

# Stevens Johnson syndrome due to nevirapine

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## Abstract

Adverse drug reactions continue to be among the important cause of morbidity and at times mortality among hospital admissions. The severity of cutaneous adverse drug reaction may vary from mild rashes to severe Stevens Johnson syndrome (SJS). Nevirapine (NVP) is an important component of antiretroviral therapy for patients having acquired immunodeficiency syndrome. It usually cause mild rash in some of these patients. This report describes a case of NVP induced SJS that was reversible on withdrawal of the drug. Possible mechanisms of NVP induced SJS and its clinical implications are also briefly discussed.

**Keywords:** Drugs, nevirapine, rashes, Stevens Johnson syndrome

## Introduction



Nevirapine (NVP), is a dipyrindodiazepinone - non nucleoside reverse transcriptase inhibitor (NNRTI) used to treat human immunodeficiency virus (HIV-1) infection. <sup>[1]</sup> NNRTIs bind allosterically the HIV reverse transcriptase enzyme at a different site distinct from the active site (where NRTI bind) termed as the NNRTI pocket making NVP ineffective against HIV-2, as the pocket of the HIV-2 reverse transcriptase where it binds has a different structure, which confers intrinsic resistance to the NNRTI class. <sup>[2]</sup> Like other antiretroviral drugs, HIV rapidly develops resistance if NVP is used alone, so recommended therapy consists of combinations of three or more antiretrovirals.

The common adverse drug reactions (ADRs) observed with NVP include skin rashes and hepatotoxicity. Skin rashes are usually mild and rarely progress to Stevens Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) in about 0.5-1% cases. <sup>[3],[4]</sup>

## Case report



A newly diagnosed 38-year-old male patient was initiated on highly active anti-retroviral therapy (HAART) with lamivudine, stavudine and NVP simultaneously in lieu of low CD4 count. NVP was started as 200 mg tablet once daily for 2 weeks and then was planned to increase to twice a day over next 2 weeks. However, on 6<sup>th</sup> day of therapy, patient developed generalized erythematous lesions that progressed over the next 4-5 days. Lesions were initially ignored by the patient. On 15<sup>th</sup> day, lesions on sun exposed part showed marked exfoliation over the face, neck and ear. Some ulcers were also observed at lips [Figure 1]. There was no conjunctival, corneal, genital and scalp involvement. A dermatologist opinion was sought immediately and provisional clinical diagnosis of NVP induced SJS was made. NVP was stopped immediately.



Figure 1: Photograph of the patient showing extensive erythematous lesions with peeling of skin over sun exposed areas and ulcers on lips

Urinalysis, blood counts, serum biochemistry including liver function tests etc., were found to be normal. Patient was managed conservatively with cold sponging, oral antihistaminics and supportive treatment. There was gradual improvement over the next 1 week and lesions completely disappeared after 2 weeks. Since the patient was already on lamivudine and stavudine, a final diagnosis of NVP induced SJS was made.

Re-challenge with NVP was not performed but a modified HAART regimen was started that included efavirenz in place of NVP. This case recorded a score of 8 on the "*naranjo probability scale*" incriminating this drug as the probable cause of the reaction. WHO-UMC also recorded this event as likely. No recurrence of rash was recorded in subsequent follow up over the next 1 year.

## Discussion



ADRs are one of the leading causes of morbidity and at times mortality among hospitalized patients and reported to occur in up to 8% of all hospital admissions as per western literature. [5] However, these may often go undetected and mostly underreported from our country. These may vary from mild rashes to severe reactions such as SJS or TEN. SJS is a severe life-threatening medical disorder caused by a variety of drugs that includes antimicrobials, antiepileptics, analgesic etc. [6] Among the antimicrobials, antiretrovirals are important group of drug associated with cutaneous drug reactions. [7] Drugs having long half-lives are more likely to cause ADRs than those with a shorter half-life. Individuals with HLA Bw44, HLA-B<sub>12</sub> and HLADQB1 × 0601 appear to be more prone to develop the disease complex of SJS. [8]

NVP is an important component on antiretroviral therapy for HIV infected patients having low CD4 counts. Therapy is generally initiated with a 2 week lead-in dose of 200 mg/day followed by 200 mg twice a day thereafter so as to lessen the frequency of rash. A 400 mg/day dose at the very

outset has also been used and found to have no significant difference in incidence of severe life-threatening skin reactions compared to the generally used escalating dose regimen. <sup>[9]</sup> The risks of cutaneous ADRs with NVP in HIV-1 infected patients are among the highest reported for any drug <sup>[10]</sup> and mainly includes skin rash and hepatotoxicity. Cutaneous reactions are usually MHC class I mediated and influenced by NVP CYP2B6 metabolism while hepatic reactions are most likely class MHC II mediated and not influenced by CYP2B6 metabolism. <sup>[11]</sup> The rash is generally mild and reported in between 32% to 48% cases but rarely progresses to SJS. <sup>[12]</sup>

There is generally high risk of SJS or TEN in HIV infected patients compared to non HIV infected individuals. In a multinational case control study at Europe between 1997 and 1999, 246 patients were found to have drug induced SJS or TEN among these, 18 patients were having HIV infection and in 83% of such patients the reaction was observed with NVP. All the patients were on escalating doses of NVP and the median reaction time was 12 days. The authors of this study suggested to discontinue the drug as early as possible in view of long elimination half-life of NVP and the severity of reaction. <sup>[13]</sup>

The mechanisms of this reaction are mostly unclear and postulated to involve drug specific cytotoxic lymphocytes. In an animal model of NVP induced skin rash, Chen *et al.* <sup>[14]</sup> found that 12-hydroxylation metabolic pathway is responsible for rash. It has also been observed that the CD4<sup>+</sup> T cells depletion reduces as well as delays the severity of NVP induced skin rash. Further IFN-gamma secretion by lymphocytes against a particular drug is also important mechanism for drug induced rash. Other possible mechanism of developing SJS in viral infections includes decrease in immunity, a genetic defect and the drug metabolites binding to proteins to trigger an immune response that leads to the cutaneous reactions of SJS. <sup>[15],[16]</sup>

The case presented here bear important clinical messages. A strict vigilance by the treating physician is utmost important in the initial months of antiretroviral therapy so as to detect and manage severe forms of ADRs. This becomes an important issue nowadays in view of decrease in incidence of opportunistic infections and large use of anti-retroviral therapy in today's era. Any ADRs including the cutaneous one should not be ignored and duly warned. Awareness of such ADRs by the treating physician is must and also significant as these may turn life threatening at any time and on the other hand may be a cause of non-adherence to treatment.

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