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Over Exposure to Efavirenz Plasma Concentrations among Beninese HIV Patients Treated by A 600 mg Daily Dose

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Abstract: Therapeutic plasma concentrations of EFV (efavirenz) are between 1,000 ng/mL and 4,000 ng/mL. Concentrations below 1000 ng/mL are associated with higher risk of treatment failure, and concentrations above 4,000 ng/mL are associated with toxicity. The aim of the study was to appreciate EFV plasmas concentrations profile and the association between plasma levels and various characteristics in Beninese patients treated by a 600 mg standard daily-dose. Blood samples were collected and EFV plasma levels were measured by liquid chromatography coupled with mass spectrometry detection in HIV-infected patients receiving EFV in combination with other antiretroviral drugs for at least 14 days. Adverse effects occurring during treatment were collected through a questionnaire. An over-exposure to EFV among Beninese HIV patients were observed, with 46.4% of patients presenting EFV concentration above 4,000 ng/mL, although adverse effects were tolerated indicating that antiretroviral treatment is safe. The measurement of plasma concentration at the steady-state could contribute to early detection of treatment failure and adapt treatment in subjects presenting serious adverse effects within context of therapeutic drug monitoring.

Key words: HIV, efavirenz, plasma concentrations, adverse effects, Benin.

1. Introduction

EFV (efavirenz, Fig 1) is a NNRTI (non-nucleoside reverse transcriptase inhibitor) mainly used in combination with others ARV (antiretroviral) agents as first-line HAART (highly active antiretroviral therapy) to control HIV-1 (human immunodeficiency virus) infection in adult, adolescent and child aged of 3 years old and more. Its long half-life (approximately 45 h) facilitates its standard posology of 600 mg by oral route once a day. According to a study performed in a group of 130 HIV-infected patients, average residual plasmatic concentration (Cmin) of the EFV at steady-state is 1,700 +/-1,000 mg/mL [1]. Conclusions of this study show that EFV plasma level is associated with the probability of virological response beyond the Cmin threshold of 1,000 ng/mL. This is an advantage in the observance and contributes to the treatment effectiveness.

However, in spite of its undeniable advantages, EFV, like any drug, presents adverse effects, which could constitute a risk for the patient. CNS (central nervous system) toxicity is the major adverse effects of EFV, which justifies the recommendation of its evening take in order to improve the tolerance degree of these effects. The prediction of the therapeutic effectiveness and the probability of developing CNS side effects were associated with efavirenz plasmatic concentrations [2, 3]. Marzolini et al. reported that a central neurological toxicity occured when EFV plasmatic concentration

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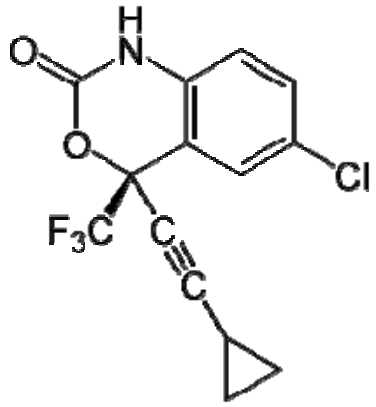

Fig. 1 Chemical structure of Efavirenz

was higher than 4,000 ng/mL [1] in Caucasian patients. Different studies showed that metabolism of ARV drugs vary according to different ethnic groups. Consequently, it cannot be excluded that Beninese exhibit particular pharmacokinetic trend due to specific pharmacogenetics, which can condition ARV plasma exposure in patients [4-9].

Moreover, therapeutic drug monitoring for EFV has shown interest in Caucasian patients [10] which remains current events in Beninese population.

The aim of this study was to appreciate whether EFV plasma concentration monitoring could predict treatment failure or CNS tolerability in Beninese patients.

2. Materials and Methods

2.1 Study Design and Patients

HIV-infected adults' patients receiving HAART based on EFV since at least 14 days treatment, both gender and of Beninese origin were included. Pregnancy women and patients known as inobservant were not included. The study was approved by the Ethics Review Committee of Institute of Applied Biomedical Sciences (ISBA), University of Abomey-Calavi, Benin, and was conducted in accordance with the principles of GCP (good clinical practices) under the number n43. All patients gave written informed consent before their participation in the study. They responded to a questionnaire in order to determine all adverse effects present simultaneously to the measurement of the plasma concentration of EFV.

2.2 Efavirenz Analysis

Venous blood samples (5 mL) were collected in a dry heparinated tube at 12 ± 2 h after the last take of EFV. After centrifugation (3,000 g, 3 minutes), plasma was collected in labeled dry tubes and stored at -20 °C until analysis. EFV plasma concentrations were determined in Pharmacology and toxicology Laboratory of CHU (centre hospitalier universitaire) Raymond Poincaré (France), by an on-line automated sample preparation using a TurboFlow® (ThermoFischer Scientific, Les Ulis, France) coupled to a LC-/MS/MS, derived from a previously published method [11]. Briefly, after addition of the internal standard, EFV-D4, precipitation with methanol and centrifugation, supernatant was directly injected onto Turboflow® device. A Cyclone® column allowed extraction of EFV and an Hypersil Gold® chromatographic column (ThermoFischer Scientific, Les Ulis, France) allowed its separation. Compounds were detected using an Access® mass spectrometer (ThermoFischer Scientific, Les Ulis, France) equipped with an electrospray ionization probe.

2.3 Analytical Validations

The method was validated for selectivity, linearity, sensitivity, accuracy, precision, matrix effect and extraction yield according to US Food and Drug Administration's recommendations. The method was accredited by the French Comity of Accreditation (COFRAC, Comité Français d'Accréditation). The method was linear between 50 and 7,700 ng/mL. Accuracies and precisions evaluated at five concentrations (50, 800, 1,400, 3,000, 6,000 ng/mL) were all > 93% and < 14% (excepted for the limit of quantification, 50 ng/mL, 17%), respectively.

2.4 Statistical Analysis

Data were treated with EpiDataversion 3.1 software

and statistical analysis was performed using Stata version 12.0 software. Chi-square test was used appropriately to compare base line parameters. Multiple linear regression analysis was done to study the association between plasma concentrations and independent variables such as age, sex, BMI, initial CD4 count, WHO clinical stage, therapeutic. Test results with a *p* value less than 0.05 were considered statistically significant.

3. Results and Analysis

3.1 Study Participants

A total of 117 patients were recruited to participate to the descriptive and analytical study depending on the inclusion and non-inclusion criteria. Among them, 5 were excluded for non-observance of the rules (n = 2) and switch of protocol (n = 3) reasons. Thus, statistical analysis was performed on 112 subjects. The characteristics and the therapeutic regimens of the patients are given in Table 1.

3.2 Adverse Effects

Average number of adverse effects per patient was 3.55. The maximum adverse effects presented by patient were 8. Eight percent of the patients did not present any AE. The frequency of adverse effects on the CNS was highest. Dizzinesses are the most dominating. The frequencies of adverse effects observed among patients according to the systems affected are summarized in Table 2.

3.3 Plasmatic Concentrations

EFV plasma concentration average is of 6,360 ± 539 µg/L with a median of 3,925 µg/L. Three patients had concentration below 1,000 ng/mL, since 52 had concentrations above 4000 ng/mL. The distribution and frequencies of all EFV plasma concentrations are summarized in Table 3.

3.4 Plasmatic Concentrations and Demographic, Clinico-Biological, Therapeutic Characteristics

The study determined whether age (a), BMI (b), WHO clinical stage (c), therapeutic regimen (d) and CD4 counted (e) before the treatment initiation are parameters likely to influence EFV plasmatic concentration measured at 12 ± 2 h. Descriptive statistics of recorded data showed that there is not any correlation between the plasmatic concentration and the various parameters (aP = 0.64; bP = 0.55; cP = 0.65; dP = 0.39; eP = 0.58, respectively).

Table 1 Characteristic about the study population.

Characteristics	Study data
Demographic	
Age (years), (mean ± SD)	38.15 ± 0.9
Sexe (percentage), (men/women)	36.61/63.39
BMI (Kg/m^2), (mean ± SD)	22.3 ± 0.45
WHO clinical stage before initiation of ART, *N* (%)	
Stage I	31 (27.68)
Stage II	38 (33.93)
Stage III	33 (29.46)
Stage IV	10 (8.93)
CD4 count at initiation ($cell/mm^3$), *N* (%)	
< 350	97 (86.6)
> 350	15 (13.4)
Patients'distribution according to therapeutic regimen, *N* (%)	
TDF + 3TC + EFV	78 (69.64)
AZT + 3TC + EFV	31 (27.68)
D4T + 3TC + EFV	03 (2.68)

SD: Standard deviation; TDF: ténofovir; 3TC: lamivudine; AZT: Zidovudine; D4T: stavudine.

Table 2 Frequency of adverse effects among patients according to systems' affected by ART (N = number of patients in percentage).

Affected system	Adverse effects	Proportion of patients N (%)	
CNS	Dizziness	81 (72.3)	97 (86.6)
	Abnormal dreams	36 (32.1)	
	Insomnia	25 (22.3)	
	Somnolence	14 (12.5)	
	Headache	30 (26.8)	
	Nervousness	21 (18.7)	
	Memory disorder	12 (10.7)	
General	Tiredness	50 (44.6)	50 (44.6)
	Prurit	22 (19.6)	
Cutaneous	Cutaneous eruptions	17 (15.2)	41 (36.6)
	Abscess	2 (1.79)	
	Nauseas, vomiting	18 (16.1)	
Gastro-intestinal	Abdominal pains	09 (8.04)	35 (31.2)
	Diarrhoea	14 (12.5)	
Others		13 (11.6)	13 (11.6)

Table 3 Efavirenz levels concentration in the study population.

Plasma concentration (µg/L)	Number	Frequency (%)
Infra therapeutic (< 1,000)	3	2.7
Normal [1,000-4,000]	57	50.9
Supra therapeutic (> 4,000)	52	46.4
Total	112	100

Table 4 Association between the plasma concentrations and the number of adverse effects.

	Concentration		
	Coefficient	IC to 95%	*p*-value
Number of adverse effects	582.90	[33.37; 1132]	0.04
	Log (concentration)		
	Coefficient	IC to 95%	*p*-value
Number of adverse effects	0.11	[0.02; 2.35]	0.02

3.5 Plasmatic Concentrations and Adverse Effects

Investigating the relationship between plasma concentration and adverse effects, it was observed that the number of adverse effects increased proportionally with plasma concentration (p = 0.04). Thus, an increase of adverse effects number unit induced an increase of 583 µg/mL of plasmatic concentration (IC95 = [33.4; 1132], $p < 0.04$) (Table 4). However, the results obtained did not permit to establish an association between plasma concentration and the nature of adverse effects.

4. Discussion

The aim of the study was to appreciate EFV plasma concentrations profile in HIV infected individuals in Benin, and to explore an association with various factors.

4.1 Efavirenz Plasma Concentrations

EFV is a molecule that shows complex pharmacokinetic characteristics resulting in a significant variability of plasma concentrations. Plasma levels measurement can contribute to better management of HIV infection in clinical practice.

Inter-individual variance of plasma concentrations observed in our study is in the same range, even lower compared with other studies. However, plasma concentration median in our study population was

higher than all others studies conducted in Africa, which is very close to that found by Gounden et al. (3,980 µg/L) in South Africa [12]. But the median observed in our study was strangely higher than those found by Sarfo et al. (1,087 µg/L) or Gunda et al. (2,112 µg/L) respectively in Ghana and Tanzania [13-14]. Plasma concentration average of our population was 6,360 µg/L ± 539 µg/L. It is definitely higher than those found by Poeta and Wyen, which were respectively 2,200 and 2,077µg/L [15-16]. In the studies preceding ours, plasma concentrations averages were included in the therapeutic index described [1,000-4,000 µg/L]. The average observed in our study was above this therapeutic index, meaning that the percentage of patients having a supra-therapeutic plasma concentration is significantly elevated, comparatively with other studies. Indeed, EFV concentrations distribution according to therapeutic interval of our study are significantly different from the distribution observed in various studies ($p < 0.05$) [1, 3, 12-14].

EFV plasma concentrations distribution according to the therapeutic interval observed in our study is very close to that found by Gounden among South African patients [12].

4.2 Plasma Concentrations and Socio-demographic Factors

Our data did not highlight a relationship between plasma levels and socio-demographic factors such as age, weight, sex, BMI ($R^2 = 0.0702$). In the same way, Gounden et al. [12] in 2010 had not found any association between the parameters cited above and EFV plasma concentrations ($R^2 = 0.107$). Our observations are also in agreement with results obtained by Kappelhoff et al. [10], who did not find any association between weight, BMI and EFV plasma concentrations. However, divergent data exist in the literature. Stohr et al. had found that a high weight induced a weak plasmatic concentration of EFV [5]. Brazilian study of Poeta et al. [15] in 2011 had also revealed that high BMI induced weak level concentration of EFV ($p = 0.001$) [15]. Also, high BMI can mean a great drug distribution volume and thus, low plasma concentration. This difference with our result could be explained by the fact that the population Poeta et al. studied was slightly in overweight (25.6 kg/m^2 against 22.6 kg/m^2 in our study). A more recent study has shown the absence of relationship between demographic characteristics or biochemical parameters and EFV concentrations using a pharmacokinetic model developed from 96 included patients [17]. This study suggests that polymorphism of CYP2B6 was the only covariates that could influence pharmacokinetic parameters of EFV.

4.3 Plasma Concentrations and Therapeutic Regimen

Three types of therapeutic regimens were used by our patients (Table 1). All therapeutic regimens have in common lamivudine and EFV. We did not observe significant difference between medians of EFV plasma concentrations among various therapeutic regimens. This indicates that neither TDF, d4T, nor AZT seems to impact significantly EFV metabolism or its distribution. Concerning the distribution of EFV concentrations in the therapeutic margin described (under therapeutic, therapeutic, supratherapeutic), there is not any difference between various regimes of our study opposite to results found by Gunda et al. [14]. Indeed, stavudine and lamivudine induced plasma concentrations of NNRTI below the therapeutic index. On the other hand, zidovudine and lamivudine associated with NNRTI drugs could cause an increase of NNRTI plasma concentration. Tenofovir and emtricitabine allowed obtaining plasma concentration included in the therapeutic margin [18].

4.4 Adverse Effects

About 87% of our study population presented adverse effects on CNS. Similar frequencies have been reported by several authors [13, 19, 20]. However, within the framework of a study carried out in Ghana in

2013, only 9.4 % of HIV-infected patients had presented AE on CNS [13]. All studies undertaken on efavirenz confirmed that it's responsible for neurosensory AE. From the results presented in Table 2, dizzinesses were most dominating. Frequency of dizzinesses found in our study is significant compared with those brought back by Gounden et al., Diop et al., and Fumaz et al. [12, 18, 21]. Moreover, a study carried out in Benin on undesirable effect of antiretroviral drugs in 130 HIV-infected patients, argues the high frequency (64.6%) of neuropsychic effects when using ART based on EFV [20].

In our study, we did not inventoried psychic affections such as anxiety, severe depression, ideas of suicide, aggressive behaviors, maniacs and paranoiac reactions. In the same way, Vrouenraets et al. [22] did not report these affections. In contrast, it has been reported cases of patients suffering from depression (17%) and delirium (13%) in other study [23]. Absence of identification of certain psychiatric AE in our study can be related to skews of questionnaire used during the data-gathering. Indeed, the patients could not appreciate themselves the nature of psychiatric effects. Moreover, the transverse nature of our study was not favorable to collect chronic psychiatric affections.

In short, AE on CNS are most relevant and documented. In 2014, several studies reported that EFV AE on CNS occurred in more than half of patients [24]. However, prevalence of this toxicity is variable because of the contradictory definition and detection method used to appreciate "CNS toxicity" [14].

In addition to neuropsychic effects, we highlighted gastro-intestinal, cutaneous and general effects in proportion of 31.2%, 36.6% and 44.6%, respectively.

4.5 Plasma Concentrations and Adverse Effects

We investigated if presence of certain AE were related to a high EFV level, in particular a concentration higher than 4000 µg/L. In any cases, subjects exhibiting supratherapeutic concentration significantly did not present any more risk to feel particular AE. As surprising as that could be, patients in our study had in general very high plasma concentrations of EFV. Opposite to several authors who have found association between EFV plasma concentration and presence of neuropsychic AE [1, 5, 25-28], we did not highlighted such an association in our study. This could be related to the transverse nature of our study involving under-notification. In addition, it has been argued that neuropsychic AE induced by EFV were light and patients' capacity to support them settled at the end of couple weeks, especially subjects having defective genotypes CYP2B6 and exhibiting high plasma levels [29]. It is most likely case of many patients of our study. Assumption according to which patient educated to AE improve their tolerance degree towards these AE is also plausible.

However, we observed a significant correlation between the number of AE and plasma concentration. This result could reinforce recommendation of daily dose reduction for patients who exhibiting supratherapeutic concentration without affecting viral charge suppression. Patients having high plasma concentration of EFV should be subjected to closely follow-up. A recent study has shown that once-daily EFV 400 mg dose was so effective than once-daily EFV 600 mg despite lower plasma concentrations obtained, even if this study was probably critical because it compared pharmacokinetic parameters and plasma concentrations obtained at week 4 or 8 and clinical outcome at week 96 [30]. This study included 606 patients with 37% of African and 33% of Asian people.

In our study, only 2.7 % of the patients exhibited plasma concentration below the therapeutic margin. Within sight of these results, we can suppose high frequency of CYP2B6 516GT, CYP2B6 516TT and 983CT alleles in our study, thus explaining the strong plasma concentrations of EFV (46.4% of the patients above 4,000 ng/mL). In fact, EFV plasma concentrations are characterized by interindividual variance which is explained partly by CYP2B6

polymorphisms [17, 19]. Alleles 516GT, 516TT and 983CT are defective, inducing a slow metabolism of EFV and consequently high plasma concentrations. Siccardi et al. in 2012 had carried out a model of extrapolation concluding that it was necessary to reduce by 200 mg dose of EFV among patients having 516GT mutation, and by 400 mg for those having 516TT mutation of CYP2B6 gene [29]. Unfortunately, we were not able to determine CYP2B6 or CYP3A4 polymorphism gene of patients because of limited technical plate for genetic tests. CYP2B6 genotype of patients could provide data even more convincing to improve patients care.

To our knowledge, our study is the first report of such over-exposure to plasma concentrations among Beninese population of HIV patients treated by a 600 mg daily dose of EFV. In 322 Chinese patients, Meng et al. have shown that with a 600 mg daily dose of EFV, average EFV plasma concentration was 2,350 ± 2,090 µg/L, with 13.1% presenting concentration below 1,000 µg/mL and only 9.3% with concentrations above 4,000 µg/mL [31]. High concentrations were associated with polymorphisms of CYP2B6.

5. Conclusions

Our study highlighted an over-exposure to EFV drug in Beninese patients treated by a 600 mg standard daily-dose. The high plasma concentrations observed were not associated with age, sex, BMI, WHO clinical stage, CD4 cells count and antiretroviral therapy. The number of adverse effects observed among patients seems to be correlated with plasma concentrations of EFV. Further studies are necessary to identify possible causes of this over-exposure. Waiting more investigations, Beninese patients administered standard daily-dose of EFV required therapeutic drug monitoring in order to reduce incidence of adverse effects.

Conflict of Interest

The authors declared no conflict of interest.

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