

PHARMACOKINETICS OF RIFAMPICIN DURING ANTIRETROVIRAL TREATMENT WITH NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

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Abstract

Introduction: Co-management of tuberculosis (TB) and HIV is complicated by pharmacologic drug interactions between rifampicin (RMP) and certain classes of antiretroviral agents. The NNRTIs Nevirapine (NVP) or Efavirenz (EFV), used to HIV infection, are known to induce the CYP 450 enzyme system. Thus when RMP is co-administered along with NVP or EFV, the bioavailability of RMP could be lowered leading to drug resistance and treatment failure.

Objectives: To study the steady state pharmacokinetics of RMP in HIV and HIV-TB patients receiving antiretroviral regimens containing NVP or EFV respectively.

Methods: The study population comprised of HIV and HIV-TB patients undergoing antiretroviral treatment with NVP and EFV containing regimens respectively. These patients were also receiving concomitant RMP. Rifampicin was estimated by HPLC in blood collected at different time points after drug administration. The pharmacokinetic variables of RMP were calculated using WinNonlin software.

Results & Conclusions: Co-administration of NVP or EFV did not alter the pharmacokinetics of RMP in HIV and HIV-TB patients, suggesting that the dose of RMP need not be altered during antiretroviral treatment with NVP or EFV.

Key words: Rifampicin; nevirapine; efavirenz; drug-drug interactions; HIV-TB

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Introduction

Tuberculosis (TB) is of particular concern in HIV-infected patients, and is the most common opportunistic infection observed in HIV-infected individuals. HIV-TB co-infected patients merit special considerations because co-management of both diseases is complicated by potential pharmacologic drug interactions between the rifamycins and non-nucleoside reverse transcriptase inhibitors (NNRTIs).^{1,2}

Rifampicin (RMP) is an important first line anti-TB drug and is usually administered for 6-8 months along with other drugs for treatment of TB. This drug is reported to undergo metabolism through the hepatic microsomal cytochrome P-450 (CYP 450) enzyme system.³

The standard therapy of HIV infection consists of 2 NRTIs and 1 NNRTI. The NNRTI could be Nevirapine (NVP) or Efavirenz (EFV). Both these drugs are known to induce the CYP 450 enzyme system.^{4,5} Thus when RMP is co-administered along with NVP or EFV, the bioavailability of RMP could be lowered leading to drug resistance and treatment failure. The best regimens and appropriate schedule for the administration of both treatments is still not clear.

Lopez et al observed that the pharmacokinetics of RMP did not change substantially in presence of EFV, even when it is administered at elevated doses.⁶ Ribera et al reported that serum RMP levels in patients receiving this drug in combination with NVP were similar to levels found in patients without NVP.⁷ Their results were consistent with that of Robinson *et al*.⁸ Similar information, to the best of our

knowledge, is lacking in HIV and HIV-TB patients in India, who are racially/ethnically different. We report the effect of NVP on RMP pharmacokinetics in HIV-infected patients and that of EFV in HIV-TB patients.

Methods

Patients: HIV and HIV-TB patients attending the outpatient clinic of the Government Hospital of Thoracic Medicine, Chennai, India, took part in the study. They were required to meet the following inclusion criteria: (i) aged 18 – 50 years, (ii) body weight not less than 30 kg, (iii) no severe hepatic or renal dysfunction (iv) non – diabetic, (v) willingness to participate in the study and give informed written consent. These studies were undertaken after obtaining clearance from the Institutional Ethics Committee. Informed written consent was obtained from all the patients.

HIV-infected patients were undergoing treatment with the fixed-dose combination containing NVP (200 mg), lamivudine (150mg), and stavudine (30/40 mg). HIV-TB patients were receiving ART regularly with EFV (600 mg) along with lamivudine (150 mg) and stavudine (30/40 mg) / zidovudine 300 mg) bi-daily. All patients were on ART for atleast two weeks prior to the study. Their anti-TB treatment consisted of RMP (450/600 mg), Isoniazid (600 mg), Pyrazinamide (1500 mg) and Ethambutol (1200 mg) thrice weekly for the first 2 months followed by RMP and INH thrice weekly according to Revised National Tuberculosis Control Program regimen (RNTCP).

Conduct of the Study

NVP-RMP study: Eligible patients were instructed to take RMP once daily (450 mg

for patients weighing less than 60 kg and 600 mg for those weighing more than 60 kg) for a period of 6 days along with their antiretroviral regimens, and they were instructed to report to the hospital on day 6 for admission into the ward. The pharmacokinetic study was conducted on day 7. On the study day, blood samples were drawn in heparinised containers predosing and at 1,2,4,6,8 and 12 hours after administration of antiretroviral drugs and RMP, under supervision.

EFV-RMP study: This study was conducted after admitting the patients to the hospital. A sample of blood was collected on the study day and the EFV and RMP were administered under supervision. Blood samples were collected at different time points after dosing, similar to the NVP-RMP study.

The blood samples were centrifuged and plasma stored at -20°C until assay.

Estimation of Plasma RMP

Plasma RMP concentrations were estimated by high performance liquid chromatography (Shimadzu Corp., Kyoto, Japan) according to a validated method.⁹ The intra- and inter-assay variations observed in the plasma rifampicin estimations were less than 3.5 % and 6.4% respectively.

Pharmacokinetic analysis

Based on the plasma concentrations of RMP at different time points, maximum concentration (C_{max}), and time to attain C_{max} (T_{max}) were determined by visual inspection of data. Other pharmacokinetic parameters like $t_{1/2}$, AUC_{0-12} and Clearance were calculated by a non-compartmental model using WinNonlin Software, version 5.1 (Pharsight Corporation., Mountain View, CA).

The pharmacokinetic variables obtained for NVP and EFV groups were compared with that of the historical controls¹⁰ by independent t-test (SPSS version 13).

Results and Discussion

The demographic details of all the patients who took part in the study are given in table 1. The steady state pharmacokinetic parameters of RMP when co-administered with NVP or EFV are given in table 2. Data reported from one of our earlier studies on the pharmacokinetics of RMP when administered alone in HIV uninfected TB patients is also given in this table for comparison.¹⁰ The pharmacokinetic parameters of RMP of patients receiving this drug in combination with NVP or EFV were similar to that found in HIV uninfected patients. A test of significance between the present study data and that obtained from a recently concluded study¹⁰ showed that none of the pharmacokinetic variables was significantly different between the TB patients and that of NVP and EFV groups

Our results are consistent with earlier reports in which co-administration of RMP along with NVP or EFV did not affect RMP plasma levels.⁶⁻⁸ This suggests that the pharmacokinetics of RMP remains unaltered when given along with NVP or EFV despite induction of CYP 3A4 by these antiretroviral drugs, and that the dose of RMP need not be altered during ART. Thus anti-TB treatment containing RMP in standard dosages can be safely used in combination with ARV regimen containing NVP or EFV. The present guidelines recommend the use of EFV when the patient is receiving RMP-containing anti-TB treatment. Ongoing studies are evaluating the safety and efficacy of NVP when used along with anti-TB treatment.

Table 1 Demographic detail of patients

Characteristics		HIV n=13	HIV-TB n=9
Sex (No.)	Male Females	9 4	7 2
Age (Year)	Mean Range	34 28-48	34 27-42
Body weight (kg)	Mean Range	58 38-91	47 34-61
Height (cm)	Mean Range	161 145-173	160 150-167
Body Mass Index (BMI)	Mean Range	22.2 17.8- 33.0	18.6 14.3- 22.4
Duration of ATT (Months)	Mean Range	-	3.8 0.3-6.0
Duration of ART (Months)	Mean Range	4.5 1-8	3.9 0.3-14.0
CD4 counts (cells/mm ³)	Mean Range	315 60-684	114 70-199

Table 2 Steady State Pharmacokinetics of Rifampicin (450/600 mg)

	Mean (range)				
	C _{max} (µg/ml)	T _{max} (hours)	T _{1/2} (hours)	AUC ₍₀₋₁₂₎ (µg/ml -hrs)	CI (litres/ min)
RMP ¹⁰ (n = 13)	7.2 (5.5- 8.9)	2.4 (1.7- 3.1)	3.0 (2.1- 3.9)	33.0* (26.7- 39.4)	15.0 (11.8- 18.2)
With NVP (n=13)	8.7 (5.6- 13.5)	2.6 (2.0- 4.0)	2.1 (1.4- 3.0)	43.7 (28.0- 66.1)	12.4 (8.6- 20.9)
With EFV (n=9)	7.7 (4.8- 11.1)	2.3 (1.0- 4.0)	2.3 (1.9- 5.1)	37.8 (15.0- 53.2)	12.8 (8.0- 29.1)

* denotes AUC_{0 to 8} (µg/ml-hrs)

C_{max}- peak concentration; T_{max}- time to attain

C_{max}; AUC-area under the plasma

concentration vs. time curve; CI – clearance

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References

1. Burman WJ, Jones BE. Treatment of HIV-related Tuberculosis in the Era of Effective Antiretroviral Therapy. *Am J Respir Crit Care Med* 2001; 164: 7-12.
2. American Thoracic Society Documents. American Thoracic Society/ Centers of Disease Control and Prevention/Infection Diseases Society of America. Treatment of tuberculosis. *Am J Respir Crit Care Med* 2003; 167: 603-662.
3. Acocella G. Clinical pharmacokinetics of rifampicin. *Clin Pharmacokinet* 1979; 3: 108-127.
4. DuPont Pharmaceuticals Company. Sustiva™ (efavirenz capsules), Prescribing information: 1998 Sep 17: <http://www.sustiva.com>. Accessed on 24 April 2007.
5. Montaner JSG, Lange JMA. Nevirapine. *AIDS Therapy Chapter 7*; 87-96.
6. Lopez-Cortes LF, Ruiz-Valderas R, Viciano P, et al. Pharmacokinetic interactions between efavirenz and rifampicin in HIV-infected patients with tuberculosis. *Clin Pharmacokinet* 2002; 41: 681-690.
7. Ribera E, Pou L, Lopez RM, et al. Pharmacokinetic interaction between nevirapine and rifampicin in HIV-infected patients with tuberculosis. *J Acquir Immun Dis Syndr* 2001; 28:450-453.
8. Robinson P, Lamson M, Gigliotti M, et al. Pharmacokinetic interaction between nevirapine and rifampicin (abstract 60623).

In Program abstracts of the XII World Conference on AIDS, Geneva, Switzerland, June 28 – July 3, 1998.

9. Hemanth Kumar AK, Chandra I, Geetha R, Silambu Chelvi K, Lalitha V, Prema G. A validated high-performance liquid chromatography method for the determination of rifampicin and desacetyl

rifampicin in plasma and urine. Ind J Pharmacol 2004; 36(4): 231-233.

10. Gurumurthy P, Ramachandran G, Hemanth Kumar AK, et al. Decreased bioavailability of rifampin and other antituberculosis drugs in patients with advanced human immunodeficiency virus disease. *Antimicrob Agents Chemother* 2004; 48: 4473-4475.