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

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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 necrolysis.

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
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, ie. 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.

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Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

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REFERENCES


