Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients

Catia Marzolini[a], Amalio Telenti[b], Laurent A. Decosterd[a], Gilbert Greub[b], Jérôme Biollaz[a] and Thierry Buclin[a]

Objective: Limited information exists on the clinical usefulness of drug level monitoring for efavirenz, a once-daily non-nucleoside reverse transcriptase inhibitor (NNRTI). The aim of this study was to determine whether efavirenz plasma concentration monitoring could predict treatment failure and central nervous system (CNS) tolerability.

Methods: Blood samples were obtained from 130 HIV-infected patients receiving efavirenz in combination with other antiretroviral agents for more than 3 months. Efavirenz plasma concentrations were measured by high-performance liquid chromatography. An evaluation of CNS side-effects was performed and the viral load, CD4 cell count and other clinical and laboratory data were assessed. In 85 patients, these measures were repeated at 3 month intervals.

Results: Efavirenz plasma levels (n = 226) were measured at an average of 14 h after drug intake. Drug concentrations ranged from 125 to 15 230 μg/l (median 2188). Large inter-patient (CV 118%) and limited intra-patient (CV 30%) variabilities were observed in efavirenz levels. Virological failure was observed in 50% of patients with low efavirenz levels (< 1000 μg/l) versus 22 and 18% in patients with 1000–4000 μg/l or more than 4000 μg/l, respectively. CNS toxicity was approximately three times more frequent in patients with high efavirenz levels (> 4000 μg/l) compared with patients with 1000–4000 μg/l.

Conclusion: Treatment failure and CNS side-effects are associated with low and high efavirenz plasma levels, respectively. The important inter-individual variability in efavirenz levels strongly argues for dose adjustment on the basis of therapeutic drug monitoring to optimize treatment.

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Keywords: CNS side effects, drug monitoring, efavirenz, plasma levels, treatment failure

Introduction

Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) with a prolonged half-life [1–3]. allowing once-daily dosing, and therefore presenting an advantage for treatment compliance and efficacy [4–10]. Despite its potency, efavirenz is a drug with a low genetic barrier as a single mutation, most frequently

From the [a]Division of Clinical Pharmacology, Department of Medicine, and [b]Division of Infectious Diseases, University Hospital of Lausanne, Switzerland.

Correspondence to: Thierry Buclin, Division of Clinical Pharmacology, Beaumont 06-633, Department of Medicine, University Hospital (CHUV), 1011 Lausanne, Switzerland.

Tel: +41 21 314 42 65; fax: +41 21 314 42 66; e-mail: thierry.buclin@chuv.hospvd.ch

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K103N in the reverse transcriptase gene, and induces a high level of phenotypic resistance [3]. The emergence of efavirenz-resistant mutants is likely to be facilitated by repeated exposure to subtherapeutic drug levels. Treatment failure seems to be more frequent in patients with low efavirenz trough levels, compared with those with high levels (> 1100 μg/l) [11]. Moreover, 20–40% of patients receiving efavirenz have central nervous system (CNS) side-effects [12]. CNS disturbances range from dizziness to hallucinations, including frequent nightmares, dreams and insomnia [1,2]. The symptoms are usually mild to moderate in severity, and are reported to subside progressively over a few weeks after the initiation of efavirenz therapy [13]. Nevertheless, efavirenz is discontinued in 4% of patients because of the severity or persistence of such adverse effects [14].

As pharmacological differences among patients introduce wide heterogeneity in the response to antiretroviral therapy [15], monitoring of the drug levels could be useful in the clinical management of HIV disease [16]. Whereas this could apply to efavirenz, no evaluation of the target concentrations to be reached to ensure treatment success and toxicity avoidance has yet been reported. The aims of this study were to evaluate the inter- and intra-patient variability, to assess the influence of various factors on efavirenz disposition, and to explore the relationship between treatment failure or CNS side-effects and efavirenz plasma concentrations, by measuring plasma concentrations of efavirenz in field conditions.

Materials and methods

Patients were recruited at the outpatient HIV clinic at the university hospital of Lausanne, Switzerland, from January 1999 to June 2000. The study was approved by the local Ethics Committee. HIV-positive individuals treated for at least 3 months with efavirenz 600 mg a day in combination with other antiretroviral agents were included.

As efavirenz is generally administered at bedtime to improve its tolerability [1], it is difficult to determine trough levels in an outpatient setting. Blood samples were thus taken during the day, between 8 and 20 h post-dosing, at the patient's convenience. A blood sample (5 ml) was collected into lithium heparin Monovettes (Sarstedt, Nümbrecht, Germany). Plasma was isolated by centrifugation, viro-inactivated in a water bath at 60°C for 60 min and stored at −20°C until analysis. Plasma efavirenz levels were determined by reverse-phase high-performance liquid chromatography according to a validated method [17], enabling the simultaneous quantification in plasma of HIV protease inhibitors (PI) and efavirenz.

Concomitant medications at the time of sample collection were recorded. A standardized evaluation of CNS side-effects (insomnia, dizziness, headache, faint) was performed, together with the determination of viral load, CD4 cell count and other clinical and laboratory variables. These measures were repeated at 3 month intervals for a subset of patients.

The efavirenz concentration results and the viral load values were log transformed. Associations with discrete factors (patient, sex, PI, CNS toxicity) were explored using one-way analysis of variance, whereas linear regression was used for continuous covariates (viral load, body mass index, efavirenz treatment duration, sampling time, CD4 cell count). The predictive value of efavirenz concentrations for viral suppression (Amplicor test, level of detection 400 copies/ml and modified ultrasensitive method, level of detection < 20 copies/ml; Roche Diagnostics, Basel, Switzerland) or CNS adverse effects was assessed by logistic regression analysis.

Results

The plasma level of efavirenz was determined at mid-interval in 130 patients (93 men) aged 23–74 years, treated either with a combination therapy of two nucleosidic reverse transcriptase inhibitors (NRTI) or PI with or without NRTI. The most frequent NRTI and PI combined with efavirenz were zidovudine, lamivudine and nelfinavir, respectively. The blood sampling occurred between 3 and 18 months after the initiation of efavirenz treatment (average 8 months). Eighty-five patients provided two to eight samples at 3 month intervals. In total, 226 drug levels were determined. Patients and treatment characteristics, laboratory values, CNS toxicity and range of efavirenz plasma levels are summarized in Table 1.

Drug concentrations ranged from 125 to 15 230 μg/l (median 2188 μg/l). The average (SD) sampling time interval was 14.0 ± 2.7 h after dose intake. The efavirenz levels were only slightly influenced by the sampling time, which explained only 3% of the total variance ($P = 0.006$) in accordance with the long plasma half-life reflected in the small log-linear slope ($0.055\ h^{-1}$) (Fig. 1a). The repeated determinations performed in 85 patients revealed a low intra-patient variability [coefficient of variation (CV) 30%] over 3 month intervals, whereas inter-patient variability was much larger (CV 118%), accounting for 90% of the total variance.

Table 1. Analysis per patient and per sample according to efavirenz concentration level.

		Efavirenz concentration			
Analysis per patient		< 1000 μg/l n = 10	1000–4000 μg/l n = 103	> 4000 μg/l n = 17	*P*
Sex	Male (%)	5 (50)	74 (72)	14 (82)	0.20
Age (years)	Mean ± SD	43 ± 12	40 ± 10	40 ± 9	0.61
BMI (kg/m^2)	Mean ± SD	23 ± 2	23 ± 3	23 ± 3	0.90
Efavirenz duration (months)	Mean ± SD	11 ± 3	8 ± 4	8 ± 3	0.20
PI co-administration	Yes (%)	4 (40)	29 (28)	7 (41)	0.45
CD4 cell count (× 10^6/l)	Mean ± SD	259 ± 222	420 ± 246	348 ± 171	0.08
Viral load (copies/ml)	Geometric mean (CV%)	1878 (6966)	166 (1661)	110 (1691)	0.035
Viral failure (> 400 copies/ml)	Yes (%)	5 (50)	23 (22)	3 (18)	0.12
CNS toxicity	Yes (%)	0	9 (9)	4 (24)	0.093
Analysis per sample		n = 19	n = 180	n = 27	
CD4 cell count (× 10^6/l)	Mean ± SD	233 ± 195	437 ± 251	335 ± 158	0.0005
Viral load (copies/ml)	Geometric mean (CV%)	1187 (5241)	134 (1534)	102 (1378)	0.005
Viral failure (> 400 copies/ml)	Yes (%)	10 (53)	40 (22)	5 (19)	0.01
CNS toxicity	Yes (%)	0	11 (6)	6 (22)	0.005

BMI, Body mass index; CNS, central nervous system; CV, coefficient of variation.

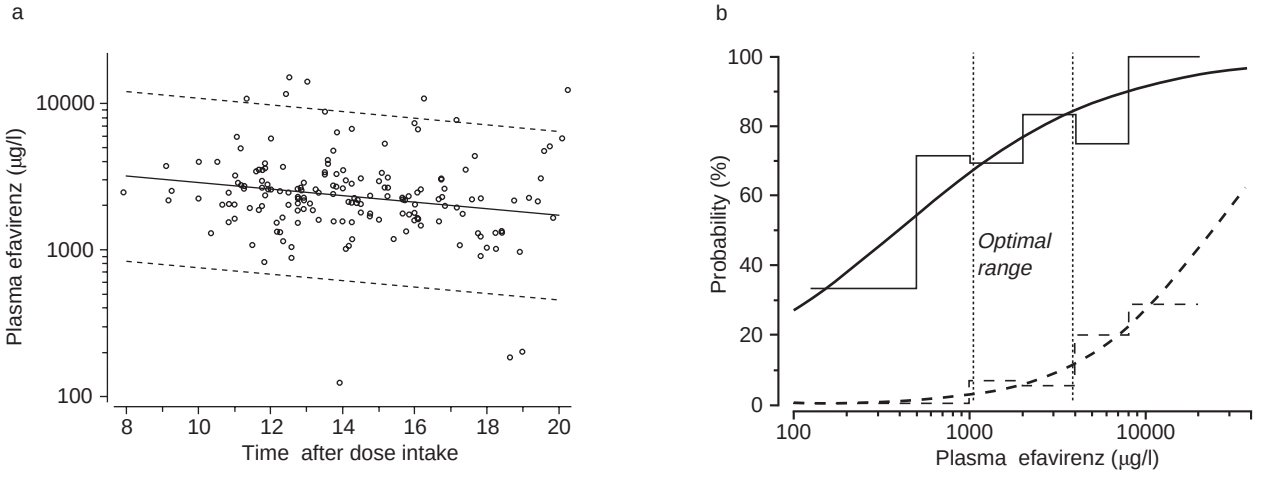

Fig. 1. (a) Efavirenz plasma concentration versus time in 171 determinations in 99 patients with viral suppression under efavirenz 600 mg a day. —— Average trend; – – 95% confidence intervals. (b) Predictive value of efavirenz concentration for the probability of viral suppression (——) and central nervous system adverse effects (– –). Both the observed frequency in predefined concentration ranges (stepped lines) and the fitted logistic regression model (curves) are indicated. An optimal range is proposed between 1000 and 4000 μg/l.

Among the covariates tested to explain the pharmacokinetic variability of efavirenz, neither sex, age, or body mass index influenced efavirenz plasma levels. Data gathered from the 40 patients receiving efavirenz in combination with a PI indicated that this co-medication did not influence efavirenz plasma levels.

Viral load values ranged from 20 to over 379 000 copies/ml; 76% had viral load levels below 400 copies/ml. A significant inverse correlation was found between efavirenz levels and viral load in this heterogeneous group of patients. Indeed, virological failure was observed in five out of 10 (50%) patients with low (< 1000 μg/l) efavirenz levels and in 23 out of 103 (22%) and three out of 17 (18%) with 1000–4000 μg/l or over 4000 μg/l, respectively. The CD4 cell count ranged from 6 to 1145 × 10^6 cells/l (median 376).

Thirteen patients (10%) had sustained adverse effects. CNS toxicity was observed in four out of 17 (24%) patients with high (> 4000 μg/l) efavirenz levels and in nine out of 103 (9%) with 1000–4000 μg/l. A range of mid-interval drug levels (1000–4000 μg/l) was proposed according to observed drug levels, toxicity and efficacy in viral suppression. This is expressed in the

predictive value of efavirenz concentration for the probability of viral suppression and CNS adverse effects (Fig. 1b).

Discussion

Clinicians are often confronted with treatment failure or side-effects, and are in need of methods to evaluate drug exposure in patients. The large range of concentrations observed underlines the pharmacokinetic differences among patients. The marked inter-patient and low intra-patient variability suggest that a therapeutic drug monitoring (TDM) strategy may be useful for individualizing the treatment. According to Joshi *et al.* [11], trough plasma levels represent an important predictor of virological failure in compliant patients. On the other hand, the trough concentration adequately predicts the extent of drug exposure as expressed by the area under the curve [18]. However, efavirenz trough sampling is not convenient because the drug is normally given at bedtime. In this study, we demonstrate that, given the long half-life of efavirenz, mid-interval sampling times between 8 and 20 h post-dose are feasible without a significant loss of information.

The patients with treatment failure had lower efavirenz concentrations than the non-failure patients. However, the overlap in plasma concentrations between the two groups is large, as previously reported [11]. One major cause of low plasma levels is non-compliance. Drug level determination could be used for treatment adherence evaluation, because efavirenz has a long half-life. Low levels would thus suggest the omission of several consecutive doses. Nevertheless, one patient in our collective had repeatedly low levels (200 μg/l) despite good compliance. This epileptic patient was on phenobarbital, a known potent inducer of cytochrome CYP 3A4, the enzyme responsible for the metabolism of efavirenz. Other conditions may also be associated with significant pharmacokinetic variations. Our data do not suggest, however, that the co-administration of PI influences the levels of efavirenz as suggested by others [18,19], despite sharing a common cytochrome P450 metabolic pathway.

In our study, 10% of patients had persistent CNS side-effects. Descriptions of CNS adverse effects included light-headedness, feeling faint, dizzy, drunk, 'out of control' or restless. A few patients had nightmares, dreams or impaired concentration. Dose splitting did not substantially shorten the duration of symptoms, or reduce their intensity [13]. However, it has been proposed that a dose-escalating regimen may provide a better tolerance profile, without evidence of decreased antiviral activity in the short term [20]. We demonstrated that CNS side-effects were more frequent in patients with high drug levels. Tolerance towards this adverse effect improved with time. In one patient, we observed exceptionally high efavirenz levels (> 10 000 μg/l) but all CNS symptoms had disappeared 9 months after the beginning of treatment, despite persisting high efavirenz levels.

Antiretroviral therapy for HIV-1 infection has become more and more complex. The numerous dosing regimens proposed, the associated toxicities, and the potential for drug–drug and food–drug interactions further complicate patient care. Patient non-compliance represents a further problem. In this situation, TDM may represent a valuable tool for the clinician, provided the drug pharmacokinetics have good intra-individual reproducibility, and the circulating levels are predictive of treatment success and tolerability. These conditions are seemingly met by efavirenz, and further studies aimed at validating the clinical usefulness of TDM for individualizing the dosing regimen are warranted. From our exploratory study, a 1000–4000 μg/l range at mid-dosing interval seems to represent a suitable target for dose individualization, which should be adapted considering the clinical condition of the patient.

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