TuPeB4565

XIV International AIDS Conference, Barcelona, July 2002

Assessment of the Effect of Nevirapine on the Pharmacokinetics of Lopinavir/ritonavir (Kaletra®) after Multiple Dosing in HIV-Infected Adults

R. Bertz, C. Foit, D. Burt, K. Grebner, T. Marsh, B. Bernstein, S. Brun, Y-L. Chiu, M. King, A. Hsu, G.R. Granneman, E. Sun
Abbott Laboratories, Abbott Park, IL

ABSTRACT

Background: Lopinavir/ritonavir (LPV/r) is an HIV protease inhibitor (PI) metabolized by CYP3A, with mean protein binding-corrected inhibitory quotient (IQ=C_{trough}/IC_{50}) >75 for wild type HIV at 400/100 mg (3 capsules) BID. The nonnucleoside reverse transcriptase inhibitor nevirapine (NVP) is a CYP3A inducer, and has been shown to reduce LPV concentrations during coadministration with LPV/r in pediatric HIV-infected subjects (ages 6 mo-12 yr). Thus, the effect of NVP on LPV pharmacokinetics (PK) in HIV-infected adults has been assessed.

Methods: A subset of HIV-infected adults with previous PI treatment (n=24), receiving LPV/r 400/100 mg BID + NVP 200 mg BID + nucleoside analogs (NRTIs) in clinical trials, participated in the PK substudy. Steady-state plasma concentrations of LPV/r were obtained over a 12 h dosing interval; concentrations were measured by LC/MS/MS. PK parameters were compared using ANOVA to those obtained in a previous study in antiretroviral naïve HIV-infected adults receiving LPV/r 400/100 mg BID + NRTIs (n=19).

Results: Coadministration of LPV/r with NVP resulted in a decrease in both LPV and ritonavir concentrations. The mean LPV AUC was 27% lower ($p<0.05$) and C_{min} was 51% lower ($p<0.01$); mean C_{max} was 14% lower ($p>0.10$). Results were consistent with those observed previously in pediatric subjects.

Conclusions: As previously noted in pediatric subjects, coadministration of NVP and LPV/r in adults results in a modest reduction in AUC and a moderate reduction in the C_{min} of LPV. A dose increase of LPV/r to 533/133 mg (4 capsules) BID should be considered during concurrent NVP use, where reduced susceptibility to LPV is clinically suspected.

INTRODUCTION

- Kaletra® (Lopinavir/ritonavir or LPV/r) is an HIV-protease inhibitor (PI) approved for treatment of HIV in combination with other antiretrovirals.
- Clinical adult dose of LPV/r is 400/100 mg (3 capsules) BID.
- At clinical concentrations, LPV/r inhibits CYP3A-mediated metabolism and is also a metabolic inducer; LPV and ritonavir (RTV) are both substrates for CYP3A.
- The LPV mean protein binding-corrected inhibitory quotient (IQ = C_{trough}/IC_{50}) is >75 for *wild-type* HIV.
- Viramune® (nevirapine or NVP) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) approved for treatment of HIV in combination with other antiretrovirals.
- NVP is an enzyme inducer of CYP-mediated metabolism and is metabolized by CYP2B6 and CYP3A.

BACKGROUND

- At clinical concentrations, NVP was shown to reduce LPV concentrations during coadministration with LPV/r in pediatric HIV-infected subjects.[1]
  - PI and/or nucleoside reverse transcriptase inhibitors (NRTI)-experienced pediatric HIV-infected subjects (ages 6 months to 12 years) received LPV/r 230/57.5 mg/m² or 300/75 mg/m² and NVP; pharmacokinetic (PK) parameters compared to PI-naïve children receiving LPV/r without NVP.
  - Steady-state PK samples were collected over a 12-hour dosing interval.
- In a previous study in healthy adult subjects, concurrent administration of NVP did not appear to significantly affect the steady-state PK parameters of LPV.[2]
  - LPV C_{max}, C_{min} and AUC central values for the combination regimen differed by <5% from those of the LPV/r alone regimen.
  - The 90% confidence intervals were broad, probably due to the parallel group design and small sample size due to study discontinuation.
  - NVP concentrations were not significantly affected by LPV/r coadministration.

Table 1. The Effect of Coadministration of NVP on LPV Point Estimates and 90% Confidence Intervals in Pediatric HIV-Infected Subjects

	C_{max} (µg/mL)	C_{min} (µg/mL)	AUC_{12} (µg•h/mL)
LPV/r 230/57.5 mg/m² BID with relative to without NVP	0.770 (0.566-1.049)	0.457 (0.247-0.846)	0.675 (0.481-0.948)
LPV/r 300/75 mg/m² BID with relative to without NVP	0.862 (0.639-1.164)	0.448 (0.246-0.815)	0.782 (0.562-1.087)

OBJECTIVE

- To assess at steady-state the effect of NVP on the pharmacokinetics (PK) of LPV/r 400/100 mg BID in HIV-infected adults.

DISCUSSION

- Coadministration of LPV/r with NVP resulted in statistically significant lower LPV AUC and C_{min} in HIV-infected adult patients when compared to historical controls receiving LPV/r and NRTIs.
- A reduction in LPV AUC (27%), C_{trough} (46%) and C_{min} (51%) was observed.
- The decreases in LPV and RTV concentrations during NVP coadministration were comparable to those observed previously in pediatric HIV-infected patients where LPV C_{min} and AUC were decreased by 55% and 22%, respectively.
- The clinical significance of the PK interaction between NVP and LPV/r has not been definitively established; however, LPV/r has been coadministered with NVP at doses of 400/100 mg (N=36) and 400/200 mg BID (N=34) in a Phase II study of single PI-experienced, NNRTI-naïve HIV-infected subjects.
  - Sustained viral suppression (<400 copies/mL) was demonstrated in 83% by on-treatment (OT), 53% by intent-to-treat (ITT) analyses of HIV-infected single PI-experienced subjects receiving LPV/r 400/100 mg BID with NVP and NRTIs after 144 weeks of therapy.[4]
  - A similar proportion of subjects receiving LPV/r 400/200 mg BID had viral loads <400 copies/mL (86% OT, 56% ITT), despite LPV concentrations approximately 50% higher than those produced by LPV/r 400/100 mg BID with NVP.[4,5]
  - These observations suggest that the reduction in LPV concentrations at LPV/r 400/100 mg BID due to NVP coadministration is not associated with markedly decreased response in single PI-experienced patients.[4,5]
- LPV/r dose may need to be increased when coadministered with NVP in treatment-experienced patients in whom reduction in LPV susceptibility is suspected by treatment history or laboratory evidence.
- Increasing the dose of LPV/r to 533/133 mg BID (4 capsules) has been shown to compensate for the similar decrease in plasma concentrations of LPV produced by efavirenz, another inducing NNRTI,[6] suggesting that increasing LPV/r to 533/133 mg BID may be an option when LPV/r and NVP are coadministered.

CONCLUSIONS

- As previously noted in pediatric subjects, coadministration of LPV/r 400/100 mg BID and NVP 200 mg BID in HIV-infected adult subjects results in a reduction in LPV AUC and C_{min}.
- A dose increase of LPV/r to 533/133 mg (4 capsules) BID should be considered during concurrent NVP use, where reduced susceptibility to LPV is clinically suspected.

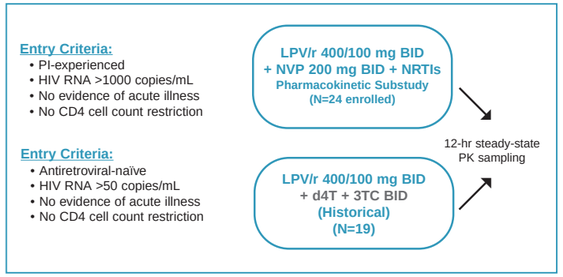
REFERENCES

1. Hsu A, et al., Poster #440, 5th International Congress on Drug Therapy in HIV Infection, Glasgow, 2000.
2. Lal R, et al., Evaluation of the pharmacokinetics (PK) of the concurrent administration of ABT-378/ritonavir (ABT-378/r) and nevirapine (NVP), 7th European Conference on Clinical Aspect and Treatment of HIV Infection, Oct 1999.
3. Bertz R, et al., Paper #126, 9th Conference on Retroviruses and Opportunistic Infections, Seattle, 2002.
4. Hicks C, et al., Poster #220, 8th European Conference on Clinical Aspects and Treatment of HIV-Infection, Athens 2001.
5. Benson, CA, et al., Safety and antiviral activity at 48 weeks of lopinavir/ritonavir plus nevirapine and 2 nucleoside reverse-transcriptase inhibitors in human immunodeficiency virus type 1-infected protease inhibitor-experienced patients, *Journal of Infectious Diseases*, 2002;185:599-607.
6. Bertz R, et al., Abstract #424, 40th ICAAC, American Society for Microbiology, Toronto, 2000.

STUDY DESIGN

- As part of a PK substudy, LPV/r plasma concentration data from two Phase II/III studies were obtained in PI-experienced, HIV-infected adults receiving LPV/r 400/100 mg BID with NVP and NRTIs.
  - 24 subjects were enrolled in PK substudy
  - 22 subjects had sufficient data for the analysis; one subject had incomplete sampling and one subject missed the previous evening's dose
- Historical data presented from a Phase II study were obtained in antiretroviral-naïve, HIV-infected adults receiving LPV/r 400/100 mg BID with the NRTIs, stavudine (d4T) and lamivudine (3TC).[3]

Figure 1. Study Schematic



METHODS

- Steady-state plasma samples were collected pre-dose and at 2, 4, 6, 8, 10 and 12 hours post dose.
- LPV and RTV concentrations were measured by LC/MS/MS.
  - LPV lower limit of quantitation (LOQ) = 5.0 ng/mL
  - RTV LOQ = 1.0 ng/mL
- Noncompartmental methods were used to calculate PK parameters: C_{max}, T_{max}, C_{min} (minimum concentration within a dosing interval), C_{trough} (morning pre-dose concentration) and AUC_{12} (using linear trapezoidal rule).
- PK parameters were compared using two-sample student's t-test to those obtained in a previous study in which antiretroviral-naïve HIV-infected adults received LPV/r 400/100 mg BID with the NRTIs, d4T and 3TC.
- Initial ANCOVA model included covariates for gender, race, age and weight; none were included in the final model.
- Bioequivalence assessments were carried out using the two one-sided test procedure *via* 90% confidence intervals on the ratio of untransformed means.

RESULTS

Table 2. Demographics

	LPV/r + NVP	LPV/r (Historical)
N	22*	19
Age (yrs)	38 (29-55)	35 (22-54)
Weight (kg)	72 (50-96)	75 (46-131)
Height (cm)	172 (153-183)	172 (152-192)
Gender	16 Males, 6 Females	13 Males, 6 Females
Race	17 Caucasian, 5 Black	10 Caucasian, 9 Black
Hepatitis B/C Infected	4 Subjects	1 Subject

* 24 subjects were enrolled; 22 subjects were included in the analysis.

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

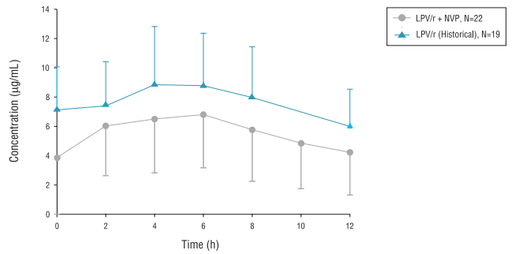


Table 3. Lopinavir Pharmacokinetic Parameter Estimates (Mean ± SD)

	LPV/r 400/100 mg BID + NVP 200 mg BID (N=22)	LPV/r 400/100 mg BID (Historical) (N=19)
C_{max} (µg/mL)	7.95 ± 3.58	9.81 ± 3.66
T_{max} (h)+	5.3 ± 3.0	4.4 ± 2.4
C_{min} (µg/mL)	2.71 ± 2.43*	5.51 ± 2.68
C_{trough} (µg/mL)	3.87 ± 3.81*	7.13 ± 2.93
AUC_{12} (µg•h/mL)	67.8 ± 37.1*	92.6 ± 36.7

* Statistically significantly different from LPV/r (Historical), p<0.05.
+ Parameter not tested statistically.

Table 4. Bioavailability of LPV with NVP Coadministration Relative to LPV/r

			Relative Bioavailability	
Test	Reference	Parameter	Point Estimate*	90% Confidence Interval
LPV/r + NVP	LPV/r (Historical)	C_{max}	0.811	0.619 – 1.051
		C_{min}	0.486	0.277 – 0.742
		C_{trough}	0.543	0.327 – 0.814
		AUC_{12}	0.733	0.534 – 0.982

* Ratio of geometric means.

Figure 3. Ritonavir Mean (SD) Concentration-Time Profiles

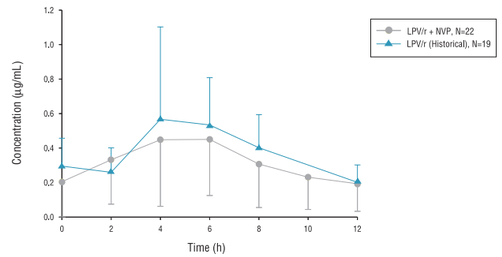


Table 5. Ritonavir Pharmacokinetic Parameter Estimates (Mean ± SD)

	LPV/r 400/100 mg BID + NVP 200 mg BID (N=22)	LPV/r 400/100 mg BID (Historical) (N=19)
C_{max} (µg/mL)	0.587 ± 0.379	0.683 ± 0.504
T_{max} (h)+	5.3 ± 2.7	4.3 ± 2.2
C_{min} (µg/mL)	0.111 ± 0.098*	0.174 ± 0.084
C_{trough} (µg/mL)	0.205 ± 0.213	0.295 ± 0.162
AUC_{12} (µg•h/mL)	3.93 ± 2.70	4.59 ± 2.37

* Statistically significantly different from LPV/r (Historical), p<0.05.
+ Parameter not tested statistically.

Table 6. Bioavailability of RTV with NVP Coadministration Relative to LPV/r

			Relative Bioavailability	
Test	Reference	Parameter	Point Estimate*	90% Confidence Interval
LPV/r + NVP	LPV/r (Historical)	C_{max}	0.860	0.532 – 1.365
		C_{min}	0.621	0.382 – 0.935
		C_{trough}	0.693	0.395 – 1.123
		AUC_{12}	0.857	0.577 – 1.255

* Ratio of geometric means.