

Carbamazepine-induced erythema multiforme major in an epileptic patient with bipolar affective disorder

Suneet K. Upadhyaya, Rangeel S. Raina¹, Archana Sharma², Vijay Thawani¹, Deepak Dimari³

Departments of Psychiatry, ¹Pharmacology, ²Obstetrics and Gynaecology, ³Dermatology, VCSG Govt. Medical Science and Research Institute, Srinagar Garhwal, Uttarakhand, India

ABSTRACT

Carbamazepine (CBZ) is frequently used for epilepsy and various psychiatric illnesses. It is known for its dermatological side effects which may range from mild rash to life-threatening reactions as Stevens Johnson syndrome or toxic epidermal necrolysis. We hereby report a rare case of 17-year-old woman suffering from generalized tonic clonic epilepsy with comorbid bipolar affective disorder, who was initially treated with sodium valproate with partial improvement. After 19 days of addition of CBZ to the therapy, the patient developed erythema multiforme major with >60% skin involvement and oral, conjunctival, intestinal, and vaginal mucosal involvement.

Key words: Carbamazepine, erythema multiforme major, Stevens-Johnson's syndrome

INTRODUCTION

Drug-induced dermatological reactions are common with the antiepileptic drugs such as carbamazepine (CBZ), phenytoin, lamotrigine, ethosuximide, and phenobarbital. Some studies also reported valproate as a factor in drug-induced cutaneous reactions.^[1] These reactions may occur in the mild form as benign rash or may be severe and life-threatening as erythema multiforme major or toxic epidermal necrolysis (TEN). Erythema multiforme major, also known as Stevens-Johnson syndrome, is usually caused by reactions to medications, rather than infections.^[2] Some less studied factors may predispose to these reactions. CBZ was originally introduced in therapeutic armamentarium as an anticonvulsant, and is known to produce

such adverse drug reaction (ADR), but the reports are rare. CBZ is still used as a first-line agent along with lithium and valproic acid in the treatment of bipolar disorder.^[3] Although there are case reports of Stevens Johnson syndrome (SJS) occurring in schizophrenia,^[4] bipolar affective disorder,^[5] and during a manic episode when treated with CBZ, we were unable to find reports of SJS in patients having epilepsy with bipolar affective disorder. SJS is a blistering disorder, characterized by mucosal erosions at two or more sites with small blisters and purpuric macules.

CASE REPORT

A 17-year-old woman was brought to Psychiatry OPD with complaints of episodes of decreased sleep, irritability, and occasional aggressive and violent behavior. She was already on sodium valproate 600 mg/day for generalized tonic-clonic seizures, since the last 2 years from a primary health centre of Uttarakhand state. She had a history of 5–10 convulsions per day for 2–3 days and then seizure free period of 10–15 days. Her episodes of behavioral abnormalities had no correlation with onset of seizures. She reported insignificant improvement

Access this article online	
Quick Response Code:	Website: www.jpharmacol.com
	DOI: 10.4103/0976-500X.95537

Address for correspondence:

Suneet Kumar Upadhyaya, S/o Shri Ashok Kumar Upadhyaya, Prankur, Opposite Idgaah, Kothun Road, Lalsot - 303 503, Dausa, Rajasthan, India. E-mail: dr_suneet12@yahoo.com

in her seizure disorder despite treatment. She accepted noncompliance to the regular treatment, thrice for 15–20 days duration each, during the last 2 years, and admitted that a further increase in seizure frequency during such breaks compelled her to resume the treatment subsequently.

On examination, her mental status was found to be normal and no psychiatric disorder was evident. She had history of frequent mood swings of mania and depression associated with episodic behavioral changes which was undoubtedly suggestive of bipolar affective disorder. Her general physical examination was unremarkable. All routine investigations were within normal limits. She was diagnosed as a case of bipolar affective disorder, currently in remission, with comorbid epilepsy. The patient was initiated on higher dose (800 mg) of sodium valproate which was further increased gradually to 1600 mg/day. At this stage, her seizure frequency was reduced to 1–2 convulsions/day on monthly intervals. A further increase in dose caused significant sedation and was intolerable. At this stage, she was referred to a neurologist which she refused to comply with.

CBZ 200 mg once daily was added to her regimen of valproate 1600 mg/day in consultation with the hospital physician, which was increased to twice daily after 5 days and then three times daily after 10 days of initiation. She tolerated the treatment well until 19th day when she returned with high-grade fever, redness of eyes, swelling all over body, eruptions on lips, face in butterfly pattern [Figure 1, 2] and was admitted in the dermatology ward. On examination, she appeared toxic. Her axillary temperature was 39°C, blood pressure was 90/60 mmHg, and the pulse rate was 70 per min and regular. The lymph nodes, liver, and spleen were not palpable. Next day she had multiple bullae formation all over the body in the symmetrical pattern which gradually increased to involve >60–65% of the body surface area. Epidermal detachment was not evident. She had severe pain during deglutition, generalized body edema, and bleeding per vagina. A mucopurulent discharge was present from oral, nasal, and conjunctival mucous membranes. She was unable to open her eyes because of matting with thick discharge. Her lips were swollen with hemorrhagic crusting. She was in the state of altered consciousness. Examination by a gynecologist revealed that she was in the menstruating phase and vaginal mucosa was found ulcerated.

Her lab investigations showed that hemoglobin was 13 g/dL, total leukocyte count 6000/mm³, platelets 1.5 lakhs/mm³, creatinine 0.9 mg/dL, urea 49 mg/dL, sodium 139 mEq/L, and potassium 4.8 mEq/L. Examination of urine revealed albumin (+) and full field RBCs, which correlated with her menstruation phase. Stool examination had RBCs and pus cells indicating mucosal involvement of the bowel. She was HIV and HBsAg negative. Biopsy was not done as her clinical presentation was

compatible with diagnosis of erythema multiforme major which was confirmed with an opinion from the pharmacologist.

Her antiepileptics were discontinued. She was treated with methylprednisolone, chlorpheniramine, and ceftriaxone parenterally, and clobetasol–gentamicin combination topically, along with IV fluids and other supportive measures. After about 2 weeks of intensive indoor management, her conditions started improving and during third week she was again put on oral valproate 200 mg with an incremental increase of 200 mg per day till it reached 1600 mg/day on eighth day of initiation. The patient again started feeling drowsy, which may have had a psychological component as the patient was already anticipating the effect due to past experience. She refused any other addition to her treatment for fear of similar reaction and agreed to bear the possibility of few convulsions per month.

Two months after discharge, the patient returned for review and the dose of sodium valproate was increased since the sedation was tolerable. Her dose was increased to 1800 mg and then to 2000 mg in the next month. With this dose she started having about 3–4 months of seizure free period and maintained on the same dose since the last 6 months.

DISCUSSION

Antiepileptic drugs are known to cause cutaneous ADRs. CBZ is known to cause hypersensitivity syndrome associated with severe cutaneous and multiorgan involvement. Cutaneous lesions mostly occur on the palms, soles, dorsum of the hands, and extensor surfaces. Mucosal involvement may include erythema, edema, sloughing, blistering, ulceration, and necrosis.

This patient had been taking valproate for 2 years, and her investigations were not suggestive of any other etiology for causation of these ADRs. Cutaneous reactions started within 3 weeks of administration of CBZ, which is the usual risk period for this ADR.^[6] This attributes the severe hypersensitivity reaction to CBZ.

The causality assessment by Naranjo's algorithm was done which revealed a score 7 suggesting a probable ADR to CBZ.^[7]

Literature search revealed only few reports of SJS after the use of CBZ. In one such a report, a 6-year-old boy developed SJS five weeks after CBZ was added to valproic acid, which he had been taking as sole antiepileptic therapy for several weeks.^[8] Another study showed the incidence of skin rashes with the same dose of CBZ in psychiatric patients (12–15%) was nearly three times more than that in neurological patients (5%).^[9] However, no study showing incidence in comorbid neurological and psychiatric patients was found during our search, hence we lack any comparison with our case report.



Figure 1: Lesions on patient's face in the butterfly pattern

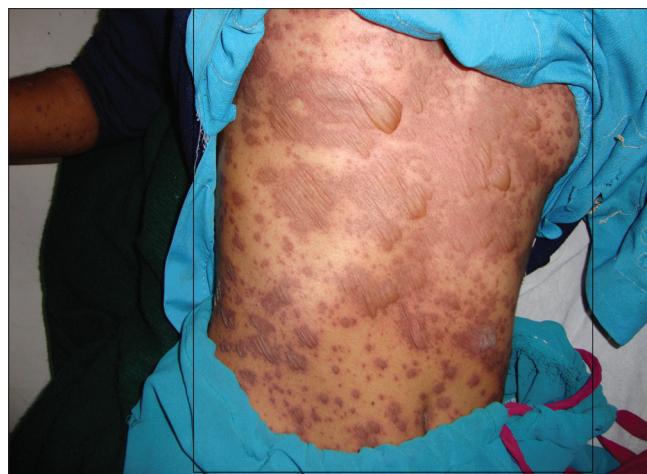


Figure 2: Lesions on patient's trunk

Our patient also received sodium valproate which is also known to cause hypersensitivity reactions,^[1] but the patient had been taking valproate since the last 2 years without any ADRs. It was only after the administration of CBZ along with a higher dose of valproic acid that this patient developed severe ADRs. Immunological reactions due to hormonal changes during menstruation trigger various hypersensitivity reactions such as mucosal ulcerations, skin rashes, asthma, etc.,^[10] so it may be an important factor in drug reactions which is yet an unreported factor and should be considered in further studies.

There are random reports of SJS with the use of CBZ. Approximately three persons per million per week may experience life-threatening dermatological syndromes with the use of CBZ.^[11]

The incidence of ADRs may increase when CBZ is given along with higher doses of valproic acid because of increased plasma concentrations of CBZ.

CONCLUSION

This was a rare case of life-threatening erythema multiforme major/Stevens Johnson's Syndrome with the use of CBZ when given along with higher doses of valproic acid. The causality assessment supported our probable diagnosis. It was perceived that menstruation, and comorbidity of neurological and psychiatric illnesses might have had predisposing roles. There is a need of continued ADR monitoring and reporting of ADRs, more so with the use of CBZ.

REFERENCES

1. Mockenhaupt M, Messenheimer J, Tennis P, Schlingmann J. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptics. *Neurology* 2005;64:1134-8.
2. Erythema multiforme. Available from: <http://www.nlm.nih.gov/medlineplus/ency/article/000851.htm> [Last accessed on 2011 May 27].
3. Freist JIL. Current use of carbamazepine and other anticonvulsants as lithium alternatives in bipolar disorder. *Int J Clin Psychopharmacol* 1990;5:27-34.
4. Jain R. Stevens-Johnson syndrome in a schizophrenic patient treated with carbamazepine. *Indian J Psychiatry* 1993;35:139-40.
5. Ramadasan P, Chaudary S, Vaishampayne S, John TR. Stevens-Johnson syndrome due to carbamazepine. *J Assoc Physicians India* 2000;48:742-3.
6. Raojeau JC, Stern RS, Wintroub BU. Cutaneous drug reactions. In: Fauci AS, Kasper DL, Longo DL, Braunwald E, Hauser SL, Jameson JL, *et al.*, editors. *Harrison's Principle of Internal Medicine*. 17th ed. New York: McGraw Hill; 2008. p. 346.
7. 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;30:239-45.
8. Keating A, Blahunka P. Carbamazepine induced Steven-Johnson Syndrome in a child. *Ann Pharmacother* 1995;29:538-9.
9. Elphick M, Lyons F, Cowen PJ. Low tolerability of Carbamazepine in psychiatric patients may restrict its clinical usefulness. *J Psychopharmacol* 1988;2:1-4.
10. Kumar P, Malhotra N. Premenstrual syndrome and other menstrual phenomena. In: Jeffcoate's *Principles of Gynaecology*. 7th ed. New Delhi: Jaypee Brothers; 2008. p. 631-3.
11. Sadock BJ, Sadock VA. Carbamazepine. In: Kaplan and Sadock's *Synopsis of Psychiatry: Behavioral, Sciences/Clinical Psychiatry*. 9th ed. Philadelphia: Lippincott Williams and Wilkins; 2003. p. 1036-9.

How to cite this article: Upadhyaya SK, Raina RS, Sharma A, Thawani V, Dimari D. Carbamazepine-induced erythema multiforme major in an epileptic patient with bipolar affective disorder. *J Pharmacol Pharmacother* 2012;3:202-4.

Source of Support: Nil, **Conflict of Interest:** None declared.