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Follow-up Measurements of Nevirapine Plasma Levels over a Prolonged Period*

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Abstract: Over a period of more than four years of treatment, 177 Nevirapine plasma levels were taken from 27 patients. The values showed a high inter-patient variability and a lower intra-patient variability. Differences in body weight turned out to be the main reason for inter-patient variability. Treatment over a prolonged period did not result in any change in plasma concentrations. Adjusting dosage by means of therapeutic drug monitoring would appear to be a reasonable way of maximising patient benefit from treatment.

Key words: Nevirapine; plasma levels

Introduction

Nevirapine (NVP) is a non-nucleoside reverse transcriptase inhibitor which acts against Human Immunodeficiency Virus Type 1 (HIV-1). Structurally, NVP is a member of the dipyridodiazepinone chemical class of compounds.

The drug is readily absorbed with a bioavailability of over 90% and distributes well to all tissues [1]. It is metabolised in the liver mainly by Cyp3A4 and CYP2B6 and is capable of inducing its own metabolism, leading to an approximate 1.5 to 2-fold increase in the apparent oral clearance during the first two-to-four weeks of treatment [2].

The usefulness of Therapeutic drug monitoring (TDM) for Nevirapine has already been outlined in sufficient detail [3, 4]. Furthermore, a correlation between plasma levels and effectiveness of therapy has been demonstrated in several publications [3, 5].

However, up to now, data describing long-term pharmacokinetics of NVP or pharmacokinetics in patients with liver impairment has been scarce [3].

In this paper, we report the results of a retrospective analysis of NVP plasma levels obtained over a period of more than four years. Also we outline the history of one patient with liver cirrhosis who was treated with low-dose NVP on a long-term basis. Finally, we suggest an adjustment of dosage in some patients on the basis of these findings.

Patients and Methods

Patients

Patients were recruited from the outpatient department of the University-Hospital, Würzburg. Subjects who had taken NVP between 1997 and May 2002 were identified by means of electronic data processing. Patients whose NVP plasma level measurements were available were included, if they had received NVP for more than four weeks. Development of a rash in the early stage of the treatment which caused treatment interruption was a reason for study exclusion.

Patients were regarded as "compliant" if no irregularity in taking the medication was documented by their physician. Patients who were admitted at least once having neglected to take the medication regularly were regarded as "non-compliant".

Nevirapine Plasma Concentrations

NVP plasma concentrations were usually measured four weeks after treatment initiation and subsequently in 12-week intervals. Blood samples were taken at random times after drug ingestion. The time interval between ingestion of the last dose and blood sampling was recorded.

Concentration of NVP in plasma was determined with a sensitive and validated gas chromatographic assay described previously [6].

Concentrations of below 1.000 ng/ml were considered in all probability to be a failure in the part of the patient to comply with the treatment and patients were therefore omitted from this study.

Statistical Analysis

Mean value and standard deviation of Nevirapine plasma levels were calculated for all patients. The mean of all standard deviations was defined as intra-patient variability and the standard deviation of all mean values was defined as inter-patient variability.

Correlations between Nevirapine plasma levels and body weight as well as time intervals after ingestion of the last dose were investigated with the Spearman rho coefficient.

To eliminate the influence of body weight regression analysis of Nevirapine plasma levels on body weight was carried out. Mann-Whitney-U-tests were used to evaluate the influence of the following factors on weight-adjusted Nevirapine plasma levels: smoking, compliance, sex and presence of viral hepatitis.

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The Spearman rho coefficient was also calculated between NVP plasma levels and time elapsed since commencement of treatment. One-way Analysis of variance (ANOVA) was used to compare measurements obtained in weeks 4-50, 51-100, 101-150 and >150.

Statistical calculations were performed using "Statistical Product and Service Solutions" (SPSS) for Windows (version 11.0). A significance level of 0.05 was used throughout.

Results

Patients

27 patients who met inclusion criteria were identified. Basic clinical characteristics are summarized in Table 1.

Increase of HI-viral load during treatment with Nevirapine was observed in two patients after 45 and 48 weeks of treatment, respectively. Nevirapine was replaced in these cases. All other patients received Nevirapine until the end of the observation period.

Nevirapine Plasma Concentrations

177 NVP plasma concentration measurements (an average of 6.6 measurements per patient) could be included for statistical analysis (Fig. 1).

The mean NVP plasma concentration was 4.465 ± 2.068 ng/ml (mean ± standard deviation).

Intra-patient variability was 34% and the inter-patient variability was 27% of the mean.

In twelve patients, at least one NVP plasma level was below 3.000 ng/ml during the first year of treatment. The mean value of these 12 patients was 3.063 ± 676 ng/ml, while the mean value of all the other patients was 5.122 ± 1.301 ng/ml.

There was a significant linear correlation between body weight and Nevirapine plasma levels. The correlation coefficient amounted to R = 0.556 (p = 0.003).

Table 1. Clinical characteristics of 27 patients included into the study.

Characteristic	**No. of patients**
Sex	
female	5
male	22
Hepatitis B/C coinfection	5
CD 4 cell count at initiation of NVP treatment	
<200 cells/mm^3	8
200-499 cells/mm^3	13
≥500 cells/mm^3	6
Previous treatment	
none	5
some previous treatment	22
Duration of Nevirapine treatment	
4-50 weeks	15
51-100 weeks	7
101-150 weeks	0
>150 weeks	5
Compliance with treatment	
Patients regarded as "compliant"	17
Patients regarded as "non-compliant"	10

The mean NVP plasma concentration in patients with body weight <70kg was 4.906 ± 1.352 ng/ml, while in patients with >80kg it was 3.111 ± 1.545 ng/ml.

There was also a significant correlation between plasma levels and time elapsed since ingestion of the last dose (R = -0.26, p = 0.005).

Mean values of Nevirapine plasma levels did not differ significantly between compliant patients and non-compliant patients (4.126 ng/ml and 5.128 ng/ml, p = 0.75), but standard deviation was more than four times higher in non-compliant patients (525 ng/ml vs. 2.322 ng/ml).

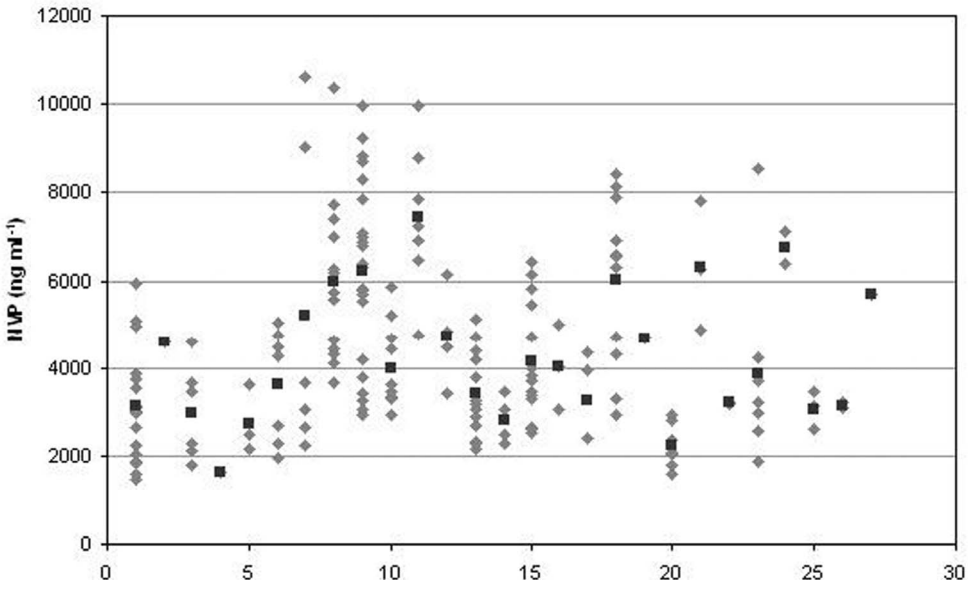

Fig. 1. Nevirapine plasma levels of 27 patients.

The mean plasma levels showed a tendency to be lower in smokers than in non-smokers.($p = 0.17$).

Differences in sex of patients and coinfection with viral hepatitis did not influence the mean of NVP plasma levels ($p = 0.33$ and $p = 0.60$, respectively).

Long-term Development of Nevirapine Plasma Levels

Fig. 2 shows NVP plasma concentrations plotted over time elapsed since treatment initiation.

The Spearman rho coefficient between the two variables was $k = 0.028$, and was not significant ($p = 0.73$).

Mean values and standard deviation of measurements taken at 50-week intervals are shown in Fig. 3. One-way Analysis of variance reveals no significant difference between the groups of values ($p = 0.63$).

We can therefore conclude that there was no tendency towards a change in plasma levels during prolonged therapy.

Case History

One patient suffering from liver cirrhosis (Child B) due to chronic Hepatitis C was administered 200 mg NVP per day on a long-term basis. Zidovudine and Lamivudine had been replaced by NVP, in order to avoid lactic acidosis. Simultaneously, the patient was given low-dose Indinavir (3*200mg/d). No other antiretroviral medication was administered during the period in which this study was carried out.

NVP plasma levels obtained from this patient are shown in Fig 4.

The mean NVP plasma level was 2.913 ± 1.338 ng/ml (65% of the mean value of the other patients).

The patient reported a respiratory infection with

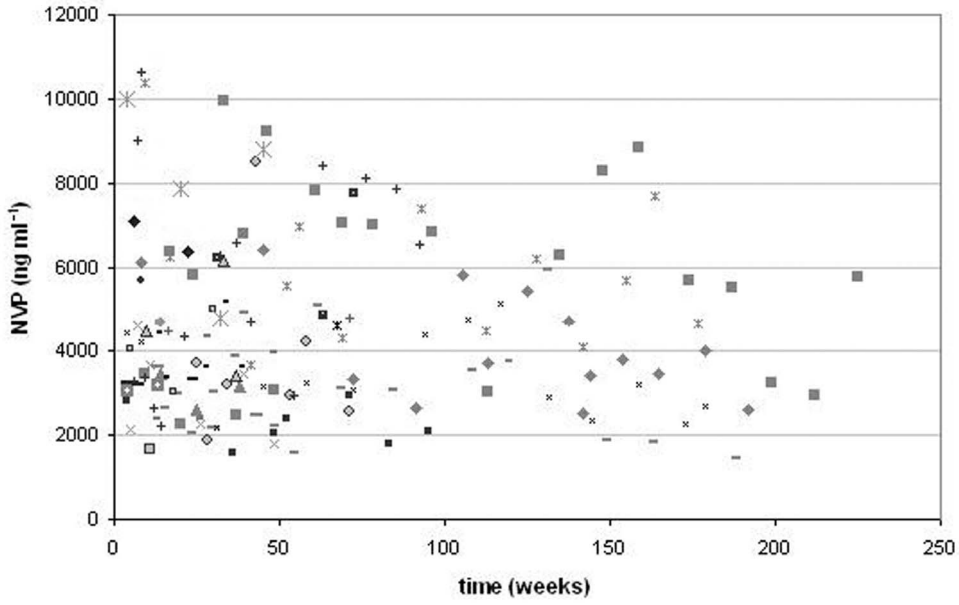

Fig. 2. Nevirapine plasma levels plotted over time after initiation of treatment.

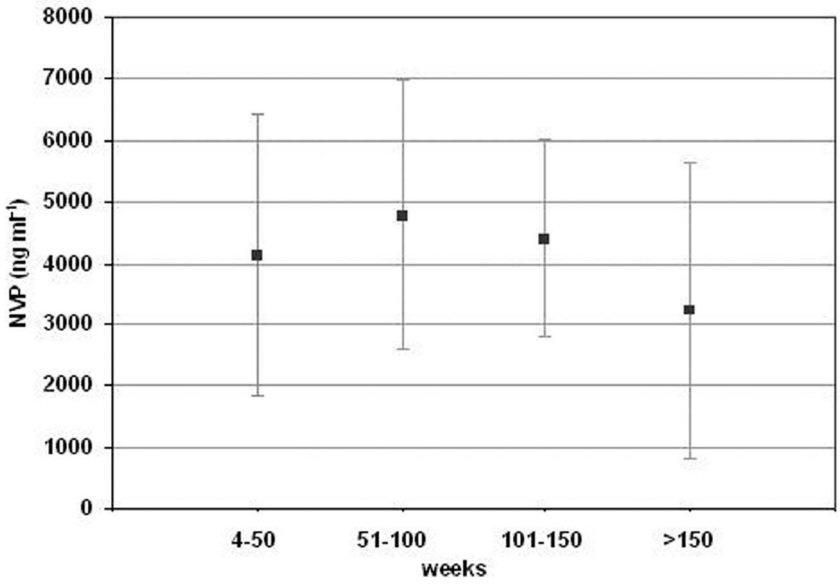

Fig. 3. Mean ± standard deviation of NVP plasma levels obtained at various time intervals. The groups of values did not differ significantly ($p = 0,63$).

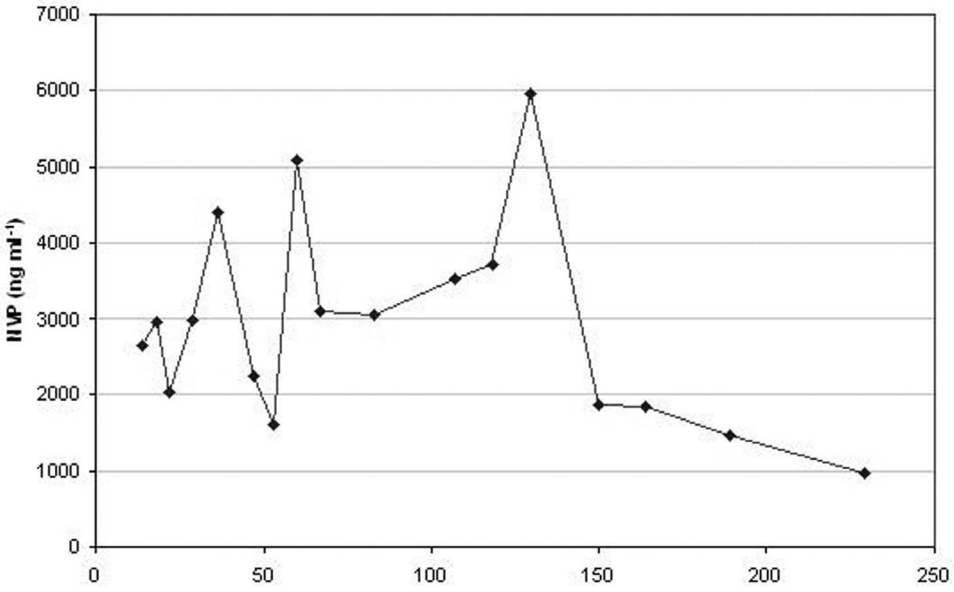

Fig. 4. Nevirapine plasma levels obtained from a patient with HCV-associated liver cirrhosis, who received a low-dose NVP (200mg qd) containing regimen.

high temperature, when low NVP plasma levels were measured (weeks 53 and 229).

The HIV-1 RNA level was below limit of detection in any measurement taken throughout the period of observation. Simultaneously, the CD 4 cell count increased from 39 (week 3) to 318 cells/μl (week 229).

Discussion

We found a high inter-patient variability and a lower intra-patient variability, in accordance with results of earlier studies [3, 7].

Variation of body weight was identified as the main reason for inter-patient variability. Plasma levels of patients with body weight >80kg were found approximately one-third below average.

The time interval between ingestion of the last dose and blood sampling was also related to the Nevirapine plasma levels. However, due to the long half-life of the drug, this factor was of minor impact. A method for eliminating the effect of time interval from Nevirapine plasma level measurements has been described previously [5].

Nevirapine plasma levels were lower in smokers than in non-smokers. Although the difference was not significant, enzyme induction caused by nicotine would be a plausible explanation for this phenomenon, in accordance with results from an earlier study [8].

Differences in compliance with treatment did not contribute to inter-patient-variability, but did contribute to intra-patient variability.

Due to induction of its own metabolism, long-term changes of pharmacokinetics of Nevirapine would appear possible in theory. However, autoinduction takes place mainly during the first 2-4 weeks of treatment [2], and the stability of NVP plasma concentrations has previously been demonstrated for a period of two years [7]. We can confirm these findings for a period of more than four years of treatment.

Pharmacokinetics of NVP in patients with liver impairment have not yet been thoroughly investigated. Theoretically, accumulation of the drug is possible as well as a decrease in plasma levels due to enhanced metabolism [2, 4]. For fear of accumulation, the patient suffering from HCV associated liver cirrhosis, as described above, was treated with low-dose NVP on a long-term basis. In fact, the mean NVP plasma level in this patient was about two thirds of the mean plasma concentration of the other patients. Different time intervals after ingestion of the drug may have contributed to higher intra-patient-variability in this patient.

Although the antiretroviral treatment with Nevirapine was effective in all but two cases of our study, a relationship between NVP plasma levels and antiviral efficacy could be shown in the same way as previously been demonstrated [3, 5].

Taken together, only certain aspects of a high inter-patient as well as intra-patient variability could be explained in this study. Major factors of lowering NVP plasma levels in this investigation were high bodyweight, insufficient compliance and smoking. The increase of NVP plasma levels in a patient with HCV associated liver cirrhosis was shown. In order to be able to predict Nevirapine plasma levels on the basis of clinical data, further investigations will be required, such as examination of genetic differences in CYP 450 and P-Glycoproteine, as well as variation of α_1-acid protein.

Guidelines for use of antiretroviral agents in HIV-1-infected adults and adolescents suggest minimum target levels for persons with wild type HIV-1 infection of 3.400 ng/ml [9]. We therefore regard dose adjustment on the basis of TDM as appropriate in optimizing the NVP treatment.

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