



Amprenavir (APV) and Ritonavir (RTV): Intraindividual comparison of different doses and influence of concomitant NNRTI on steady state pharmacokinetics in HIV-infected patients.



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Introduction

Amprenavir (APV) and ritonavir (RTV) are substrates and inhibitors of CYP3A4. RTV is used to increase plasma concentrations of different other protease inhibitors such as indinavir and saquinavir and may also reduce the metabolism rate of APV via CYP3A4. It has been shown that low dose RTV markedly increases APV plasma concentrations.

The addition of the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz (EFV) leads to a significant decrease in plasma levels of APV.

The impact of nevirapine (NVP) on APV plasma level has not been assessed so far.

In this study we investigated the pharmacokinetics of APV in combination with RTV with or without concomitant use of EFV or NVP in patients on a salvage therapy regimen.

Material and Methods

- The steady-state pharmacokinetic of APV and RTV was analysed in 17 HIV-infected patients.
- Serial blood samples over a period of 8 h. The first sample was obtained 12 h after the evening dose of the preceding day and directly before the next dose.

PK Measurement

Blood samples were centrifuged at 3000 rotations/min for 15 min, the serum was extracted and centrifuged at 5000 rotations/min for 15 min.

The plasma levels of the protease inhibitors were determined by liquid chromatography/ mass spectrometry (LC-MS). 100 µl of serum were diluted with 200 µl of 0.1 M ammonia acetate buffer containing 5 % of acetonitril. Following addition of the internal standard N-ethyl-diazepam (Biorad, Munich) the samples were mixed and centrifuged. 100 µl were injected into the LC-system (Merck-Hitachi, Darmstadt). Following on-line extraction employing a column switching technique with an ADS (activated diol silica)-RP 4 column (Merck, Darmstadt) the samples were introduced into a tandem mass spectrometer (API 365, Perkin-Elmer, SCIEX, Toronto) through an APCI (atmospheric pressure chemical ionisation) source. The fragments of the protease inhibitors and the internal standard were detected simultaneously.

Results

- 17 pts. were included, 16 were male
- Median age was 42 years (Range 31-64)
- CDC/ WHO Stage: 5/17 B3, 1 B2, 11/17 C3.

Treatment Details

- All 17 pts. had been treated with APV450 mg BID and RTV 200 mg BID for a median of 5 weeks (range 4-7), all patients received ≥ 2 NNRTI.
- 10/17 pts. received additional EFV 600 mg QD
- 2/17 NVP 200 mg QD
- 5/17 no concomitant NNRTI

Pharmacokinetic Parameters

The pharmacokinetic parameters of APV for all pts. (n=17) at the doses of 450/200 mg APV/RTV BID are listed in **Table 1** and **Fig.1**. The C_{min} , C_{max} and AUC of APV were high and stable in all patients regardless of the concomitant administration of NNRTI. Even the plasma concentration of APV from the patient with the lowest C_{min} (950 ng/ml) was evidently higher than observed at a standard dose of 1200 mg BID (326 ng/ml pooled data from PROA1002, PROA1012 and PROA1013, Sadler et al., CROI 2000).

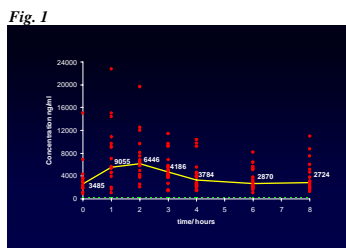


Fig. 1: Plasma concentration of APV for all pts. (n=17) at the dose of 450/200 mg APV/RTV BID, green: Cmin of APV (326 ng/ml at the standard dose of 1200 mg BID)

Results cont.

Intraindividual Comparison

- In 5/17 pts. (4 EFV, 1 NVP) the dose was changed to 600/100 mg APV/ RTV BID after a median duration of 34 weeks (range 24-48). The main pharmacokinetic parameters before and after dose adjustment are listed in (**Table 2**).
- PK measurements were performed median 28 days after switch (range 21-56).
- C_{min} decreased by 80% from 2493 ng/ml to 496 ng/ml, C_{max} by 80% from 9055 ng/ml to 1781 ng/ml, and AUC_{0-8} by 77% from 33939 ng/ml to 7860 ng/ml (median values).

Table 2

APV/RTV (n=)	C_{min} (ng/ml) Range	C_{max} (ng/ml) Range	AUC_{0-8} (ng/ml) Range	t_{max} (h) Range
450/200 (n=5)	2493 1635-5553	9055 5418-15041	33939 21229-70687	1-2
600/100 (n=5)	496 196-2030	1781 721-3899	7860 3610-19840	1-2

Table 2: Intraindividual comparison from plasma concentration of APV in 5 pts. before (450/200 mg) and after dose modification (600/100mg). Medians values typed in bold

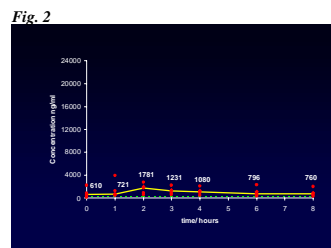


Fig. 2: Plasma concentration of APV for 5 pts. at the dose of 600/100 mg APV/RTV BID, green: Cmin of APV (326 ng/ml at the standard dose of 1200 mg BID)

Table 1

	C_{min} (ng/ml) Range	C_{max} (ng/ml) Range	AUC_{0-8} (ng/ml) Range	t_{max} (h) Range
All patients (n=17)	2049 950-8183	7529 4265-22746	30688 21229-103234	1-4
With EFV (n=10)	2366 950-8183	9076 4573-22746	32313 16990-103234	1-2
With NVP (n=2)	1368 1101-1635	8878 5773-11983	38842 21229-56455	2-2
Without NNRTI (n=5)	2049 1178-2049	6380 4265-14399	29888 20254-50651	2-4

Table 1: Main pharmacokinetic parameters of APV for all pts. at the dose of 450/200 mg. Medians values typed in bold

Results cont.

Figure 3a and 3b shows the intraindividual comparison of C_{min} and C_{max} at the different doses in 5 pts..

Fig. 3a

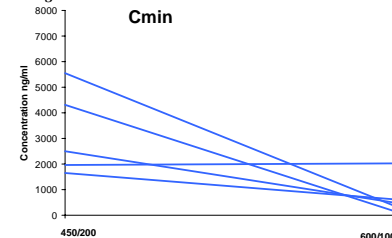
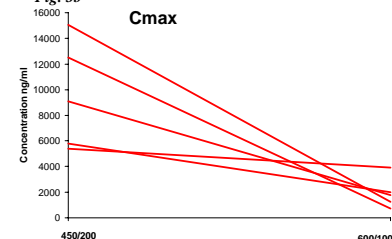


Fig. 3b



Conclusions

The dose 450mg APV + 200mg RTV BID exhibits high and stable APV plasma levels with or without concomitant NNRTI. The lowest C_{min} of 950 ng/ml was >3 times above the C_{min} observed at the standard dose of 1200mg BID (320 ng/ml). The intraindividual comparison with 600mg APV+ 100 mg RTV BID shows a decrease of APV plasma levels by 80% of C_{min} , 80% of C_{max} and 77% of AUC_{0-8} . 100 mg RTV might not be sufficient to fully counteract the effect of NNRTI's on the clearance of APV. Especially in salvage patients high plasma levels may be required for optimal virological response. 450 mg APV with 200 mg RTV BID ensure a higher drug exposure in combination with NNRTI's.

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