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Stevens Johnson Syndrome - Toxic Epidermal Necrolysis Induced by A Combination of Lamotrigine and Valproic Acid: A Case Report

Serap Oflaz[1], Hira S. Kalkan[2], Esra Gokce[2], Cagatay Karsidag[3], M. Salih Gurel[4]

ÖZET:

Lamotrijin ve valproik asit kullanımına bağlı gelişen Stevens Johnson sendromu-toksik epidermal nekroliz: olgu sunumu

Stevens-Johnson sendromu (SJS) ve toksik epidermal nekroliz (TEN) deri ve mukozayı etkileyen, nadir olarak görülen ve hayatı tehdit eden akut allerjik reaksiyonlardır. Bu yazıda lamotrijin ve valproik asit kullanan hastada, lamotrijin titrasyonun uygunsuz olması sonucu gelişen SJS-TEN vakası bildirilmiştir. Bu vaka, lamotrijin ile birlikte diğer psikiyatrik ilaçların kullanımı sonucunda, daha sık ve daha ciddi cilt reaksiyonlarının oluşabileceğini vurgulamaktadır. Bu nedenle lamotrijin kullanırken çoklu psikiyatrik ilaç kullanımından kaçınmalı, herhangi bir cilt reaksiyonu görülmesi halinde lamotrijin kesilmelidir.

Anahtar sözcükler: Stevens-Johnson sendromu, toksik epidermal nekroliz, lamotrijin, valproik asit

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ABSTRACT:

Stevens Johnson Syndrome - Toxic epidermal necrolysis induced by a combination of lamotrigine and valproic acid: a case report

Both Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare and life-threatening acute allergic reactions affecting the skin and mucous membranes. We report a case with SJS-TEN likely induced by inappropriate lamotrigine titration during the use of a lamotrigine and valproic acid regimen. The present case report supports the clinical evidence that combination of lamotrigine with other psychiatric drugs increases the frequency and severity of skin reactions. Therefore in polypharmacy, lamotrigine should be used more carefully and lamotrigine should be discontinued if any rash appears.

Key words: Stevens-Johnson syndrome, toxic epidermal necrolysis, lamotrigine, valproic acid

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[1]M.D., Specialist of Psychiatry, Istanbul University, Istanbul Faculty of Medicine, Department of Psychiatry, Istanbul-Turkey
[2]M.D., Resident at Department of Psychiatry,
[3]M.D., Specialist of Psychiatry, Bakirkoy Research and Training Hospital of Psychiatric and Neurological Diseases, Istanbul-Turkey
[4]M.D., Associate Professor of Dermatology, Istanbul Research and Training Hospital, Deparment of Dermatology, Istanbul-Turkey

Yazışma Adresi / Address reprint requests to: Serap Oflaz, M.D., Istanbul University, Istanbul Faculty of Medicine, Department of Psychiatry, İstanbul-Turkey

Telefon / Phone: +90-505-894-4436

Faks / Fax: +90-212-634-1204

Elektronik posta adresi / E-mail address: drserapb@yahoo.com

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INTRODUCTION

Lamotrigine, a new antiepileptic drug, is currently indicated as adjunctive therapy for partial seizures and generalized tonic-clonic seizures. It is also indicated for maintenance treatment of bipolar disorder and neuropathic pain (1). In patients taking lamotrigine, 5-10% experience rash and ≤14% of patients comedicate with valproic acid (1).

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are both rare and life-threatening conditions. They are thought to be caused by a hypersensitivity complex affecting the skin and the mucose membranes (2). Stevens-Johnson syndrome is considered to be a milder form of TEN and the affected body surface area is less than 10%. If the affected body surface is more than 30% of the total body surface area, the condition is called TEN. If the affected body surface area is 10-30%, this condition is considered to be SJS-TEN. Both SJS and TEN are associated with high morbidity and mortality (3).

Here, we present a case of SJS-TEN that occurred after addition of lamotrigine to the valproic acid regimen.

CASE REPORT

A 24-year-old female patient with psychotic depression was referred to the emergency room with suicidal plans, swelling on her eyelids and lips, oral mucosal lesions, and generalized rash which had appeared at the end of the second week of lamotrigine treatment. The patient had experienced 3 depressive episodes within 8 years, but she did not seek any medical attention during those 3 episodes. She had been referred to a psychiatry clinic two months ago, because of new complaints including anhedonia, increased need for sleep, and auditory hallucinations during the previous 6 months. Risperidone (3 mg/day) was started. In follow-up visits, lithium (900 mg/day) and valproic acid (1000 mg/day) were subsequently added due

to sustained depressive symptoms. The risperidone dose was increased to 6 mg/day along with the addition of biperiden (4 mg/day). Due to continued depressive symptoms, lamotrigine (25 mg/day) was added to the treatment regimen and the dose was gradually raised to 100 mg/day during the following 3 weeks. Her family history was positive for psychiatric disorders. Her father and elder brother had bipolar I disorder, and her mother had obsessive compulsive disorder. She had no history of alcohol use, smoking, or any drug addiction.

Initial psychiatric examination showed agitation, mildly decreased spontaneous speech, psychomotor activation, depressive mood, suicidal plans, auditory hallucinations, paranoid delusions, and lack of judgment and insight. According to the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria, she was diagnosed with psychotic depression. Her vital signs were as follows: temperature (axillary), 36.5ºC;pulse rate, 88/min; respiration rate, 18/min; blood pressure, 110/80 mmHg.

Physical examination showed erythematous papules and vesicules. Flask bullous lesions prone to merge and also erosive and crusted lesions and diffuse atypical target-like purpuric macules and papules were detected on her face, extremities, body, and hips. Sharply but irregularly limited erosive lesions, and blistered, irregular shaped white plaques were also seen diffusely in the oropharynx. She had hemorragic crusted erosive areas. Flask bullae

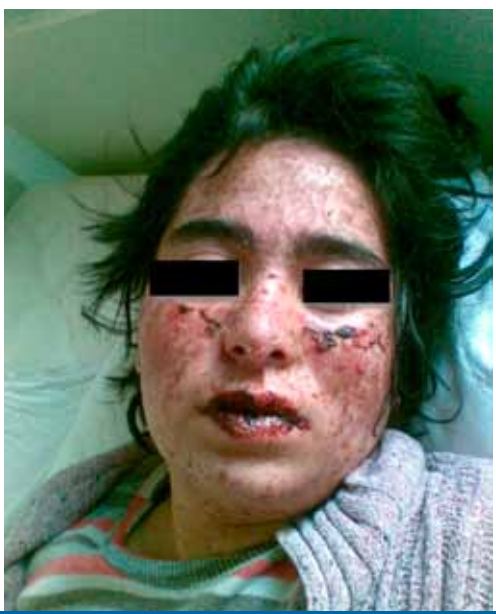

Figure 1: Skin lesions on the face and neck

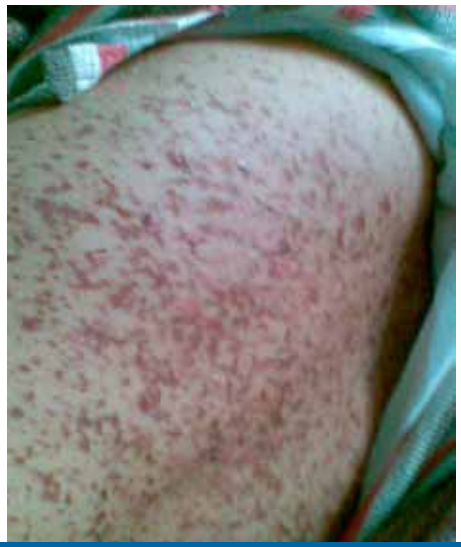

Figure 2: Skin lesions on the trunk

(the largest one 1x1.5 cm in diameter) were seen on the base of the foot and on the big toe. Edema and purulent leakage on the eye lids and conjunctiva were detected. Nicolsky's sign was positive. Lesions covered about the 30% of the body surface on skin examination (Fig. 1 and 2).

Laboratory examination revealed normal complete blood count and serum biochemistry, moderately elevated erythrocyte sedimantation rate (42 mm/h), normal C-reactive protein, negative rheumatoid factor, normal thyroid function and serum coagulation tests. Serum serology testing, including VDRL, TPHA, HbsAg, anti Hbs, anti HCV, and anti HIV, was found to be negative. Urinalysis showed pyuria (leucocyte 1+). Chest X-ray was normal.

Following her initial assessment by a psychiatrist in the emergency room, consultations by a dermatologist, an internist, an ophthalmologist and an otorhinolaryngologist were conducted. Considering the rapid arise of the lesions, the presence of atypical target-like lesions, the intense bullous reaction with Nicolsky positivity, the oral mucosa and conjunctiva involvement and the clinical course, the patient was diagnosed with lamotrigine related SJS-TEN.

The patient was hospitalized in the dermatology clinic and her treatment involved fluid-electrolyte replacement (isotonic solution, 1000 cc/day, 5% dextrose solution, 500 cc/day), antiaggregants (clexan 0.4U 1x1), steroids (prednizolone, 60 mg/day), a prophylactic antibiotic (cephazolin 1x3 gr) due to the risk of S.aureus and other

opportunistic skin infections and sepsis, mouth care (nystatin oral suspension and chlorhexidine gluconate gargle), topical wound care (hydrocortisone acetate cream), eye care (prednisolone acetate forte eye drops 5x1/day, lomefloxacin eye drops 4x1/day and oxytetracycline HCl eye ointment 2x1/day). The patient's previous psychiatric medications were discontinued, an antipsychotic (haloperidol 10 mg/IV) was added. Her blood pressure, pulse rate and body temperature remained within normal limits. The patient's lesions started to improve after the 4th day of her hospitalization; however, the patient became excited on the 5th day of her hospitalization and she reported that she would like to kill herself or her children. She attempted to jump from the window and the stairs and was therefore referred to our psychiatry in-patient unit. Her dermatological symptoms resolved within 15 days. Seven sessions of electroconvulsive therapy were applied for psychotic depression following improvement of her general medical condition. After 30 days of hospitalization, the patient had achieved partial remission and was discharged on a combination of risperidone (3 mg/day) and venlafaxine (225 mg/day). The patient provided written informed consent.

DISCUSSION

Antiepileptics such as phenytoin, phenobarbital, and carbamazepine play an important role in the development of drug-induced serious skin reactions such as SJS and TEN. Lamotrigine, a relatively new antiepileptic drug, has been reported as having similar potential to cause serious cutaneous reactions (4). These reactions generally appear in the first 8 weeks of treatment, and the risk is most acute during the first 2-8 weeks of antiepileptic treatment (5). Rash of any type occurred in 10% of subjects receiving lamotrigine in controlled trials (6). The incidence of rash appears to increase with the magnitude of the initial dose and the subsequent rate of dose escalation and in patients receiving concomitant therapy with valproic acid (7). Occasionally the cutaneous reaction is more severe and may progress to desquamation with mucous membrane involvement (8).

The product information for lamotrigine states that the incidence of severe rashes (i.e., SJS or TEN) is approximately 1/1000 in adults (9). Concomitant use of valproic acid with lamotrigine significantly increases the risk for development of adverse cutaneous reactions (7). It is known that valproic acid interacts with lamotrigine metabolism, leading to a reduced total clearance and therefore to an increased elimination half-life of lamotrigine, resulting in higher serum concentrations (9). Therefore concominant admistration of these drugs necessitates a much slower titration, 25 mg every other day for the 1st and 2nd weeks, 25 mg/day for the 3th and 4th weeks. Unfortunately, the starting dosage of lamotrigine in our case was 25 mg/day, and dosage had been increased rapidly to 100 mg/day. The initial dose and rapid dose escalation of lamotrigine with concomitant use of valproate may have induced SJS-TEN in this patient.

The mortality rate due to TEN in the acute phase varies between 20-66% (10). Mortality usually results from sepsis due to e pulmonary or skin infections by Pseudomonas or Staphilococcus. Gastrointestinal hemorrage, pulmonary edema, and fluid-electrolyte imbalances are other reasons which increase the mortality rate (11).

In conclusion, the present case report supports the clinical evidence that a combination of lamotrigine and valproic acid increases the frequency and severity of skin reactions. This case also supports the recommendation that if lamotrigine is added to current valproic acid treatment, it should be initiated at a low dose and then increased slowly and the treatment should be discontinued if any rash appears.

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