

Drug-Drug Interaction Between Lopinavir/Ritonavir and Rosuvastatin

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Abstract

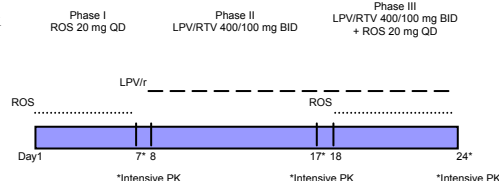
Subjects

Exclusion Criteria:

- Current drug or alcohol abuse
- Active cardiovascular, renal, hematologic, hepatic, neurologic, gastrointestinal, psychiatric, endocrine, or immunologic disease(s)
- Any chronic gastrointestinal conditions that might interfere with drug absorption
- The use of investigational, prescription, or over-the-counter medications within 14 days of study entry with the exception of aspirin, acetaminophen, diphenhydramine, multivitamins, mineral supplements, or hormonal contraceptives
- Pregnancy, the intention to become pregnant, or breastfeeding
- Post-menopausal women requiring hormone replacement therapy

Study Design

Open-label, single-arm, three phase intensive pharmacokinetic (PK) study



Intensive PK Visits:

- On days 7, 17, and 24 subjects underwent intensive 24-, 12-, and 24-hour intensive PK studies, respectively
- Study drug administration was observed following breakfast
- Samples were obtained at the following time points:
 - For ROS quantification on days 7 and 24: 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 20, 24 hours
 - For LPV/r quantification on days 17 and 24: 0, 1, 2, 3, 4, 5, 6, 8, 12 hours

Safety and Tolerability Assessments:

- Clinical adverse effects were assessed using a questionnaire
- Subjects rated adverse effects as mild, moderate, or severe
- Laboratory tests were performed at baseline and on all three intensive PK visits
- Clinical and laboratory adverse events were graded using the 1992 Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Experiences

Lipid Measurements:

- Each subject's fasting total cholesterol, high density lipoprotein (HDL), and triglycerides (TG) were measured at baseline and at the end of Phase I, II, and III of the study. LDL was calculated.

Laboratory Analyses

- LPV and RTV determined using a simultaneous, validated HPLC-UV method (Antiviral Pharmacology Laboratory, Denver, CO)
- ROS determined using a validated HPLC-MS method (Covance Laboratories, Madison, WI)

Data Analyses

- The primary endpoint for this study was ROS and LPV/r AUC_[0,τ] and Cmax bioequivalence when given alone and in combination.
- 18 subjects provided 98% and 84% power for ROS and LPV AUC_[0,τ] and Cmax, respectively, in order that the 90% confidence interval for the geometric least square means ratio (GMR) was contained within the interval of 0.7 to 1.43.
- The geometric least square means were determined for ROS, LPV, and RTV PK parameters, and hypotheses evaluated by examining their 90% confidence intervals. Paired t-tests were done to clarify results.
- A secondary endpoint was a comparison of the percent LDL decrease from Baseline to Phase I to the percent LDL decrease from Phase II to Phase III. Other lipid measures were exploratory. Paired t-tests were used to evaluate these changes.
- SAS version 9.1 was used for data analysis.
- ROS, LPV, and RTV PK were determined by noncompartmental methods using WinNonLin v5.0.1 (Pharsight Corp, Mountain View, CA).

Results

Patients

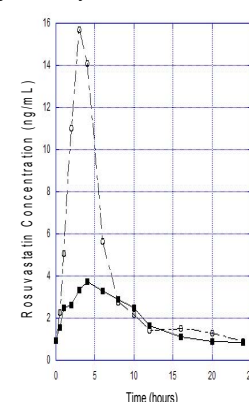
- 20 subjects enrolled, 15 completed all three phases of the study. Of the 5 who were not included in PK analyses, one withdrew consent on day 10 due to personal reasons, one subject discontinued due to neutropenia, one subject was non-adherent with LPV/r, one subject discontinued due to rash, and one subject's ROS samples from the Phase I intensive PK study were lost.
- Among the 15 eligible for PK analyses, 9 were female and 7 were oral contraceptives. 3 subjects were Hispanic, the remaining subjects were Caucasian.
- The median (range) age, weight, height, and body surface area of subjects was 27 years (23-40), 71 kg (54-103), 176 cm (158-196), and 1.8 m² (1.5-2.3), respectively.

Table 1. ROS PK (n=15)

	AUC _[0,τ] (ng*hr/mL)	Cmax (ng/mL)	Tmax (hrs)	C _{min} (ng/mL)	CL (L/hr)	Half-life (hrs)
Phase I*	47.6	4.34	3.9	0.74	420	9.5
Phase III*	98.8	20.2	2.7	0.77	202	8.6
Difference (fold-change) Phase III vs. Phase I	2.08	4.66	0.69	1.04	0.48	0.91
90% CI	1.66-2.4	3.4-4.4	0.47-0.99	0.9-1.2	0.39-0.6	0.64-1.2†
p value**	<0.0001	<0.0001	0.0031	0.6545	<0.0001	0.6078

* Geometric means. ** Based on paired t-test. † No adjustments were made for multiple comparisons

Figure 2. Rosuvastatin Area-Under-the-Concentration-Time Curves in the Absence and Presence of Lopinavir/Ritonavir in 15 HIV Seronegative Healthy Volunteers



ROS alone (black squares; solid line) and ROS+LPV/r (open circles; dashed line)

LPV/r PK

- LPV and RTV AUC_[0,τ] and Cmax were bioequivalent when given alone and with ROS.

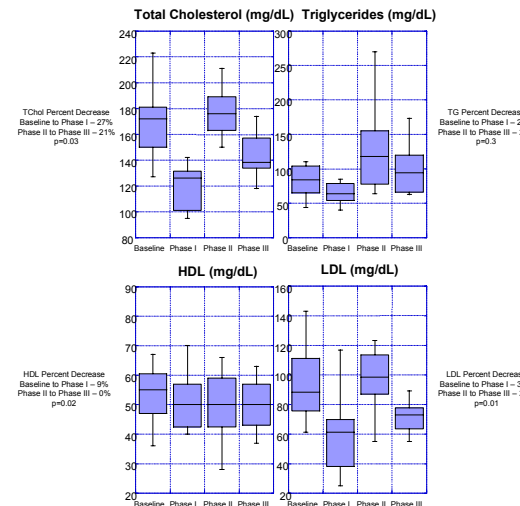
Safety and Tolerability – Clinical Adverse Events

- All clinical adverse events as graded by study subjects were considered mild or moderate in severity.
- The most commonly reported adverse events were nausea/vomiting/abdominal pain and diarrhea reported during LPV/r monotherapy or with the combination.

Safety and Tolerability – Laboratory Abnormalities

- Increases in total bilirubin were the most commonly observed laboratory abnormality, noted during all three phases of the study.
- Four study subjects experienced increases in CPK. A Hispanic male, had a CPK of 3300 U/L (16.9xULN) on the day of the Phase III intensive PK visit. He was not symptomatic and his previous CPK values had been within normal limits.
- One subject had LFTs within 1.1-2.5xULN on the day of the Phase III intensive PK visit.
- One subject, a black female, had an absolute neutrophil count of 600/mm³ during Phase II and was discontinued from study.
- Two male subjects had decreases in hemoglobin (≤ 2 g/dL) during all three phases of the study.

Figure 3. Median (±IQR) fasting total cholesterol, TG, HDL, and LDL at baseline (no drug), Phase I (ROS alone), Phase II (LPV/r alone), and Phase III (ROS+LPV/r)



Conclusions

- ROS AUC and Cmax were unexpectedly increased 2.1 and 4.7-fold, respectively, in the presence of LPV/r.
- Studies are needed to elucidate the mechanism for this interaction.
- LPV and RTV AUC and Cmax were bioequivalent when given alone and with ROS.
- ROS LDL-lowering effects were attenuated with LPV/r despite increased exposures, thus decreasing the dose of ROS with LPV/r may affect the cholesterol-lowering efficacy.
- ROS+LPV/r should be used with caution until the safety, efficacy, and appropriate dosing of this combination have been demonstrated in larger populations.

Acknowledgements

This research was supported by a grant from the Investigators-Sponsored Study Program of Astra Zeneca and M01 RR00051. The authors wish to acknowledge the study participants, the nurses and staff of the University of Colorado Hospital General Clinical Research Center, Dr. Thomas Delahanty, PhD, with the University of Colorado Antiviral Pharmacology Laboratory (director Dr. Courtney V. Fletcher, Pharm.D.) for analyzing the lopinavir and ritonavir concentrations, Dr. Connie Azymya, PhD, with Astra Zeneca for supplying the rosuvastatin concentrations, and Dr. Susan Trieu, Pharm.D., Regional Medical Scientist with Astra Zeneca for her assistance with this project.

Introduction

- Rosuvastatin (ROS) would be a welcome addition to our armamentarium of agents for the treatment of dyslipidemia in patients with HIV because the low density lipoprotein (LDL)-lowering effects of ROS exceed those achieved with atorvastatin, simvastatin, and pravastatin, and less than 10% of a dose of ROS undergoes metabolism by CYP enzymes. (Jones PH, et al. Am J Cardiol 2003;92:152-160, Crestor® prescribing information).
- We hypothesized that ROS and lopinavir/ritonavir (LPV/r) would not interact because ROS is not metabolized by CYP enzymes.
- The primary objective of this study was to determine the bioequivalence of ROS and LPV/r when used alone and in combination.
- Secondary objectives included assessments of safety and tolerability and changes in lipid levels throughout the course of the study.

Methods

Subjects

Inclusion Criteria:

- HIV negative male and female subjects
- 18-60 years
- Within 30% (±) of their ideal body weight and weigh ≥ 50 kg
- Hematologic, metabolic, renal and hepatic function tests all within normal limits, and a creatine phosphokinase (CPK) < 3 times the upper limit of normal (ULN)