Cent. Eur. J. Med. • 5(6) • 2010 • 733-736
DOI: 10.2478/s11536-010-0001-1

VERSITA

Central European Journal of **Medicine**

Stevens-johnson syndrome caused by combined use of lamotrigine and fluoxetine and review of the literature

Case Report

Mehmet Uluğ[1*], Nuray Can Uluğ[2], Mustafa Kemal Celen[3], Mehmet Faruk Geyik[4], Celal Ayaz[3],

[1] *BSK Anadolu Hospital, Department of Infectious Diseases and Clinic Microbiology, 43100 Kütahya, Turkey*

[2] *BSK Anadolu Hospital, Department of Neurology, 43100 Kütahya, Turkey*

[3] *Dicle University Medical School, Department of Infectious Diseases and Clinic Microbiology, 21280 Diyarbakir, Turkey*

[4] *Düzce University Medical School, Department of Infectious Diseases and Clinic Microbiology, 81100 Düzce, Turkey*

Received 14 May 2009; Accepted 9 December 2009

Abstract: Stevens-Johnson syndrome (SJS) is a rare, life-threatening acute allergic drug reaction presenting with target lesions and blebs of epidermis. Although a variety of etiologies such as infections and underlying malignancies have been implicated as potential causes of SJS, drugs remain the predominant inciting agent. This report presents a SJS case due to combined use of lamotrigine and fluoxetine. A 41-year-old man was admitted to our clinic with fever, skin eruptions (especially on the face and trunk) and lesions around the mouth. The patient's history revealed lamotrigine and fluoxetine use during the previous three weeks for major depression. Dermatological examination revealed a typical clinical picture of SJS; his psychotropic medications were all stopped. While topical and ocular prednisolone (1mg/kg/day) cares were initiated, steroid dosage was reduced within 15 days. The condition of patient rapidly improved through this treatment. Effective management of SJS begins with prompt recognition of the entity, combined with attention to each of the major organs that may be affected, potential comorbidities and withdrawal of all potentially causative drugs. Clinicians should bear in mind the possibility that drugs with potential risk in developing SJS must be used carefully.

Keywords: *Stevens - Johnson syndrome • Lamotrigine • Fluoxetine • Medical treatment*

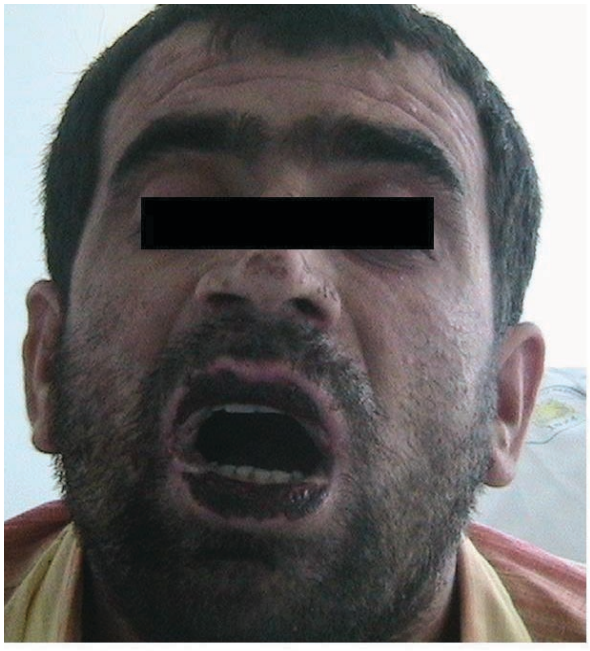
1. Introduction

Cutaneous drug eruptions are one of the most frequent manifestations of adverse drug reactions [1]. Severe cutaneous adverse reactions of drugs are affected about 1 per 1000 hospitalised persons [2].

Stevens-Johnson syndrome (SJS) is a life-threatening inflammatory mucocutaneous drug reaction [3] and occurs at a rate of approximately 1-7 cases per million people per year [2]. The eruptions usually occur in the form of a late hypersensitivity reaction and are rare in a erythematous or maculopapular manner [4]. In adults, drugs are major precipitating factors [5]. The most commonly implicated drugs are sulfa derivatives, non-steroidal anti-inflammatory agents, penicillin-related and cephalosporin antibiotics, antiepileptics, allopurinols, and terbinafines. Antiepileptics pose relatively greater risks than many other drugs; each one may lead to SJS

* *E-mail: mehmetulug21@yahoo.com*

Figure 1. Erythematous macules, bullae and erosion on face, and hemorrogic crust on lips.



alone. The frequency of SJS in patients who are treated with lamotrigine (LTG) is estimated to be 1:1000 [6].

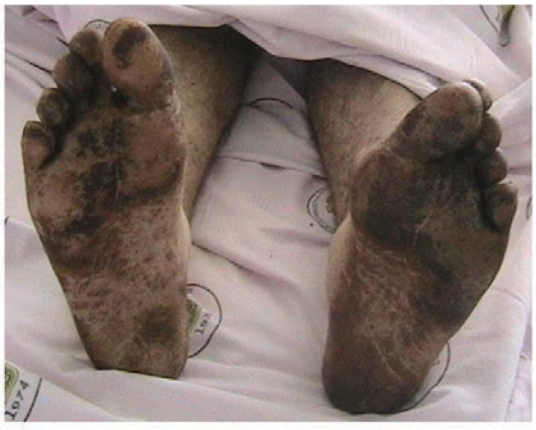
The mortality rate for SJS is up to 50%, with sepsis and Gram-negative pneumonia as the leading causes of death [7]. This report presents a SJS case triggered by use of LTG and fluoxetine together.

2. Case Report

A previously healthy 41-year-old man with complaints of fever, fatigue, myalgia, skin eruptions (especially on the face and trunk) and lesions around the mouth was admitted to our clinic. The history of him revealed the use of LTG (50 mg/day) and fluoxetine (20 mg/day) during the previous three weeks for major depression. Apart from his diagnosis of major depression, the patient's medical history was unremarkable; no previous history of drug or food allergy was observed. The patient was not on any other prior or concomitant medications.

On the day of admission, physical examination revealed that he was in pain, feverish (38.5°C), and in poor general appearance. Blood pressure, pulse and respiratory rate were 130/80 mmHg, 94/minute, and 18/minute, respectively. His physical examination was normal except of the dermatological portion. Dermatological examination revealed severe bilateral conjunctivitis, erosion of the lips with hemorrhagic crusts, pale erythematous papules, bulla and erosion on the face (Figure 1), gingivitis and severe erosions of the

Figure 2. Erythematous typical target macules tending to combine with each other and scattered Nikolsky's sign positive blisters on the legs.



pharynx. There was a bias towards pale erythematous typical target maculaes and scattered Nikolsky's sign positive blisters on the acral areas, trunk, back, and legs (Figure 2). The nose was severely involved and the other mucosal surfaces were normal.

Laboratory findings included a hemoglobin level of 13.5g/dl, total leukocyte count of 8000/mm^3 (80% polymorphonuclear cells), and platelet count 1.95 x 10^5 K/Ul. Erythrocyte sedimentation rate was 78 mm/h with a C-reactive protein, measuring 143 mg/dl. In biochemical studies, liver function tests such as ALT: 224 U/l (range, 10-35 U/l) and AST: 230 U/l (range, 10-40 U/l) were elevated.

In the light of the cutaneous lesions and mucosal involvement of the conjunctivae, a preliminary diagnosis of SJS was made. Skin biopsy was then performed on the patient and the typical histopathological appearance of SJS (e.g., apoptosis and necrosis of keratinocytes along with dermoepidermal detachment and lymphocytic infiltration of perivascular regions) were seen.

At that time, all of his psychotropic medications were stopped. Additional treatment (i.e., fluid replacement, prednisolone (1 mg/kg/day), antibiotic eye drops and ointment (polymyxin B sulfate ointment combined with neomycin sulfate), steroid ointment for lips, mupirosin for skin, bicarbonate and clorhexidine mouth wash for oral mucosal lesions, wet dressing for epidermal surfaces) was given. In response to these treatments, his critical condition improved and was finally stabilised.

He responded well to treatment, his fever subsided five days after starting the treatment. When his biochemical values and general condition improved along with the absence of new lesions, the steroid dosage was gradually reduced and completely stopped. He was discharged following complete recovery on the 21st day of treatment. When he discharged, tianeptine sodium

(37.5 mg/day) was administered for major depression. At the 6-month follow-up visit, no residual cutaneous scarring or end-organ damage was observed.

3. Discussion

SJS is a serious mucocutaneous illness with systemic symptoms characterised by the presence of flat, atypical target lesions and epidermal detachment, which is <10% of the total surface area [1]. Although a variety of etiologies, such as infections and underlying malignancies, have been implicated as potential causes of SJS, drugs remain the predominant inciting agent [8]. The drugs most reported in inciting SJS are antibiotics (40%), antiepileptics (11%) and analgesics (5-23%) [4]. Among antiepileptics, phenytoin, carbamazepine, phenobarbital and LTG have recently been cited as causes [9]. LTG, a new anticonvulsant drug, has chemical properties different from those of other antiepileptics [4]. It can be also used in major depression [10]. On the other hand, selective serotonin reuptake inhibitor (SSRIs) such as fluoxetine is widely used in the treatment of depressive disorders because of their low-frequency adverse effects [11]. Adverse cutaneous effects of SSRIs are rare but the knowledge of these reactions is important because SJS had been reported during fluoxetine treatment [12].

The exact pathophysiologic mechanism of SJS remains unknown. Various theories have implicated both immunological and non-immunological mechanisms, with the prevailing evidence suggesting primary involvement of the immunologic response [8]. In immunological mechanisms, LTG metabolites have been claimed to assume the role of hapten and lead to immunological reactions, particularly to T-cell-originated reactions and cell-associated cytotoxicity [4]. On the other hand, genetic factors may play a role in the development of SJS in non-immunological mechanisms [8]. It has been postulated that patients with slow intrinsic acetylation rates and those taking medications such as azoles, protease inhibitors, SSRIs, and quinolones are at increased risk of developing SJS [13]. Slow acetylation may be a factor in the development of a number of adverse cutaneous drug reactions, as the reduced rate of acetylation causes the accumulation of reactive metabolites that induce cell-mediated cytotoxic reactions directed against the epidermis, thereby resulting in keratinocyte apoptosis [8,14]. In the light of these findings, we think that LTG and fluoxetine exert a synergistic effect in developing SJS.

SJS caused by LTG alone is a very well-described phenomenon, but the role of fluoxetine in SJS is not clear. Bodokh *et al.* [12] reported that fluoxetine can cause SJS; consistent with this finding, studies conducted in France suggested fluoxetine as a potential causative agent in SJS [15,16]. However, LTG was associated with a high risk for SJS, but there was no evidence of risk for fluoxetine in the Mockenhaupt *et al* study [17].

Effective management of SJS begins with prompt recognition of the entity, combined with attention to each of the major organs that may be affected as well as potential co-morbidities. Since medications are the most common cause of SJS, a thorough drug history must be obtained, and all potential offending agents must be immediately discontinued [8]. In this study, the patient's psychotropic medications were discontinued.

Treatment with corticosteroids, while effective in most other acute inflammatory disorders, is controversial [18]. Furthermore, numerous other anti-inflammatory, immunosuppressive, and immunumodulatory agents (such as cyclosporine, cyclophosphamide and thalidomide) as well as intravenous immunoglobulin have been administered as possible means to arrest underlying immunological mechanisms promoting SJS [19]. However, the efficacy of these agents in the treatment of SJS has not been demonstrated in any controlled clinical trial. In the absence of strong evidence, none of those regimens can be definitely proposed as a treatment of choice [8]. In this study, according to the result of skin biopsy prednisolone was given to him and his response was very well to the treatment.

In spite of this, SJS has a significant impact on public health because of its high mortality rate [7,17]. In this study, the patient did not die and was followed-up after 6 months; there is no residual cutaneous scarring or end-organ damage due to appropriate supportive care, prompt recognition and treatment of systemic corticosteroids.

4. Conclusion

SJS is a rare but serious adverse cutaneous reaction most commonly due to medications. Prompt recognition is critical for the initiation of appropriate care. Comprehensive SJS treatment requires a skilled, collaborative and multidisciplinary approach that addresses the highly complex, systemic response to condition. If corticosteroids are considered in more severe cases, they should be used early before blistering occurs in moderate-to-high doses and stopped within days if there is no dramatic response. In conclusion, clinicians should bear in mind the possibility that drugs increasing the risk of developing SJS must be used carefully.

References

[1] Sharma VK, Sethuraman G, Minz A. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) and SJS-TEN overlap: A retrospective study of causative drugs and clinical outcome. Indian J Dermatol Venerol 2008; 74: 238-240

[2] Roujeau JC, Stern RS. Severe cutaneous adverse reactions to drugs. N Engl J Med 1994; 331:1272–1285

[3] Hussain W, Craven NM. Toxic epidermal necrolysis and Stevens-Johnson syndrome. Clin Med 2005; 5:555-558

[4] Karıncaoglu Y, Ozcan H, Saglam H, Seyhan M. A case of Stevens-Johnson syndrome trigged by combined use of antiepileptics. T Klin Dermatoloji 2004; 14:162-165

[5] Wolkenstein P, Revuz J. Toxic epidermal necrolysis. Dermatol Clin 2000; 18:485-495

[6] Messenheimer JA. Rash in adult and pediatric patients treated with lamotrigine. Can J Neurol Sci 1998; 25:14-18

[7] Weber DJ, Cohen MS, Rutala WA. The acutely iII patient with fever and rash. In: Mandell GL, Bennet GE, Dolin R eds. Principles and Practice of Infectious Diseases. 6th ed. Philadelphia: Churchill Livingstone. 2005:729–746

[8] Hazin R, Ibrahimi OA, Hazin MI, Kimyai-Asadi A. Stevens-Johnson syndrome: Pathogenesis, diagnosis, and management. Ann Med 2008; 40:129-138

[9] Fritsch PO, Sidoroff AA. Drug-induced Stevens-Johnson syndrome/toxic epidermal necrolysis. Am J Clin Dermatol 2000; 1: 349-360

[10] Barbee JG, Jamhour NJ. Lamotrigine as an augmentation agent in treatment-resistant depression. J Clin Psychiatry 2002; 63:737-741

[11] Krasowska D, Szymanek M, Schwartz RA, Myslinski W. Cutaneous effects of the most commonly used antidepressant medication, the selective serotonin reuptake inhibitors. J Am Acad Dermatol 2007; 56:848-853

[12] Bodokh I, Lacour JP,Rosenthal E et al. Lyell syndrome or toxic epidermal necrolysis and Stevens-Johnson syndrome after treatment with fluoxetine. Therapie 1992; 47:441

[13] Chung WH, Hung SI, Hong HS et al. Medical genetics: a marker for Stevens-Johnson syndrome. Nature 2004; 428:486

[14] Evans DA. Survey of the human acetylator polymorphism in spontaneous disorders. J Med Genet 1984; 21:243-253

[15] Beauquier B, Fahs H. Secondary dermatologic effects of serotonin reuptake inhibitor antidepressants: hypothesis of cross-reacting allergy. Encephale 1998; 24:62-64

[16] Richard MA, Fiszenson F, Jreissati M, Jean Pastor MJ, Grob JJ. Cutaneous adverse effects during selective serotonin reuptake inhibitors therapy: 2 cases. Ann Dermatol Venerol 2001; 128:759-761

[17] Mockenhaupt M, Viboud C, Dunant A, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: Assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-Study. J Invest Dermatol 2008; 128:35-44

[18] Hynes AY, Kafkala C, Daoud YJ, Foster CS. Controversy in the use of high-dose systemic steroids in the acute care of patients with Stevens-Johnson syndrome. Int Ophthalmol Clin 2005; 45:25-48

[19] Metry DW, Jung P, Levy ML. Use of intravenous immunoglobulin in children with Stevens-Johnson syndrome and toxic epidermal necrolysis. Pediatrics 2003; 112:1430-1436