A Retrospective Study of Spectrum of Nevirapine Induced Cutaneous Drug Reactions in HIV Positive Patients

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Abstract: BACKGROUND: Nevirapine, a NNRTI (non-nucleoside reverse transcriptase inhibitor), is most commonly used as a part of the combination therapy for HIV (human immunodeficiency virus) infection because of its efficacy and good tolerability. But it is the major culprit in causing adverse drug reactions ranging from mild maculopapular rash to severe toxic epidermal necrolysis. AIM: To observe the spectrum of adverse cutaneous reactions to Nevirapine. METHODOLOGY: This is a retrospective study from the year 2006-2013. RESULTS: 120 cases presented with adverse cutaneous reactions to NVP (Nevirapine). Out of 120 patients, females outnumbered males (68:52). Majority of them were in the age group of 31-40 years. 63 (52.5%) patients developed maculopapular rash, 37 (30.8%) cases of SJS/TEN (Steven Johnson Syndrome/Toxic epidermal necrolysis), 13 (10.8%) patients developed diffuse erythema, urticarial rash in 3 (2.5%), angioedema in 3 (2.5%), 1 (0.9%) developed serum sickness like reaction. CONCLUSION: Managing HIV infection is a double edged sword, and the benefits of ART have to be balanced against the risks of drug toxicity.

Key words: Nevirapine, adverse drug reactions, anti retroviral therapy, toxic epidermal necrolysis, Steven Johnson.

1. Introduction

Patients with HIV infection are at increased risk for adverse drug reactions. The reason for this is unclear. The mechanism probably involves drug specific cytotoxic lymphocytes. NVP (Nevirapine) was the first NNRTI (non nucleoside reverse transcriptase inhibitor) approved by the US Food and Drug Administration for the treatment of HIV (Human Immunodeficiency Virus) infection in 1997. Nevirapine based regimens of highly active antiretroviral therapy have been widely used in resource limited countries because of their efficacy, accessibility and comparatively low cost [1]. NVP (Nevirapine) binds directly to RT (reverse transcriptase) and blocks the ribonucleic acid-dependent and DNA (deoxyribonucleic acid)-dependent DNA polymerase activities by causing a disruption of the enzyme’s catalytic site [2]. NVP is notorious to cause adverse drug reactions when compared to other antiretroviral drugs. Cutaneous adverse reaction is the most common adverse drug reaction associated with NVP which usually appears within 4-6 weeks of therapy. The incidence of rash varies between 9% and 32% and discontinuation of the drug is required in about 67% of cases [3]. Hence this observational study was done to know the different patterns of cutaneous drug eruptions to nevirapine.

2. Materials and Methodology

This is a retrospective study, data collected from the year 2006-2013. All the retro positive patients who were on ART (Anti Retroviral Therapy) and developed toxicity to nevirapine were included in the
study. Out of all the patients taking ART drugs, 120 patients developed toxicity to Nevirapine. The following data were tabulated and analyzed: name, age, sex, baseline CD4 (Cluster differentiation 4) count, CD4 count at the time of rash, date of starting the drug, date of developing reaction, type of regimen, type of rash, presence of hepatotoxicity, and any other associated toxicities developed were looked for. Baseline investigations, including hemogram, ESR (Erythrocyte sedimentation rate), urine examination, VDRL (venereal disease research laboratory test), serum HBsAg (Hepatitis B Antigen), liver function tests and renal function tests, were carried out in each patient. Chest X-ray and ultrasonography abdomen were done in all cases to rule out focus of tuberculosis.

3. Results

120 cases presented with adverse cutaneous reactions to NVP. Out of 120 patients, females outnumbered males (68:52) (Fig. 1), majority of them were in the age group of 31-40 yrs. Baseline CD4 count of majority of them (70 patients) was in the range of 100-400 cells. 82% of the patients were in low socio economic status (Fig. 1). Literacy level of the patients and risk factors are shown in Fig. 1. 63 (52.5%) patients developed maculopapular rash, 37 (30.8%) cases of SJS/TEN (Steven Johnson Syndrome/Toxic epidermal necrolysis), 13 (10.8%) patients developed diffuse erythema, urticarial rash in 3 (2.5%), angioedema in 3 (2.5%), 1 (0.9%) developed serum sickness like reaction. (Fig. 2). Clinical photographs are shown in Appendix A.

4. Discussion

NNRTIs are included in most of the 1st line ART regimens, either NVP or EFV (Efavirenz). NVP is the most commonly used NNRTI because of its cost effectiveness compared to EFV however, NVP is notorious to produce adverse cutaneous reactions, ranging from mild maculopapular rashes to fatal SJS/TEN, and is also hepatotoxic.
HIV patients are more vulnerable to develop drug reactions when compared to non HIV patients. Chosidow et al proposed that drugs or their metabolites disturb the balance between cytotoxic and regulatory phenomena, allowing resurgence of cytotoxicity against virally infected cutaneous cells, where the target of cytotoxic reactions would be viral antigens rather than drug haptens as per this hypothesis [4].

NVP rash may be classified as: (1) grade 1—erythema with or without pruritus; (2) grade 2—diffuse erythematous macular or maculopapular rash or dry desquamation with or without pruritus or typical target lesions without blistering, vesicles or ulcerations in the lesions; (3) grade 3—urticaria or diffuse erythematous macular or maculopapular rash or moist desquamation with or without pruritus together with any of the four constitutional findings possibly related to the drug, namely raised liver function tests, fever, blistering and mucosal lesions; angioedema; exfoliative dermatitis; and serum sickness-like reactions; and (4) grade 4—diffuse cutaneous eruptions usually starting on the face, trunk or back often with prodromal symptoms plus one of the following: cutaneous bullae, Nikolsky’s sign, SJ (Stevens Johnson) syndrome, erythema multiforme major or TEN (toxic epidermal necrolysis) or two or more anatomically distinct sites of mucosal erosions [5].

European Agency for Evaluation of Medicinal products recommends that “NVP must be discontinued permanently in case of severe cutaneous drug reaction” (EMEA/11260/00, London, and 12 April 2000).

Recent advances in treatment and modified lifestyles have prolonged the life span of HIV infected patients but adverse drug reactions to ART continue to be a matter of concern. Therefore, treating physicians need to keep in mind the risk of such life-threatening cutaneous reactions while prescribing nevirapine-based ART regimens.

5. Conclusion

Managing HIV infection is a double edged sword, and the benefits of ART have to be balanced against the risks of drug toxicity. A strict vigilance during the initial two months of ART regimen is mandatory for timely intervention and management of such serious life-threatening reactions. Recognizing and managing these adverse reactions to ART drugs at an early stage will reduce morbidity and mortality and compliance to the ART in the long run.
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References


Appendix A  Photographs of various morphological patterns of adverse drug reactions to Nevirapine

![Urticarial rash](image1)

![Blanchable erythema](image2)

![Maculopapular rash](image3)

![TEN](image4)

![Angioedema with erythema multiforme](image5)
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SJS before and after photographs