Lamotrigine is said to be safe but be cautious: A case report

Shri Niwash Jangir, Rajeshwari Suthar, AK Singhal, Smita N Deshpande

**ABSTRACT**

Introduction: Severe hypersensitivity reactions of lamotrigine are very uncommon conditions. We present this case of rapid development of toxic epidermal necrolysis. Case Report: A 37-year-old female of bipolar affective disorder on lamotrigine presented with acute skin eruptions with fever which involved almost whole body in next 7-10 days. There was massive peeling of the skin involving more than 50% of the body surface. Discussion: The case was diagnosed as lamotrigine induced toxic epidermal necrolysis and treated conservatively. Conclusion: Watchfulness of the clinicians and educating the patient about the doses schedule and adverse reaction of lamotrigine is key to prevent severe cutaneous reactions.

Keywords: Lamotrigine, Bipolar affective disorder, Stevens-Johnson syndrome, Toxic epidermal necrosis.

**INTRODUCTION**

Lamotrigine is being widely used in the treatment of partial seizures and generalized tonic-clonic seizures, either as monotherapy or as adjunctive treatment. It has a distinct place in the management of bipolar disorder, with the potential to treat and prevent bipolar depression. The strongest evidence for its efficacy lies in the prevention of bipolar depression [1].

Of all the adverse events associated with lamotrigine, rash has been the greatest concern. Indeed, before its launch in the United States in 1994, lamotrigine trials were complicated by severe rashes, presenting as Stevens-Johnson syndrome, toxic epidermal necrolysis or severe hypersensitivity syndrome. This led to the inclusion of a black-box warning in the prescribing information. The relatively high incidence of serious rash was attributed to a high initial dose and rapid escalation, which compelled the manufacturer to recommend the policy of start with low and go slow. Thus, the starting dose of lamotrigine was cut from 50 mg/day to 12.5 mg/day, when used as adjunct therapy with valproic acid, and from 100 mg/day to 50 mg/day, when added to a regimen of enzyme-inducing antiepileptic drugs [2].

**CASE REPORT**

A 37-year-old, illiterate female with bipolar depressive disorder was admitted in the emergency department with an acute skin eruption over legs and
body, temperature 101°F and bilateral inguinal and
submandibular lymphadenopathy. She was evaluated
and received one dose of sodium phosphate
betamethasone and dexchlorpheniramine maleate 5.3
mg, intravenously along with oral antipyretics with
partial relief of her symptoms. A detailed history was
taken from the patient, her relatives and medical records.
She had been prescribed lamotrigine for bipolar
depression 25 mg every day; subsequently up titrated to
200 mg/day during the next two months. Her depression
improved and she discontinued the medications on her
own. After a symptom free period of about four months,
depressive symptoms reappeared and the patient
resumed the old prescription - escitalopram 20 mg/day
and lamotrigine 200 mg/day in two divided doses. The
skin eruptions developed after 7-10 days of starting the
medication.

We discontinued the clinically suggested causative
drug lamotrigine immediately but the rash continued to
progress. We shifted the patient to dermatology care and
treated conservatively. The lesions disseminated very
rapidly all over the body including the palms and soles
with almost bilateral symmetry, in the form of
erythematous papules, papulovesicles, bullae and
necrotic erosions. Even the oral mucosa and tongue were
not spared and developing erosions and aphthous ulcers.
The lips had thick hemorrhagic crusting (figure 1). The
nasal mucosa was also affected. Her postnasal and oral
secretions were highly purulent. Both conjunctivae were
hyperemic with purulent secretions. Ophthalmologic
examination revealed bilateral conjunctivitis with no
corneal involvement and epithelial detachment in the
conjunctiva. The Nikolsky’s sign was found positive.
Erosions and erythematous papules also developed on
genitalia. The lesions lead to massive peeling of the skin
affecting face, neck, trunk and extremities. The
underlying denuded skin was red and exquisitely tender
(figure 2 A, B). The body surface area detachment was
approximately 50%, as per estimation by rule of nine.

Initially, the laboratory assessments suggested strong
inflammatory reaction: leucocytosis, elevated erythrocyte
sedimentation rate and increased C-reactive protein level
with peripheral blood eosinophilia, while other
investigations i.e. hepatic enzyme levels, renal function,
and serum electrolyte levels were within normal limits.
Urine, blood, and throat cultures were sterile. Later, a
biopsy specimen from a lesion showed edema and scanty
mononuclear inflammatory cell infiltration in the
perivascular region with total necrosis and complete
separation of the epidermis from the underlying dermis,
suggestive of toxic epidermal necrolysis. Almost all
epidermal structures were obliterated. The patient
managed to survive with fluid replacement, nutritional
support, dressings and systemic as well as local culture
specified anti-infective treatment.

**DISCUSSION**

Stevens-Johnson syndrome (SJS) and toxic
epidermal necrolysis (TEN) are rare life-threatening
mucocutaneous reactions of a continuous severity
spectrum with incidence estimated to be 1-2 cases per
million population per year [3]. More than 70% of cases

---

Figure 1: Showing massive erosions and aphthous ulcers on oral mucosa and tongue and hemorrhagic crusting over the lips.

Figure 2: A, B) Large areas of epidermal shedding, and red and exquisitely tender underlying denuded skin over the trunk, neck, face, ear and extremities.
of TEN are drug induced and the common culprit drugs are carbamazepine, phenytoin, phenobarbital, lamotrigine, sulfonamides, oxicam, nevirapine and allopurinol [4].

Lamotrigine is said to be well-tolerated, having an adverse-event profile by and large comparable to placebo [5]. Though, simple maculopapular rashes are common (3-15%) but the rare severe cutaneous reactions such as SJS and TEN have always been the greatest concern and most frequent reason for discontinuation of the drug in clinical practice [6]. The risk factors more commonly associated with adverse reactions are: first eight weeks of treatment, exceeding the recommended starting dose, rapid dose escalation and concomitant use of sodium valproate. However, the forecast of the progression of the rashes is difficult [7].

SJS and TEN are often drug induced idiosyncratic cutaneous reactions of similar histology. It has been proposed that they represent a spectrum of the same pathogenic mechanism. The pathogenesis of both the disorders is still unclear; however, immunological hypersensitivity, particularly T-cell-dependent reactions such as cell-mediated cytotoxicity has been suggested [3]. Mechanisms for lamotrigine-induced hypersensitivity reaction are less implicit than those for older anti epileptics such as carbamazepine; however, they are structurally similar and are likely to share mechanisms similar to sulphonamides, i.e. they have drug bio-activation that triggers clonal expansion of T cells in skin, liver and other injury sites. HLA linkages have not been performed for patients with lamotrigine-induced hypersensitivity. One patient with lamotrigine-induced hypersensitivity showed direct binding of T-cell receptors with lamotrigine [8]. Lamotrigine binding of T cells subsequently triggered clonal production of CD4+ cells and some CD8+ cells in culture. It remained unclear, however, whether direct T-cell–receptor binding was the result of previous sensitization and whether initial lamotrigine-induced hypersensitivity reactions are major histocompatibility complex dependent [9]. Most of the patients report the reaction within 14 days, which is also compatible with the development of immune sensitization [10].

Another possible mechanism is altered drug metabolism resulting in reactions mediated by toxic intermediate metabolites [10]. Lamotrigine is predominantly metabolized by glucuronidation by liver. Valproate increases the half-life of this drug by decreasing its glucuronidation through competition [11]. Most reported cases of SJS or TEN due to lamotrigine have occurred in patients who were co-medicated with these two drugs [8]. The findings suggest a possible diversion of lamotrigine from glucuronidation to an oxidative elimination pathway, as found in rodents, with production of a reactive epoxide intermediate; however, this hypothesis remains to be demonstrated in humans [12]. This is why the combination of lamotrigine and valproate may be toxic and a cautious use of the combination, by adjusting the dosages, has been recommended by the manufacturer [2].

When rash develops during lamotrigine treatment, the drug should be stopped immediately. Unless the rash can be clearly attributed to another cause, lamotrigine should be permanently withdrawn from the regimen. Also any other drug that may cause skin reactions, like ampicillin, should be avoided. If the patient has fever or shows severe oral ulceration, lymphadenopathy, skin desquamation, blistering or other systemic signs, patient should be hospitalized.

In the above case, we had no doubt that lamotrigine caused the rash, because of the sudden resumption of the drug in relatively high doses. No other proximate reasons could be found. This case reiterates that lamotrigine doses should not only be up titrated very slowly, but patients and care givers should also be cautioned not to resume the same regimen in case the drug is discontinued for any reason.

CONCLUSION

Watchfulness of the clinicians and educating the patient about the doses schedule and adverse reaction of lamotrigine is the key to prevent severe cutaneous reactions.

********

Author Contributions
Shri Niwash Jangir – Conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Final approval of the version to be published
Rajeshwari Suthar – Acquisition of data, Analysis and interpretation of data, Critical revision of the article, Final approval of the version to be published
A.K. Singhal – Analysis and interpretation of data, Critical revision of the article, Final approval of the version to be published
Smita N. Deshpande – Analysis and interpretation of data, Critical revision of the article, Final approval of the version to be published

Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

Copyright
© Shri Niwash Jangir et al. 2011; This article is distributed under the terms of Creative Commons attribution 3.0 License which permits unrestricted use, distribution and reproduction in any means provided the original authors and original publisher are properly credited. (Please see www.jケースreportsandimages.com /copyright-policy.php for more information.)
REFERENCES

1. Ng Felicity, Hallam Karen, Lucas Nellie, Berk Michael. The role of lamotrigine in the management of bipolar disorder. Neuropsychiatr Dis Treat 2007;3(4):463-74.
2. Messenheimer JA, Mullens EL, Giorgi L. Safety review of adult Clinical trial experience with lamotrigine. Drug Saf 1998;18:281–96.
3. Roujeau J-C, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med 1994;331:1272–85.
4. Auquier-Dunant A, Mockenhaupt M, Naldi L, Correia O, Schroder W, Roujeau JC. Correlations between clinical patterns and causes of erythema multiforme majus, Stevens- Johnson syndrome, and toxic epidermal necrolysis: results of an international prospective study. Arch Dermatol 2002;138(8):1019–24.
5. Bowden CL, Asnis GM, Ginsberg LD, Bentley B, Leadbetter R, White R. Safety and tolerability of lamotrigine for bipolar disorder. Drug Saf 2004;27(3):173–84.
6. Calabrese J. R., Sullivan J. R., Bowden C. L., Suppes T., Goldberg J. F., Sachs G. S. et al. Rash in multicenter trials of lamotrigine in mood disorders: clinical relevance and management. J Clin Psychiatry 2002;63(11):1012-9.
7. Schlienger RG, Shapiro LE, Shear NH. Lamotrigine induced severe cutaneous adverse reactions. Epilepsia 1998;39(Suppl 7):S22–S26.
8. Rahman M, Haider N. Anticonvulsant hypersensitivity syndrome from addition of lamotrigine to divalproex. Am J Psychiatry 2005;162:1021.
9. Pichler WJ. Delayed drug hypersensitivity reactions. Ann Intern Med 2003;139:683–93.
10. Friedmann PS, Strickland I, Pirmohamed M, Park BK. Investigation of mechanisms in toxic epidermal necrolysis induced by carbamazepine. Arch Dermatol 1994;130:598–604.
11. Park BK, Kitteringham NK, Pirmohamed M, Tucker GT. Relevance of induction of human drug-metabolizing enzymes: pharmacological and toxicological implications. Br J Clin Pharmacol 1996;41:477–91.
12. Maggs JL, Naisbitt DJ, Tettey JN, Pirmohamed M, Park BK. Metabolism of lamotrigine to a reactive arene oxide intermediate. Chem Res Toxicol 2000;13:1075-81.