

Lamotrigine induced Stevens-Johnson syndrome: a case report

Lamotrijin kullanımına bağlı Stevens-Johnson sendromu: vaka sunumu

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Abstract

This case is about a young girl who had lamotrigine induced Stevens Johnson syndrome which is known to occur but is rare. Lamotrigine was started when the patient was also receiving valproate for several years; no adverse effects, including any minor skin rash, were recorded while on valproate monotherapy. Valproate is known to augment lamotrigine availability via reduced glucuronidation, which increases the risk of serious rash if patients are concomitantly given lamotrigine. This suggests that a drug-drug interaction between lamotrigine and valproate did contribute to the development of Stevens-Johnson syndrome. Stevens-Johnson syndrome was linked in this case with a higher dose of lamotrigine, suggesting a dose-dependent toxicity. We emphasize that a rapid dose escalation of lamotrigine, even a single higher dose, could expose to an unacceptable risk of Stevens-Johnson syndrome, particularly in patients taking valproate.

Keywords: Drug interactions; drug reaction; lamotrigine; Stevens Johnson syndrome.

Özet

Vaka sunumu, lamotrijin kullanımına bağlı nadiren olduğu bilinen Stevens Johnson sendromunu gelişen bir kız çocuğunu bildirmektedir. Birkaç yıldır valproat tedavisi alan bu esnada herhangi bir deri döküntüsü olmayan hastaya lamotrijin tedavisi başlandı. Valproat kullanan hastaya lamotrijin verildiğinde, azalan glükuronizasyon nedeni ile lamotrijin düzeyini ve ciddi döküntü riskini artırdığı bilinmektedir. Stevens Johnson sendromu gelişimi, lamotrijin ve valproat arası bir ilaç etkileşimini düşündürmektedir. Bu vakada Stevens Johnson sendromu gelişimi, lamotrijin yüksek dozuna bağlı bir doza bağlı toksisiteye bağlanmıştır. Biz, lamotrijinin hızlı doz artırımın, hatta tek yüksek dozunun, özellikle valproat alan hastalarda kabul edilemez bir risk taşıdığını düşünmekteyiz.

Anahtar kelimeler: İlaç etkileşimi; ilaç reaksiyonu; lamotrijin; Stevens Johnson sendromu

Introduction

Lamotrigine (LTG) is a triazine compound that is chemically unrelated to any of the other antiepileptic drugs (AEDs). It was developed as an antifolate agent on the basis of a theory that the mechanism of some AEDs is related to their antifolate property (1). Valencia et al.(2) in their study of 72 patients, found that most common adverse event with LTG was rash (7%) and rate of discontinuation of LTG was around 8%. Rashes though most commonly are erythematous, maculopapular or morbiliform benign rashes but at times, albeit rarely can take up the life threatening form of Stevens-Johnson syndrome (SJS) or more fatal, toxic epidermal necrolysis (TEN).

Case

Our patient was a 16 year old girl, student by occupation, resident of a semiurban area, known case of idiopathic seizure disorder for the last nine years for which she was on anti-epileptics who presented to our hospital with 7 days history of fever followed by generalized rash. Fever was moderate to high grade, documented to be 102°F, intermittent associated with rigors, chills, malaise and headache. Three days after the onset of fever she started developing a burning and pruritic rash over her face and upper torso and which over a period of one day spread to involve the whole body. Rash was erythematous and maculopapular to begin with but later vesicles and bullae started to develop over the face and lips and buccal mucosa

followed by desquamation. In addition patient had red eyes with sensations of burning, grittiness, tearing and photophobia. Vagina and peri anal area was spared.

Patient had been on sodium valproate (500 mg daily) for the last 8 and half years. Her seizures were controlled until 20 days prior to presenting to us she had a fresh episode of seizure after which she was put on oral lamotrigine 25 mg alternate days and was advised to increase the dose after one week to 25 mg daily while valproate was continued at the usual dose. The rash developed on the 10th day of use of lamotrigine concurrent with the time she started to take increasing doses of lamotrigine.

The extent of desquamation was less than 10 percent. On the basis of history and clinical examination a diagnosis of Stevens-Johnson syndrome due to use of lamotrigine was made and was confirmed on punch biopsy of skin.

Investigations revealed normal blood counts, high sedimentation rate and C reactive protein, sterile swab cultures from the desquamated areas and sterile blood and urine cultures. Chest roentgenogram was normal and there were no signs of pneumonitis.

Our patient had a score of 9 on the Naranjo scale for adverse drug reactions which is definitive evidence for causality of the rash to the drug, in this case, lamotrigine.

Patient was managed symptomatically and supportive treatment was started. Lamotrigine was immediately

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discontinued and patient was started on intra-venous fluids. Chlorhexidine mouth washes were used. Topical anesthetics helped in reducing pain and allowed the patient to take orals. Areas of denuded skin were covered with compresses of saline. Tetanus prophylaxis was given. Eye lubricants were used. Anticoagulation with heparin was started and antacids were used to prevent stress ulcers.

For infection control local antiseptic 0.5% silver nitrate was used. No systemic antibiotic was used. As the role of steroids in Stevens-Johnson syndrome is controversial so steroids were not used.

With aggressive supportive care patient started to improve in few days and had no complications.



Figure 1. An image of the patient showing the desquamating erythematous rash of Stevens Johnson syndrome.

Discussion

Lamotrigine is a triazine compound that is chemically unrelated to any of the other AEDs. It was developed as an antifolate agent on the basis of a theory that the mechanism of some AEDs is related to their antifolate property (1). LTG's major mechanism of action is blocking voltage-dependent sodium channel conductance. It has been found to inhibit depolarization of the glutaminergic presynaptic membrane, thus inhibiting release of glutamate. It has a weak antifolate effect that is unrelated to its antiseizure efficacy. Valencia et al.(2) in their study of 72 patients, found that most common adverse event with LTG was rash (7%) and rate of discontinuation of LTG was around 8%. Incidence of rashes varies from 0.08-3%, least in adults with mood disorder when LTG was used as monotherapy and maximum with children treated with LTG for epilepsy (3). Rashes usually occur in two to eight weeks of treatment initiation (4). Rashes though

most commonly are erythematous, maculopapular or morbiliform benign rashes but at times, albeit rarely can take up the life threatening form of Stevens-Johnson syndrome or more fatal, TEN. TEN and SJS are mucocutaneous disorders with an estimated incidence of 0.4-1.2 patients per year (5,6).

Stevens-Johnson syndrome (SJS) is an immune-complex-mediated hypersensitivity complex that typically involves the skin and the mucous membranes. While minor presentations may occur, significant involvement of oral, nasal, eye, vaginal, urethral, gastrointestinal, and lower respiratory tract mucous membranes may develop in the course of the illness. GI and respiratory involvement may progress to necrosis. Stevens-Johnson syndrome is a serious systemic disorder with the potential for severe morbidity and even death. Although several classification schemes have

been reported, the simplest breaks the disease down as follows (7).

- Stevens-Johnson syndrome (SJS) - A "minor form of TEN," with less than 10% body surface area (BSA) detachment
- Overlapping Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) - Detachment of 10-30% BSA

- Toxic epidermal necrolysis (TEN) - Detachment of more than 30% BSA

The 4 etiologic categories for Stevens Johnson syndrome are as follows:

- Infectious
- Drug-induced
- Malignancy-related
- Idiopathic



Figure 2. Another image of the same patient showing the maculopapular nature of the rash at an earlier stage of Stevens Johnson syndrome .

Drugs including allopurinol, antibiotics, anticonvulsants and non-steroid antiinflammatory drugs are the main cause of SJS/TEN in most cases. Phenytoin, carbamazepine, oxcarbazepine, valproic acid, lamotrigine, barbiturates are some of the anti convulsants that are incriminated in causing Stevens Johnson syndrome. Mockenhaupt et al. (8) stressed that most anticonvulsant-induced SJS occurs in the first 60 days of use. There is an association with Herpes simplex and Mycoplasma pneumoniae infections (9).

The overall incidence of lamotrigine-induced serious rash is approximately 0.3 percent in adult patients with epilepsy receiving adjunctive therapy, and this risk seems to be largely confined to the first months of treatment (10).

Most reported cases of SJS or TEN due to LTG have occurred in patients who were co-medicated with lamotrigine and valproate. Chaffin and Davis (5) reported a case of TEN after LTZ was added to carbamazepine. Bocquet et al. (11) reported two children

who developed SJS when LTZ was added to valproate and clonazepam.

Our case history along with the lack of other potential confounding factors was highly suggestive of lamotrigine-induced Stevens-Johnson syndrome; use of the Naranjo scale indicated a definite relationship of causality (12).

When lamotrigine was started the patient was also receiving valproate for several years; no adverse effects, including any minor skin rash, were recorded while on valproate monotherapy. However, valproate is known to augment lamotrigine availability via reduced glucuronidation, which increases the risk of serious rash if patients are concomitantly given lamotrigine (13). Very low valproate concentrations may inhibit lamotrigine clearance and this is **maximal** when patients are taking valproate 500 mg/day (14). After one weeks of up-titration therapy our patient took lamotrigine 50

mg, and even though lamotrigine levels were not measured we postulate that concentrations were elevated in coincidence with the onset of Stevens-Johnson syndrome. This suggests that a drug-drug interaction between lamotrigine and valproate did contribute to the development of Stevens-Johnson syndrome. Stevens-Johnson syndrome was linked in this case with a higher dose of lamotrigine, suggesting a dose-dependent toxicity.

We emphasize that a rapid dose escalation of lamotrigine, even a single higher dose, could expose to an unacceptable risk of Stevens-Johnson syndrome, particularly in patients taking valproate.

References

1. Cunnington MC. The International Lamotrigine pregnancy registry update for the epilepsy foundation. *Epilepsia*. 2004;45(11):1468.
2. Valencia I, Pinol-Ripoll G, Khurana DS, Hardison HH, Kothare SV, Melvin JJ, et al. Efficacy and safety of lamotrigine monotherapy in children and adolescents with epilepsy. *Eur J Paediatr Neurol* 2009;13(2):141-5.
3. Seo HJ, Chiesa A, Lee SJ, Patkar AA, Han C, Masand PS, et al. Safety and tolerability of lamotrigine: results from 12 placebo-controlled clinical trials and clinical implications. *Clin Neuropharmacol* 2011;34(1):39-47.
4. Sussman N. Anticonvulsants: other anticonvulsants. In: Sadock BJ, Sadock VA, eds. *Kaplan&Sadock. comprehensive textbook of psychiatry*. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2000. 2299-2304.
5. Chaffin JJ, Davis SM. Suspected lamotrigine-induced toxic epidermal necrolysis. *Ann Pharmacother* 1997;31(6):720-3.
6. Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995;333(24):1600-7.
7. French LE. Toxic epidermal necrolysis and Stevens Johnson syndrome: our current understanding. *Allergol Int* 2006;55(1):9-16.
8. Mockenhaupt M, Messenheimer J, Tennis P, Schlingmann J. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptics. *Neurology* 2005;64(7):1134-8.
9. Tay YK, Huff JC, Weston WL. *Mycoplasma pneumoniae* infection is associated with Stevens-Johnson syndrome, not erythema multiforme (von Hebra). *J Am Acad Dermatol* 1996;35(5 Pt 1):757-60.
10. Rzany B, Correia O, Kelly JP, Naldi L, Auquier A, Stern R. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis during first weeks of antiepileptic therapy: a case-control study. Study group of the international case control study on severe cutaneous adverse reactions. *Lancet* 1999;353(9171):2190-4.
11. Bocquet H, Farmer M, Bressieux JM, Barzegar C, Jullien M, Soto B, et al. Lyell syndrome and Stevens-Johnson syndrome caused by lamotrigine. *Ann Dermatol Venereol* 1999;126(1):46-8.
12. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30(2):239-45.
13. Yalcin B, Karaduman A. Stevens-Johnson syndrome associated with concomitant use of lamotrigine and valproic acid. *J Am Acad Dermatol* 2000;43(5 Pt 2):898-9.
14. Gidal BE, Sheth R, Parnell J, Maloney K, Sale M. Evaluation of VPA dose and concentration effects on lamotrigine pharmacokinetics: implications for conversion to lamotrigine monotherapy. *Epilepsy Res* 2003;57(2-3):85-93.