Phenytoin Induced Steven Johnson Syndrome: A Case Report

Syed Zia Inamdar[1,*], Swapnapriya Chirasani[1], Ajit Janagond[2], Sushilkumar Londhe[1], Pradeepthi Katragadda[1], Mallinath Paramagond[1], Raghavendra Vinayakarao Kulkarni[1], Akram Naikwadi[3], Anant Khot[3], Arvind Patil[4]

[1]Department of Pharmacy Practice, BLDEA's SSM College of Pharmacy and Research Centre, Vijayapura, Karnataka, INDIA.
[2]Department of Dermatology, Shri BM Patil Medical College Hospital and Research Centre, Vijayapura, Karnataka, INDIA.
[3]Department of Pharmacology, Shri BM Patil Medical College Hospital and Research Centre, Vijayapura, Karnataka, INDIA.
[4]Department of Surgery, Shri BM Patil Medical College Hospital and Research Centre, Vijaypur, Vijayapura, INDIA.

ABSTRACT

Stevens-Johnson syndrome (SJS) is a disastrous consequence of hypersensitivity reaction precipitated by certain drugs and viral infections. It is an idiosyncratic drug reaction usually associated with drugs like anti-epileptics, non-steroidal anti-inflammatory compounds and antibiotics. The syndrome is characterized by purpuric macules and bullous eruptions involving the mucous membrane which may be followed by systemic manifestations. We report here a case of phenytoin induced SJS, the clinical features of this condition and management of the patient are described in brief. The Naranjo adverse drug reaction causality assessment yielded "probable" causal association between the suspected drug and the adverse drug reaction and severity of the reaction was found to be of "moderately" severe in nature.

Key words: Adverse Drug Reaction, Phenytoin, Steven Johnson Syndrome, Antiepileptics Naranjo, Idiosyncratic Drug Reaction, Toxic Epidermal Necrolysis

INTRODUCTION

Antiepileptic drugs are associated with severe skin reactions such as Stevens-Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN). Phenytoin is one of the most commonly prescribed antiepileptic agent and is known to cause a plethora of adverse effects.[1] According to WHO, adverse drug reaction is defined as "any response to drug which is noxious or unintended and occurs at a dose normally used in man for prophylaxis, diagnosis or treatment of diseases or for modification of physiological function".[2] The relative risk of SJS/TEN as an important severe cutaneous adverse reactions have been reported with the use of sulfonamide antibiotics, aromatic antiepileptic (phenytoin and carbamazepine), lamotrigine and oxicam NSAIDs. SJS/TEN are rare and severe manifestations of idiosyncratic reaction to certain drugs and are more likely to occur in people infected with human immunodeficiency virus (HIV), with an estimated incidence of 1/1000. They are also rarely associated with vaccination and infections such as mycoplasma, cytomegalovirus and dengue, but are more commonly associated with drugs. SJS and TEN are two entities of the same condition differing only in the percentage of body surface area (BSA) involvement. Usually <10% BSA involvement is seen in SJS, 10-30% BSA in SJS-TEN overlap and >30% BSA detachment is seen in TEN. SJS can present as a nonspecific febrile illness (malaise, headache, cough, rhinorrhea) with polymorphic lesions of skin and mucous membrane characterized by acute blisters and erosions. SJS is associated with a mortality rate of 1-5% which increases to 25-35% in case of TEN.[3,4] Among hospitalized patients approximately about 0.3 to 7% of deaths were reported to be caused by adverse drug reactions (ADR). The spectrum of drug reactions can differ from mild to severe such as SJS which is an uncommon, but with a serious skin-mediated hypersensitivity reaction. Drug induced SJS is one of the

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Address for correspondence:
Dr. SZ Inamdar
Professor and Clinical Pharmacist, Department of Pharmacy Practice, BLDEA's SSM College of Pharmacy and Research Centre, Vijaypur-586103, Karnataka, INDIA.
Phone no: +91 9986666016
Email Id: syedzia.inamdar@gmail.com

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most common forms of SJS. Antimicrobials (37.27%) have been found to be the most frequent class to cause drug induced SJS, followed by antiepileptic drugs (35.73%) and NSAIDs (15.93%) respectively.[5]

CASE REPORT

A 60 years old male patient was apparently alright 15 days back when he developed lesions over the face which was insidious in onset and gradually progressed to involve lips and mouth. Lesions were also associated with difficulty in swallowing. Patient developed fluid filled lesions over back and bilateral upper and lower extremities, few of which ruptured spontaneously leaving behind erosions [Figure 1-3]. Patient also complaints of reduced sleep and appetite and burning micturition since 2 days. Detailed past history suggested that, the patient had sustained a head injury one and half months back for which he was on *phenytoin* and *nimodipine*. CT scan of brain revealed minimal inter hemispheric bleed, symmetric hypo densities /ischemic changes in frontal white matter bilaterally, extra cranial soft tissues swelling over right frontal region. Patient had also received *amoxyclav* orally for 10 days post the development of lesions. Further, patient took medication (*phenytoin and nimodipine*) for nearly one and half month till the day of admission and it was after that multiple bullae over bilateral thighs, multiple hyper pigmented purperic patches over face, trunk and bilateral upper and lower extremities, diffuse crusting over lips and erosions over bucal mucosa started developing. The patient was immediately admitted in dermatology intensive care unit for further management.

The suspected drug *phenytoin* was stopped. Multiple therapies were prescribed to the patient, On dermatological consultation intravenous fluids of *dextrose normal saline, normal saline* and *ringer lactate* solution was given 8th hourly once a day for 3 days, *mupirocin* ointment, *liquid paraffin* and *1% GV* lotion were applied topically, *triamcinolone* oral paste and *betadine* gargle were used to treat oral ulcer and throat infection, fever was managed by *paracetamol* (650mg) twice a day for 7 days and *cyclosporine (200mg)* was given orally once a day for 7 days to treat skin lesions. *Protein supplement* was started on 3rd day of treatment and anemia was managed with oral iron and vitamin supplements. On the day of hospitalization, the laboratory investigation revealed a marginal elevation of *ESR-60, TC- 21990, eosinophils- 20.4* and decrease in *hemoglobin- 10.2, RBC- 3.83, PCV- 30.9* and *Liver function test* showed decrease *Serum protein- 6.2, serum albumin- 2.8*, increased *SGPT- 101 and SGOT- 65*. Serum electrolyte analysis showed decreased *bicarbonate- 15.7* and Peripheral blood smear report showed *normocytic normochromic* anemia with mild *leucocytosis*. The systemic examination of *BSA reveals 15% involvement* with *SCORTEN severity score of 3*. The immunosuppressant's *(cyclosporine)* doses were tapered appropriately with gradual resolution of the symptoms and the patient was discharged after complete ablation of rashes with proper instructions regarding the possible relapse with the use of aromatic antiepileptic.

DISCUSSION

SJS/TEN are serious adverse cutaneous drug reactions characterized by mucocutaneous tenderness and usually hemorrhagic erosions, erythema and more or less serious epidermal detachment presenting as blisters and areas of denuded skin regions. *Acute generalized exanthematou's pustulosis* (*AGEP*), erythema multiforme (*EM)* major,

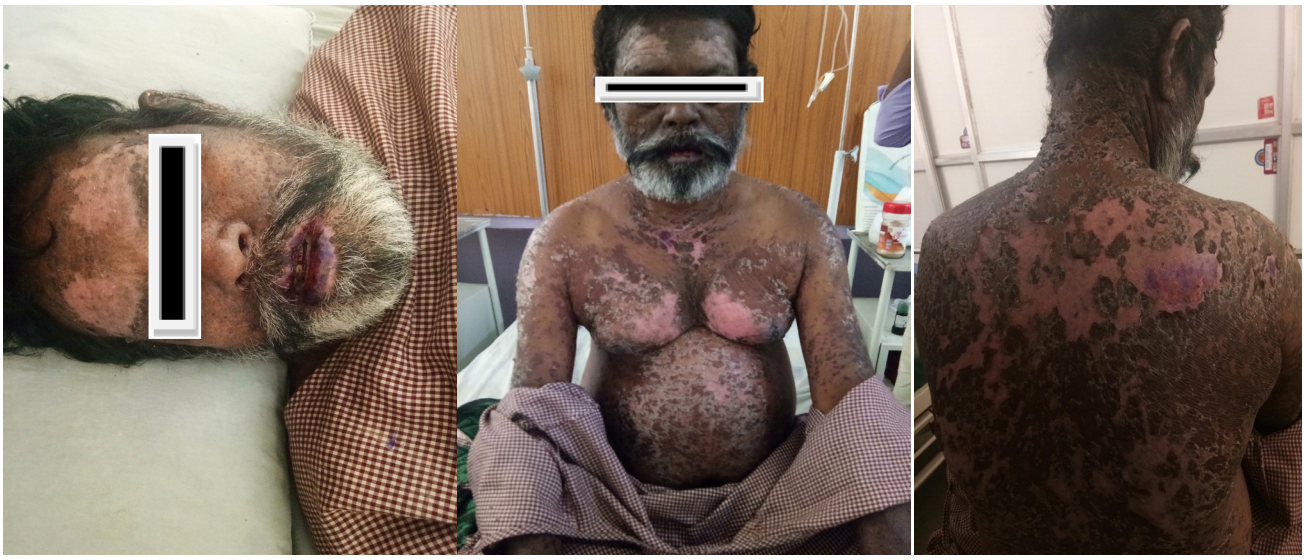

Figure 1: Phenytoin induced SJS Hyper pigmented purpuric patches over face, trunk and bilateral upper and lower extremities, diffuse crusting and erosions over lips.

staphylococcal scalded skin syndrome, *pemphigus vulgaris, pemphigus foliaceus*, *severe cutaneous adverse reactions (SCAR) viz; drug hypersensitivity syndrome (DHS)* and *other forms of drug eruption* and acute graft versus host disease are some conditions that might need consideration for differential diagnosis. Some typical drug class have been recognized as the major cause of SJS/TEN in majority of the cases, but *mycoplasma pneumonia* and herpes infections are also well acknowledged.

A large number of drugs are at higher risk of causing SJS/TEN includes: *allopurinol, trimethoprim-sulfamethoxazole* and other *sulfonamide antibiotics, aminopenicillins, cephalosporins, quinolones, carbamazepine, phenytoin, phenobarbital and* oxicam *NSAIDs.* Amongst anti-epileptics, *phenytoin and carbamazepine* have been reported to be the most common cause.[2] SJS/TEN are rare but lethal manifestations of a type IV hypersensitivity reaction with an approximate incidence of 1-2/million/year.[1] In the early stages of the disease progression, the epidermis becomes infiltrated with macrophages and CD8 T-lymphocytes, while the dermis of skin shows CD4 cells in high proportion. It is assumed that the lymphocytes liberate cytokines, which mediate epithelial cells inflammatory response and apoptosis. It should be stressed, however, that the mechanism of hypersensitivity syndrome is believed to engage deficiency or abnormality of the epoxide hydroxylase enzyme that detoxifies the metabolites of aromatic anticonvulsants, associated reactivation of herpes-type viruses and ethnic predisposition with certain human leukocyte antigen subtypes. In the metabolism of aromatic anticonvulsant drugs, the toxic intermediates are capable of accumulating and trigger cell death immediately, or, as prohaptens which bind to T cells evoking immune response.[5,6]

In the acute phase, sepsis is the most common serious risk of SJS/TEN. Organ failure may occur, including pulmonary, hepatic and renal systems.[7] The most common long-term complications of SJS/TEN are ocular (including blindness), cutaneous (pigmentary changes and scarring) and renal. Mucosal involvement with blisters and erosions can lead to strictures and scarring.[8]Patient with SJS/TEN requires multidisciplinary management approach and supportive care that includes; cessation of the suspected causative drug(s), hospitalization (preferably to an intensive care), fluid replacement (crystalloid), nutritional assessment, temperature control, pain relief etc. In the current case, the suspected causative drug *phenytoin* was immediately withdrawn and the patient was managed symptomatically. Cyclosporine (3mg/kg/day) an immunosuppressant drug was given orally once a day for 7 days and tapered appropriately. *Cyclosporine* has encouraging role in the management of uncomplicated cases of SJS, SJS-TEN overlap or TEN.[9] The ideal therapy of SJS/TEN still remains a matter of debate as there are only a limited number of studies of good quality comparing the usefulness of different specific treatments. Though, the expert group recommends prompt withdrawal of the culprit drug, meticulous supportive care and judicious and early (preferably within 72 h) initiation of moderate to high doses of oral or parenteral corticosteroids (prednisolone 1-2 mg/kg/day or equivalent), tapered rapidly within

Table 1: Causality assessment of suspected adverse drug reaction using Naranjo scale.

Question	Yes	No	Don't Know/ NA	Score*
Are there previous conclusive reports on this reaction?	+1	0	0	1
Did the adverse event appear after the suspected drug was administered?	+2	-1	0	2
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	1
Did the adverse event reappear when the drug was re-administered?	+2	1	0	0
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	2	0	2
Did the reaction reappear when a placebo was given?	-1	1	0	0
Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0	1
Total				7

**Score: Definite: ≥ 9, Probable: 5-8, Possible: 1-8, Doubtful: 0 Report: The suspected ADR found to be Probable on Naranjo scale assessment.*

7-10 days. Cyclosporine (3-5 mg/kg/day) for 10-14 days may also be used either alone, or in combination with corticosteroids.[7,8]

It is unknown whether systemic corticosteroids are beneficial, but they are often prescribed in high dose for the first three to five days of admission. The management also involves the use of antibiotics for secondary infection but is best avoided prophylactically. Granulocyte colony-stimulating factor (G-CSF) may be of benefit in patients with severe neutropenia. Other drugs reported effective include; *TNF-alpha inhibitors, N-acetylcysteine* and intravenous *immunoglobulins*, however, their role remains controversial.[7,8]

SJS/TEN is potentially very serious with high mortality; however, there has been a trend towards improved mortality in recent years attributed mainly to improvised supportive care against older approaches. People who have survived SJS/TEN must avoid the causative drug or structurally related medicines (*anticonvulsants beta-lactam and NSAIDs and sulfonamides*) for cross-reactivity.[8]

The Naranjo causality assessment for the present case yielded a total score of 7, which indicates that there was a "probability" that the adverse reaction was caused due to the suspected drug (phenytoin) [Table 1] and the Hartwig's severity assessment categorized the observed adverse reaction to level 4 indicating "moderately severe reaction" requiring hospitalization.

CONCLUSION

The suspected ADR was found to have "probable" causal relationship between the suspected drug phenytoin and severity nature of "moderate" category. The report suggests close monitoring of phenytoin usage among population for the occurrence of SJS/TEN type adverse effect and patients should be educated for aromatic anticonvulsants adverse effect and cross reactivity with similar structural molecules.

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CONFLICT OF INTEREST

The author declares no conflict of interest exists.

ABBREVIATIONS

SJS: Stevens–Johnson syndrome; **TEN:** Toxic epidermal necrosis; **ADR:** Adverse drug reaction; **WHO:** World Health Organization; **HIV:** Human Immunodeficiency Virus; **BSA:** Body Surface Area; **NSAIDs:** Non steroidal anti-inflammatory drugs; **CT:** *computerized* tomography; **ESR:** erythrocyte sedimentation rate; **TC:** Total count,: **RBC:** Red blood cells; **PCV:** Packed cell volume; **SGPT:** Serum Glutamic Pyruvic Transaminase; **SGOT:** Serum glutamic-oxaloacetic transaminase; **SCORTEN:** SCORe of Toxic Epidermal Necrosis; **SCAR:** Severe cutaneous adverse reactions; **DHS:** Drug hypersensitivity syndrome; **AGEP:** Acute generalised exanthematous pustulosis; **EM:** Erythema Multiforme; **CD:** Cluster of differentiation; **G-CSF:** Granulocyte colony-stimulating factor; **TNF:** *Tumor necrosis factor*.

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