Phenytoin induced Stevens-Johnson syndrome in a 38 year male patient: A Case Report

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Abstract
Adverse drug reactions (ADRs) are one of the leading causes of death among hospitalized patients and occur in 0.3 to 7 per cent of all hospital admissions. These may vary from mild rashes to severe reactions such as Stevens-Johnson syndrome (SJS). Antiepileptic drugs-induced SJS is a life-threatening severe cutaneous adverse reaction. We report here a case of phenytoin induced SJS in a 38 year old male patient presenting at emergency room. The patient responded to the treatment and was prescribed tab. Levetrecitam and remained symptom free since then.

Keywords: Phenytoin, Drug induced Stevens - Johnson syndrome, Levetrecitam, Anti-Epileptics, and Drug Reaction.

Introduction

Approximately 0.3 to 7 % of the deaths amongst hospitalized patients have been reported to be caused by adverse drug reactions (ADR). The spectrum of drug reactions may range from mild to severe such as Johnson syndrome (SJS) which is a rare, but with severe cutaneous, cell-mediated hypersensitivity reaction that is usually induced by medication or a virus. Drug induced SJS is one of the most common forms of SJS and Antimicrobials (37.27%) have been the most common drug associated with drug induced SJS, followed by Anti-epileptic drugs (AEDs) (35.73%) and NSAIDs (15.93%).[1]

Epilepsy affects about 1% of the human population. There are 50 million patients with this disease and 2 million new cases per year are observed. The necessary treatment with AEDs increases the risk of adverse reactions. In 70% of the patients receiving AEDs, the seizures are well controlled but however simultaneous occurrence of ADRs are the the most challenging feature associated with the treatment. In case of 15% of people receiving AEDs, cutaneous reactions, like maculopapular or erythematous pruritic rash, may appear within four weeks of initiating therapy with AEDs.[2] Varying incidences of SJS (13.37% and 3.33%) with phenytoin have been reported by various authors.[3]

Case Report

A 38 years old, male patient presented to the emergency with chief complaints of rashes, oral ulceration and fever. When detailed history was taken, patient revealed onset of chief complaints from past 8-10 days beginning with fever (99-101 degrees Celsius), followed by rashes and difficulty in eating/swallowing due to oral ulcerations. Patient had previous history of pulmonary tuberculosis for which he had undergone treatment.

Patient was diagnosed with General Tonic Clonic Seizures approximately 1 month back, for which he was prescribed Tab. Phenytoin 100 milligrams thrice a day from a local doctor. After 12-13 days of administration, patient developed fever for which he self-medicated with Tab. Paracetamol but with no effect. After 3-4 days patient started developing rashes beginning from trunk and progressing towards neck and then involving both arms and flexor surface of forearms over a period of 3-4 days with progressing intensity and severity along with oral ulcerations and red eye, finally presented to the emergency of our institute in the above mentioned condition.

On physical examination, the patient was well-oriented, had hyperpyrexia, generalized, maculopapular rash all over the body and bullous eruptions on the neck, face and back. The trunk and extremities were having well developed variably sized target like lesions. Intraoral examination revealed ulcerations of the vermilion surface of lips, labile mucosae, tongue and palate. The ulcers were hemorrhagic and tender on palpation. Ophthalmic examination showed acute...
conjunctivitis and sub conjunctival hemorrhages. Hemorrhagic ulcers over the eyelids were also noted.

On general examination, BP was 110/80 mm of Hg, Pulse-94 beats/min, Respiratory rate- 16/min, chest auscultation and abdominal palpation did not reveal any significant finding. Bilateral submandibular lymph nodes were palpable, tender, mobile and firm in consistency.

The patient was immediately admitted with diagnosis of drug induced Steven Johnson’s Syndrome and Tab. Phenytoin and Tab. Paracetamol were immediately stopped. Patient was started with Intravenous fluids (1.5 liters/day), Intravenous Cefotaxime (1 gram every 12 hourly) for infection prophylaxis, Inj. Pheniramine Maleate 25 mg and inj. Prednisolone 10 mg qid. Oral ulcer was managed with the candid mouth paint and choline salicylate. Ofloxacin eye drops 0.3% was advised for eye lesion and Lotion Calamine was applied gently over the skin with strict aseptic measures.

Causality assessment using Naranjo’s algorithm categorized the adverse drug reaction as probable (score=6). The reaction was labeled as severe (level 5 using Hartwig severity scale). The drug reaction was not a preventable ADR (using modified schumlock and thronton preventability scale). The average rate of mortality was 3.2%, with a SCORTEN (Score of Toxic Epidermal Necrosis) score of 0.

Patient started showing improvement after 2 days of treatment, had normal body temperature with BP-130/80 mm of Hg, Pulse 80 beats/minute, Respiration at 16/minute, urinary output of 1.5-1.8 liters/day and with an overall improved general condition. Tab. Levetiracetam 500 mg bid was started from day 3rd as an alternative to Tab. Phenytoin and intravenous fluid was also stopped as patient was comfortable taking orally. Systemic steroid, Inj. Prednisolone 10 mg qid for 7 days, which was gradually tapered to 10 mg tid for 7 days, 10 mg bid for 5 days, then Tab Prednisolone 10 mg once daily for 5 days respectively. Inj. Cefotaxime was also stopped after 7 days. Patient recovered completely after 22 days and was advised to continue Tab. Levetiracetam

**Discussion**

Now considered as a clinically distinct disorder, earlier SJS was considered to be part of a spectrum of erythema multiforme (EM) and is part of the SJS-toxic epidermal necrolysis (SJS-TEN) spectrum, characterized by heterogeneous cutaneous bullous eruptions which can result in sloughing of the epidermis. SJS and TEN involve <10% and >30% of the body surface area respectively. The third condition named as SJS-TEN overlap falls in-between SJS and TEN. Patient may initially present with SJS, which subsequently evolves into TEN or SJS-TEN overlap. [4]

In the initial stages of the disease process, the epidermis becomes infiltrated with CD8 T-lymphocytes and macrophages, while the dermis shows CD4 predominance cells. It is postulated that the lymphocytes release cytokines, which mediate the inflammatory reaction and apoptosis of epithelial cells. It should be stressed, however, that the mechanism of hyper sensitivity syndrome is thought to involve deficiency or abnormality of the epoxide hydroxylase enzyme that detoxifies the metabolites of aromatic amine anticonvulsants, associated reactivation of herpes-type viruses, and ethnic predisposition with certain human leukocyte antigen subtypes. The toxic intermediates in the metabolism of anticonvulsant drugs can accumulate and directly cause cell death, or, as prohaptens, bind to T cells evoking immune response. [5]

Prodromal features includes fever, cough, sore throat, headache, myalgia, and burning sensation. As described by Sanmarkan et al., skin lesions preceded mucosal lesions in 50% of patients. Oral, conjunctiva and genital mucosa were involved in 43.47% of patients. [6] Our reported case had also developed generalized rash which was followed by mucosal lesions in the form of oral ulcerations and conjunctival lesions. Previous studies have shown female predominance for drug induced SJS/TEN and a mean age group of 10-40 years. [7, 8] However, our reported case is a 38 year old male patient who experienced fever as the first symptom after approximately 13 days of exposure to Tab. Phenytoin, Patel et al; 2011 had reported the average time between the 1st administration and development of SJS/TEN of 1- 5 weeks in majority of the cases. [3]

First symptom reported by the patient was fever for which the patient did not consult the prescribing physician, but instead started self-medicating with Tab Paracetamol, which however was not effective. When patient presented to our institute, after approximately 1 week of onset of fever, he was still febrile with full blown SJS. In a systematic review of the published evidence of the drug-induced SJS and TEN in Indian population by Patel TK et al., 2013, reported that among the NSAIDs, paracetamol and nimesulide were most commonly reported. [9] Similarly SCAR (severe cutaneous adverse reaction) study has found an overall risk of SJS with oxicam derivatives. It reports increased risk with paracetamol from Germany, Italy, and Portugal except France. There is no increased risk with diclofenac, salicylates and pyrazolone derivatives. [10] EuroSCAR (European Severe Cutaneous Adverse Reaction) study found weak association of paracetamol with SJS. [11] Paracetamol is confounded by its use to treat nonspecific symptoms such as fever or pain, the early signs of the adverse reaction or infection both. However, paracetamol is found to be a potential risk factor in children when data from pediatric patients from the SCAR and EuroSCAR studies are pooled. Similarly, various other studies have also found paracetamol as a suspected agent in drug induced SJS. [6-8, 12-14]

**Conclusion**

As soon as the diagnosis of Phenytin induced SJS was confirmed, patient was taken off from Tab. Phenytoin and
after 2 days was started with Tab. Levetrecitam 500mg twice a day as an alternative to phenytoin. It is believed that phenytoin induces cytochrome P450 3A and produces oxidative reactive intermediates that are involved in the hypersensitivity reaction. Additionally, it is thought that the aromatic chain in the chemical structure of phenytoin and other agents undergo a detoxification pathway mediated by epoxide hydrolases. Anticonvulsants that do not commonly cause SJS are metabolized differently. Since Carbamazepine, Valproic Acid and barbiturates have shown cross-sensitivity with Phenytoin, Gabapentin was recommended as a substitute Anti-Epileptic Drug for a suspected sensitive patient. Gabapentin related SJS reactions, however, have been reported in the literature. Nonetheless, they are rare events. Another alternative, Levetiracetam, is increasingly being used as a phenytoin replacement.

What this case report adds:

1. What is known about this subject?
Antiepileptic drugs-used in epilepsies are associated drug induced skin eruptions.

2. What new information is offered in this study?
We report here a case of phenytoin induced SJS in a 38 year old male patient presenting at emergency room. The patient responded to the treatment and was prescribed tab. Levetrecitam and remained symptom free since then.

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