THERAPEUTIC DRUG MONITORING (TDM) OF EFAVIRENZ IN HIV-INFECTED PATIENTS TREATED BY SUSTIVA® ASSOCIATED OR NOT WITH RITONAVIR

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OBJECTIVE

Efavirenz (EFV) is a Non Nucleoside Reverse Transcriptase Inhibitor (NNRTI) usually associated with Nucleoside Reverse Transcritase Inhibitors (NRTI) as antiretroviral (ARV) first line treatment.

In heavily pretreated patients, EFV is also combined with Protease Inhibitors (PI) and consequently often administered with ritonavir (RTV), used as enzymatic inhibitor of cytochrome P450 3A to increase PI plasma concentrations. Moreover EFV shows a metabolic inductive effect with a self-induction of its own metabolism

➢ Because of these drug interactions, a therapeutic monitoring of EFV must be required to evaluate plasma levels and optimize dosage regimen in the aim to ensure antiviral efficacy and to limit adverse events.

➢ The monitoring of EFV plasma concentrations was conducted for a half year in patients receiving Sustiva ® and data from TDM were analysed depending on association with RTV as PI booster.

PATIENTS AND METHOD

❖ The study was performed by measuring EFV plasma levels in 48 HIV-infected patients treated by Sustiva® with a 600 mg once a day dose.

❖ When used, RTV was prescribed at a 100 mg BID dose.

❖ ARV associated drugs were specially INTI when no RTV was administered, and PI when RTV was included.

❖ The EFV concentrations were obtained at steady-state, at least 8 hours after drug intake.

❖ EFV plasma levels were analysed according to RTV association or not:

- ➢ group EFV (without RTV) : 27 patients (10 F - 17 M)
- ➢ group EFV + RTV : 21 patients (2 F et 19 M).

❖ **Usual therapeutic zone** retained for EFV trough concentration:

1,500 mg/L < EFV trough C < 5,000 mg/L

❖ The **analytical determination of EFV** was carried out by a reverse phase high performance liquid chromatography with spectrophotometric detection, after liquid/solid plasma extraction.

	EFV group	EFV + RTV group
patients	27	21
associated antiretroviral treatments	22 patients : + 2 INTI 3 patients : + 3 INTI 1 patient : + 4 INTI 1 patient : + 1 INTI + 1 IP	19 patients : + 1 à 2 IP 2 patients : + 1 INTI
weight (kg)	63,18 ± 8,806 [51,00-80,00]	62,95 ± 13,86 [32,00-92,00]
EFV dosage (mg/kg) OD	9,384 ± 1,552 [7,792-13,04]	9,342 ± 2,373 [5,797-13,95]

RESULTS

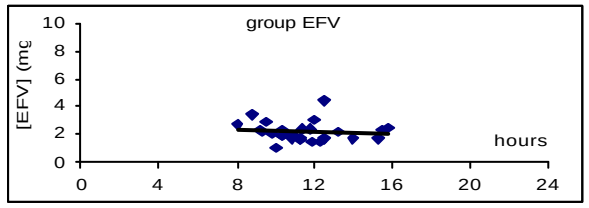
In all 48 patients, the mean plasma level of EFV was **2,66 ± 1,42 mg/l** at a mean time of **11,8 hours** after EFV administration.

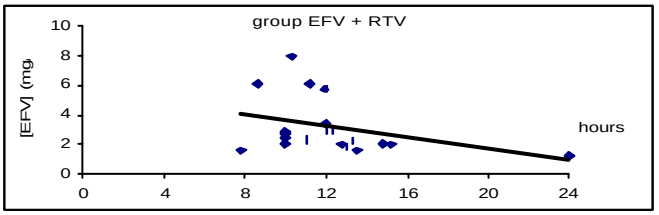
EFV concentrations were in the therapeutic range for 43 out of 48 patients, independently of drug associations.

❖ In the **EFV+RTV group**, mean plasma level is significantly higher than that observed in the **EFV group**:
3,15 ± 1,82 mg/L versus **2,22 ± 0,70 mg/L** ($p < 0,05$), at a mean time of 12,2 and 11,8 hours, respectively.

❖ Metabolic inhibition due to RTV is greater than inductive effect of EFV.

❖ 5 patients out of 21 from EFV+RTV group show plasma concentrations above therapeutic range (5,000 mg/L). In spite of drug interactions no dosage regimen of Sustiva® was necessary.





CONCLUSION

❖ With a Sustiva ® 600 mg OD dose, an optimal EFV plasma level is observed in 90% patients, with any combined treatment. The increase of the EFV concentrations of about 40% in the EFV+RTV group did not justify any dosage adjustement. However, EFV plasma levels must be controlled when RTV is administered because of the potential risk of adverse effects.

❖ The relations between EFV concentrations and adverse effects must be farther accessed.

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