400/100 mg twice daily were eligible for participation. Informed consent was obtained from all subjects. Subjects were excluded from participation into this open-label, pharmacokinetic (PK) trial of orally administered LPV/r given with and without omeprazole. PK studies were conducted 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. Comparison of period 1 vs. period 2 of pharmacokinetic parameters were completed using the paired, nonparametric Wilcoxon signed rank test.

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Objective
Primary: To compare the PK parameters of Kaletra (lopinavir/ritonavir) with lopinavir/ritonavir given with and without omeprazole.
Secondary: To examine the safety and tolerability of Kaletra (lopinavir/ritonavir) combined with lopinavir (omeprazole).

Study Design

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<thead>
<tr>
<th>Entry Criteria</th>
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<td>HIV-infected subjects</td>
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<td>Age 18 – 65</td>
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<td>CD4 &gt; 200 cells/mm³</td>
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<td>VL &lt; 1000 copies/mL</td>
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<td>Stable HAART including LPV/r 400/100 mg BID</td>
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<td>Not receiving reducing therapy</td>
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<td>Blood samples collected for PK: Predose 1, 2, 3, 4, 6, 8, 10 and 12 hours post dose</td>
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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
- 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 were supervised taking their Kaletra tablets and omeprazole tablets with a sip of water.
- Blood samples for PK were collected at 0 hour (predose), 1, 2, 3, 4, 6, 8, 10, and 12 hours post dose.

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 (RP-HPLC) with UV detection. This methodology has been approved by the ACTG QA/QC committee and undergoes 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: Cmax, Tmax, C0, AUC0-t, AUC0-t, MRTi, MRT, Cmin, Cmax, ↓Cmax, V/F, Q, CL.

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

Conclusions
- There were 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.

References
4. BMS388241 (ralpivirabine) Rebello M, Sykes S, Product Information.