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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

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Incidence and risk factors for nevirapine-associated rash

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Abstract *Objective*: To determine the incidence of rash in HIV-1 infected individuals starting a nevirapine-containing regimen in an unselected outpatient clinic population. Possible risk factors including plasma concentrations of nevirapine were evaluated for their relationship with the occurrence of a rash.
Methods: The occurrence of rash was extracted from the outpatient medical records or based on a prescription of the antihistaminic cetirizine as documented by the community pharmacy within the first 90 days of nevirapine use. During regular visits to the clinic blood samples were collected for the determination of nevirapine plasma concentrations. Possible risk factors such as demographics, immunology, virology, clinical chemistry and antiretroviral pretreatment were collected at baseline for each patient. In addition, concomitantly used drugs during the nevirapine-based regimen were recorded. The association between these factors and the occurrence of rash was studied. Primary outcome was the onset of rash within the first 90 days after initiation of a nevirapine-containing regimen.
Results: Data from 216 HIV-1-infected patients were used in this study. Thirty-eight patients (17.6%) developed a rash of some grade that led to discontinuation of nevirapine in seven patients (3.2% of the included patients). The median time to occurrence of rash was 26 days (interquartile range 17–46 days). The multivariate analysis showed that patients pretreated with antiretroviral drugs less than 12 months before the initiation of a nevirapine-containing regimen had a more than 2.5-fold increased risk of developing rash. Furthermore, nevirapine plasma concentrations were also significantly related to the occurrence of rash. A more than twofold increased risk for developing rash was observed for patients with nevirapine plasma concentrations above 5.3 mg/l.
Conclusions: This is the first study demonstrating that patients with antiretroviral pretreatment less than 12 months and with nevirapine plasma concentrations above 5.3 mg/l during the first 90 days of treatment are at a higher risk for the development of rash. It is therefore advised to monitor this group of patients carefully when initiating nevirapine-containing therapy.

Keywords Nevirapine · Rash · Incidence · Risk factors

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Introduction

Cutaneous disorders occur with a relatively high frequency in HIV-infected patients and show an increase in incidence and severity as the disease progresses [1, 2]. A number of drugs currently available for the treatment of HIV are involved in skin reactions including all licensed nonnucleoside reverse transcriptase inhibitors (NNRTI; nevirapine, efavirenz, delavirdine), the nucleoside reverse transcriptase inhibitor (NRTI) abacavir, and the protease inhibitor (PI) amprenavir [3]. Rash is the most frequently observed adverse event with nevirapine, which manifests as a maculopapular eruption with or without constitutional symptoms such as fever, edema, myalgia, and arthralgia. This rash is in general mild and transient. However, severe fatal reactions such as Stevens-Johnson syndrome may occur [4, 5]. Nevirapine-associated rash has been reported to be as high as 48% after a starting dose of 400 mg/day [6]. Nevirapine shows autoinduction of cytochrome P450 isoenzymes,

resulting in a decrease in the terminal half-life in plasma from 45 h following a single dose to 24–30 h with multiple dosing [7, 8]. To account for this phenomenon an initial dose of 200 mg once daily was administered during the first 2 weeks before escalation to 400 mg/day in several clinical studies. With this strategy the incidence of rash reduced to 9–32% [9, 10, 11, 12, 13]. Other strategies that have been evaluated to reduce the occurrence of rashes include the use of corticosteroids and antihistamines as prophylaxis and the use of a slower induction phase of treatment [14, 15, 16, 17]. The use of prophylaxis when initiating therapy with nevirapine remains controversial as contradictory results have been reported [14, 15, 16, 17]. However, a slowly escalating dose of nevirapine (e.g., nevirapine 100 mg for the first week, and increasing 100 mg daily per week until achieving the full nevirapine dose by the fourth week) diminished the incidence of rash by approximately 40% compared to patients using the advised escalation dose (200 mg once daily the first 2 weeks) [14].

We are unaware of studies that examined the incidence of rash in an unselected outpatient clinic population (thus without any strict inclusion criteria) including both antiretroviral naive and pretreated patients. Such studies may be very important to determine the real incidence of rash in daily practice as well as to identify potential risk factors. Therefore the aim of this study was to assess the incidence of rash in HIV-1 infected individuals starting a nevirapine-containing regimen in an unselected outpatient clinic population and to identify possible risk factors. Furthermore, the observation that strategies administering slowly escalating doses of nevirapine are successful in diminishing the incidence of rash suggests that exposure to nevirapine is correlated with the occurrence of rash. Data on the effect of nevirapine plasma concentrations on the occurrence of rash are, however, lacking. Therefore the second aim was to investigate whether nevirapine plasma concentrations are associated with the occurrence of rash.

Methods

Patients and data collection

Ambulatory HIV-1 infected patients from the outpatient clinic of the Slotervaart Hospital, Amsterdam, who initiated a nevirapine-containing regimen between June 1997 and May 2001 were included in the study. In addition, to be included in the study patients had to have a follow-up of at least 90 days after initiation of nevirapine unless the drug was discontinued before 90 days of therapy due to a cutaneous rash. Finally, patients needed to give written permission to obtain their pharmacy records from the community pharmacy for a complete overview of their drug use. Data from 216 HIV-1 infected patients were available for analysis. Of these, 183 had at least one nevirapine plasma concentration available for analysis in the first 90 days after initiation of nevirapine and in the case of rash before the rash.

For all included patients, age, gender, race, and hepatitis status (B and C) were collected. Patients were considered to have chronic hepatitis B (HBV) when hepatitis surface antigen was detected at baseline [18]. When hepatitis C antibodies (anti-HCV) were present at baseline, patients were considered to have a chronic HCV infection [19]. In addition, clinical chemistry parameters collected at baseline included alkaline phosphatase, γ-glutamyltransferase (GGT), total bilirubin, aspartate aminotransferase, alanine aminotransferase, creatine kinase, and amylase. Furthermore, CD4 and CD8 cell count, HIV-RNA load, eosinophilic leukocyte count, and pretreatment with antiretroviral drugs before start with nevirapine were recorded at baseline. The complete antiretroviral drug regimen in addition to nevirapine was assessed from the outpatient medical record. Additionally, the community pharmacy records were used to obtain a complete overview of coadministered drugs (other than antiretroviral drugs) including antibiotics, antihistamines, antimycotics, steroids, and pentamidine. The use of pentamidine was also extracted from the hospital records as nebulized pentamidine was generally administered at the day ward clinic of our hospital.

The occurrence of rash was extracted from the outpatient medical records and prescriptions of the antihistaminic cetirizine (exclusively used for this indication) within the first 90 days after initiation of nevirapine. Not all patients contact the infectious disease specialist directly when a rash occurs but instead contact the aids nurse. The standard approach is then a prescription of the antihistamine drug cetirizine. None of these patients initiated another drug concomitantly with the nevirapine-containing regimen that could have caused the rash. In addition, allergic rhinitis and conjunctivitis as the reason for cetirizine prescription in these patients was ruled out. Therefore when no cutaneous event was described in the outpatient medical record, but a prescription of cetirizine was documented within the first 90 days (but after initiation of nevirapine use), it was assumed that the patient developed a rash due to nevirapine.

Pharmacokinetic analysis

At each visit to the clinic a single blood sample was obtained for the quantitative determination of nevirapine plasma concentration. The time after ingestion was recorded according to the protocol of our routine therapeutic drug monitoring program. Concentrations of nevirapine in plasma were quantitatively assessed by a validated high-performance liquid chromatographic method [20]. Population pharmacokinetics were described with a one-compartmental model with first-order absorption and elimination using a nonlinear mixed-effect modeling analysis (NONMEM) version V (double precision, level 1.1) as described earlier [21]. For each nevirapine plasma sample oral clearance (CL/F), (oral) volume of distribution (V/F), and the absorption rate constant (k_a) of nevirapine were calculated using a Bayesian approach taking both the individual observation and the population pharmacokinetic parameters into account (POSTHOC option of NONMEM). Bayesian analysis was also used to estimate plasma trough concentrations (C_{12h}) of nevirapine at each sampling occasion. The area under the plasma concentration vs. time curve during 24 h (AUC_{24h}) was calculated for each occasion by dividing the daily dose by the Bayesian estimate of CL/F.

Study definitions

The primary outcome measure of this study was the onset of cutaneous adverse reactions within the first 90 days of nevirapine-containing therapy. The date of onset of rash was defined as the earliest date of rash documented in the outpatient medical record or the first date of cetirizine prescription. Furthermore, it was recorded whether patients had to discontinue nevirapine because of the rash. The use of cetirizine and corticosteroids was considered to be prophylactic when initiated before or simultaneously with nevirapine.

Statistical analysis

Statistical calculations were performed with SPSS for Windows, version 10 (SPSS, Chicago, Ill., USA). A P value of 0.05 or less was considered statistically significant. Baseline characteristics of

patients with and without rash during the study period were tabulated. Group comparisons were performed using the Mann-Whitney U test for continuous data and the χ^2 statistic or Fisher's exact test for categorical data.

Relationships between the occurrence of rash and possible risk factors were tested univariately with logistic regression. Both fixed (baseline characteristics) and time-dependent variables were included in the model. Factors considered in the univariate analyses were baseline characteristics including gender, age, race, duration of prior exposure to antiretroviral drugs before start with nevirapine, pretreatment with a PI, HCV infection, HBV infection, clinical chemistry parameters, CD4 and CD8 cell counts, nadir CD4 cell count, eosinophil leukocyte count, and plasma HIV RNA load. In addition, time-dependent variables were concomitant use of a PI (each PI also individually tested), a NRTI (each NRTI individually tested), an antibiotic, an antihistaminic, an antimycotic, a steroid (administered dermatologically or systemically), and the pharmacokinetic parameters of nevirapine (CL/F, k_a, AUC_{24h}, C_{12h}, plasma concentration). Age, CD4 and CD8 cell counts, nadir CD4 cell count, plasma HIV-RNA load, duration of prior exposure to antiretroviral drugs, and pharmacokinetic parameters of nevirapine were examined as continuous variables, and CD4 cell count, plasma HIV-RNA load, nevirapine plasma concentration, and duration of prior antiretroviral exposure were also transformed to dichotomous variables and tested. CD4 cell count was dichotomized to less than 200 cells/μl vs. more than 200 cells/μl, HIV-RNA load to detectable (>200 copies/ml) vs. undetectable, nevirapine plasma concentration to less than median plasma concentration vs. greater than median plasma concentration, and duration of prior antiretroviral exposure to less than 1 year vs. longer than 1 year. Gender, race, pretreatment with a PI, HCV infection, HBV infection, and concomitant use of the above drugs or drug categories were examined as dichotomous variables. The baseline clinical chemistry parameters were transformed to dichotomous variables (above vs. below the upper limit of normal, ULN). For patients who developed rash due to nevirapine covariates that were determined after the start of nevirapine could be included in the logistic regression only if they were determined before the occurrence of rash.

When multiple significant ($P<0.1$) covariates were identified univariately, (forward) multivariate logistic analysis was performed. Significance of the logistic regression models was assessed with the Wald statistic. The multiple logistic regression model was adjusted for gender and age.

Results

Patient characteristics

Baseline characteristics are presented in the first column of Table 1. The population had a median age of 40 years and was predominantly male and white. Of the 216 patients 20.8% were antiretroviral treatment naive at the start of the nevirapine-containing regimen. A minority

Table 1 Baseline characteristics [*ALAT* alanine aminotransferase (normal range 0–21), *AMY* amylase (35–133), *AP* alkaline phosphatase (34–105), *ARV* antiretroviral, *ASAT* aspartate aminotransferase (0–19), *CK* creatine kinase (0–70), *GGT*γ-glutamyltransferase (6–25), *HCV* chronic hepatitis C infection, *HBV* chronic hepatitis B infection, *IQR* interquartile range, *PI* protease inhibitor, *TBR* total bilirubin (0–17)]

	All patients ($n=216$)	No rash ($n=178$)	Rash ($n=38$)	P^a
Age (years), median (IQR)	39.9 (34.8–47.4)	39.5 (34.0–47.0)	40.4 (36.3–48.4)	0.46
Gender: % male	88.4	88.2	89.5	1.00
Race (%)				
White	81	79.8	86.8	0.31
Black	10.6	11.8	5.3	0.38
Asian	2.8	1.7	7.9	0.069
Latino	5.6	6.7	0	0.13
Clinical chemistry, median (IQR)				
ALAT (U/l)	15 (10–22)	16 (11–23)	13 (9–21)	0.031
AMY (U/l)	74 (53–105)	74 (53–106)	74 (61–97)	0.69
AP (U/l)	72 (60–88)	71 (59–90)	72 (62–84)	0.94
ASAT (U/l)	13 (11–17)	13 (11–18)	11 (9–16)	0.028
CK (U/l)	47 (32–69)	47 (32–73)	50 (33–60)	0.94
GGT (U/l)	17 (11–35)	18 (12–36)	12 (9–27)	0.043
TBR (μmol/l)	13 (10–17)	13 (10–17)	14 (10–17)	0.88
Clinical immunology, median (IQR)				
CD4/CD8 ratio	0.30 (0.18–0.489	0.30 (0.18–0.51)	0.30 (0.18–0.43)	0.90
CD4 cell count (10^6/l)	325 (200–480)	300 (198–465)	350 (220–490)	0.58
Nadir CD4 cell count (10^6/l)	170 (80–290)	165 (70–290)	220 (120–290)	0.37
CD8 cell count (10^6/l)	1020 (730–1420)	1000 (710–1420)	1125 (800–1400)	0.36
Log_{10} HIV-1 RNA (copies/ml)				
Median (IQR)	<2.30 (<2.30–4.48)	<2.30 (<2.30–4.48)	2.87 (<2.30–4.49)	0.30
Detectable (>200 copies/ml, %)	50.2	47.4	63.2	0.079
Eosinophilic leukocytes (10^6/l), median (IQR)	108 (63–174)	107 (64–175)	100 (55–216)	0.78
ARV experience (months), median (IQR)	21.3 (6.3–36.5)	22.3 (7.6–37.6)	13.0 (0–31.1)	0.061
>12 months (%)	66.2	69.1	52.6	0.051
ARV naive (%)	20.8	18.5	31.6	0.072
PI pretreated (%)	76.4	78.1	68.4	0.20
HCV (%)	6.5	6.2	7.9	0.72
HBV (%)	5.6	5.6	5.3	1.00

[a] χ^2 statistic/Fisher's exact test or Mann-Whitney U test comparing rash with no rash

Table 2 Coadministered drugs during the first 90 days of the nevirapine-containing regimen (*PI* protease inhibitor, *NRTI* nucleoside reverse transcriptase inhibitor)

Coadministered drug	n	%
PI[a,b]	28	13.0
Indinavir	10	4.6
Nelfinavir	8	3.7
Ritonavir	8	3.7
Saquinavir	7	3.2
NRTI[a]		
Abacavir	10	4.6
Didanosine	15	6.9
Lamivudine	184	85.2
Stavudine	92	42.6
Zidovudine	109	50.5
Hydroxyurea[a]	4	1.9
Cotrimoxazole[c]	56	29.0
Pentamidine[a]	14	7.3
Antihistamines[c]	11	5.7
Cetirizine	6	3.1
Antimycotics[c]	37	19.2
Antibiotics[c]	38	17.6
Steroids[c]		
Dermatological	18	9.3
Systemic	6	3.1

[a] $n = 216$
[b] Patients can use more than one PI
[c] $n = 193$

of patients (13.0%) were using a protease inhibitor concomitantly with nevirapine (Table 2). Lamivudine was most frequently part of the antiretroviral regimen, predominantly combined with either stavudine or zidovudine. Cetirizine or corticosteroids were administered prophylactically in 3.1% of the patients.

Rash

The total incidence of rash in this population was 17.6% (38/216). Of these patients eight were included based on cetirizine prescription within the first 90 days of nevirapine use. Rash developed after a median of 26 days (interquartile range, IQR, 17–46). The median time to development of rash in the patients that were included based on cetirizine prescription was 42 days (IQR 29–53) vs. 23 days (IQR 14–44) in the other patients ($P = 0.086$). For one patient the exact date of the onset of rash could not be determined. In seven patients (18.4%, 7/38; 3.2% of the total studied population) nevirapine was discontinued after the occurrence of the rash.

Risk factors for rash

As shown in Table 1, there were a few differences in baseline characteristics between the patients who developed rash and who did not. The 38 patients who developed rash within 90 days after start with the nevirapine-containing regimen had lower baseline alanine aminotransferase, aspartate aminotransferase, and GGT values ($P < 0.05$), and were less often pretreated with antiretroviral drugs longer than 12 months ($P = 0.05$).

Parameters that had a P value less than 0.1 in the univariate analyses, and the results of the multiple logistic regression analysis are shown in Table 3. None of the covariates was significantly related with the development of rash in the univariate analyses, although both Asian race and time on antiretroviral treatment longer than 12 months showed a trend of a higher risk and a lower risk for the development of rash, respectively. Adjusted for age and gender in the multivariate analysis, patients pretreated with antiretroviral drugs longer than 12 months (OR 0.39, IQR 0.17–0.89, $P = 0.025$) and patients with nevirapine plasma concentrations above 5.30 mg/l (OR 2.31, IQR [1.02–5.22, $P = 0.045$) appeared to be independent predictors of the occurrence of rash. Patients who developed rash had a median nevirapine plasma concentration of 5.60 mg/l (IQR 4.86–6.52) compared to 5.08 mg/l (IQR 4.16–6.48) for patients who did not develop a rash.

Discussion

The incidence of rash observed in this unselected outpatient clinic population was 17.6%. Although this study is the first with an unselected outpatient clinic population including both antiretroviral naive and pretreated patients, the observed incidence was comparable to that reported in several clinical trials [9, 10, 11, 12, 13, 14] and retrospective analyses [16, 22, 23, 24]. Only seven patients (3.2%) in this population discontinued nevirapine because of rash, which is fairly low compared to other studies and reports [9, 10, 11, 12, 13, 14, 16, 22, 23].

Table 3 Factors associated with rash during the first 90 days of a nevirapine-containing regimen in the univariate analyses ($P < 0.1$) and in the multivariate analysis (*ARV* antiretroviral, *CI* confidence interval, *PI* protease inhibitor, *OR* odds ratio)

	Univariate			Multivariate		
	OR	95% CI	P	OR[a]	95% CI	P
Asian race	5.00	0.97–25.78	0.055	–	–	–
Baseline HIV-RNA detectable	1.90	0.92–3.92	0.081	–	–	–
Concomitant use of PI	0.15	0.02–1.15	0.068	–	–	–
Concomitant use of antibiotics	0.27	0.06–1.20	0.085	–	–	–
Plasma concentration nevirapine (mg/l)[b]	1.88	0.89–4.23	0.094	2.31	1.02–5.22	0.045
ARV treatment naive	2.03	0.93–4.43	0.076	–	–	–
Time on ARV therapy > 1 year	0.50	0.24–1.01	0.054	0.39	0.17–0.89	0.025

[a] Adjusted for age and gender
[b] < 5.3 mg/l vs. > 5.3 mg/l

The difference in median time to occurrence of rash after start with nevirapine between the two types of outcome of this study, i.e., 23 days for outpatient medical record vs. 42 days for prescription of cetirizine, is noteworthy. Patients included on basis of cetirizine prescription were all pretreated with antiretroviral drugs, compared to only 60% of the patients included based on documentation of rash in the outpatient medical records. These pretreated patients may be well known with cutaneous reactions and wait with seeking medical attention, and if they do (because of persistence or worsening), contact the nurse specialist HIV/AIDS care for a cetirizine prescription. It could also be a delayed mild cutaneous reaction that developed in these patients.

No variable was significantly related to the development of any grade of rash in the univariate analyses (Table 3). In addition, no relationship to the prophylactic use of antihistamines or steroids and the development of rash was demonstrated. This may be caused by the low percentage of patients using these drugs, making the statistical power to detect a difference low. However, reports on the effectiveness of these drug categories in the prevention of rash are not consistent. Barreiro et al. [14, 25] showed that the use of antihistamines and steroids was beneficial in the prevention of nevirapine-associated rash. In contrast, several other studies have reported increased rash in patients using steroids and/or antihistamines during the first weeks of nevirapine treatment [15, 16, 17]. Although gender was not related to the development of rash in this study, we adjusted for both gender and age in the multivariate analyses as strong relationships have been reported between gender and nevirapine-associated rash [18, 24].

The main interest of this study was determining whether nevirapine plasma concentrations are related to rash occurrence. Havlir et al. [6] compared plasma concentrations of nevirapine in patients with and patients without rash and did not find a relationship, but this study was a phase I/II study investigating nevirapine at a dosage of 400 mg/day (without slow escalation after initiation) and included only 21 patients. Our results show that nevirapine plasma concentrations above 5.3 mg/l were significantly related to the development of rash during the first 90 days. None of the other pharmacokinetic parameters (CL/F, k_a, AUC_{24h} or C_{12h}) was significantly related to rash.

The use of antiretroviral regimens longer than 12 months before initiation of a nevirapine-containing regimen compared to pretreatment less than 12 months, including no antiretroviral pretreatment, was associated with a lower risk of developing rash. The patients with antiretroviral pretreatment of more than 12 months showed a trend of having higher GGT values than patients with antiretroviral pretreatment less than 12 months ($P = 0.08$). Higher values of GGT represent more induction of enzymes and may thus result in lower nevirapine plasma concentrations. Another explanation could be the difference in HIV-RNA load. Patients with antiretroviral pretreatment of more than 12 months had more often undetectable HIV-RNA levels than patients pretreated less than 12 months ($P < 0.0001$). In addition, although not statistically significant, patients pretreated more than 12 months had higher CD4 cell counts than patients pretreated less than 12 months ($P = 0.07$). This would suggest a contribution of immune reconstitution related to the initiated potent antiretroviral regimen in the occurrence of rash. Immune reconstitution might possibly lead to an increased likelihood of drug hypersensitivity, as was also suggested by Wit et al. [23] who found a diminished incidence of rash in patients with undetectable HIV-1 RNA levels at baseline.

In conclusion, the observed incidence of rash in this unselected outpatient clinic population was 17.6% but led to discontinuation in only 3.2% of the included patients. Antiretroviral pretreatment of more than 12 months and nevirapine plasma concentrations were significantly related to the development of rash within 90 days after initiation of nevirapine. The observed relationship between the occurrence of rash and nevirapine plasma concentrations questions the allergic character of the rash. Intrinsic toxicity of nevirapine may play a part in this adverse effect. Physicians need to be aware of an increased risk of rash in patients with antiretroviral pretreatment less than 12 months and those with nevirapine plasma concentrations above 5.3 mg/l.

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