

Phenytoin Induced Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in a Tertiary Care Hospital: A Case Series

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Abstract: Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) are rare but potentially life threatening cutaneous adverse drug reactions. Drugs commonly implicated are anti-microbials, anti-epileptics and non-steroidal anti-inflammatory drugs (NSAIDs).

We report here a case of SJS due to phenytoin. Adverse drug reactions (ADRs) are one of the leading causes of death in hospitalized patients. ADR is a response to a drug which is noxious, unintended and occurs at doses normally used in human for prophylaxis and treatment. Steven Johnson syndrome is an immune complex mediated hypersensitivity complex that typically involves the skin and mucous membranes. Steven Johnson syndrome and toxic epidermal necrolysis are rare (TEN 90% SJS less than 10% body surface area detachment) but life threatening cutaneous adverse drug reactions. Drugs like antiepileptics (Phenobarbitone, phenytoin, lamotrigine), antibiotics (penicillin, cephalosporins, sulphonamides) anti gout drug allopurinol are considered as one of the most common causative factor for these serious ADRs.

SJS and TEN are potential adverse drug reactions. Most common offending drugs are antibiotics and Antiepileptics. Among antiepileptics Phenytoin is most common drug which frequently causes SJS and TEN. Removal of offending agents and treating the inflammation and hypersensitivity reactions with corticosteroids is best treatment for SJS and TEN.

Keywords: Adverse drug reaction, Steven Johnson syndrome, Toxic epidermal necrolysis, Phenytoin

1. Introduction

Stevens Johnson syndrome /toxic epidermal neurolysis (SJS/TEN) is a severe skin reaction most often triggered by particular medication. SJS represents the less severe end of disease spectrum and TEN represents the more severe end. SJS/TEN is a rare disease, affecting 1 to 2 per million people each year. [1] Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are diseases within the spectrum of severe cutaneous adverse reactions (SCAR) affecting skin and mucous membranes. Although different in clinical pattern, prognosis and etiology, erythema multiforme with mucosal involvement, also called erythema exsudativum multiforme majus (original term still used in Europe), erythema multiforme majus (EMM) or bullous erythema multiforme is part of this

spectrum. According to China National knowledge infrastructure (CNKI) and Wanting data base from 2006 -2016 among total of 166 patient, 70 were SJS, 2 were overlap of SJS/TEN and 94 were TEN. The most common offending drugs were antibiotics (29.5%), Anti Convulsant (24.1%). [2] Carbamazepine, Allopurinol, Probation and penicillins were the most common single offending drugs. The most common clinical manifestations of SJS/TEN Rashes, fever, oral ulcers, edema, eye symptoms, myalgia, oral mucosa involvement, genital involvement, Hepatitis, microscopic haematuria [3]. Treatment regimen includes Dexamethasone IV, Prednisolone oral, Antibiotics and fluid resuscitation [4]. In case reports and case series, a variety of drugs have been reported to be associated with SJS and TEN, but risk estimates for certain drugs and drug groups to induce SJS/TEN were not available before the epidemiological studies [5].

A. Case: 01

A 35 yr. old female patient came into the dermatology OPD with chief complaints of skin lesions, and fluid filled blisters for the last 1 day and oral lesions. before the patient was admitted in a public health care hospital for reason of seizures and had started treatment with phenytoin(IV). The patient had developed mild skin lesions within an hour which flared up in the last day with abdominal, oral, chest, both upper and lower limb involvement. Diagnosis was phenytoin-induced SJS made by the dermatologist. Patient is on T. Frisium 5mg, T. Leveteracetam. and patient had 1 episode of GCTS frothing+, tongue bite+, but there is no proper dermatological intervention at present.

On examination, she was conscious & coherent, her BP was 110/70mmHg, PR was 70/min, CVSS1S2+, R/S-BAE+ all other vitals were normal. She was provisionally diagnosed as phenytoin induced drug rash as she was on the anti-epileptic therapy. She was advised with MRI scan (brain), Complete Blood Picture, renal function test, EEG, & Liver function Tests.

On the second day her vitals were normal, PR: 76/min. On day 3, She was conscious/coherent, Bp: 110/70mmHg, PR: 76/min. On day 4 all her vitals were normal and she was advised with a high protein diet. On day 5 all her vitals were normal and

PR: 88/min. Based on her complaints of rash (fluid filled in nature), she was confirmed with phenytoin induced fluid filled blisters.

Here, the ADR in this patient can be confirmed by:

1. disappearance of the reaction progressing after stopping the administration of the suspected drug (phenytoin).
2. Recovery of the patient on withdrawal on the drug with other drugs give for the reaction developed.



B. Case: 02

A 44 years old male patient was admitted in dermatology inpatient department with chief complaints of fever since 5 days associated with chills and rigours, difficulty in swallowing, developed rashes all over the body since 1week. And known case of hypersensitive with old cerebral vascular attack with right hemiparesis, Patient was diagnosed with Toxic epidermal neuralgia phenytoin induced. Patient is on T. leveteracetram, Injury. monocef 1gm, Lactocalamime lotion. As patient developed rashes due to phenytoin levipril was added for treating seizures, other medications Moisol cream, Mucipain ointment, T. Chloroxidine was prescribed for skin interventions.

On examination, patient was conscious and coherent, B.P was 90/60 mmHg, P.R was 80mins CVS-S1S2+, P/A- Soft and all other vitals were normal. She was provisionally diagnosed as drug allergy and advised for Complete blood picture, liver function tests Renal function tests and ECG. On the next day patient was conscious and coherent -92 mins, B.P- 110/80 mmHg. On day 3 vitals were normal and soft diet was maintained, On day day 4 P.R -102, B.P-110/70mmHg, on day 5 P.R-108, B.P-110/70mmHg, On day 6 Patient was conscious and coherent, P.R-106mins, B.P- 110/70mmHg. Based on chief complaints of rashes all over patient was confirmed with phenytoin induced toxic epidermal neuralgia.

Here, the ADR in the patient can be confirmed by:

1. Disappearance of the reaction progressing after stopping the administration of the suspected drug (phenytoin).
2. Recovery of the patient on withdrawal on the drug with other drugs given for the reaction developed.

C. Case: 03

A 2 years old male child was admitted in paediatric ward with Chief compliant of seizures of generalised tonic clonic type associated with uprolling of eyes and complaint of ear discharge since 10 months and rash all over the body has developed rash has persisted for many days. And patient had history of head trauma one year ago and patient was diagnosed with Meningitis and phenytoin induced hypersensitivity reaction. Patient was on

Injection phenytoin 200mg in 20cc NS, injection ceftriaxone 500mg IV BD, injection amikacin 50mg IV BD, injection midazolam 1mg in 2cc NS, injection ranitidine 0.5c IV BD and injection dexamethasone 1.5mg. As patient was developed phenytoin induced rash sodium valproate was given as alternative treatment and calamine lotion was given for skin manifestation.

On examination child was drowsy, pulse rate- 153/min, RR- 24/min, CVS-S1, S2+ve, and RS- Bilateral air entry positive and blood pressure- 90/60mmHg and CNS tone- Normal. Child was provisionally diagnosed as meningitis and status epilepticus and rash due to drug allergy and advised for electro encephalogram, color doppler study of transcranial nerve, complete blood picture and serum electrolytes level and on second day child was conscious and coherent PR-102/min, Bp- 100/70mmHg, RR- 22/min and others vitals were stable. On 3-day child was conscious and BP- 100/70mmHg and RR- 24/min and other vitals were stable and on 4th day child was conscious and BP- 100/70mmHg and RR- 22/min, PR-98/min and other vitals were stable and child was kept on soft diet and on 5th day child was conscious all vitals were stable and pulse rate was 98/min. Based on compliant of rash all over the body child was confirmed with phenytoin induced skin rash.

Here the ADR in the patient was confirmed by:

1. Disappearance of reaction progression after stopping the administration of suspected drug (phenytoin).
2. Recovery of patient on withdrawal on the drug with other drugs given for the reaction developed.

2. Discussion



Steven Johnson syndrome and Toxic epidermal necrolysis are adverse hypersensitivity that affect the skin and mucous membrane [6]. They are described by characterized by erythematous macules and hemorrhagic erosions of the mucus membranes described by Adeegbenroo on trying John Dakota et al in 2018 [7]. Serious allergic cutaneous reactions especially SJS/TEN are major complications of antiepileptic drug therapy. Phenobarbital, Phenytoin, lamotrigine is most widely used anticonvulsants for seizure prophylaxis [8].

According to National Medical insurance review system in a total of 1,167(938 SJS and 229 TEN) we're newly diagnosed from 2010-2013.[9]The age and sex standardized annual incidences estimated in this study were 3.96 to 5.03 in SJS and

0.94 to 1.45 in TEN per million described Min -Suk Yang 2016.[10]

Females are more prone to SJS/TEN compare to men population. Single drug was to cause the adverse cutaneous reactions n patient don't have any history of drug intake prior to preceding the onset Stated by the Vinod k. sharma et. al. in 2008 [11]. cutaneous adverse reactions. Hypersensitivity to phenytoin is not unusual [12].

Phenytoin (or its prodrug, fosphenytoin) is a widely used medication for common types of epileptic seizures, especially when accompanied by focal brain lesions. Available in parenteral and oral forms, phenytoin is widely used. Despite the inherited risk of dose-related toxicity attributed to its zero-order pharmacokinetics, phenytoin is still considered a first-line therapy for some types of seizures [13].

Thus, therapeutic monitoring of a patient's phenytoin serum level is crucial to assure the safety and efficacy of phenytoin therapy stated by Qsama M. Al-Quteiment in 2016.

Usually, the acute phase lasts from 8 to 12 days. 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. 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 stated by Qsama M. Al-Quteiment in 2016 and Archana Vijendra in 2013 [13], [14].

A precise clinical history of the patient is needed to determine the presence of the drug in the body at the time of onset of the adverse reaction stated by Ratan J. Lihite in 2016 [15].

Early recognition and prompt treatment with corticosteroids might improve the outcome [16], [17]. Because of the variety and the rarity of adverse systemic reactions to AEDs, physicians initiating AEDs should counsel patients to notify their physician if they develop any new or unusual symptoms by Shereen Elazzazyin 2013 [18]. Also, patient education regarding the possibility of adverse drug reaction is essential. Rare association of myocarditis with or without SJS is to be kept in mind [19].

3. Conclusion

SJS and TEN are severe life threatening complications

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. Regular monitoring of such ADRs, educating physicians and patients can help in early diagnosis and prevent the development of serious consequences of this idiosyncratic reactions.

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