Steady-State Pharmacokinetics of Nevirapine in HIV-1 Infected Adults in India

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Background and Objectives: **A variety of demographic factors, sex, and degree of immunosuppression can influence antiretroviral drug concentrations. The authors studied the influence of immune status, sex, and body mass index (BMI) on the steady-state pharmacokinetics of nevirapine delivered as a fixed-dose combination in HIV-1-infected patients in India.** ***Methods:*** **Twenty-six HIV-1-infected adult patients undergoing treatment with nevirapine-based highly active antiretroviral therapy regimens participated in the study. Pharmacokinetic variables were compared between patients divided based on CD4 cell counts, sex, and BMI.** ***Results:*** **Patients with higher BMI had lower peak and trough concentration and exposure of nevirapine than those with lower BMI; none of the differences in the pharmacokinetic variables of nevirapine between the various patient groups was statistically significant.** ***Conclusions:*** **Patients' immune status, sex, or BMI had no impact on the pharmacokinetics of nevirapine. Plasma nevirapine concentrations were maintained within the therapeutic range of the drug in the majority of the patients.**

Keywords: ***pharmacokinetics; nevirapine; India; immune status; sex; BMI***

Access to antiretroviral drugs for HIV-1-infected patients in developing countries is a global public health priority. The World Health Organization currently recommends first-line therapy with 2 nucleoside reverse transcriptase inhibitors (NRTIs) and 1 non-NRTI (NNRTI)—a combination with good efficacy, tolerability, simplicity, and low cost.[1] Generic fixed-dose combinations (FDCs) of such regimens are widely regarded as crucial for scaling up AIDS treatment in developing countries. Two triple-drug combinations consisting of nevirapine and lamivudine with either stavudine or zidovudine as the third agent are available as FDCs in the developing world. A vast majority of HIV-infected patients in India receive nevirapine-based highly active antiretroviral therapy (HAART), the common co-drugs being lamivudine and stavudine.[2] A few studies have reported the effectiveness and safety of generic FDCs for treatment of HIV-1-infected adults.[2-5] It has been suggested that a variety of demographic factors such as age, body size, and weight can influence antiretroviral drug concentrations.[6] Sex-based differences in the pharmacokinetics of nevirapine have also been observed.[7] Keating et al reported that malabsorption correlates significantly with the degree of immunosuppression.[8] We undertook a study to obtain information on the pharmacokinetics of nevirapine in HIV-infected patients on treatment with FDCs in India, as well as the influence of immunological status, sex, and body mass index (BMI) on the pharmacokinetics of these drugs, as very limited information is available on this aspect.

Methods

Patients

The study participants were composed of HIV-infected patients of ethnic Indian origin who were participating in a controlled clinical trial and were being followed

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Table 1. Baseline Characteristics of Study Participants

Characteristic	*Value*
Gender (No.)	
Males	16
Females	10
Age (years)	
Mean	36
Range	26-50
Body weight (kg)	
Mean	53
Range	35-91
Height (cm)	
Mean	159
Range	140-173
BMI	
Mean	20.8
Range	15.1-33.0
Duration of ART (months)	
Mean	4.6
Range	1-17
CD_4 counts (cells/mm^3)	
Mean	230
Range	25-684
≥ 200 cells/mm^3 (No.)	13
< 200 cells/mm^3 (No.)	13

BMI = body mass index; ART = antiretroviral therapy.

up at regular intervals. During each follow-up visit, they underwent a complete medical examination and were tested for biochemical and hematological parameters and CD4 cell counts. The patients were required to meet the following inclusion criteria: (1) 18 to 50 years of age, (2) body weight not less than 30 kg, (3) no severe hepatic or renal dysfunction (serum transaminases within 2 1/2 times the upper limit of normal range and creatinine < 1.2 mg/dl), (4) nondiabetic (random blood glucose between 80 and 140 mg/dl), (5) undergoing treatment with generic FDC of antiretroviral drugs (nevirapine 200 mg/lamivudine 150 mg/stavudine 30/40 mg bi-daily) for a minimum period of 2 weeks, (6) not suffering from any serious opportunistic infection that could cause malabsorption of drugs, and (7) willingness to participate in the study and provide informed written consent. Chronic alcoholics and female patients on hormonal birth control pills were excluded from the study.

Conduct of Study

The study was conducted at the Government Hospital of Thoracic Medicine, Tambaram, Chennai, India. Eligible study participants were admitted to the hospital at least a day prior to start of the study. On the day of the study, blood samples (3 ml) were drawn in heparinized containers before dosing (0 hour) and serially at 0.5, 1, 2, 4, 6, 8, and 12 hours after administration of the FDC pill (Cipla/Ranbaxy/Alkem/Emcure) with 200 ml water. The blood samples were centrifuged immediately and plasma was stored at −20°C until estimation of nevirapine was undertaken. The study was conducted after obtaining clearance from the Institutional Ethics Committee. Informed written consent was obtained from all the patients.

Estimation of Plasma Nevirapine

Estimation of plasma nevirapine was carried out by HPLC (Shimadzu Corporation, Kyoto, Japan) according to validated methods described earlier.[9]

Pharmacokinetic Analysis

Maximum concentration (C_{max}), minimum concentration (C_{min}), and time to attain C_{max} (T_{max}) were determined by visual inspection of data. Drug concentration-time data were analyzed by noncompartmental model following first-order kinetics using WinNonlin software (Version 4.1) (Pharsight Corporation, Mountain View, CA). The linear trapezoidal rule was used to compute the exposure (AUC_{0-12}). Elimination half-life (t ½) was obtained by dividing 0.693 with elimination rate constant (K_{el}).

Statistical Evaluation

Analysis of data was performed using SPSS (version 10) package. The significance of differences in the pharmacokinetic parameters of nevirapine between various groups of patients was calculated using nonparametric Mann-Whitney test. A *P* value of ≤ .05 was considered to be statistically significant. Pearson's correlation test was used to evaluate the correlation between C_{max} and AUC_{0-12} of nevirapine with that of patients' body weight. Repeated measures analysis was used to study the trend of plasma nevirapine levels over time (0 to 12 hours) versus BMI.

Results

The baseline characteristics of study participants are provided in Table 1. The mean CD4 cell counts at baseline, 6 months, and 12 months were 99, 320, and 414 cells/mm^3, respectively. Comparison of pharmacokinetic variables of nevirapine in patient groups divided based on CD4 cell counts (< and ≥ 200 cells/mm^3), sex (males and females), and BMI (< 18.5 and ≥ 18.5) were made. The normal range of BMI was taken as 18.5 to 24.9.[10] It was observed that patients with a BMI ≥ 18.5 had lower C_{max} (7.48 vs 8.95 µg/ml), C_{min} (4.70 vs 5.81 µg/ml), and AUC_{0-12} (69.31 vs 85.74 µg/ml) than those with a BMI < 18.5; however, these differences were not statistically significant (Table 2).

Table 2. Steady-State Pharmacokinetics of Nevirapine

		Mean ± SD				
Variable	*N*	C_{max} (µg/ml)	C_{min} (µg/ml)	T_{max} (h)	AUC_{0-12} (µg/ml.h)	t ½ (h)
Sex						
Males	16	8.38 ± 2.45	5.47 ± 2.06	1.53 ± 0.97	79.67 ± 27.68	33.74 ± 26.46
Females	10	8.70 ± 2.55	5.46 ± 2.10	1.15 ± 0.47	82.38 ± 26.87	23.55 ± 18.07
BMI						
< 18.5	18	8.95 ± 2.43	5.81 ± 2.04	1.42 ± 0.86	85.74 ± 27.31	29.57 ± 22.44
≥ 18.5	8	7.48 ± 2.29	4.70 ± 1.92	1.31 ± 0.80	69.31 ± 23.47	30.40 ± 21.24
CD4 cell counts (cells/cu.mm)						
< 200	13	8.66 ± 2.44	5.48 ± 2.17	1.62 ± 0.94	82.25 ± 29.46	28.74 ± 15.41
≥ 200	13	8.34 ± 2.53	5.45 ± 1.98	1.15 ± 0.66	79.13 ± 25.09	34.90 ± 16.11
Overall	26	8.50 ± 2.44	5.05 ± 2.04	1.38 ± 0.83	80.69 ± 26.85	29.82 ± 11.66

C_{max} = peak concentration; C_{min} = trough concentration; T_{max} = Time to attain C_{max}; AUC = area under the plasma concentration versus time curve; t ½ = half-life; BMI = body mass index.

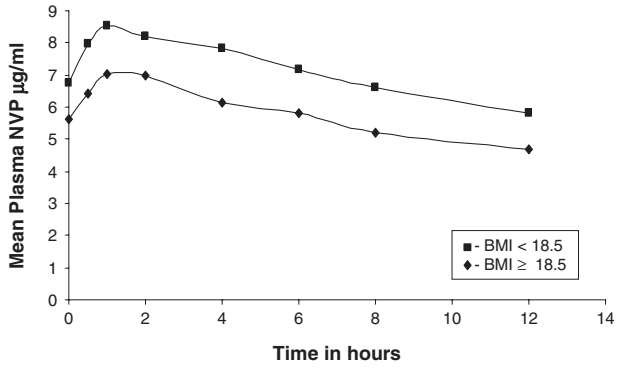

Figure 1 Mean plasma nevirapine (NVP) over time (0 to 12 hours) versus body mass index (BMI). Trend analysis of plasma NVP versus BMI in 26 HIV-infected patients.

Repeated measures analysis showed that there was a significant trend in plasma nevirapine over time in patients with a BMI < and ≥ 18.5 ($P < .05$) (Figure 1). But the difference in plasma nevirapine between the 2 groups of patients was not significant. None of the differences in the pharmacokinetic variables of nevirapine between the various patient groups was statistically significant. We did not observe a significant correlation between patients' body weight and C_{max} and AUC_{0-12} of nevirapine.

Discussion

Antiretroviral drug concentrations are among the most important determinants of clinical response to a drug accounting for both toxicity and efficacy. This study presents the pharmacokinetic profile of nevirapine taken as a generic FDC in HIV-infected patients in India. All the patients were obtaining antiretroviral drugs from the government antiretroviral therapy (ART) clinic. The majority of the patients had adequate nevirapine concentrations, which were within the therapeutic range of the drug (3-12 µg/ml). Four patients had nevirapine peak concentrations above the upper limit of the therapeutic range of 12 µg/ml. Three of the 4 patients had a BMI of > 21, whereas in 1 patient the BMI was 17.5. None had any obvious symptoms related to drug toxicity. However, hepatotoxicity was not monitored prospectively in these patients and transient liver enzyme abnormalities could have been missed. A similar observation has been made by Kappelhoff et al,[11] who did not observe any relationship between nevirapine exposure and development of adverse events. Three patients who had their nevirapine trough concentrations below 3 µg/ml showed a significant increase in their CD4 cell counts.

Several studies have found that sex can have a modest influence on the pharmacokinetic profile of some antiretroviral drugs. Exposure of nevirapine has been reported to be 20% higher in females than in males.[7] However, our study did not observe any significant difference in the pharmacokinetics of nevirapine between males and females. Keating et al observed that malabsorption and increased intestinal permeability are common in AIDS patients and that malabsorption correlated significantly with the degree of immune suppression and BMI.[8] The study findings demonstrate that adequate nevirapine levels are maintained in blood irrespective of the stage of immune suppression and BMI.

Peak and trough concentrations and exposure of nevirapine observed in the present study are markedly higher in the Indian population of HIV-infected patients than those reported in the American and European populations.[12-17] This could be due to the

fact that Indian patients weigh less than Europeans and Americans and that nevirapine clearance is dependent on body weight.[18] However, the present study data are very similar to that observed in Malawians, who had a mean peak concentration of 9.3 µg/ml.[14] It would therefore be interesting to explore pharmacogenetic differences that could impact drug levels in different populations.

The effectiveness of nevirapine-based HAART delivered as a generic FDC has been reported.[2-5] A limitation of this study is that although all the patients were receiving treatment at the same ART center, they could have received drugs from different companies, which we were not able to control. Our study has clinical implications for treatment of HIV-infected patients in resource-constrained settings. Earlier, we had shown that malabsorption of antituberculosis drugs occurs in patients with advanced HIV disease with and without diarrhea.[19] Adequate plasma concentrations of nevirapine that are not influenced by the stage of immune suppression, sex, and BMI observed in this study are encouraging. Hence, if patients take regular treatment, chances of failure due to inadequate drug levels are low. A regular follow-up of these patients has shown a steady increase in their CD4 cell counts following treatment. Although a majority of the patients started antiretroviral therapy at advanced stages of HIV infection, there was still remarkable improvement in CD4 counts, indicating the potency of generic FDC regimens. Finally, this study provides one more piece of evidence that generic fixed drug combinations manufactured and widely used in the developing world (in this case, through the Indian government-run antiretroviral treatment program) are effective and, if used regularly, can improve the health status of millions of patients who require antiretroviral therapy.

References

1. World Health Organization. *Scaling Up Antiretroviral Therapy in Resource Limited Settings: Treatment Guidelines for a Public Health Approach—2003 Revision.* Geneva: World Health Organization; 2003. Available at: http://www.who.int/hiv/pub/prev_care/en/arvrevision2003en.pdf.
2. Kumarasamy N, Solomon S, Chaguturu SK, et al. The changing natural history of HIV disease: before and after the introduction of generic antiretroviral therapy in Southern India. *Clin Infect Dis.* 2005;41:1525-1528.
3. Calmy A, Pinoges L, Szumilin E, et al. Generic fixed dose combination antiretroviral treatment in resource-poor settings: multicentric observational cohort. *AIDS.* 2006;20: 1163-1169.
4. Laurent C, Kouanfack C, Koulla-Shiro S, et al. Effectiveness and safety of a generic fixed-dose combination of nevirapine, stavudine, and lamivudine in HIV-1-infected adults in Cameroon: open-label multicentre trial. *Lancet.* 2004;364:29-34.
5. Pujari SN, Patel AK, Naik E, et al. Effectiveness of generic fixed-dose combinations of highly active antiretroviral therapy for treatment of HIV infection in India. *J Acquir Immun Defic Syndr.* 2004;37:1566-1569.
6. Phair JP, Flexner CW. *Factors Associated With Pharmacokinetic Variability in HIV-Infected Patients.* Chicago, IL: Northwestern University, Feinberg School of Medicine, Office of Continuing Medical Education, iMedOptions; 2004.
7. La Porte C, Burger D, Gyssens I, Sprenger H, Koopman P. Gender differences in Nevirapine pharmacokinetics, fact or fiction? Program and abstracts of the 4th International Workshop on Clinical Pharmacology in HIV therapy; 2003; France.
8. Keating J, Bjarnason I, Somasundaram S, et al. Intestinal absorptive capacity, intestinal permeability and jejunal histology in HIV and their relation to diarrhea. *Gut.* 1995;37:623-629.
9. Moyer TP, Temesgen Z, Enger R, et al. Drug monitoring of antiretroviral therapy for HIV-1 infection: method validation and results of a pilot study. *Clin Chem.* 1999;45:1465-1476.
10. National Institute of Nutrition (Indian Council of Medical Research). Hyderabad, India, 2005.
11. Kappelhoff BS, van Leth F, Robinson PA, et al. Are adverse events of nevirapine and efavirenz related to plasma concentrations? *Antivir Ther.* 2005;10:489-498.
12. Donnerer J, Kronawetter M, Kapper A, Haas I, Kessler HH. Therapeutic drug monitoring of the HIV/AIDS drugs abacavir, zidovudine, efavirenz, nevirapine, indinavir, lopinavir, and nelfinavir. *Pharmacology.* 2003;69:197-204.
13. Havlir D, Cheeseman SH, McLaughlin M, et al. High-dose nevirapine: safety, pharmacokinetics and antiviral effect in patients with human immunodeficiency virus infection. *J Infect Dis.* 1995;171:537-545.
14. Hosseinipour MC, Corbett A, Kanyama C, et al. Pharmacokinetic comparison of generic and trade formulations of lamivudine, stavudine and nevirapine in HIV-infected Malawian subjects. 12th Conference in Retroviruses and Opportunistic Infections; 2005; Boston.
15. van Heeswijk RPG, Veldkamp AI, Mulder JW, et al. The steady-state pharmacokinetics of nevirapine during once daily and twice daily dosing in HIV-1 infected individuals. *AIDS.* 2000;14:F77-F82.
16. van Praag RME, van Weert ECM, van Heeswijk RPG, et al. Stable concentrations of zidovudine, stavudine, lamivudine, abacavir and nevirapine in serum and cerebrospinal fluid during 2 years of therapy. *Antimicrob Agents Chemother.* 2002;46: 896-899.
17. Ribera E, Pou L, Lopez RM, et al. Pharmacokinetic interaction between nevirapine and rifampicin in HIV-infected patients with tuberculosis. *J Acquir Immun Defic Syndr.* 2001;28:450-453.
18. de Maat MM, Huitema AD, Mulder JW, Meenhorst PC, van Gorp EC, Beijnen JH. Population pharmacokinetics of nevirapine in an unselected cohort of HIV-1 infected individuals. *Br J Clin Pharmacol.* 2002;54:378-385.
19. Gurumurthy P, Ramachandran G, Hemanth Kumar AK, et al. Decreased bioavailability of rifampin and other anti-TB drugs in patients with advanced HIV disease. *Antimicrob Agents Chemother.* 2004;48:4473-4475.