

Stevens Johnson Syndrome precipitated by Phenytoin and aggravated by oral cefixime – A rare case report from tertiary medical college in North India.

ABSTRACT:

Stevens–Johnson syndrome (SJS) is a rare, life-threatening mucocutaneous hypersensitivity reaction most commonly triggered by medications. It is characterized by epidermal necrosis, detachment, and involvement of multiple mucosal surfaces. Among drug-induced causes, antiepileptics and antibiotics are frequently implicated. We report a rare Paediatric case of SJS precipitated by phenytoin and subsequently aggravated by oral cefixime. A clinical diagnosis of SJS secondary to phenytoin was made based on temporal association. The patient initially improved with supportive care and was discharged. However, within 48 hours of initiating oral cefixime, he returned with worsening cutaneous lesions, desquamation, and exacerbation of oral ulcers. No other new medications were reported. Cefixime-induced aggravation of SJS was suspected, and the drug was promptly discontinued. This case highlights a rare instance of sequential drug-induced SJS, with phenytoin as the precipitating agent and cefixime as a potential aggravating factor. While cephalosporins are associated with SJS, clinicians should remain vigilant regarding their potential role, especially in patients with recent other drug hypersensitivity. Early recognition, prompt withdrawal of offending agents, and appropriate supportive management are crucial to improving outcomes. This report underscores the importance of careful drug selection and monitoring in paediatric patients at risk for severe cutaneous adverse reactions.

KEYWORDS:

Steven Johnson syndrome, Phenytoin, Cefixime, Mucocutaneous lesions, Cephalosporins.

INTRODUCTION:

Stevens-Johnson syndrome (SJS) is an uncommon yet life-threatening disorder affecting the skin and mucous membranes. It is characterized by widespread keratinocyte apoptosis leading to epidermal detachment. The condition represents a delayed-type hypersensitivity reaction mediated primarily by

cytotoxic T lymphocytes and natural killer cells, which release inflammatory and cytotoxic mediators. (1)

Clinically, SJS typically involves less than 10% of the total body surface area and may affect multiple mucosal sites, including the oral cavity, eyes, respiratory tract, and genital region. The reported incidence ranges from approximately 1 to 6 cases per million population annually, with slightly higher rates observed in Asian populations. (1)

A variety of triggers have been implicated, most notably medications, which account for the majority of cases. Other contributing factors include infections, immunizations, radiation exposure, graft-versus-host disease, and certain environmental agents. Drug-induced cases constitute around 50–80% of SJS, while an even greater proportion of Toxic Epidermal Necrolysis (TEN) cases are attributed to medications. (2)

Among pharmacological triggers, antibiotics—particularly cephalosporins—have been associated with SJS, although reports involving specific agents such as cefixime remain limited. (3,4)

There have been just 2 case reports implicated in causation of SJS by Cefixime, however we have not been able to find any cases reported in literature where SJS has been precipitated by Phenytoin and found to be aggravated by cefixime. Therefore, we are reporting this rare case of a 7-year-old boy from Nepal presenting with SJS which was precipitated by Phenytoin and aggravated by Cefixime.

Case description

A 7-year-old male child, was admitted with chief complaints of fever, cutaneous lesions associated with burning and itching sensation, and painful perioral and oral lesions.

The patient had previously been admitted to a hospital in Nepal with complaints of seizures. He received intravenous Phenytoin for seizure control, following which he developed multiple coalescing erythematous and purpuric macules and papules over the trunk, face, and upper limbs, associated with burning sensation and pruritus. These lesions were accompanied by swelling, redness, and crusting of the lips. The patient subsequently presented to the Emergency Department of our hospital.

On detailed history taking, there was no prior history of similar manifestations. No family history of similar illness was present. The patient had no known autoimmune disease, allergy history, active malignancy, or significant prior drug exposure.

On examination, multiple hyperpigmented and reddish-purple macules and papules were present over the face, trunk, back, and upper limbs, involving <10% of the body surface area (BSA). The rash was erythematous with blister formation and areas of necrotic epidermal detachment. Nikolsky sign was positive. Examination of the oral cavity revealed multiple ulcers along with haemorrhagic crusting and erosions over the labial mucosa. Eyes and genital mucosae were spared. The cutaneous manifestations were associated with fever (103°F), odynophagia, and dysphagia. SCORTEN at the time of admission was 1, corresponding to an estimated mortality rate of 3%. Vital parameters were otherwise within normal limits.

On investigation, haemoglobin was 11.1 g/dL (normal male range: 13–18 g/dL), C-reactive protein was 38.5 mg/L (normal range: 0–5 mg/L), and random blood sugar was 96 mg/dL. In view of the prior history of seizures, lumbar puncture, electroencephalography, and magnetic resonance imaging of the brain were performed, all of which were within normal limits.

Dermatology consultation was obtained, and a clinical diagnosis of Stevens–Johnson syndrome precipitated by Phenytoin was made based on the temporal relationship between drug administration and onset of symptoms. Accordingly, phenytoin was discontinued. The patient was managed conservatively with intravenous fluids, injection meropenem, injection dexamethasone 2.5 mg every 24 hours, Mucopain oral gel, Nadibact ointment, Mometasone cream, tablet fexofenadine 180 mg once daily and other supportive treatment.

After 5 days of conservative management, the patient showed clinical improvement. The lesions progressed to the healing stage, and the oral ulcers reduced significantly. The patient was discharged after 5 days of hospitalization.

104 At discharge, oral cefixime was prescribed, while topical medications and
105 nutritional supplements were continued.

106 However, 48 hours after discharge, the patient returned to the triage with
107 aggravation of the cutaneous and oral lesions. Peeling and desquamation were
108 noted over the facial and truncal lesions, along with marked swelling of the lips
109 and haemorrhagic crusting. Multiple oral ulcers were again present. On detailed
110 history, the patient had taken only the medications prescribed at discharge.
111 There was no history of intake of NSAIDs or any antibiotic other than
112 Cefixime. Therefore, aggravation of Stevens–Johnson syndrome secondary to
113 cefixime was suspected, and the drug was discontinued immediately.

114 The patient was urgently readmitted, and after consultation with the
115 Dermatology and ENT teams, treatment was initiated with injection
116 methylprednisolone 2 mg/kg for 5 days, tablet fexofenadine 180 mg once daily,
117 intravenous fluids, and supportive care. Gradual improvement in the lesions was
118 observed, and the patient was subsequently discharged in stable condition.

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121 IMAGES : Are taken after due consent from the patient and patient identity has
122 been concealed.



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124 IMAGE 1 : Multiple pigmented maculopapular lesions present over the face and
125 haemorrhagic crusting present over the lips.

126



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IMAGE 2 : Hyperpigmented coalescent purpura like maculopapular rash present over the abdomen.

DISCUSSION

Stevens–Johnson syndrome (SJS) is a severe, potentially fatal, immune-mediated hypersensitivity reaction that is most commonly triggered by medications, although infections may also be responsible.(1) The presence of the HLA-B*1502 allele has been strongly linked to carbamazepine-induced SJS.(5) Infectious agents such as herpes simplex virus and *Mycoplasma pneumoniae*, as well as vaccinations such as the measles vaccine, have also been implicated as potential triggers.(6)

It represents a significant proportion, approximately 30–50%, of serious cutaneous adverse drug reactions. (7) Several predisposing factors have been identified, including immunocompromised states such as HIV infection, (1) underlying malignancies, autoimmune or collagen vascular disorders, and genetic susceptibility. (1)

SJS and Toxic epidermal necrolysis (TEN) are considered part of a continuous clinical spectrum, most often resulting from adverse drug reactions. They are primarily differentiated based on the extent of epidermal detachment:(1)

1. SJS: involvement of less than 10% of total body surface area (BSA)
2. SJS–TEN overlap: epidermal detachment involving 10–30% of BSA
3. TEN: more extensive involvement affecting over 30% of BSA

Cutaneous adverse drug reactions (CADRs) represent a wide spectrum of clinical and immunological manifestations. These range from relatively common and mild conditions, such as maculopapular drug eruptions, to severe and potentially fatal disorders including Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and Drug reaction with eosinophilia and systemic symptoms (DRESS)(8). With increasing life expectancy, a higher burden of comorbid illnesses, and widespread use of multiple medications, the occurrence of CADRs has risen.

The onset of reactions following administration of the offending drug is typically around 4–28 days. In our case, the patient had received intravenous Phenytoin at another hospital, which precipitated the skin reaction. After discontinuation of phenytoin, there was an initial healing phase followed by

aggravation of lesions within 48 hours of starting oral Cefixime, which differs from the usual onset duration of SJS reported in the literature (9). There is evidence regarding the association of cephalosporins as causative agents for SJS/TEN. This group of drugs is considered the fifth most common class of antibiotics implicated in SJS/TEN. (9)

Phenytoin is highly protein-bound in plasma (approximately 90%), which means that even small increases in dose can significantly raise free drug levels and lead to toxicity, especially near the therapeutic range. In addition, it acts as a hepatic enzyme inducer, altering the metabolism of several concomitant medications. The risk of developing Stevens–Johnson syndrome (SJS) is highest during the early phase of treatment, particularly within the first two months. This adverse reaction is thought to be related to the formation of reactive drug metabolites that can trigger immune-mediated damage to keratinocytes, ultimately leading to widespread epidermal injury. (10,11)

Given the high mortality associated with SJS/TEN, significant efforts have been directed towards developing reliable prognostic tools. The SCORTEN (Severity-of-Illness Score for Toxic Epidermal Necrolysis), introduced by Bastuji-Garin et al. in 2000, is the most widely used system for predicting in-hospital mortality (12). It incorporates seven clinical and laboratory parameters: age ≥ 40 years, presence of malignancy, epidermal detachment $>10\%$ of total body surface area, heart rate $\geq 120/\text{min}$, blood urea nitrogen $>10 \text{ mmol/L}$, serum bicarbonate $<20 \text{ mmol/L}$, and serum glucose $>15 \text{ mmol/L}$. Although SCORTEN has been extensively validated and remains clinically useful, recent studies suggest that its predictive performance may vary in current clinical practice. (12)

The cornerstone of management in Stevens–Johnson syndrome is the prompt identification and immediate withdrawal of the offending drug. Subsequent care is largely supportive and should prioritize maintenance of airway patency, hemodynamic stability, adequate fluid and electrolyte balance, pain control, and meticulous wound care (13). Various systemic therapies have been explored to modify disease progression. These include corticosteroids, cyclosporine, intravenous immunoglobulin (IVIG), and tumor necrosis factor- α (TNF- α) inhibitors.

IVIG at a dose of 2 g/kg has been found to be effective in one meta-analysis. However, the role of corticosteroids remains controversial because of inconsistent evidence regarding their impact on mortality (14).

Emerging evidence has highlighted the role of TNF- α inhibitors such as etanercept, with studies showing mortality rates lower than those predicted by severity scoring systems such as SCORTEN. (15) Additionally, combination regimens—such as cyclosporine or IVIG used alongside corticosteroids—have been associated with improved survival outcomes in certain analyses. (16)

The strength of this article lies in highlighting a rare occurrence of Stevens–Johnson syndrome precipitated by Phenytoin with possible aggravation by Cefixime, emphasizing a clinically important drug interaction pattern that has not been reported previously. Unlike typical reports focusing on a single offending agent, this case suggests a possible two-hit phenomenon—initial sensitization by phenytoin followed by subsequent exacerbation by cefixime—thereby adding depth to the existing literature.

The limitation of our article is that it is a single case report; therefore, the findings cannot be generalized to a larger population. Larger studies and meta-analyses are required to establish definitive causality.

CONCLUSION

As both Phenytoin and Cefixime are rampantly used in Paediatric clinical practice throughout the world owing to their availability and cost effectiveness for their respective clinical indications, therefore a clinician should be mindful of the drug hypersensitivity reactions that can occur due to both used in succession.

CONFLICTS OF INTEREST :NIL

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