


Carbamazepine-Induced Stevens-Johnson Syndrome in an Epilepsy Patient: Case Report

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ABSTRACT

Introduction: As a first-line antiepileptic drug for partial and tonic-clonic seizures, carbamazepine requires long-term use. This drug carries a risk of Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) reaction. **Case**: A 23-year-old woman with a history of seizures had reddish rashes on the face, neck, chest, back, and left and right upper extremities covering 10% of the body surface area (BSA) after taking carbamazepine 200 mg twice a day for her seizures. **Discussion:** The patient was given methylprednisolone 16 mg tablets twice a day, IV diphenhydramine twice a day, and other symptomatic drugs. After 9 days, the patient was discharged with phenytoin 100 mg tablets twice a day as a substitute for carbamazepine. Early treatment with high-dose systemic steroids provides benefits of rapid recovery, especially in SJS patients where skin damage is not too extensive and can be restored by the anti-inflammatory effects of steroids. The main treatment of SJS/TEN is early recognition and immediate discontinuation of the drug. **Conclusion**: Carbamazepine is often a risk factor for SJS, thus an alternative treatment is needed.

Keywords: Carbamazepine, case report, Stevens-Johnson syndrome, toxic epidermal necrolysis.

ABSTRAK

Pendahuluan: Sebagai lini pertama obat antiepilepsi untuk bangkitan parsial dan tonik-klonik, *carbamazepine* digunakan jangka panjang. Obat ini berisiko menimbulkan sindrom Stevens-Johnson (SJS) ataupun *toxic epidermal necrolysis* (TEN). **Kasus**: Perempuan berusia 23 tahun dengan riwayat kejang; mengalami kemerahan pada wajah, leher, dada, punggung belakang, dan ekstremitas atas kiri dan kanan seluas 10% *body surface area* (BSA) setelah mengonsumsi *carbamazepine* 200 mg 2 kali sehari untuk kejang. **Diskusi:** Pasien diterapi tablet *methylprednisolone* 16 mg 2 kali sehari dan *diphenhydramine* IV 2 kali sehari, serta obat simtomatik lain. Setelah dirawat 9 hari, pasien dipulangkan dengan *phenytoin* 100 mg 2 kali sehari sebagai pengganti *carbamazepine*. Pengobatan awal dengan steroid sistemik dosis tinggi memberikan manfaat berupa pemulihan yang lebih cepat, terutama pada pasien SJS dengan kerusakan kulit yang belum terlalu luas dan masih dapat diperbaiki melalui efek antiinflamasi dari steroid. Penatalaksanaan utama SJS/TEN adalah pengenalan dini dan penghentian segera obat penyebab. **Simpulan**: *Carbamazepine* sering menjadi faktor risiko SJS sehingga memerlukan terapi alternatif. **Charity Harlim, Kelvin, Agung Triana Hartati. Sindrom Stevens-Johnson pada Pasien Epilepsi Terkait *Carbamazepine*.**

Kata Kunci: *Carbamazepine*, laporan kasus, sindrom Stevens-Johnson, *toxic epidermal necrolysis*.

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INTRODUCTION

Carbamazepine has long been known as the first-line therapy for partial and tonic-clonic seizures.[1] Its structure is similar to tricyclic antidepressants, so it is also an option for depression or mania for its mood-stabilizing properties.[1] Carbamazepine can induce hypersensitivity reactions, especially Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN).[1]

The phenomena of SJS and TEN are rare and the affected locations also vary.[2] SJS occurs due to severe delayed hypersensitivity reactions and is usually caused by exposure to drugs such as antibiotics, antiretrovirals, anticonvulsants. The incidence of SJS is reported to range from 1–6 and TEN ranges from 0.4–1.2 per million people per year. The average mortality rate for TEN is 25%–35% while for SJS it is 1%–5%.[3,4] Manifestations of SJS/TEN are often preceded by fever, mucositis, anorexia and skin pain, followed by skin lesions in the form of vesicles and bullae and extensive and rapid skin peeling.[5] SJS and TEN carry a high mortality risk. We report a case of a 23-year-old woman with SJS and epilepsy.

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CASE

A 23-year-old woman came to the emergency room with reddish rashes on the face, neck, chest, lower back, and left and right upper extremities. The patient had seizures since 2 weeks before being admitted to the hospital, the seizures only lasted a few minutes and only on one part of the body. The patient has a history of recurrent seizures since the age of 1 year, usually on one side of the body and sometimes the whole body accompanied by decreased consciousness during seizures. She was given carbamazepine 200 mg twice a day, diazepam, mecobalamin, and folic acid at the clinic. On the 10th day of medication, symptoms of a sore throat, fever, cough, pain in the lips, loss of appetite, increased eye discharge, and a rash on the chin area began to appear. Then on the 14th day (at admission to the hospital), the rash had spread throughout the body. The rash is estimated to affect <10% of the Body Surface Area (BSA). The patient did not have any history of previous drug allergies. The patient also complained of lip erosion with bleeding and pain, as well as swallowing or opening her mouth because of the pain. On physical examination, both eyes were red with yellow discharge. On dermatological examination, multiple erythematous macules were found in the face, neck, chest, back, and left and right upper extremities with a generalized distribution. Nikolsky's sign was positive.

Based on the anamnesis and examination, the diagnosis was Stevens-Johnson syndrome caused by carbamazepine, so carbamazepine was stopped and the patient was given methylprednisolone tablets 16 mg twice a day orally and diphenhydramine 10 mg IV twice a day. To maintain fluids and nutrition, the patient was given Ringer's lactate and complete parenteral nutrition 1440 mL (amino acids 34 g, electrolytes, dextrose 97 g and lipid 51 g injectable emulsion) with total energy 1000 kcal every 24 hours. Gentamicin IV 80 mg twice a day was also given. Eye secretions were cleaned and covered with warm water gauze, treated with ofloxacin eye drops 6 times a day. Mometasone furoate 0.1% ointment was applied twice a day for rashes on the face. Body rash was covered with gauze containing NaCl 0.9% for 15 minutes and then given a combination of 0.25% desoxymethasone ointment and 2% mupirocin twice a day. Lip erosions were treated with 0.9% NaCl, followed by triamcinolone acetonide plus 2% mupirocin ointment, applied four times a day. The patient was also given other symptomatic drugs such as diphenhydramine IV 10 mg twice a day, methylprednisolone IV 32.5 mg twice a day, cetirizine oral 10 mg once a day, lansoprazole oral 30 mg once a day, vitamin D3 oral 5000 IU once a day, curcuma oral three times a day, artificial tears every 3 hours, VIP albumin oral (*Ophiocephalus striatus* extract 500 mg) once a day. After 9 days of hospitalization, the patient's condition improved, and the patient was discharged and asked for a check-up 2 weeks later. The patient was given phenytoin 100 mg tablets twice a day as a substitute for carbamazepine.

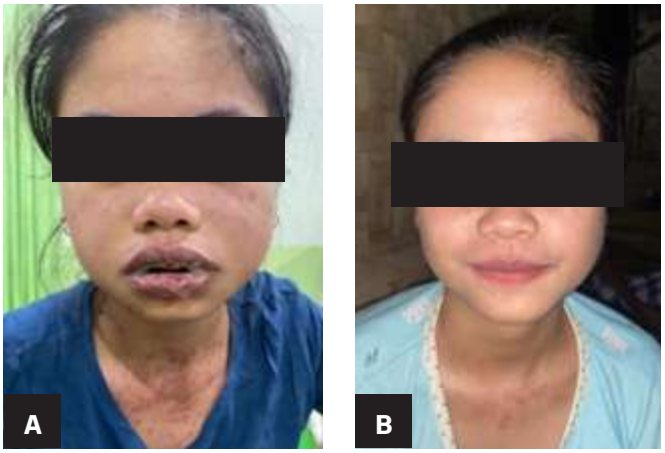

*Photo documentation by Charity Harlim.

Figure 1. Comparison of SJS rash in patients on day 1 in hospital (A) and 1 month after discharge (B).

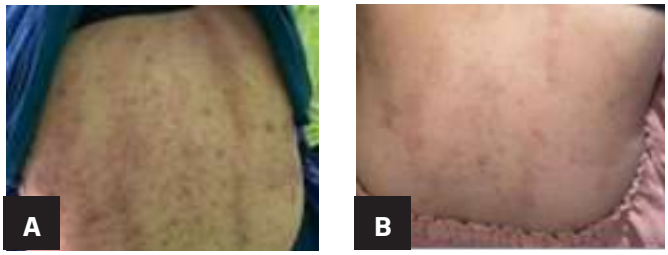

*Photo documentation by Charity Harlim.

Figure 2. Comparison of SJS rash in patients on day 1 in hospital (A) and 1 month after discharge (B).

DISCUSSION

The phenomena of SJS and TEN are severe drug hypersensitivity reactions, and their pathogenesis is still unknown, mostly caused by drug exposure.[5] Carbamazepine as a cause of SJS/TEN has long been studied. It usually occurs after 4–21 days of exposure in a genetically susceptible patient. Many studies recommend the human leukocyte antigen B*15:02 (HLA-B*15:02) allele screening before using carbamazepine to prevent the occurrence of SJS and TEN, especially in the Asian population (India, China, Thailand, and Malaysia).[6] Carbamazepine is one of the first-generation anti-epileptic drugs.

Stevens-Johnson syndrome/toxic epidermal necrolysis is defined as a widespread vesicobullous rash with epidermal peeling and necrosis, with involvement of the mucous membranes, namely the eyes, oral cavity, and skin.[7] In 1956, Alan Lyell described 4 cases of skin eruptions, one of which was TEN or also called Lyell's syndrome. SJS/TEN is considered a spectrum of severe diseases and a life-threatening form of drug-induced skin reaction. The classification is based on the following: SJS if < 10% affected, SJS/TEN overlap if 10%–30% and TEN if > 30% body surface area was affected.[4,6] The incidence of SJS is reported from 1–6 and TEN from 0.4–1.2 per million people per year. The average mortality rate for TEN is 25%–35% while for SJS it is 1%–5%.[3,4] Studies show an increasing incidence of SJS/TEN with age, which is usually accompanied by increasing


drug use such as carbamazepine, lamotrigine, sulfamethoxazole, allopurinol, and NSAIDs of oxicam-type. The ratio of women to men is 3:2, and the average age reported is between 46 and 63 years. Other risk factors reported are human immunodeficiency virus (HIV)-1 infection, bone marrow transplant recipients, and systemic lupus erythematosus (SLE).[8] The rash in this patient was < 10%, so it was classified as SJS.

The most common clinical features of SJS are fever, myalgia, and general weakness for 1 to 3 days before the appearance of skin lesions.[4] Almost all SJS/TEN patients have mucosal involvement in the eyes, mouth, and genitalia. Wang, *et al.*, found that the majority of cases (79.5%) reported involvement of the mucous membranes, including the oropharynx, conjunctiva, genitalia, and/or anus. Other organ systems such as the cardiovascular, pulmonary, gastrointestinal, and urinary tract systems can also be affected.[9,10] The initial location of skin involvement includes the trunk, presternal, face, palms and soles of the feet. Approximately 90% of the patients have involvement of the oral mucosa, genitals and/or digestive tract as erythematous macules and erosions. The second phase is characterized by extensive separation of the epidermis, so epidermis sheets are peeled off.[2] A more detailed skin examination is to apply tangential mechanical pressure to many erythematous areas, if there is a detachment of the epidermis after pressure, Nikolsky's sign is positive. However, the Nikolsky's sign can also be positive in other autoimmune conditions such as pemphigus vulgaris.[8] SJS in this patient involves the eye and oral mucosa; the rash occurs on the face, neck, chest, back, and left and right upper extremities. These symptoms are also accompanied by other systemic symptoms such as sore throat, fever, cough, pain in the lips, loss of appetite, and increased eye discharge. Nikolsky's sign was positive.

The pathophysiology of SJS/TEN is still not fully understood, it is believed that SJS/TEN is a type IV hypersensitivity reaction mediated by T cells. Several studies support the occurrence of an immune response in SJS, namely the hapten/pro-hapten concept, the pharmacological interaction concept, and the altered peptide concept. T cell activation is still believed to be a response to drugs or infections and downstream epidermal necrosis.[2]

Diagnosis of SJS/TEN as a result of drug exposure uses the Naranjo score (**Table 1** and **Table 2**).[11] In this case, carbamazepine

Table 1. Questionnaire for Naranjo score.[11]

	Question	Yes	No	Do Not Know	Score
1.	Are there previous conclusive reports on this reaction?	+1	0	0	
2.	Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3.	Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4.	Did the adverse event reappear when the drug was readministered?	+2	-1	0	
5.	Are there alternative causes that could on their own have caused the reaction?	-1	+2	0	
6.	Did the reaction reappear when a placebo was given?	-1	+1	0	
7.	Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	
8.	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9.	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10.	Was the adverse event confirmed by any objective evidence?	+1	0	0	
		Total Score			

Table 2. Interpretation of Naranjo score.[11]

Score	Interpretation of Scores
Total Score ≥9	**Definite.** The reaction (1) followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues, (2) followed a recognized response to the suspected drug, and (3) was confirmed by improvement on withdrawing the drug and reappeared on reexposure.
Total Score 5 to 8	**Probable.** The reaction (1) followed a reasonable temporal sequence after a drug, (2) followed a recognized response to the suspected drug, (3) was confirmed by withdrawal but not by exposure to the drug, and (4) could not be reasonably explained by the known characteristics of the patient's clinical state.
Total Score 1 to 4	**Possible.** The reaction (1) followed a temporal sequence after a drug, (2) possibly followed a recognized pattern to the suspected drug, and (3) could be explained by characteristics of the patient's disease.
Total Score ≤0	**Doubtful.** The reaction was likely related to factors other than a drug.


is suspected of causing SJS/TEN with a Naranjo score of 8. This assumption is supported by the European Study of Severe Cutaneous Adverse Reactions (EuroSCAR).[12] Fukasawa, *et al*., who conducted research on more than 5 million subjects, reported 71 SJS/TEN cases. A significantly increased odds ratio (OR) for SJS/TEN was found among new carbamazepine users (OR 68.00). The cumulative incidence of SJS/TEN was 93.83 for carbamazepine. Diazepam which is also consumed by the patient is very unlikely to cause SJS/TEN because the cumulative incidence of SJS/TEN was 1.23 for diazepam.[13]

The main treatment of SJS/TEN is early recognition and immediate discontinuation of the drug.[4] Acute treatment includes systemic corticosteroids, intravenous immunoglobulins, and tumor necrosis factor-α (TNF-α) inhibitors. Other supportive care includes the protection and restoration of skin barrier function, maintaining fluid balance, protecting the airway, eye recovery, nutrition, and preventing infection.[7] Corticosteroid use is still highly debated, as it can increase the risk of sepsis (especially due to *Staphylococcus aureus*, *Pseudomonas spp*., gram-negative bacilli, or fungi) and delay healing. Early treatment with high-dose systemic steroids provides benefits of rapid recovery, especially in SJS patients, where skin damage is not too extensive and can be restored by the anti-inflammatory effects of steroids.[4] In this case, carbamazepine was stopped and replaced with phenytoin twice daily.

CONCLUSION

SJS/TEN is a serious condition that requires immediate treatment. Carbamazepine is often a risk factor in epilepsy patients. Replacing carbamazepine with an alternative and early treatment of SJS/TEN can prevent further skin damage. Acute and supportive treatment is needed in this case.

REFERENCES

1. Dadwai A, Navar K, Bagilipeddola M, Rajannagari R, Nittu SR. Pharmacogenomics and adverse drug reactions: carbamazepine induced Steven Johnsons syndrome. Indian J Pharm Pract. 2021;14(2):145–7. doi: 10.5530/ijopp.14.2.27.
2. Frantz R, Huang S, Are A, Motaparthi K. Stevens–Johnson syndrome and toxic epidermal necrolysis: a review of diagnosis and management. Medicina (Kaunas). 2021;57(9):895. doi: 10.3390/medicina57090895.
3. Malik MN, Ullah AM, Ahmad ME, Riaz R, Syed TIS. Pancytopenia in a patient with Stevens-Johnson syndrome: a case report with literature review. Cureus. 2019;11(5):e4702. doi: 10.7759/cureus.4702.
4. Pramita NYM, Sudarsa PSS, Nukana RP. Steven Johnson syndrome induce by carbamazepine in epileptic patient: a case report. Bali Dermatol Venereol J. 2019;2(1):1–3. doi: 10.51559/dz26cj70.
5. Al Rajaibi R, Al Rumhi T, Al Abri AM. Carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis overlap treated successfully with oral cyclosporin: case report and literature review. Sultan Qaboos Univ Med J. 2021;21(3):491–4. doi: 10.18295/squmj.4.2021.002.
6. Shrestha O, Pant P, Devkota N, Gurung D, Shrestha DB. Carbamazepine induced toxic epidermal necrolysis and Stevens-Johnson syndrome overlapping during pregnancy in a South-East Asian patient: a case report. Ann Med Surg. 2021;68:102616. doi: 10.1016/j.amsu.2021.102616.
7. Shanbhag SS, Chodosh J, Fathy C, Goverman J, Mitchell C, Saeed HN. Multidisciplinary care in Stevens-Johnson syndrome. Ther Adv Chronic Dis. 2020;11:2040622319894469. doi: 10.1177/2040622319894469.
8. Fakoya AOJ, Omenyi P, Anthony P, Anthony F, Etti P, Otohinoyi DA, et al. Stevens - Johnson syndrome and toxic epidermal necrolysis; extensive review of reports of drug-induced etiologies, and possible therapeutic modalities. Open Access Maced J Med Sci. 2018;6(4):730–8. doi: 10.3889/oamjms.2018.148.
9. Chang HC, Wang TJ, Lin MH, Chen TJ. A review of the systemic treatment of Stevens–Johnson syndrome and toxic epidermal necrolysis. Biomedicines 2022;10(9):2105. doi: 10.3390/biomedicines10092105.
10. Wang L, Varghese S, Bassir F, Lo YC, Ortega CA, Shah S, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: a systematic review of PubMed/MEDLINE case reports from 1980 to 2020. Front Med. 2022;9:949520. doi: 10.3389/fmed.2022.949520.
11. Adverse drug reaction probability scale (Naranjo) in drug induced liver injury. LiverTox: clinical research information on drug-induced liver injury [Internet]. 2019 May 4 [cited 2025 Nov 21]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548069/.
12. Capule F, Tragulpiankit P, Mahasirimongkol S, Wichukchinda N, Jittikoon J, Alentajan-Aleta LT, et al. Carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis overlap in a Filipino with positive HLA-B75 serotype. BMJ Case Rep. 2018;2018:bcr2018225028. doi: 10.1136/bcr-2018-225028.
13. Fukasawa T, Takahashi H, Takahashi K, Tanemura N, Amagai M, Urushihara H. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with anticonvulsants in a Japanese population: matched case–control and cohort studies. Allergol Int. 2021;70(3):335–42. doi: 10.1016/j.alit.2021.01.004.