

CASE REPORT

LAMOTRIGINE INDUCED TOXIC EPIDERMAL NECROLYSIS IN A PATIENT WITH BIPOLAR DISORDER

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ABSTRACT: Stevens-Johnsons syndrome and toxic epidermal necrolysis are the most severe cutaneous adverse reactions to medications. These are characterized by the detachment of dead epidermis and the erosion of mucus membrane. Lamotrigine is an antiepileptic drug used in the management of various forms of seizures. Lamotrigine is also useful in preventing the depressive phase of manic depressive disorder. We present a case of toxic epidermal necrolysis induced by Lamotrigine to increase the awareness to this life threatening adverse drug reaction to Lamotrigine, as Steven Johnson syndrome and Toxic epidermal necrolysis have a significant impact on public health in view of their high mortality and morbidity.

KEY WORDS: Antiepileptic, Manic – depressive illness, Severe cutaneous adverse reaction,

INTRODUCTION: Toxic epidermal necrolysis (TEN), a serious life threatening bullous cutaneous disease with a mortality rate reaching 30% consists of epidermal detachment greater than 30%, generally considered as immune mediated reaction to drugs.¹ In case reports and studies, more than 100 drugs have been implicated as causes of Stevens Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).² Approximately 50% of cases of SJS and 80-90% of cases of TEN are drug induced.³ Common causative agents include sulfa drugs, antiepileptic drugs, antibiotics and NSAIDS.⁴

Lamotrigine is an anti epileptic drug that is structurally unrelated to aromatic antiepileptics. It acts on voltage sensitive sodium channels, stabilizes neuronal membranes and inhibits the release of excitatory neurotransmitters, glutamate or aspartate. The drug is considered effective for multiple types of seizures.⁵ Lamotrigine has been reported to be useful in preventing the depression that often follows the manic phase of bipolar disorder.⁶ Lamotrigine is also prescribed for bipolar disorder

Dizziness, ataxia, blurred vision, nausea, vomiting and rash are the most common adverse effects of Lamotrigine. A few cases of Stevens Johnson syndrome and disseminated intravascular coagulation have been reported.⁷ We present a case of TEN induced by Lamotrigine to increase the awareness to the life threatening adverse reactions.

Lamotrigine is also reported as a common culprit drug to cause serious reaction in western population.^{8,9} Due to its limited utilization it is not reported as a culprit in Indian population.¹⁰ We present a case of Lamotrigine induced toxic epidermal necrolysis in a patient

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with bipolar disorder to create awareness about the increasing incidence of this adverse reaction.

CASE HISTORY: A 45 year old woman, a known case of bipolar disorder since 5 years. She was initially treated with Escitalopram 10mg twice daily along with sodium valproate 500 mg once daily orally for the first 2 years, then followed by the same dose of escitalopram, and sodium valproate reduced to 250mg for the next 3 years. She was continued on tablet sodium valproate 250mg and tablet tolazapine 2.5mg once daily and a fixed dose combination of escitalopram 10mg and clonazepam 0.25mg were added. No adverse reactions were reported during this period for any of these drugs. To this regimen, lamotrigine was introduced with an initial dose of 37.5mg in three divided doses on day 1 and day 2, 75mg in three divided doses on day 3 and day 4. From 5th day, the dose was increased to 100mg given once a day.

Three weeks following the intake of Lamotrigine, she developed fever with chills, rashes all over the body associated with itching. She consulted a dermatologist in a local hospital and was prescribed topical and parenteral corticosteroids, antihistaminics for 6 days, with which the skin lesions did not subside. She was then referred to our hospital.

The examination revealed multiple erosive lesions present all over the body, with multiple flaccid bullae on lower limbs and thighs. Crusted plaques were present all over the body (fig 1). Later denudation was seen (fig2). Urine output was normal. All the vitals including pulse rate and blood pressure were within normal limits.

Laboratory investigations showed Normocytic, hypochromic anaemia with neutrophilia and a high ESR (75mm/hr). Urine examination showed traces of proteins, 1-2 pus cells, no casts. Based on the positive drug history of Lamotrigine administration and the clinical picture, a diagnosis of TEN (Naranjo score - 6) secondary to Lamotrigine was made by the dermatologists of our hospital.

The patient was treated with adequate supportive measures including wound care, nutritional support, fluid and electrolyte management, temperature management, pain control, ocular care. Gradually, the patient showed signs of improvement and was subsequently discharged.

DISCUSSION: TEN and SJS are rare, life threatening, bullous cutaneous diseases generally considered as immune mediated reactions to drugs. These severe cutaneous adverse reactions (SCAR) are characterized by epidermal necrosis, extensive detachment of the epidermis, erosions of the mucous membranes and severe constitutional symptoms. There is evidence that SJS and TEN are a single disease with common causes and mechanisms.^{11,12} Cutaneous reactions are the most frequent manifestations of delayed drug induced hypersensitivity.¹³ They comprise a broad spectrum of clinical features, spanning benign disease such as maculopapular exanthema to life threatening severe reactions. Among them, SJS and TEN are the most severe forms of drug induced skin diseases.¹⁴ Rash is a common side effect of lamotrigine therapy, occurring in 10% of patients in clinical trials.¹⁵

Although rare(2 cases / million population/Y), SJS and TEN have a significant impact on public health in view of their high mortality (20% - 25%) and morbidity.

Drug exposure and a resulting hypersensitivity reaction is the cause of the majority of cases of SJS/TEN. In a multinational case control study in Europe covering more than 100 million inhabitants, the investigators paid special attention to newly marketed drugs and in

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addition, identified nevirapine, lamotrigine and sertraline as drugs with a significantly increased risk of inducing SJS and TEN.¹⁶ The risk of lamotrigine induced hypersensitivity syndrome has also been attributed to valproic acid combination.⁵ Lamotrigine is metabolized by uridine glucuronyl transferase(UGT), sodium valproate inhibits UGT and decreases clearance of Lamotrigine. This concomitant sodium valproate therapy may lead to high plasma concentration of Lamotrigine and also increases the risk of developing allergic reactions.^{17,18} Our analysis showed a possible association between TEN and Lamotrigine according to the Naranjo probability scale. Although the occurrence is rare, the widespread use of lamotrigine could result in an increase of incidence and physicians should be aware of the possibility of lamotrigine associated TEN. The possible role of other drugs (tolazapine, escitalopram, clonazepam) was excluded, since the patient was on these drugs for a long duration of 5 years and the only adjuvant to this prescription was Lamotrigine, which was discontinued after the patient reported about the rash to the physician. The incidence of lamotrigine induced rash increases with age, a high initial dose, rapid dose escalation and concomitant administration of sodium valproate, as is the situation in this case. The most crucial interventions in TEN are discontinuation of the offending drug and intensive supportive care, which was done so in this case. We have reported this case to highlight the initial symptoms like rash and fever, which might be mistaken for other diseases.

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