

PHENYTOIN INDUCED TOXIC EPIDERMAL NECROLYSIS: A CASE REPORT

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ABSTRACT

Toxic Epidermal necrolysis (TEN) is a rare, life threatening dermatological disorder that is usually induced by medications. Anti-convulsants such as phenytoin, carbamazepine and phenobarbital have been enlisted as high risk drugs for causing TEN. A 25 year old man, a known case of epilepsy, who consumed inadvertently escalated daily dose of 600 mg/day of phenytoin for 10 days, developed TEN which involving more than 30% of body surface area with mucosal involvement. Rigorous treatment of 18 days using systemic and topical antibiotics along with glucocorticoids helped in complete recovery of the patient. Causality analysis of this Adverse Drug Reactions (ADR) showed a probable association on both World Health Organisation (WHO) – Uppsala Monitoring Centre (UMC) scale and Naranjo's probability scale and Severity scale of 5 on Modified Hartwig and Siegel scale. Medication error is an important cause of such life threatening reactions which requires concern of all health care professionals.

KEY-WORDS: Adverse Drug Reaction (ADR); Hypersensitivity Reaction; Medication Error; Phenytoin; Toxic Epidermal Necrolysis

Introduction

Toxic epidermal necrolysis (TEN) also known as "Lyell's syndrome", is a rare, life-threatening dermatological condition that is usually induced by a reaction to medications. Incidence of Steven Johnson Syndrome (SJS) and TEN is 0.05 to 2 persons per million, population per year.^[1,2] It is characterized by the detachment of the dermis from the epidermis all over the body. Cases with epidermal detachment in less than 10% of body surface area (BSA) are designated as SJS; those with more than 30% of BSA are labelled as TEN; while cases between 10 and 30% of involvement are defined as SJS-TEN overlap.^[3] Both these terms are covered under Erythema Multiforme spectrum of diseases. TEN presents with a prodromal period mimicking an upper respiratory tract infection, followed by poorly defined erythematous macules or diffuse ill-defined erythema. The affected skin may develop flaccid bullae and may detach irregularly, sometimes in large sheets with just a sliding touch (Nikolsky's sign). The consequences of such a massive loss of epidermis include dehydration, increased energy expenditure and local or systemic infection such

as septicaemia. The common causes for Toxic Epidermal Necrolysis are medications that are taken for a short period of time, such as antibiotics co-trimoxazole, quinolones and cephalosporins or the medications used for prolonged period such as anticonvulsants like phenytoin, lamotrigene, carbamazepine etc. Some rare causes are Malignancy and Idiosyncrasy. We report an interesting case of phenytoin induced TEN, details of which are given below.

Case Report

A 25 year old male, known case of epilepsy and was on tablet phenytoin in the dose of 300mg/day, intermittently (during the attacks only), for the past 14 years. With his recent epileptic attack he unknowingly consumed 600 mg/day (2 tablets of 300 mg) of phenytoin instead of the regular dose for a span of 10 days. One week following the medication overdose, he developed wide-spread erythematous bullous lesions all over the body involving more than 30% of BSA (Body Surface Area). Some of these had burst-out with scraping of sheets of skin, on a sliding touch (Nikolsky's sign positive) (figure 1). Few purpuric lesions

over the chest and oral mucosal lesions were also seen (figure 2). The patient had developed conjunctivitis and pseudo membrane formation in the eyes. He also suffered from fever; pruritus and swelling of the upper lip. It was anaphylactic type of reaction. He then visited a neurophysician in a private set-up who replaced tablet phenytoin with tablet oxcarbazepine 600mg/day and tablet clobazam 5mg/day. Despite these measures, the patient's complaints got aggravated and he came to department of Medicine of a tertiary care teaching rural hospital with bed strength of 1250 after three days of the changing the medications. His physical examination was within the normal physiological range with temperature - 100° F (37.7° C); pulse rate - 90/min and systolic blood pressure of 100 mmHg. His blood investigations were white blood cell count (WBC) of 3700/ μ l, haemoglobin 11.1g/dl and serum sodium 125mEq/L. Tests for HIV, HbsAg and HCV were negative. A diagnosis of phenytoin induced toxic epidermal necrolysis was made. Patient was admitted in the Intensive Care Unit (ICU) for further management. To begin with, oxcarbazepine and clobazam were put on hold immediately. Concurrent correction of fluid and electrolyte imbalance was done. He then received parental glucocorticoids i.e., intravenous dexamethasone 8mg/day for 5 days followed by gradual tapering of the dose, over a period of 15days, to 2mg/day. This was followed by tablet prednisolone in the dose of 10mg/day for another 5 days (2days before and 3 days after discharge) before complete stoppage of steroid therapy. Antibiotics used were parental ceftriaxone in a dose of 1g/day and amikacin 750mg/day. Seizure control was achieved by midazolam. Framycetin skin ointment and gatifloxacin eye drops were used for the topical treatment of skin and eye infections respectively.

The patient responded favourably to the treatment and recovered from this fatal adverse reaction after rigorous treatment for 18 days. He was discharged from the hospital with the advice to continue tablet clobazam in a dose of 5mg/day regularly for the treatment of epilepsy, oral prednisolone 10 mg per day as mentioned above and topical antibiotics for residual skin infections. On follow-up visit, after a week the skin and eye lesions had completely healed (Figure 3) and he

had no fresh complaints. The patient was given an "alert card", mentioning about various medications which were to be avoided.



Figure-1: Drug Reaction before Management (Nikolsky's Sign Positive)



Figure-2: Spreading Lesions All Over the Body



Figure-3: Improvement in the Lesions of Skin and Oral Mucosa after Treatment

The association between phenytoin and TEN was evaluated using World Health Organisation (WHO) – Uppsala Monitoring Centre (UMC) causality

assessment criteria, Naranjo's Probability Scale and Modified Hartwig and Siegel Severity Scale. According to WHO-UMC scale the reaction was of 'probable' nature. Naranjo's Scale revealed a score of 8, also signifying a probable association. According to Modified Hartwig and Siegel Severity Scale, the ADR was placed at level 5, wherein the patient required intensive medical care.

Discussion

Toxic epidermal necrolysis (TEN) and Steven Johnson Syndrome (SJS) are considered to be two ends of a spectrum of severe, life threatening epidermolitic cutaneous adverse drug reactions, differing only by their extent of skin detachment. Anticonvulsants are a major cause of TEN and other severe cutaneous reactions. We have attempted to co-relate the findings in our patient with the available facts related to the same.

Phenytoin induced TEN can occur at any time between 2 and 8 weeks after initiation of the treatment and may progress despite discontinuation of the drug. Factors associated with increased risk of this reaction include the use of higher than recommended dose, more rapid dose escalation and concomitant use of valproate.^[4] This patient has also developed reaction after consuming higher than usual dose of phenytoin unknowingly instead of regular dose for a period of 10 days. Moreover it was found that the Cutaneous Adverse Drug Reaction (CADR) continued despite the discontinuation of phenytoin although the use of oxcarbazepine, as replacement for phenytoin by the local doctor of the patient, remains a confounding factor. Oxcarbazepine, a 10-keto derivative of carbamazepine, which was considered to carry a lower risk, seems to significantly cross-react with carbamazepine.^[5]

Pathophysiology of SJS/TEN is still unclear and more than one mechanism has been proposed. It may involve hypersensitivity due to toxic metabolites of suspected drug/s. Arene oxides derived from aromatic anticonvulsants bind to cell constituents if they are not rapidly detoxified by epoxide hydrolase. These metabolites act as haptens and render the keratinocytes antigenic by binding to them.

Genetic basis for these ADRs like SJS/TEN have been attributed to inherited or acquired deficiency in phase 2 detoxification enzymes or from an elevated cytochrome P450 (CYP 450) isoform(s). Few studies have also indicated an association between HLA*1502 and phenytoin induced SJS/TEN.^[6] Family history of such reactions should always be asked by the prescribing doctor before prescribing these medicines.

Additionally, this case reflects an important aspect of pharmacotherapy namely "Medication Errors." In this case the patient suffered from TEN as a result of sudden dose escalation, which could be attributed to inadequate communication between the patient, doctor and the pharmacist. Such medication errors due to negligence account for about 1% of all hospital admissions which could be prevented.^[7] The optimal management of this life-threatening disease is by early recognition and withdrawal of the offending drug(s) and supportive care in an appropriate hospital setting. Many drugs have been implicated in the prevention of progression of this condition like systemic prednisolone, intravenous immunoglobulin and cyclosporine A, but none of them have been standardized. In our patient however, intravenous prednisolone along with antibiotics for treatment of infective lesions on the skin might have led to the recovery of the patient impeding further progression.

Conclusion

TEN is a severe life threatening complication associated with use of anticonvulsants like phenytoin which may have familial tendency. Moreover, proper communication to the patient regarding the use of medications is of utmost importance, in such life threatening conditions where treatment guidelines remain hazy. In short, it should be ensured that "right" patient is receiving the "right" drug in a "right" dose at the "right" frequency and duration of time. It is also advisable to give personal "allergy card"- in the true sense being an alert card about the description of ADR to the patient who suffered from such serious reactions.

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