

Phenytoin Induced Toxic Epidermal Necrolysis: A case Report

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Abstract: Toxic Epidermal Necrolysis is a fatal skin disease induced by the drug with 30 -40% skin detachment involved. Drugs that may induce this syndrome are such as nonsteroidal anti-inflammatory drugs, allopurinol, antimetabolites (methotrexate), antiretroviral drugs and anticonvulsants. Here is a case of 49 yrs old female of TEN induced by phenytoin. Phenytoin is an anticonvulsant drug.

Keywords: TEN, Toxic epidermal Necrolysis Phenytoin, Naranjo scale.

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I. Introduction

Toxic epidermal necrolysis is a cutaneous drug induced reaction with the mortality rate of 30-40% [1]. This disease is characterized by erythema, necrosis and bullous detachment of the epidermis and mucous membrane involving the filling of dermal layer with fluid, due to negative response to antibiotic and then, skin begins to detach from the body and gives the peeled off look in great swaths . The drugs most implicated in TEN are antibiotics such as sulfonamides, nonsteroidal anti-inflammatory drugs, allopurinol, antimetabolites (methotrexate), antiretroviral drugs, corticosteroids, chlormezanone (anxiolytic), and anticonvulsants such as phenobarbital, phenytoin, carbamazepine, and valproic acid [2].

II. Case Report

A 49 year old female admitted in the skin OPD with the history of the multiple well to ill defined papular plaques with central peeling and edema showing epidermal peeling on the back, sole, extremities and thigh. In addition to this, multiple erosion and ulceration over tongue, buccal mucosa and alveolar mucosa was documented (Fig. 1, 2, 3). A complete drug history revealed that she was taking phenytoin for brain metastasis. After approx 28 days of administration of the phenytoin, she developed the reddish oozy lesion behind both the ears. The assessment of the reaction was carried out by the Naranjo ADR probability Scale [Table 1]. Dermatologist confirmed the reaction

Table 1: The Naranjo adverse drug reaction probability scale: Questionnaire	Yes	No	Do not know	Score
1.Are there previous conclusive reports of this reaction?	+ 1	0	0	+1
2. Did the adverse event appear after the drug was given?	+2	-1	0	+2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	+1	0	0	+1
4.Did the adverse reaction reappear upon readministering the drug?	+2	-1	0	0
5.Were there other possible causes for the reaction?	-1	+2	0	+2
6.Did the adverse reaction reappear upon administration of placebo?	+1	0	0	0
7.Was the drug detected in the blood or other fluids in toxic concentrations?	+1	0	0	0
8.Was the reaction worsened upon increasing the dose? Or, was the reaction lessened upon decreasing the dose?	+1	0	0	0
9.Did the patient have a similar reaction to the drug or a related agent in the past?	+1	0	0	0
10.Was the adverse event confirmed by any other objective evidence?	+1	0	0	0
			Total	+6

to be toxic epidermal necrolysis. Phenytoin was regarded as the suspected medication and was withdrawn immediately after the appearance of the lesions. . Pathological studies were found to be normal except for low total protein (4.8g/dl) and albumin (2.8 g/dl) content. She was started with Dexamethasone 8mg injection, flutibact ointment (Fluticasone propionate 0.005 %W/W+Mupirocin 2 %W/W) and Pantoprazole 40 mg injection. After this she was continued with the amoxyclav tablet 625 mg TDS, fusidic acid BD, glycomet PG2, glycomet 1GM and leveysy 500 mg BD. She was recovered and discharged after a month.

Scoring
>9 = definite ADR 5-8 = probable ADR 1-4 = possible ADR 0= doubtful ADR

III. Discussion

Toxic epidermal necrolysis (TEN) is a cutaneous drug induced reaction with the mortality rate of 30-40% [1]. There are erosions with blisters in various parts of the body like mouth, vagina, eyes, back, thigh and sometimes, may lead to even blindness. If not managed properly it can lead to death due to sepsis. 95 % of the patient with TEN has the history of medication use. The drugs most implicated in TEN are antibiotics such as sulfonamides, nonsteroidal anti-inflammatory drugs, allopurinol, antimetabolites (methotrexate), antiretroviral drugs, corticosteroids, chlormezanone (anxiolytic), and anticonvulsants such as phenobarbital, phenytoin, carbamazepine, and valproic acid. The difference between the SJS and TEN is the percentage of skin detachment. In SJS below 10% of skin detachment occurs while in TEN 30% of the skin detachment occurs [2].

Underlying mechanism resulting in TEN is still to be evaluated, but there are certain studies available to explain the mechanism. Like some studies suggest that there is the cell death throughout the body in this syndrome. The hallmark of this disease is the widespread sloughing due to keratinocyte apoptosis [2]. Another study suggest abnormal metabolism of the culprit drug in TEN patients leading to increased production of reactive metabolite. This metabolite is then, suggested, to behave as haptens adhering to carrier proteins on the epidermal cell membrane and induces an immune response [3]. Others suggest the abnormal expression of HLA class II in the epidermal cells [4].

Phenytoin belongs to hydantoin class of anticonvulsant drugs. Study conducted by Neil.H.Sheer et.al revealed that CYP 450 is involved in the metabolism of phenytoin into reactive aromatic epoxide intermediates (arene oxides). Arene oxides may be responsible for cellular toxicity and the initiation of immunologic reactions. Epoxide hydrolases are cellular enzymes critical for the detoxification of arene oxides. A defect in these enzymes could lead to an accumulation of reactive metabolites [5]. Another study has shown a significant association between human leukocyte allele and the hypersensitivity syndrome. The presence of this allele increased the risk from 5% to 26 % while the absence of this allele reduced the risk from 0.5% to 3.8% [6, 7]. Phenytoin is associated with the HLA B*51:01 [8]. Thereby, it is recommended to first screen the patients for this particular allele before starting with antiepileptic drugs. Some pharmacogenetic studies have revealed the association of inherited deficiency of epoxide hydrolase and phenytoin hypersensitivity syndrome [9] while others suggest inherited or acquired deficiency in phase 2 detoxification enzymes or an elevated CYP450 isoform [8].

In the present case report patient developed the reddish oozy lesion behind both the ears that later broke out in a serious fluid filled lesion all over the body with the pedal edema 28 days after the administration of phenytoin orally at the dose of 300 mg for prophylactic management of brain metastasis. The drug was immediately stopped and was diagnosed to have allergic reaction induced by phenytoin by dermatologists. Based on the Naranjo Scale [10], the probability score obtained was +6. So, the patient was categorized as “probable ADR”.

TEN is the rare condition seen. And as this can be fatal, so proper management should be provided. Patient should be informed about medicine, suspected as culprit and should be informed avoid the re-challenge.



Fig 1

Fig 2



Fig 3

References

- [1]. P Saraogi, CS Nayak, R Pereira, RS Dhurat, Inadvertent provocative oral ondansetron use leading to toxic epidermal necrolysis in an HIV-infected patient, *Indian J Dermatol*, 57(6), 2012, 503.
- [2]. P Tiwari, R Panik, A Bhattacharya, D Ahirwar, A Chandy, Toxic epidermal necrolysis: an update, *Asian Pac J Trop Dis*, 3(2), 2013,85-92.
- [3]. NH Shear, SP Spielberg, DM Grant et al, Differences in metabolism of sulfonamides predisposing to idiosyncratic toxicity, *Ann Intern Med*, 105, 1986, 179-84.
- [4]. G Villada, J Roujeau, T Clerici et al, Immunopathology of toxic epidermal necrolysis, *Arch Dermatol*, 128, 1992,50-3.
- [5]. N Shear, S Spielberg, Anticonvulsant Hypersensitivity Syndrome:In Vitro Assessment of Risk, *J Clin Invest*, 82, 1988,1826-32.
- [6]. [6]M Cormack, A Alfirevic, S Bourgeois, J Farrell, D Kasperaviciute, M Carrington et al, HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans, *N Engl J Med*,364, 2011, 1134-43.
- [7]. Y Cheung, S Cheng, J Chan, S Lo, M Ng, P Kwan, HLA-B alleles associated with severe cutaneous reactions to anti-epileptic drugs in Han Chinese. *Epilepsia*,54, 2013,1307-14.
- [8]. N Kaniwa, E Sugiyama, Y Saito, K Kurose, K Maekawa, R Hasegawa et al, Specific HLA types are associated with antiepileptic drug-induced Stevens- Johnson syndrome and toxic epidermal necrolysis in Japanese subjects. *Pharmacogenomics*,14, 2013,1821e31.
- [9]. A Vijayendra, N Modi, K Vaidya, R Shah, S Desai, Phenytoin induced toxic epidermal necrolysis: A case Report. *International Journal of Medical Science and Public Health*, 2(3), 2013,763-66.
- [10]. CA Naranjo, U Busto, EM Sellers, P Sandor, I Ruiz and EA Roberts, A method for estimating the probability of adverse drug reactions, *Clinical Pharmacology and Therapeutics*, 30, 1981, 239-245.

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