Antiepileptic Drugs-induced Stevens–Johnson syndrome: A case Series

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ABSTRACT

Stevens–Johnson syndrome (SJS) is an acute life-threatening mucocutaneous reaction, characterized by extensive necrosis and detachment of the epidermis from the skin. The overall incidence of SJS is seen in five cases per million people per year. SJS is typically caused by drugs and is a kind of idiosyncratic reaction. Adverse drug reactions such an SJS have a remarkable effect on patient's safety issues. We encountered nine cases of antiepileptic drug (AED)-induced SJS, specifically with carbamazepine, oxcarbazepine, and phenytoin. To manage the reaction, the clinician withdrew the drug in all 8 cases, and in 1 case, the patient was shifted to valproate and symptomatic treatment was provided. There is still a controversy whether or not all AEDs can cause SJS. Recent studies have investigated the role of genetic factors - HLAB*1502 allele in the development of AED-induced SJS in patients of Asian ancestry.

Key words: Adverse drug reactions, antiepileptic drug, Stevens–Johnson syndrome

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INTRODUCTION

Stevens–Johnson syndrome (SJS) is an idiosyncratic, life-threatening, mucocutaneous reaction, characterized by necrosis and detachment of the epidermis. Although the overall incidence is only 5 cases per million people yearly, adverse drug reactions (ADRs) such as SJS have remarkable effects on patient's safety issues.[1,2] We encountered nine cases of antiepileptic drug (AED)-induced SJS, specifically with carbamazepine (CBZ), oxcarbazepine, and phenytoin. The association of SJS with phenytoin and CBZ is well known, but it is not so well reported for other antiepileptic agents including some newer ones such as oxcarbazepine. According to the Food and Drug Administration, the incidence of oxcarbazepine-induced SJS is estimated to be anywhere between 5 and 6 cases per million people per year within a general population.[3] There is still controversy as to whether or not all AEDs can cause SJS. Recent studies have investigated the role of genetic factors - HLAB*1502 allele in the development of AED-induced SJS in patients of Asian ancestry.[4]

CASE REPORTS

All nine cases of AED-induced SJS have been reported to the nearest ADR monitoring center under the Pharmacovigilance Programme of India (PvPI).

Case 1: Suspect drug - oxcarbazepine

An 18-year-old female patient came to the skin outpatient department (OPD) with the chief complaints of orogenital lesion, maculopapular rashes, and lymphadenopathy for the past 7 days since she started taking tablet oxcarbazepine 200 mg OD and tablet clonazepam 5 mg OD for seizure treatment. Diagnosis of oxcarbazepine-included SJS going into toxic epidermal necrolysis (TEN) was made by a dermatologist. Tablet oxcarbazepine was withdrawn on the same day, and the patient had completely recovered in 12 days. Injection Dexona (dexamethasone) 1 ml intravenous (IV) BD, injection Avil (pheniramine) 2 ml 4 hourly, injection Zantac (ranitidine) 2 ml 12 hourly, injection Febril (paracetamol), and candid mouth paint (clotrimazole) for local application BD were given to treat the patient. No rechallenge was attempted. The WHO causality assessment was performed, and this case was put in the probable category. It was reported to PvPI with the unique ID number 23455.

Case 2: Suspect drug - carbamazepine

A 21-year old male patient was admitted with fever, vomiting, watering from eyes, erosion on lips and mucosal candidiasis, bleachable erythematous rashes on face and neck, erythematous macular rashes on the chest and upper and lower limbs. He had a history of epileptic attacks and had a seizure 8 days before he presented himself. He was prescribed tablet CBZ 200 mg TDS, tablet levetiracetam 250 mg TDS, tablet clonazepam 5 mg OD, and tablet norfloxacin 400 mg BD. He had also taken antidepressant medication for 3–4 months. After 8 days of medication, symptoms of TEN appeared due to CBZ; hence, previous all medications were stopped. Despite giving appropriate symptomatic treatment which consisted of putting the patient on a ventilator and treating him with Piptaz (piperacillin + tazobactam) 4.5 mg IV BD, injection Acipant (pantoprazole), injection Perinorm (domperidone) IV BD, injection Febril (paracetamol) 2 ml IV 8 hourly, injection Dexona (dexamethasone) 2 ml IV BD, injection human immunoglobulin (Ig) 5 g IV 5–6 hourly, and Fusicare (fusidic acid) 20 mg application, the patient died 4 days later. The WHO causality assessment was performed, and this case was put in

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the probable category. It was reported to PvPI with the unique ID number 00497.

Case 3: Suspect drug - carbamazepine

A 20-year old pregnant female presented herself to the Dermatology and Venereal Disease OPD with chief complaints of skin lesions on the face, trunk, abdomen, extremities, and genitals for the past 6 days. The patient was on tablet valproate since 2 years for epilepsy. When the patient became pregnant, the obstetrician changed the drug to CBZ 200 mg TDS. A diagnosis of CBZ-induced SJS was made by the dermatologist.

CBZ was withdrawn and the patient was prescribed injection Dexona (dexamethasone) 1 ml IV BD, injection Avil 2 ml 4 hourly, injection acyclovir 500 mg in 100 ml normal saline (NS) 8 hourly, injection Zantac (ranitidine) 2 ml 12 hourly, injection Emeset (ondansetron) 1 ml IV 8 hourly, injection Febril (paracetamol) if T >101 F, tablet Lacoste (lacosamide) 100 mg 12 hourly, and candid mouth paint (clotrimazole) for local application BD and subsequently recovered 3 days following the initiation of treatment.

No rechallenge was attempted. The WHO causality assessment was performed, and this case was put in the probable category. It was reported to PvPI with the unique ID number 19343.

Case 4: Suspect drug - oxcarbazepine

A 58-year old male patient came to the Dermatology Department with chief complaints of multiple skin lesions over both extremities, lips, and eyes and mucosal lesions in the oral cavity for 3 days. He is a known case of epilepsy and was on phenytoin for the last 2 years. Oxcarbazepine was added just 4 days before he presented with the chief complaints. Diagnosis of oxcarbazepine + phenytoin-induced SJS was made by the dermatologist.

The dermatologist advised to discontinue both oxcarbazepine and phenytoin and prescribed a treatment consisting of injection Dexona (dexamethasone) 1 cc IV OD, Syrup Levocet (levocetirizine) 5 ml BD, Caldew (calamine) lotion for local application BD, T-Bact ointment (mupirocin 2%) for local application BD, and gatifloxacin eye drops 2 drops 6 times a day. The patient recovered after 13 days and no rechallenge was attempted. The WHO causality assessment was performed, and this case was put in the probable category. It was reported to PvPI with the unique ID number 06558.

Case 5: Suspected drug - phenytoin

A 65-year old female patient came to the skin OPD with complaints of skin and oral lesions in the past 7 days. The patient had an intracerebral hemorrhage 1 month before and was therefore put on a 1-month phenytoin therapy. Diagnosis was phenytoin-induced SJS was made by the attending physician. No rechallenge was attempted and the patient recovered following treatment with injection NS 1 L IV, injection ceftriaxone 1 g IV BD, injection Dexona 1 cc IV BD, injection Avil 1 amp IV BD, injection Zantac (ranitidine) 2 ml BD, injection Febril (paracetamol) if T >101 F, candid oral paste (co- trimoxazole) for mouth, tablet Levipil (levetiracetam) 500 mg, tablet clonidine 100 mg BD, and tablet telmisartan 80 mg OD. The WHO causality assessment was performed, and this case was put in the probable category. It was reported to PvPI with the unique ID number 17000.

Case 6: Suspected drug - phenytoin

A 12-years old male patient came to the skin OPD with chief complaints of rashes for 3 weeks. He was a known case of epilepsy and was on phenytoin therapy for the last 6 months. The dermatologist diagnosed it as phenytoin-induced SJS, so the drug was withdrawn and replaced phenytoin with valproic acid 12.5 mg/kg OD. He was put on a treatment consisting of injection Dexona (dexamethasone) 1 cc IV in the morning, injection Avil (pheniramine) 1 amp IV 12 hourly, injection Zantac (ranitidine) 1 amp IV 12 hourly, tablet chlorpheniramine 2.5 mg 1 h, tablet cetirizine 2.5 mg OD, betadine gargle after meals, xylocaine before meals, and tablet co-trimoxazole 8 mg/kg + 40 mg/kg 12 hourly. The WHO causality assessment was performed, and this case was put in the probable category. It was reported to PvPI with the unique ID number 17385.

Case 7: Suspected drug - phenytoin

A 65-year-old male patient came into the dermatology OPD with chief complaints of skin lesions for the last 2 days and oral lesions for 30 days. Before 1.5 months, the patient was admitted to the neurosurgery department, was operated on for subarachnoid hemorrhage, and had started phenytoin. The patient had mild skin lesions for 7 days which flared up in the last 2 days with abdominal, oral, chest, and conjunctival involvement. Diagnosis was phenytoin-induced SJS made by the dermatologist. Injection ceftriaxone 1 g IV BD, injection Dexona 1 cc IV BD, injection Avil 1 amp IV BD, injection Zantac (ranitidine) 2 ml BD, and injection Febril (paracetamol) were given to treat the patient. No rechallenge was attempted. The WHO causality assessment was performed, and this case was put in the probable category. It was reported to PvPI with the unique ID number 17948.

Case 8: Suspected drug - phenytoin

A 27-year-old male patient came to the hospital on March 17, 2016, with chief complaints of oral ulceration for 3 days and skin lesions for 1 day. On February 21, 2016, the patient was involved in a road traffic accident and was prescribed tablet phenytoin 100 mg BD and he was on the same medication since then. On March 17, 2016, the patient was prescribed Mucopain ointment for local application, but the patient did not improve. In fact, his condition worsened as he developed skin lesions all over his body. He was advised to withdraw from phenytoin and was admitted for the management of SJS after which he fully recovered. The management consisted of injection ceftriaxone 1 g. IV BD, injection Dexona (dexamethasone) 2 cc IV BD, injection Avil (pheniramine) 1 amp IV BD, injection pantoprazole 40 mg IV BD, and Fusicare (fusidic acid) cream for local application. No rechallenge was attempted. Diagnosis was phenytoin-induced SJS. The WHO causality assessment was performed, and this case was put in the probable category. It was reported to PvPI with the unique ID number 16154.

Case 9: Suspected drug - phenytoin

A 30-year-old male patient was a known case of epilepsy for the past 25 years and was taking tablet phenytoin 100 mg BD for the last 2 months. He presented himself to the emergency department with complaints of erythematous skin lesions all over his body with itching and acute respiratory distress syndrome. Phenytoin was kept on hold and tablet clobazam 5 mg BD was started for the epilepsy treatment. Since the reaction subsided when the drug was withdrawn, diagnosis of phenytoin-induced SJS was made by the attending physician. After withdrawal of the drug, the patient was put on symptomatic therapy of injection Dexona (Dexamethasone) 1 ml IV BD and injection Avil (pheniramine) 1 amp IV BD. No rechallenge was attempted. The WHO causality assessment was performed, and this case was put in the probable category. It was reported to PvPI with the unique ID number 16159.

DISCUSSION

More than 90% of SJS occurs within the first 2 months of AED use. Commonly, some of the drugs such as CBZ and phenytoin have a high incidence to cause SJS, and also, these kinds of reactions are independent of dose or the drug and are idiosyncratic.[5] Recent studies have suggested a strong association between HLA-B*1502 and AED-induced SJS in patients of Chinese/Asian ethnicity.[4] There is nearly a 100% association of HLA-B*1502 with CBZ-induced SJS/TEN which implies that HLA-B*1502 is not only a genetic marker but also a participant in the pathogenesis of SJS.[4] Since oxcarbazepine possesses a structure similar to that of CBZ, it might share a pathogenesis similar to CBZ-induced SJS/TEN. In the case of oxcarbazepine, HLA-B*1518/B*4001 is the causative factor, and although it differs from HLA-B*1502, HLA-B*1518 is still an HLA-B15 variant.[6] Despite the cascade of immune mechanisms underlying SJS remaining unclear, the $CD8^+$ T-cell-mediated cytotoxic responses appear to be the major event causing SJS/TEN. It has been suggested that HLA-B allele may illicit an immune response by presenting peptides bound to the drug and/or its metabolites to specific T-cells, resulting in proliferation of the cytotoxic cells. Whether this implies a similar immune response against the different AEDs will need to be confirmed in larger studies. The mechanism of cross-reactivity is thought to be due to an accumulation of toxic hydroxylated aromatic metabolites from the aromatic AEDs such as CBZ and phenytoin.[3]

One of the steps to reduce the occurrence of SJS is to identify the population with an HLA-b status. Since such a facility was not available at our set up, this genotyping could not be performed. This is a limitation of the case series.

CONCLUSION

We found 2 cases of CBZ-induced, 2 cases of oxcarbazepine-induced, and 5 cases of phenytoin-induced SJS and used the WHO causality assessment to categorize it under "Probable" in order to establish the association between SJS and AEDs. Knowledge of this association might be used to help prevent life-threatening SJS, especially for increased screening of patients for HLA-B*1502 before prescribing these high-risk AEDs. In the Indian context, careful titration of the drug and early recognition of the side effects will help to avoid life-threatening conditions such as SJS and other side effects associated with the drugs. Our findings of nine cases of AED-induced SJS draw attention to the need for future studies. Ultimately, studies will lead to improved personalization of therapy and also to the development of safer drugs.

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Conflicts of interest

There are no conflicts of interest.

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