RESEARCH PAPER

Serum Nevirapine and Efavirenz Concentrations and Effect of Concomitant Rifampicin in HIV Infected Children on Antiretroviral Therapy

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Objective: To determine factors affecting serum levels of Efavirenz and Nevirapine and analyze the effect of Rifampicin on Nevirapine drug levels.

Methods: A cross-sectional study was conducted on 30 HIV infected children on Antiretroviral therapy (ART) with Nevirapine or Efavirenz. Patients on simultaneous Rifampicin and Nevirapine were given higher doses of Nevirapine with regular monitoring of liver function tests. Trough levels (before morning dose of Nevirapine) and levels after 2 hours of administration of Nevirapine and levels of Efavirenz were assessed using HPLC and were checked to see if they fall within the therapeutic range.

Results: Thirty patients (14 males) were enrolled in the study with 20 on Nevirapine and 10 (33.3%) on Efavirenz. Seven (23.3%) patients were simultaneously taking rifampicin. The mean Nevirapine dose given to the patients was 350.9±59.8mg/m^2/day (on simultaneous rifampicin) and 309.2±54.6mg/m^2/day (not on concurrent rifampicin). Thirteen (81.3%) of the 16 patients with trough Nevirapine had values in the normal range, 1 (6.3%) had low Nevirapine trough levels and 2 (12.5%) had high Nevirapine trough levels. Of the post 2 hours Nevirapine levels, 1 (5%) had low levels and 3 (15%) had high Nevirapine blood levels. Factors like age (*P*=0.4, *P*=0.4087), nourishment (*P*=0.2679, *P*=0.4132), ART combination (*P*=0.4199, *P*=0.4132), form of the drug (tablet/syrup) (*P*=0.1964, *P*=0.4696) or if it was being given as single or in a fixed dose combination (*P*=0.4179, *P*=0.4696) and even concurrent rifampicin administration (*P*=0.284, *P*=0.472) did not significantly affect the trough and post 2 hours Nevirapine values, respectively. All the five patients being given concurrent rifampicin had normal trough and post 2 hours levels of Nevirapine. The Efavirenz drug levels were 1.9±1.1 g/mL. Of the 10 patients on Efavirenz, 2 (20%) had high and 1 (10%) had low blood levels.

Conclusion: Concurrent Rifampicin administration does not alter blood levels of Nevirapine; provided the dose of Nevirapine is increased by 20-30%. Formulation of drugs does not alter the blood levels provided drug administered is in the recommended dose.

Key words: *Anti-retroviral, Drug levels, Efavirenz, Nevirapine, Rifampicin therapy*

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Antiretroviral drugs exhibit significant between-patient pharmacokinetic variability. Over the past years, data have emerged demonstrating a link between antiretroviral drug concentrations and efficacy or side-effects. Many previous studies have provided evidence that plasma concentrations contribute to therapeutic response. As a result, the issue of therapeutic drug monitoring (TDM) for these compounds is arisen [2]. There is also an increasing interest in knowing whether antiretroviral therapy can be individualized in patients, based on measurement of drug levels [3-6]. Nevirapine (NVP) and Efavirenz (EFV) are non-nucleoside reverse transcriptase inhibitors used in antiretroviral regimens to treat HIV infection. The

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pharmacokinetic parameters of EFV vary depending on patients' race, baseline bilirubin level, and geographical location. Drug interactions and resistance mutations can also be confounders in the pharmacokinetic parameters of these drugs [7]. Concomitant rifampicin substantially decreases concentration of both NVP and EFV; however, for EFV this effect is more than counterbalanced by the effect of ethnicity and increased EFV dose [8]. Pharmacokinetic data for non-nucleoside reverse transcriptase inhibitors in children are limited and none in children reported from India [9-11]. Thus, we undertook this study to determine factors affecting serum levels of EFV and NVP and analyze the effect of concomitant Rifampicin on NVP levels.

METHODS

This cross-sectional study was conducted on 30 HIV infected children on ART with NVP or EFV, attending the pediatrics HIV outpatient department at our hospital, after approval from the hospital academic council. Written informed consent was taken from the parents/guardians for the study.

The subjects' demographic data, details of drugs prescribed, baseline and latest CD4 count (and percentage, if available), baseline and latest viral load count (if available) were recorded. The height and weight of the patients was taken, and if either was found to be less than the 3rd percentile [12,13], they were classified as malnourished. On the day of the study, a sample of blood (2 mL) was drawn in a heparinised vacutainer (0 hour–trough concentration) prior to NVP intake. ART was then administered under supervision and blood samples were collected 2 hours (post 2 hours concentration) after administration of the drug containing NVP. Patients on simultaneous rifampicin and NVP were given higher doses of NVP (increased by 30% till the patient was on rifampicin) and monitoring of liver function tests was done periodically to look for adverse effects. Regular doses of NVP, without rifampicin, prescribed were 300 mg/m^2/day in 2 divided doses. In patients on EFV based regimen, EVF was administered to the patients at night and their blood samples were collected the following morning. Disposable syringes and needles were used for drawing blood. The child could have regular food/snacks during the study period (two hours). The blood samples were centrifuged immediately, plasma separated and stored at -20^{o}C until analysis. Plasma NVP and EFV estimations were carried out by HPLC [10,11].

The statistical analysis was done using SPSS version 15.0 and OpenEpi software. Chi-square test and Fischer's exact test were used for analysis of proportions. *P* value of <0.05 was taken as significant. *t* test and ANOVA-1 were applied to find the factors significantly affecting the trough and the post 2-hours levels of NVP, and levels of EFV. These included age, gender, nutritional state, ART combination, dose of drug, drug formulation, single or fixed drug combination, associated rifampicin use, CD4 count, and viral load.

RESULTS

Demographic data of patients is depicted in ***Table* I**. The NVP and EFV levels of each patient are depicted in ***Fig.* 1**.

Out of the 20 patients given NVP, the trough NVP dose value was measured in 16 patients and post 2 hours NVP levels were measured in all 20 patients. The trough NVP levels were 5.9 ± 4.8 μg/mL and post 2 hours NVP levels were 8.2 ± 4 μg/mL. Thirteen (81.3%) of the 16 patients with trough NVP had values in the normal range. Amongst the remaining, 1 (6.3%) had low NVP trough levels and 2 (12.5%) had high NVP trough levels. Of the post 2 hours NVP levels, 1 (5%) had low levels and 3 (15%) had high NVP blood levels, of which none were on rifampicin. In our study, factors like age, nourishment, ART combination, form of the drug (tablet/syrup) or if it was being given as single or in a fixed dose combination, and concurrent rifampicin administration did not affect the trough and post 2 hours NVP values in the patients (***Table* II**), except gender, which was seen as the only factor affecting the post 2 hours NVP levels. Boys had a higher post 2 hours NVP value as compared to girls (10.1 ± 5.8 *vs* 5.8 ± 2.9; *P* value = 0.035). All the five patients being given rifampicin along with NVP had normal trough and post 2 hours levels of NVP.

The EFV drug levels were 1.9 ± 1.1 μg/mL. Of the 10 patients on EFV, 2 (20%) had high and 1

TABLE I DEMOGRAPHIC DATA OF PATIENTS

Demographic data	Value
Males	14
Age, mean ±SD	8.1 ± 3.3 years
Age less than 7 years	11 (36.7%)
Malnourished	19 (63.3%)
Patients on NVP	20 (66.7%)
ART combinations	
AZT+3TC+NVP	7 (24.1%)
d4T+3TC+NVP	13 (44.8%)
AZT+3TC+EFV	4 (10.3%)
d4T+3TC+EFV	5 (17.2%)
ABC+TDF+EFV	1(3.4%)
Mean duration of ART	1.9±1.7 years
NVP dose , mean	319.5±57.0 mg/m^2/day
In patients on rifampicin	350.9 ± 59.8 mg/m^2/day
In patients not on rifampicin	309.2±54.6 mg/m^2/day
EFV dose, mean	17.4±10.2 mg/kg/day
Tablets	25 (83.3%)
Single drugs preparations	15 (50%)
Patients on simultaneous Rifampicin	7 (23.3%)
Baseline CD4 count (*n*=29)	532.9±455.5/mm^3
Baseline CD4% (*n*=24)	17.4±14%
Baseline viral load (*n*=3)	439400±344916 copies/mL

NVP: nevirapine; EFV: efavirenz; AZT: zidovudine; 3TC: lamivudine; D4T: stavudine; ABC: abacavir; TDF: tenofovir; FDC: fixed dose combination

(10%) had low EFV blood levels, of which none was receiving rifampicin. None of the factors were seen to affect the TDM levels of EFV including concurrent Rifampicin administration (***Table* II**).

The baseline viral load, CD4 count, duration of ART and dose of ART did not affect the trough/post 2 hours dose NVP TDM values or the EFV TDM values.

DISCUSSION

Nevirapine is metabolized faster in children and thus the drug needs to be given as per body surface area. However, since calculation as per body surface area is cumbersome, recommendations as per weight bands have been devised for ease in prescribing the medicine [15,16]. In our study, we prescribed NVP

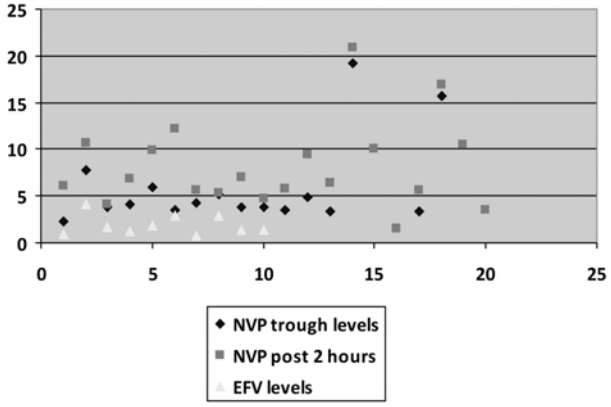

FIG. 1 *Drug levels in each individual patient.*

doses similar to the PENTA guidelines *i.e.* 300 mg/m^2/day and 80.3% of the children had normal trough NVP levels while 80% had normal post 2 hours levels. We prescribed EFV as per weight bands and in our study 70% of children had normal EFV levels.

Rifampicin is known to decrease plasma levels of NVP and EFV [17-19]. There have been studies documenting that adequate drug levels of NVP and EFV can be achieved even with rifampicin therapy by increasing the dose of NVP [20-24]. We gave a dose of 350mg/m^2/day of NVP to the patients taking rifampicin. We found no instance of toxicity in our patients with this dose of NVP. There was no significant difference in the drug levels of NVP and EFV, with or without concomitant rifampicin therapy.

The FDC pediatric formulation of lamivudine, nevirapine, and stavudine is bioequivalent to the individual liquid formulations [25]. Similarly, we found that giving a drug in combination with other anti-retrovirals did not significantly alter the drug levels in the patient's blood, as compared to the drugs being given singly. The drug formulation did not significantly affect the drug levels of NVP in our study.

Concurrent rifampicin administration was not found to alter blood levels of NVP; provided the dose of NVP is increased by 20-30% and adverse effects are usually not seen with this increase in dose. However larger studies will be required to confirm these findings. Formulation of drugs be it tablet/syrup or FDC/single does not alter the blood levels.

TABLE II FACTORS AFFECTING DRUG LEVELS OF NEVIRAPINE AND EFAVIRENZ IN THE STUDY POPULATION

Factor		Trough levels of NVP (*n*=16)No. (%)		Post 2 hours levels of NVP (*n*=20)No. (%)			Drug levels of EFV (*n*=10)No. (%)	
		Abnormal *n* (%)	Normal *n* (%)	Abnormal *n* (%)	Normal *n* (%)	P value	Abnormal *n* (%)	Normal *n* (%)
Gender	Male	3(30%)	7(70%)	3(27.3%)	8(72.7%)	0.306	2(66.7%)	1(33.3%)
Age	<7years	2(25%)	6(75%)	2(18.2%)	9(81.8%)	0.408	0	0
Malnourished	Yes	1(10%)	9(90%)	3(23.1%)	10(76.9%)	0.413	1(16.7%)	5(83.3%)
ART Combination	AZT+3TC+NVP	1(20%)	4(80%)	1(14.3%)	6(85.7%)	0.413	-	-
	AZT+3TC+EFV	-	-		-	-	1(25%)	3(75%)
	D4T+3TC+NVP	2(18.2%)	9(81.8%)	3(23.1%)	10(76.9%)	-	-	
	D4T+3TC+EFV	-	-	-	-		2(40%)	3(60%)
	ABC+TDF+EFV	-	-		-	-	0	1(100%)
Drug formulation	Tablet	2(16.7%)	10(83%)	3(20%)	12(80%)	0.469	3(30%)	7(70%)
Single Drug	Single	2(15.4%)	11(84%)	3(20%)	12(80%)	0.469	0	0
Associated Rifampicin	Yes	0	4(100%)	0	5(100%)	-	0	2(100%)

NVP: nevirapine; EFV: efavirenz; AZT: zidovudine; 3TC: lamivudine; D4T: stavudine; ABC: abacavir; TDF: tenofovir; FDC: fixed dose combination; None of the factors studied had a significant effect on drug levels studied.

Contributors: IS and SS were involved in study design. IS and ML collected blood samples. SS, GR, AKH did testing of the blood. UC, AG, ST and IS did review of literature and wrote the manuscript. IS will act as guarantor of paper.
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WHAT THIS STUDY ADDS?

- Concurrent administration of rifampicin does not affect the bioavailability of nevirapine, provided the dose of nevirapine is increased by 20-30%.

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