Poster #A-1823

42nd Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, California, September 2002

Pharmacokinetics (PK) of Two Adjusted Dose Regimens of Lopinavir/Ritonavir (LPV/r) in Combination with Rifampin (RIF) in Healthy Volunteers

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ABSTRACT

Background: Major PK interactions occur between drugs for tuberculosis (TB) and for HIV, resulting in few therapeutic options for patients coinfected with TB and HIV. Because combining LPV/r 400/100 mg BID with rifampin (RIF) leads to subtherapeutic LPV exposure (and therefore is contraindicated), we explored the PK of adjusted doses of LPV/r with RIF. **Methods:** 32 Healthy subjects (subj.) participated in a 2-group (gr.), 2-period longitudinal dose finding study. All subj. took LPV/r 400/100 mg BID from day 1 to 15. On days 11 – 15 RIF 600 mg QD was added. From day 16 – 24, subj. were randomised to take either LPV/r 800/200 mg BID (gr. A) or LPV/r 400/400 mg BID (gr. B) together with RIF. All drugs were taken with food. Appropriate PK were assessed on days 10 and 24. **Results:** 12 Out of 32 subj. withdrew from the study. 3 Subj. withdrew before randomisation, 3 in gr. A (liver enzyme elevations, n=2; vomiting, n=1), 6 in gr. B (liver enzyme elevations, n=5; total discomfort, n=1). PK data of 1 subj. (gr. A) were not evaluable due to vomiting of study drugs on day 24. Geometric mean (GM) ratios + 90% CI of day 24 vs. day 10 for LPV AUC(0-12), C_{max} and C_{min} were as follows; in gr. A (n=10): 0.84 (0.64-1.10), 1.02 (0.85-1.23) and 0.43 (0.19-0.96); in gr. B (n=9): 0.98 (0.81-1.17), 0.93 (0.81-1.07) and 1.03 (0.68-1.56). GM + 90% CI for LPV C_{min} in gr. A were 6.2 (5.2-7.4) and 2.7 (1.1-6.6) mg/L on day 10 and 24, respectively (p=0.09). On day 24, 3 (gr. A) vs. 1 (gr. B) subj. had a LPV C_{min} <2 mg/L; all C_{min} were >2 mg/L on day 10. Other observed changes in LPV PK parameters were not significant (p>0.27). Ritonavir $AUC_{(0-12)}$ on day 24 in gr. B exceeded that in gr. A (GM 37.9 vs. 8.9 h*mg/L). RIF GM C_{max} (13.5 mg/L) was comparable with literature data. **Conclusion:** Increased doses of LPV/r in conjunction with therapeutic drug monitoring may allow concurrent use of rifampin.

INTRODUCTION

- Kaletra® (Lopinavir/ritonavir or LPV/r) is an HIV-protease inhibitor approved worldwide for treatment of HIV in combination with other antiretroviral agents.
- Adult clinical dose of LPV/r is 400/100 mg BID.
- Both LPV and ritonavir (RTV) are primarily metabolized by CYP3A.
- Rifampin is an antimicrobial agent of the rifamycin group approved for the treatment of tuberculosis.
- Adult clinical dose of rifampin is 600 mg QD (for body weight >50 kg).
- At clinical concentrations, rifampin induces CYP3A-mediated metabolism.

BACKGROUND

- Co-infection with tuberculosis (TB) is frequently observed in HIV patients in African and Asian countries.[1,2]
- Major PK interactions occur between drugs for TB and for HIV, resulting in few therapeutic options for patients coinfected with TB and HIV.
- Combining LPV/r 400/100 mg BID with RIF leads to subtherapeutic LPV exposure (LPV C_{min} and AUC decreased by 99% and 75%, respectively); therefore these two agents should not be coadministered at standard doses.[3]
- PK of adjusted doses of LPV/r with RIF needs research.

1. Msamanga GI, Fawzi WW. The double burden of HIV infection and tuberculosis in sub-Saharan Africa. *NEJM*,1997;337(12):849-51.
2. Schluger NW. Issues in the treatment of active tuberculosis in human immunodeficiency virus-infected patients. *Clinical Infectious Diseases*, 1999;28:130-5.
3. Bertz R, Hsu A, Lam W, et al. Pharmacokinetic interactions between Kaletra (lopinavir/ritonavir or ABT-378/r) and other non-HIV drugs. Fifth International Congress on Drug Therapy in HIV Infection, Glasgow, UK, 22-26 October 2000. Poster 438.

OBJECTIVES

- To evaluate the PK of two LPV/r BID regimens when co-administered with rifampin and to compare the PK of each of these regimens to those of LPV/r 400/100 mg BID in the absence of rifampin.
- To evaluate the safety of each of the combinations of LPV/r and rifampin multiple-dose regimens.

STUDY DESIGN

- Multiple-dose, open-label, single-center, two arm sequential study.
- Healthy male and female subjects (N=32) were enrolled.

	Timescale (Days)				
	1-10*	**11-15**	**16**	**17**	**18-24***
Arm 1 (n=16)	LPV/r BID 400/100 mg	LPV/r BID 400/100 mg + RIF QD	LPV/r BID 533/133 mg + RIF QD	LPV/r BID 667/167 mg + RIF QD	LPV/r BID 800/200 mg + RIF QD
Arm 2 (n=16)	LPV/r BID 400/100 mg	LPV/r BID 400/100 mg + RIF QD	LPV/r BID 400/200 mg + RIF QD	LPV/r BID 400/300 mg + RIF QD	LPV/r BID 400/400 mg + RIF QD

LPV/r = lopinavir/ritonavir
RIF = rifampin 600 mg
*On Days 10 and 24, full 12-hour pharmacokinetic curves were recorded.

- 20 subjects completed; 12 subjects discontinued due to adverse events including 7 for liver enzyme elevations, 3 for a complex of events (abdominal pain, vomiting and diarrhea), 1 for hyperbilirubinemia and 1 for hyperlipidemia. An additional subject vomited after taking study medication on Day 24 and was not included in the PK analysis.

METHODS

- Plasma samples were collected pre-dose and at 2, 4, 6, 8, 10 and 12 hours post dose, on Study Days 10 and 24.
- Additional samples for RIF were drawn at 1 and 3 hours post dose, on Study Day 24.
- Additional pre-dose (trough) plasma samples were collected on Study Days 1, 3, 7, 13, 16, 18, 20 and 22.
- RIF, LPV and RTV concentrations measured by HPLC.
  - RIF limit of quantitation (LOQ) = 0.5 mg/L
  - LPV LOQ = 0.04 mg/L
  - RTV LOQ = 0.04 mg/L
- Noncompartmental methods were used to calculate PK parameters.
- Effect of RIF on LPV/r was assessed using a paired t-test on the log-transformed PK data.
- 90% confidence intervals for the bioavailability of LPV and RTV for each of the combination regimens relative to LPV/r alone were obtained for log-transformed C_{max}, C_{min}, C_0 and AUC_{0-12}.

Table 1. Demographics

	Arm 1 (Escalation to LPV/r 800/200 mg BID + RIF)	Arm 2 (Escalation to LPV/r 400/400 mg BID + RIF)
Subjects used in PK	N=10*	N=9*
Age (yrs)	37 (22-70)	36 (25-47)
Weight (kg)	71 (62-77)	75 (61-85)
Height (cm)	170 (161-185)	180 (158-190)
Gender	9 Caucasian, 1 Black	9 Caucasian
Race	4 Male, 6 Female	7 Male, 2 Female

*Subjects used in the PK evaluation of LPV/r and RIF.
Note: Age, weight and height are presented as mean(range).

RESULTS

Figure 1. Lopinavir Trough (Mean ± SD) Concentration-Study Day Profiles

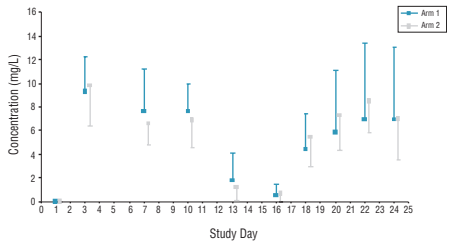

Figure 2. Mean (SD) Lopinavir Concentration-Time Profiles (Arm 1)

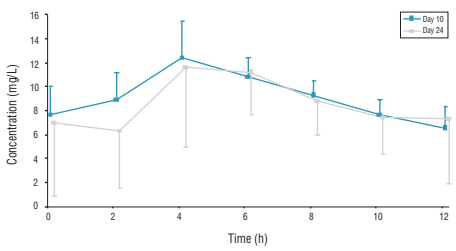

Figure 3. Summary of Individual Lopinavir C_{min} Values (Arm 1)

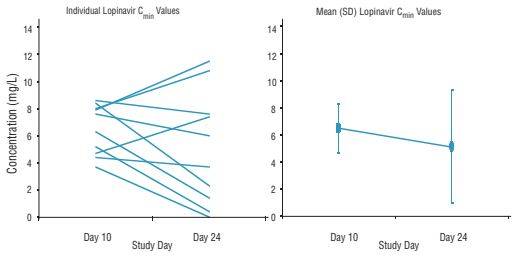

Table 2. Lopinavir Pharmacokinetic Parameter Estimates (Arm 1)

Parameter	Day 10 (N=10)	Day 24 (N=10)
T_{max} (h)	4.6 ± 0.9	5.4 ± 2.5
C_{max} (mg/L)	12.9 ± 2.5	13.8 ± 4.9
C_{min} (mg/L)	6.5 ± 1.8	5.1 ± 4.2
C_0 (mg/L)	7.6 ± 2.4	7.0 ± 6.1
AUC_{0-12} (mg•h/L)	111.8 ± 19.0	104.5 ± 46.9

Pharmacokinetic parameter estimates presented as mean ± SD.
*Statistically significantly different from LPV alone (p<0.05).

Table 3. Bioavailability of LPV/r 800/200 mg BID + RIF Relative to LPV/r 400/100 mg BID Alone (Arm 1)

	Study Day		Relative Bioavailability	
Parameter	Test	Reference	Point Estimate*	90% CI
C_{max}	24	10	1.02	0.85-1.23
C_{min}	24	10	0.43	0.19-0.96
C_0	24	10	0.46	0.19-1.10
AUC_{0-12}	24	10	0.84	0.64-1.10

*Ratio of geometric means.

RESULTS

Figure 4. Mean (SD) Lopinavir Concentration-Time Profiles (Arm 2)

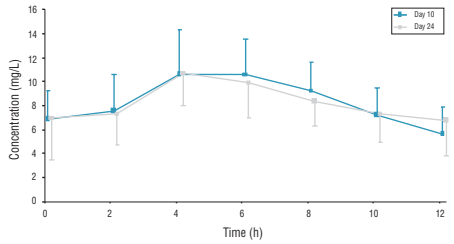

Figure 5. Summary of Individual Lopinavir C_{min} Values (Arm 2)

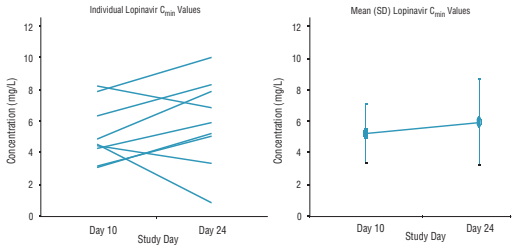

Table 4. Lopinavir Pharmacokinetic Parameter Estimates (Arm 2)

Parameter	Day 10 (N=9)	Day 24 (N=9)
T_{max} (h)	4.5 ± 1.3	5.1 ± 1.0
C_{max} (mg/L)	12.3 ± 3.2	11.5 ± 3.1
C_{min} (mg/L)	5.2 ± 1.9	5.9 ± 2.7
C_0 (mg/L)	6.9 ± 2.3	7.0 ± 3.5
AUC_{0-12} (mg•h/L)	102.9 ± 26.1	100.7 ± 26.8

Pharmacokinetic parameter estimates presented as mean ± SD.
*Statistically significantly different from LPV alone (p<0.05).

Table 5. Bioavailability of LPV/r 400/400 mg BID + RIF Relative to LPV/r 400/100 mg BID Alone (Arm 2)

	Study Day		Relative Bioavailability	
Parameter	Test	Reference	Point Estimate*	90% CI
C_{max}	24	10	0.93	0.81-1.07
C_{min}	24	10	1.03	0.68-1.56
C_0	24	10	0.89	0.56-1.40
AUC_{0-12}	24	10	0.98	0.81-1.17

*Ratio of geometric means.

Table 6. Ritonavir Pharmacokinetic Parameter Estimates (Arm 1)

Parameter	Day 10 (N=10)	Day 24 (N=10)
T_{max} (h)	4.6 ± 0.9	5.2 ± 2.5
C_{max} (mg/L)	1.37 ± 0.73	2.50 ± 1.37*
C_{min} (mg/L)	0.19 ± 0.10	0.24 ± 0.32
C_0 (mg/L)	0.28 ± 0.15	0.47 ± 0.58
AUC_{0-12} (mg•h/L)	6.64 ± 2.25	10.68 ± 5.83

Pharmacokinetic parameter estimates presented as mean ± SD.
*Statistically significantly different from Day 10 (p<0.05).

Table 7. Ritonavir Pharmacokinetic Parameter Estimates (Arm 2)

Parameter	Day 10 (N=9)	Day 24 (N=9)
T_{max} (h)	4.5 ± 1.3	4.5 ± 0.9
C_{max} (mg/L)	1.16 ± 0.60	9.63 ± 4.86*
C_{min} (mg/L)	0.17 ± 0.05	0.96 ± 0.57*
C_0 (mg/L)	0.24 ± 0.09	1.39 ± 0.97*
AUC_{0-12} (mg•h/L)	5.62 ± 1.91	41.45 ± 16.83*

Pharmacokinetic parameter estimates presented as mean ± SD.
*Statistically significantly different from Day 10 (p<0.05).

Figure 6. Mean (SD) Rifampin Concentration-Time Profiles

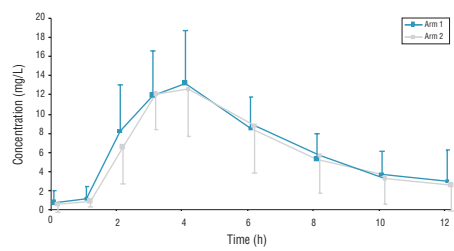

Table 8. Rifampin Pharmacokinetic Parameter Estimates (Day 24)

Parameter	Arm 1 (N=10)	Arm 2 (N=9)
T_{max} (h)	3.4 ± 0.7	3.6 ± 1.2
C_{max} (mg/L)	14.0 ± 5.9	15.0 ± 3.8
C_{min} (mg/L)	0.62 ± 0.93	0.41 ± 0.68
C_0 (mg/L)	0.74 ± 1.22	0.50 ± 0.84
AUC_{0-12} (mg•h/L)	79.18 ± 33.84	76.29 ± 31.87

Pharmacokinetic parameter estimates presented as mean ± SD.

RESULTS

Table 9. Most Commonly Reported Adverse Events (>50% of Subjects)

	Overall Study Days 1-24 (n=32)	Arm 1 Study Days 16-24 (n=14)	Arm 2 Study Days 16-24 (n=15)
Headache	21 (66%)	7 (50%)	5 (33%)
Nausea	21 (66%)	8 (57%)	6 (40%)
Diarrhea	19 (59%)	3 (21%)	4 (27%)
Fatigue	18 (56%)	5 (36%)	5 (33%)
Abdominal pain/cramps	17 (53%)	3 (21%)	3 (20%)
Urine discoloration	29 (91%)	–	–

Laboratory Abnormalities

During the study, 6 subjects (2 in Arm 1, 4 in Arm 2) had Grade 2 ALAT/SGPT elevations (>2.6 x upper limit of normal, ULN) and 3 subjects (1 in Arm 1, 2 in Arm 2) had Grade 3 elevations (>5.1 x ULN). Five of these subjects experienced concurrent Grade 2 ASAT/SGOT elevations (>2.6 x ULN). Seven of the 9 subjects with Grade 2/3 ALAT/SGPT elevations were prematurely discontinued from the study (2 in Arm 1, 5 in Arm 2). The other 2 subjects had initial liver enzyme elevations that occurred on or after Study Day 24.

All Grade 2/3 ALAT and ASAT elevations had onset after the initiation of RIF, none of which were associated with Grade 2+ elevations in total bilirubin or alkaline phosphatase. After study medication discontinuation, all such elevations declined below Grade 2 toxicity, with only 2 remaining above the ULN at the final study evaluation.

One subject was prematurely discontinued from the study for Grade 2 total bilirubin elevations (>31 µmol/L) consisting predominantly of indirect bilirubin. However, this subject did not have concurrent Grade 2+ ALAT, ASAT or alkaline phosphatase elevations. One additional subject was prematurely discontinued from the study for Grade 3 cholesterol (>7.77 mmol/L) and triglyceride (>8.48 mmol/L) elevations, both of which subsequently declined below Grade 3 following study medication discontinuation.

DISCUSSION & CONCLUSIONS

Pharmacokinetics

- The combination of LPV and RTV, when coadministered with RIF (600 mg QD) as either LPV/r 800/200 mg BID or 400/400 mg BID, both result in substantially higher LPV concentrations as compared to historical data with LPV/r 400/100 mg BID coadministered with RIF.
- The LPV/r regimen of 400/400 mg BID with RIF produced comparable pharmacokinetic results relative to LPV/r 400/100 mg BID without RIF.
- The LPV/r regimen of 800/200 mg BID with RIF resulted in substantial pharmacokinetic variability, particularly in LPV C_{min}, providing a greater likelihood of LPV concentrations lower than those observed with the clinical dose of 400/100 mg BID.
- Therapeutic Drug Monitoring (TDM) may prove useful in clinical practice for ensuring adequate LPV exposure during RIF coadministration.
- RTV concentrations increased from Study Day 10 to 24 for both LPV/r regimens, due to the increase in RTV dosing from 100 mg BID on Study Day 10 to 200 mg BID (Arm 1) or 400 mg BID (Arm 2) by Study Day 24. RTV AUC was increased by 1.4- and 7-fold after LPV/r 800/200 mg BID and 400/400 mg BID, respectively.
- RIF exposure was comparable between Arm 1 and Arm 2, and RIF concentrations observed in this study are comparable to previously reported data.

Safety

- All treatments given in this study resulted in numerous adverse events; however most (87%) were considered to be mild by the investigator.
- The frequency and character of adverse events was similar between the two LPV/r dosing arms.
- A number of subjects prematurely discontinued the study, owing to elevations in liver function tests with onset after initiation of LPV/r + RIF combination therapy, with a greater number of discontinuations occurring in the LPV/r 400/400 mg BID + RIF arm.
- The study design does not allow for an assessment of whether the frequency or magnitude of liver function test elevations seen with LPV/r + RIF combination therapy in this study is higher than would be seen when dosing RIF alone in healthy volunteers.
- Based on the toxicity profile observed when increased dosing regimens of LPV/r are used with RIF, treatment with these agents in combination should be approached cautiously with close monitoring of liver function tests.

ACKNOWLEDGMENTS

The authors would like to thank the following individuals:

- Laboratory technicians of the Department of Clinical Pharmacy UMC St Radboud, Nijmegen, The Netherlands.
- D. Voncken and supportive personnel at Farma Research BV, Nijmegen, The Netherlands.
- A. Bergshoeff, J. Droste, R. Rosmalen and M. Schoots van de Siepkamp.