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PHENYTOIN INDUCED TOXIC EPIDERMAL NECROLYSIS: A CASE REPORT

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Abstract

The drug induced Toxic epidermal necrolysis (TEN) is an acute emergency and is potentially life threatening if not treated promptly. It is obvious that patients with TEN demand much more meticulous and aggressive therapy for better outcome. Adverse drug reactions (ADRs) are one of the most leading causes of death among hospitalized patients; these may vary from mild rashes to severe reactions such as Stevens-Johnson syndrome (SJS) and Toxic epidermal necrolysis. Though the Phenytoin is an anti-epileptic drug, there is increased risk of TEN and other skin related problems. Thus utmost care should be taken while handling with the Phenytoin.

Introduction

Epilepsy is a common neurological disorder that affects people worldwide. It is relatively common condition characterized by a tendency for recurrent seizures, which is due to the disturbance of spread of electrical discharge of the cortical neurons.[1] Phenytoin (5,5-diphenylhydantoin) is one of the most effective and widely prescribed drug for the treatment of epilepsy, which was found to cause Toxic epidermal necrolysis (TEN) more frequently[2]. Despite the inherited risk of dose related toxicity attributed to its zero-order pharmacokinetics, Phenytoin is still considered a first line drug therapy for some types of seizures.[3]

Adverse drug reactions (ADRs) are one of the most leading causes of death among hospitalized patients and occur in between 0.3 to 7 per cent of all hospital admissions.[4] these may vary from mild rashes to severe reactions such as Stevens-Johnson syndrome (SJS) and Toxic epidermal necrolysis etc. Mostly Anti-Epileptic Drugs are associated with increased risk of adverse reactions. [4] In 70% of the patients receiving Anti-Epileptic Drugs (AEDs), the seizures are well controlled but however simultaneous occurrence of ADRs are the most challenging feature associated with the treatment. In case of 15% of people receiving AEDs, cutaneous reactions, such as maculopapular or erythematous pruritic rash, may appear within four weeks of initiating therapy with AEDs.[3]

Toxic epidermal necrolysis also known as Lyell's syndrome can be defined as rapidly developing extensive erythema, necrosis, and detachment of the epidermis and mucous membranes that result in severe and fatal systemic complications such as sepsis, if left untreated. TEN is commonly considered a drug induced reaction rather than a skin disease.[5] Thus, therapeutic monitoring of a patient's Phenytoin serum level is crucial to assure the safety and efficacy of Phenytoin therapy.[5]

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Case Study

Patient's Medication History: A 25-year old male patient was admitted to a Shri B M. Patil Medical College Hospital and Research Centre with chief complaints of skin lesion over the face, trunk and extremities since from one week. He had a past medical history of Alcoholic Hepatitis for which he was consulted local hospital where he had multiple episode of seizure for which he was started on Phenytoin. The patient was apparently normal for two weeks after initiation of the Phenytoin therapy; there on he developed red colored skin lesion associated with pain, over face **(Fig. 01)** and trunk insidious in onset. This gradually progressed to involve the extremities **(Fig. 02)** and genitalia. The lesion was become fluid filled and ruptured spontaneously to leave behind raw areas. The patient was then brought to dermatology ward of the hospital when the above symptoms were accompanied with other chief complaints of high grade fever, continuous in nature associated with chills and rigor. The patient appeared to be conscious, coherent, cooperative, moderately built and nourished. He confirmed the use of alcohol and tobacco for two years. The patient sticks to vegetarian diet with a reduced appetite and sleep.

General Physical Examination: On cutaneous examination multiple purpuric, dushy red patches along with erosions and crusting were found over the face, trunk, scalp and extremities. Bullae were present over both the legs. Erosion of buccal mucosa and hemorrhagic crust over the lips were also seen. Increased eye discharge, pedal edema and longitudinal ridges over finger and toe nails were also observed.

Laboratory finding: On admission, the patient was conscious, and his blood pressure was 120/80 mmHg, pulse rate of 80/min and his abdomen was soft and non-distended with no tenderness or hepatic splenomegaly. No focal deficits were seen on neurological examination. His lab investigations were: White blood cell 5,840cells/cmm, red blood cell 4.36x106/mm3, hemoglobin 13 g/dl, erythrocyt sedimentation rate, 15mm/1st in hour, platelets count 4.7lakh/cmm, serum creatinine 0.6 mg/dl, blood urea 18 mg/dl, bilirubin (total 0.5 mg/dl, direct 0.3 mg/dl, and indirect 0.2 mg/dl).

Diagnosis: Toxic Epidermal Necrolysis (TEN) Secondary to Phenytoin.

Table 01. Treatment Chart

Brand Name	Generic Name	Dose (mg)	Frequency	Indication	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Tab Psorid	Cyclosporine	100	1-0-0	Immune suppressant	✓	✓	✓	✓	-	-	-
Inj. Levipil	Levetiracetam	500	1-0-1	Seizures	✓	✓	✓	✓	✓	✓	✓
Tab Dolo	Paracetamol	650	1-0-1	Fever	✓	✓	✓	✓	-	-	-
Ont. Flomo	Moxifloxacin	0.5% w/w	1-0-1	Bacterial Eye infection	✓	✓	✓	✓	✓	✓	✓
Inj. Advent	Amoxicillin	1200	1-0-1	Antibiotic	✓	✓	✓	✓	-	-	-
Tab Anxit	Alprazolam	0.25	0-0-1	Anxiety	-	-	-	✓	-	-	-
Inj. Tazomac	Pipercillin/ Tazobactam	4500	1-0-1	Antibiotic	-	-	-	-	✓	-	-
Inj. Rantac	Ranitidine	50	1-0-0	H_2 Antagonist	-	-	-	-	✓	✓	✓
Tab Zocon	Flucanazole	50	3-0-0	Anti-Fungal	-	-	-	-	✓	✓	✓

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Tab Chymerol	Tripsin-Chymotripsin		1-1-1	Swelling	-	-	-	-	✓	✓	✓
Inj. OmniKacin	Amikacin	500	1-0-1	Antibiotic	-	-	-	-	-	✓	✓

Supportive Treatment: Saline compressors, Econorm (Sacharomuces Boulordi) Sachets, Relub Eye Drops (Carboxymethy cellulose), Candid (Clotrimazole) Mouth Paint, Betadine mouth gargle, Bioline jelly and Nasoclear nasal drops were given as supportive treatment. After implementation of treatment regimen the patient was shown improved in his condition graded fashion of days.

Discussion

Phenytoin has a narrow therapeutic index of 10-20 mcg/ml.[2] At plasma concentrations below 10 mcg/ ml, elimination follows first order. However, at higher concentrations, including those in the therapeutic range (10-20 mcg/ml), the metabolic pathway becomes saturated and elimination shifts to zero order. Half-life of Phenytoin varies between six and twenty-four hours at plasma concentrations less than 10 mcg/ml, but increases with higher concentrations. As a result, the plasma concentration rises disproportionally even with small increase in the dose. Toxicity generally correlates with the increasing plasma levels. The increased half-life due to zero order pharmacokinetics can also result in prolonged duration of toxic symptoms.[2]

Currently TEN is considered as a clinically distinct disorder, earlier SJS was considered to be part of a spectrum of erythema multiform (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]

Frequently, TEN and SJS are characterized initially by unspecific signs and symptoms such as fever, stinging eyes, and discomfort on swallowing. Thereafter, cutaneous manifestations start to appear a few days later; cutaneous involvement typically starts to affect the trunk, face, palms, and soles. In this case the patient was presented with red colored skin lesion associated with pain, over face and trunk which is insidious in onset. This gradually progressed to involve the extremities and genitalia. The lesion then became fluid filled and ruptured spontaneously to leave behind raw areas. Likewise, there are reports of Phenytoin induced Hypersensitivity reactions,[6] Erythematous lesions.[4] More than 90% of cases include mucocutaneous involvement of the buccal, genital, and/or ocular mucosa. Late phase signs and symptoms of TEN occur later in the course of the disease and include hyper and hypo pigmentation of the skin, nail dystrophies and ocular complications. Fifty percent of TEN patients will develop late ocular complications including severe dry eyes, trichiasis, symblepharon, distichiasis, visual loss, entropion, ankyloblepharon, lagophthalmos and corneal ulceration.

As soon as the diagnosis of Phenytoin induced TEN was confirmed, patient was discontinued for the same and was replaced with Levetiracetam 500mg twice a day as an alternative to Phenytoin. It is believed that Phenytoin induces cytochrome P-450 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 TEN are metabolized differently. Nonetheless, they are rare events. Levetiracetam is increasingly being used as an alternative when there comes a need for Phenytoin replacement.[4] Hence in the current case the replacements of Phenytoin with Levetiracetam was a right decision for better patient care and reduce further consequences of Phenytoin toxicity.

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Conclusion

This case report of Phenytoin toxicity helps to alert physicians about the toxic manifestations of Phenytoin in patients on long term drug therapy. Long term therapy with Phenytoin should be individualised based on the patient's clinical response, plasma drug levels and signs of toxicity. There is also need for regular follow up to assess compliance and response to therapy. This report also highlights the importance of educating Physicians, patients and their caretakers about the clinical manifestations of Phenytoin toxicity, so that it can be recognized early and treated appropriately..

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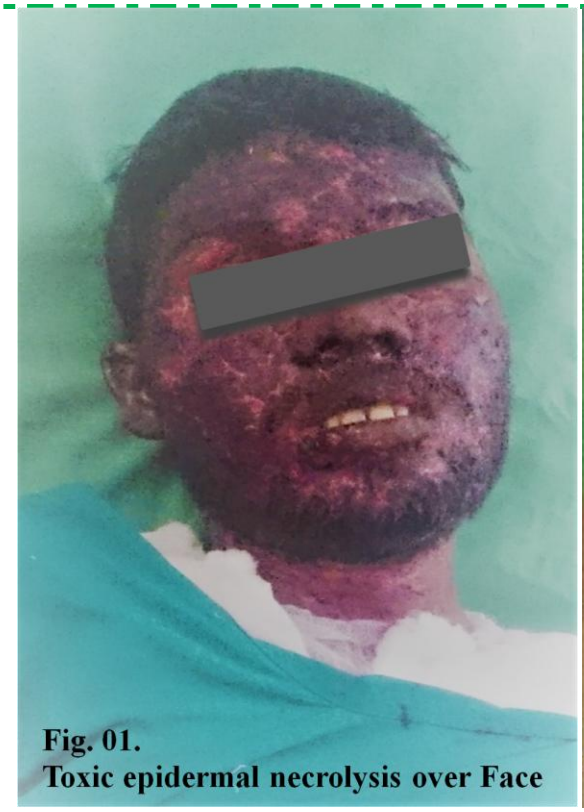

Fig. 01.
Toxic epidermal necrolysis over Face

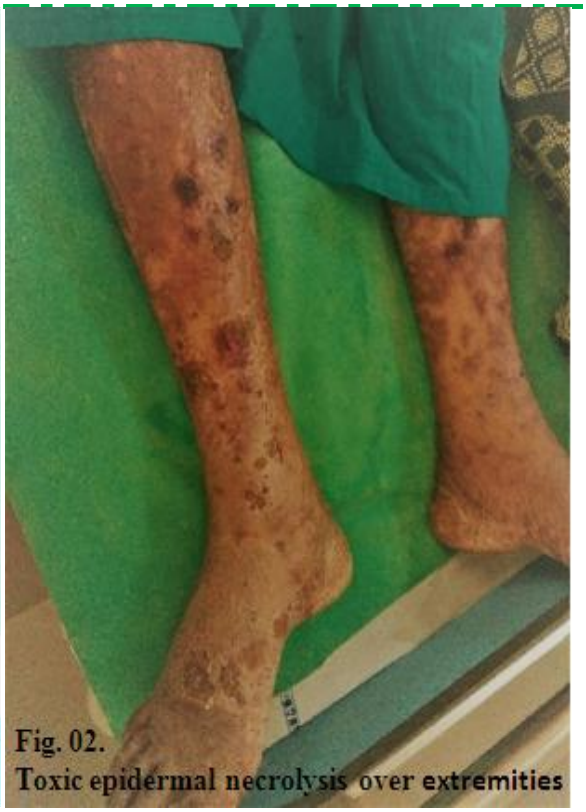

Fig. 02.
Toxic epidermal necrolysis over extremities