Nevirapine (NVP) Plasma Concentrations are Still Detectable after More Than Two Weeks in the Majority of Women Receiving Single Dose NVP: Implications for Intervention Studies

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ABSTRACT

Background: NVP in a single 200mg dose is a highly cost-effective strategy to reduce perinatal HIV-1 transmission. Its major disadvantage is the selection of NVP resistance in 20-30% of women, probably due to the long elimination half-life of NVP. In order to develop intervention strategies it is of crucial importance to know the interpatient variability in NVP half-life in women receiving a single dose of NVP, and factors that may influence this.

Methods: HIV-negative, healthy, non-pregnant Dutch women were eligible for this study which was conducted as a prelude to a subsequent study in Tanzania. After receiving a single 200mg dose of NVP (Day 1), blood was sampled for measurement of NVP twice-a-week for a total of 21 days. NVP plasma levels were determined by a validated HPLC method with a lower limit of quantification of 0.15 mg/L. The primary endpoint was the first sample with an undetectable NVP concentration.

Results: Forty-four subjects participated. The median age, height and body weight (+ interquartile range) were 26 (21-33) yr, 1.72 (1.68-1.75) m, and 64 (59-75) kg, respectively. Median elimination half-life of NVP was 56.7h with a range of 25.6 to 164h. The time to the first undetectable NVP plasma concentration was 11 days in 4 subjects, 15 days in 12, 18 days in 12, and 21 days in 9 subjects. In the remaining 7 subjects NVP was still detectable on day 22, the last day of sampling. Time to an undetectable NVP plasma concentration was not influenced by age, height, body weight, body surface area, alcohol use or smoking.

Conclusions: The majority of women who received a single NVP dose of 200mg still had detectable plasma concentrations of NVP after more than 2 weeks. This information, if confirmed in the African setting, is valuable for designing intervention studies to prevent the development of NVP resistance.

INTRODUCTION

A single dose of NVP for the mother followed by a single dose for the infant is a highly cost-effective strategy to reduce perinatal HIV-1 transmission, esp. for mothers who present late during pregnancy (e.g. just before delivery). Several programs are running to implement this preventive strategy in developing countries and the manufacturer of NVP, Boehringer Ingelheim, has provided NVP for free in these programs.

One of the major disadvantages of this single-dose NVP strategy is the selection of NVP resistance in about 20-30% of women. The mechanism behind this is probably the long elimination half-life of NVP which leads to low NVP plasma levels during several days after delivery, which creates a perfect environment for the development of resistance.

In the near future, one may consider interventions that will maintain the benefits of the single-dose NVP preventive strategy while reducing the risk for the development of NVP resistance. For such interventions it is crucial to know the interpatient variability in NVP half-life in these women, and the factors that may influence this.

METHODS

As a prelude to a subsequent study in Tanzania, we conducted a study in HIV-negative, healthy, non-pregnant Dutch women, aged 18-40 years. All study subjects received a single dose of 200mg of NVP at Day 1. At subsequent visits on Days 4, 8, 11, 15, 18, and 22, blood was drawn for measurement of NVP plasma levels. Additionally, saliva was collected at the same time using a Salivette (Sarstedt). Plasma and saliva NVP concentrations were determined by HPLC. The lower limit of quantification of the assay was 0.15 mg/L.

The primary endpoint was the first plasma sample with an undetectable NVP concentration.

RESULTS

A total of 44 subjects participated in this study. One subject discontinued after 11 days for personal reasons and her data were excluded from the analysis. Subject characteristics are given in Table 1.

Table 1 Subject characteristics (n=43)

Parameter (units)	Age (yr)	Body weight (kg)	Length (m)	Body surface area (m^2)	Race (n,%)	Smokers (n,%)	Using alcohol (n,%)	Using oral contraception (n,%)
Median	26	64	1.72	1.75	Caucasian 41 (95%) Asian 1 (2%) Mixed 1 (2%)	8 (19%)	28 (65%)	17 (40%)
Interquartile range	21-33	59-73	1.68 – 1.75	1.68 – 1.87				

RESULTS (continued)

The median plasma and saliva NVP concentration vs. time curves are depticted in figure 1. The time to first undetectable NVP plasma or saliva concentration is presented in figure 2. Median values for NVP pharmacokinetic parameters in plasma and saliva are given in table 2.

The time to undetectable plasma NVP concentration was not influenced by age, height, body weight, body surface area, smoking or the use of alcohol. In contrast, subjects using oral contraception had a significant longer time to undetectable NVP plasma concentrations than subjects not using oral contraception (table 3)

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Figure 1 Plasma and saliva NVP concentrations vs. time curves

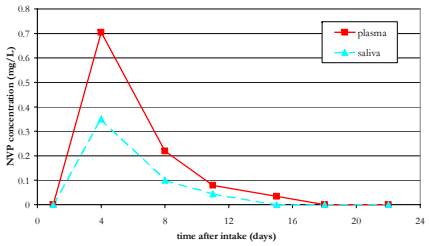


Figure 2 Time to first undetectable plasma or saliva NVP concentration

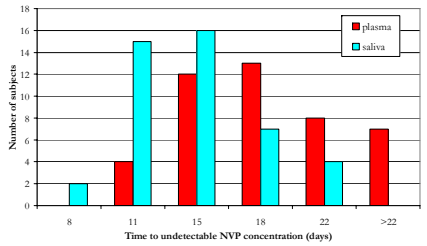
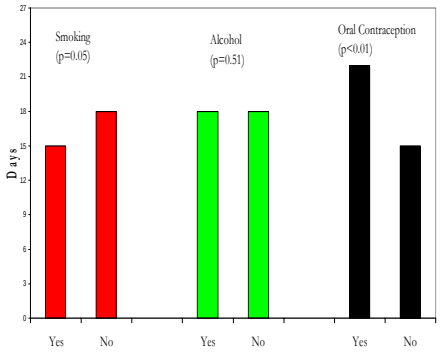


Table 2 Pharmacokinetic parameters (median + range) of NVP in plasma and saliva

Parameter	Units	Plasma	Saliva
CL/F	L/h	2.36 (0.81-5.66)	4.57 (1.59-10.35)
T-half	H	56.7 (25.6-164)	77.1 (36-265)
Vd/F	L	177 (49-370)	363 (201-798)
Cmax	mg/L	0.71 (0.36-1.59)	0.35 (0.03-0.77)
Time to undetectable concentration	Days	18 (11 - >22)	15 (8-22)

Figure 3 Correlation analysis of factors possibly influencing time to undetectable plasma NVP concentration



CONCLUSIONS

The majority of women who received a single NVP dose of 200mg still had dectectable NVP plasma concentrations after more than 2 weeks (and some even after 3 weeks)

Saliva appeared to be a good alternative for plasma when following the decay of NVP concentrations in a subject; undetectable saliva levels occurred on average 3 days before they became undetectable in plasma

Use of oral contraceptives was associated with a longer time to undetectable NVP plasma concentration, but this is not relevant for the setting of prevention of mother-to-child transmission.

If the data are confirmed in the target population of pregnant, HIV-infected African women, interventions to prevent the development of NVP resistance should last at least 2 weeks