Case Report

PHENYTOIN INDUCED TOXIC EPIDERMAL NECROLYSIS (TEN) IN A STROKE PATIENT: A CASE REVIEW.

G. Ramya Naidu, Sushanta Kr. Das, Walli Mohammed, V Uma Maheswara Rao

Department of Pharm. D., CMR College of Pharmacy, Kandlakoya (V), Hyderabad, India

Submitted on: 17.08.2014 Revised On: 20.08.2014 Accepted on: 24.08.2014

Abstract:

Background: Some of the serious cutaneous Adverse Drug Reactions (ADRs) include Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and overlap category of SJS and TEN. Drugs are considered as one of the most common causative factor for these serious ADRs especially with Phenytoin. We present a patient who developed TEN after Phenytoin treatment.

Case report: A 50yr old female was admitted in female general medicine ward in Gandhi Medical College & Hospital, Secunderabad with complaints of rashes all over the body and unable to swallow & food intake for past 2 days. She is a known case of CVA with IC bleeding and was prescribed with Phenytoin for seizure one and half month before alongside regular medicine. She develops erythematous rash was all over the body (more than 70%) with mucosal (oral and conjuctival) involvement skin peeling of face. Aggressive symptomatic and supportive treatment was given for the management of TEN. Patient was discharged after 23days treatment in hospital

Conclusion: Although TEN is a rare toxicity it must always be considered during phenytoin therapy and such patient should be managed appropriately by implying standard guideline and by using procedure which have published previously so that patient care can be paramount.

Key words: Adverse Drug Reactions, Toxic Epidermal Necrolysis, Phenytoin.

Corresponding Author: Dr. G. Ramya Naidu. B. Pharm., Pharm. D. (PB)

Ph- +91-9949901098

Email: ramyapharmd66@gmail.com

Indian Research Journal of Pharmacy and Science; 2(2014) 117-123;
Journal home page: https://www.irjps.in

Introduction:

Cutaneous drug eruptions are most occurring complication of adverse drug reactions (ADRs) [1]. It affects around 2-3% of all hospitalized patients. Drugs are considered as one of the most common causative factor for these serious ADRs [2]. Some of the serious cutaneous ADRs include Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and overlap category of SJS and TEN. TEN is a life-threatening serious muco-cutaneous illness associated with high fever and confluent erythema followed by necrolysis where two or more mucosal sites are usually affected; whereas SJS is characterized by presence of flat, atypical target lesions and epidermal detachment is < 10% of total body surface area (BSA). Flat, atypical target lesions may also be seen with TEN (TEN with spots) and sometimes, extensive necrolysis can occur without target lesions (TEN without spots). In SJS-TEN overlap category, epidermal detachment is 10-30% of the total BSA. These reactions are often associated with significant mortality [3]. The drugs commonly concerned as the cause of SJS/TEN are Anticonvulsants, Sulfonamides, Non-steroidal anti-inflammatory drugs and Antibiotics [4][5]. In this case report we will discuss Phenytoin (Anticonvulsants) induced TEN occurred at a tertiary care teaching hospital.

Case discussion:

A 50 yr old female was admitted in the female general medicine ward in Gandhi Medical College & Hospital, Secunderabad on 28/12/2013 with complaints of rashes all over the body and unable to swallow & food intake for past 2 days.

On examination

Patient was-

- Disoriented
- Febrile
- Erythematous rash was positive all over the body with mucosal (oral and conjuctival) involvement
- Skin peeling of face was also found
- BP-130/90 mmHg, pulse rate-98 beats/min, cardiovascular sound-S_1&S_2 positive, lungs-bilateral air entry positive.

Past medical and medication history

She is a known case of hypertension for past 5 years and on Anti-hypertensive medication but taking irregular medication & developed cerebro vascular accident (CVA) with intra cranial bleeding before one and half month (14/11/2013) along with weakness in both right upper & lower limb, deviation of mouth to left side, several episodes of vomiting and 2 episodes of seizures. She was prescribed with following medication for 30 days:

1. Tab. Atorvastatin 20 mg od hs
2. Tab. Ramipril 5 mg bid pc
3. Tab. Amlodipine 5 mg od pc
4. Tab. Citicoline 500 mg bid pc
5. Tab. Phenytoin 100 mg 1tab in morning – 2tabs in night
6. Tab. Folic acid 5 mg od pc
7. Protein-X powder 2tsf bid mixed with milk

After review all information regarding the patient, she was provisionally diagnosed as: **?drug induced SJS may be due to Phenytoin.**

On admission she was prescribed with

1. Intravenous fluid; DNS 2 pint & RL 1 pint
2. Intravenous fluid; D25 tid

3. Inj. Dexamethasone 8mg iv bid
4. Lot. Calamine for local application
5. Tab. Atorvastatin 20 mg od hs
6. Inj. Ranitidine 50 mg iv bid
7. Inj. Optineuron (Vit. B-Complex) 3ml in 125 ml normal saline od
8. Inj. Ceftraxone 1gm iv bid
9. Inj. Paracetamol 500 mg iv bid

Laboratory test results

Shows abnormalities in Hemoglobin - 10.5 gm/dl (11.0 -16.5 gm/dl), RBC – 3.4 X 10^6 / mm^3 (3.8 – 5.8 X 10^6 / mm^3), WBC – 11.0 X 10^3 / mm^3 (3.5 – 10.0 X10^3/ mm^3) and HCT – 31.4 % (35.0 – 44.1 %) other parameters were normal.

Same medication was continued for the next day. On day 3rd (30/12/2013) patient was referred to dermatologist for consultation and was finally diagnosed as **Phenytoin induced TEN** & advised to keep under medical care. Dermatologist added Soframycine cream (Framycetin Sulphate) bid & Saline compress along with existing prescription. On day 4th (31/12/2013) patient was afebrile, disoriented and lip bleeding was positive. Paracetamol was removed and Zytee gel (Benzalkonium chloride + Coline salicylate) was added in the existing medications. From day 5th to day 11th (01/01/2014 to 07/01/2014) patient was stable, general condition was fair; bleeding was decreased and was responding to verbal communication. Same medications were continued for this period. On day 12th (08/01/2014) patient was normal and same medication was continued with addition of Tab.Vitamin C 500 mg od. Same treatment was continued for next day (13th day) also (09/01/2014). On day 14th (10/01/2014) patient general condition was fair and erythematous rash was cured so calamine lotion was stopped from the prescription. On the same day patient visited to the dermatologist again and was found to be bleeding present with lips other were normal at diagnosis and was prescribed freshly with following prescription.

1. Inj. Dexamethasone 4mg iv bid for 2days, followed by 4mg iv od for 2days, followed by 2mg iv od and stopped.
2. Cream Moizen (soft paraffin + light liquid paraffin), application over lips
3. Cream. Fusiderm-H (Fusidic acid + hydrocortisone), application over lips
4. Liquid paraffin, for eye application morning and evening.

From day 15th to 20th (11-01-2014 to 17-01-2014) patient general condition was fair with lip bleeding was continuous, and same prescription was continued by gradual decreasing the Dexamethasone dose and by addition of Cefotaxim 1gm iv bid, Metronidazole infusion iv bid and Ranitidine 150 mg iv bid. On day 21st (18-01-2014) patient re-visited dermatology department and was found to be recovering from the TEN with no fresh lesion present and hypo&hyper pigmentation all over the body. Patient was freshly prescribed with the following prescription.

1. Cream Moizen (soft paraffin + light liquid paraffin), application over lips
2. Cream. Fusiderm-H (Fusidic acid + Hydrocortisone), application over lips
3. Liquid paraffin, for eye application morning and evening.
4. Tab. Ciprfoxacin 500 mg bid
5. Tab. Vitamin C 500 mg od

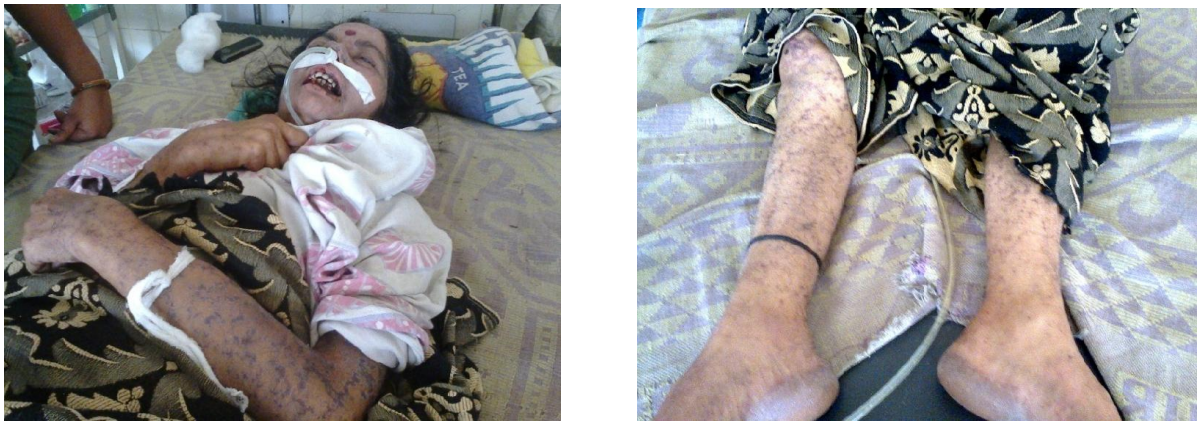
Same medication was continued for next day (22nd day) 19-01-2014 as patient was normal and ready for discharge. On day 23rd (20-01-2014) patient was fit to discharge as no further complains regarding skin eruption was present. Following are discharge medication prescribed for 2weeks and asked for

revisit in dermatology out-patient.

Discharge medication:

1. Cream Moizen (Soft paraffin + Light liquid paraffin), application over lips
2. Cream. Fusiderm-H (Fusidic acid + Hydrocortisone), application over lips
3. Liquid paraffin, for eye application morning and evening.
4. Tab. Pantoprazole 40mg od before breakfast.
5. Tab. Vitamin C 500 mg od
6. Tab. B-complex

Picture:



Pic 1. Picture shows rashes all over the body

Pic.2 Picture shows lip bleeding and facial skin peeling.

Discussion:

As drugs are most common causes of SJS and TEN it is top most priority to identify the medication causing the condition and stopping the drug as early as possible. Necessary precautions should be adopted to prevent re-occurrence from unintended re-challenge [6]. Previous study also reported that, short term usage of Phenytoin increase the risk of SJS and TEN for a period of less than eight week. In such cases, offending drug should be withdrawn [7]. The time between fist administration and development of SJS/TEN is 1-4 weeks in majority of cases [8]; this is same in this case, where TEN has developed due to Phenytoin within 4 weeks of therapy.

Some report suggests steroids are treatment of choice in severe cases, to limit the inflammatory process, along with prophylactic systemic and topical antibiotics. However, in cases of Phenytoin reactions, Carbamazepine, and Phenobarbitone should be avoided as they can cross react in such patients [9]. Same as this case, where Dexamethasone were used along with systemic antibiotics as the situation was critical and aggressive therapy were required to manage the situation.

SJS/TEN is a life threatening condition and therefore supportive care is an essential part of the therapeutic approach. A multicenter study conducted in the USA, and including 15 regional burn centers with 199 admitted patients, showed that survival rate - independent of the severity of disease (APACHE-score and TBSA=Total body surface area) - was significantly higher in patients who were transferred to a burn unit within 7 days after disease-onset compared with patients admitted after 7 days (29.8% vs 51.4% ($p < 0.05$)). This positive association of early referral and survival has been confirmed in other studies [10]. Same in our case patient got admitted within two days of onset of cutaneous adverse reactions which has saved the life of the patient.

Few other reports also suggests the treatment as mainly supportive with removal of the precipitating agent, good nursing care preferably on a ripple bed, care of the eyes and mouth to prevent scarring and infection and maintenance of fluid and electrolyte balance. Patient should be put on a high protein diet 2-3 gms/kg daily. Naso-gastric feeding is preferable in severely ill patients [8]. In this case patient was also provided with supportive therapy as cream for skin lesion and other bleeding. Fluid supplement and protein powder was also added in the prescription as per reported, additionally appropriate nursing care as saline compresses for skin lessions and ryles tube was fitted for naso-gastric feeding.

Recovery is slow over a period of 14-28 days and relapses are frequent. There is a tendency for scarring in all but the mildest of cases. Mortality is 25%-50% and rises with age, being more than 50% above 60 years of age. Half the deaths occur due to secondary infection. Pulmonary edema, pulmonary embolism and gastrointestinal hemorrhage are other important causes of mortality. Reticulate skin pigmentation may occur over the affected areas [6]. In this case it reflects the same which is reported earlier, as it took total 23 days for the patient being discharge from hospital.

Conclusion:

Our case emphasizes that, physicians should be aware of the potentially life threatening complications of Phenytoin like TEN, which is a common prescribing habit. And such patient should be managed appropriately by implying standard guideline and by using procedure which have published previously so that patient care can be paramount.

Acknowledgement:

We sincerely convey our thanks and regards to the entire staffs of Department of General Medicine, Gandhi Medical College & Hospital, Secunderabad for their constant support and help during the period of this case collection. Without their help this work could not be completed at all.

Authors contribution:

Author # 1 and 3 were completely involved in collection of case and related documents for the write-up process.

Author # 2 have been involved in drafting the manuscript critically for important intellectual content .

Author # 4 have given final approval of the version to be published.

Informed consent form:

Informed consent form obtained from the patient for publication. A copy of consent form is available with author.

Reference(s):

1. Sharma. V.K., Sethuraman. G., Kumar. B., **Cutaneous adverse drug reaction patterns to antimicrobial drugs in North India.** *J Assoc Physicians India* 1998; 46:1012-5.
2. Sharma. V.K., Sethuraman. G., **Adverse cutaneous reactions to drugs: An overview.** *J Postgrad Med* 1998; 42:15-22
3. Bastuji-Garin. S., Rzany. B., Stern. R.S., Shear. N.H., Naldi. L., Roujeau. J.C., **Clinical classification of cases of toxic epidermal necrolysis, Stevens Johnson Syndrome and erythema multiforme.** *Arch Dermatol* 1993; 129:92-6.
4. Roujeau. J.C., Guillaume. J.C., Fabre. J.P., Penso. D., Flechet. M.L., Girre. J.P., **Toxic epidermal necrolysis (Lyell syndrome). Incidence and drug etiology in France, 1981-1985.** *Arch Dermatol* 1990; 126:37-42.
5. Chan. H.L., Stern. R.S., Arndt .K.A., Langlois. J., Jick. S.S., Jick. H., *et al*., **The incidence of erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.** Arch *Dermatol* 1990; 126:43-7.
6. Roujeau. J.C., Chosidow. O., Saiag. P., Guillaume. J.C., **Toxic epidermal necrolysis (Lyell's syndrome).** *J Am Acad Dermatol* 1990; 23**:**1039-1058.
7. Revuz. J., Penso. D., Roujeau. J.C., **Toxic epidermal necrolysis: clinical findings and prognostic factors in 87 patients.** *Arch Dermatol* 1987; 123**:**1160-1165.
8. Roujeau. J.C., Revuz. J., **Recent advances in dermatology.** 8th edition. Edited by Champion RHPye RJ. Churchill-Livingstone. 1990. 85-99.
9. Ahmad. F.U., Mahapatra A.K., **Phenytoin-induced toxic epidermal necrolysis in a neurosurgical patient.** *Neurol India* 2007; 55:181-2.
10. Thomas .Harr., **and** Lars. E. French. , **Toxic epidermal necrolysis and Stevens-Johnson syndrome**. *Orphanet Journal of Rare Diseases* (Review) 2010, 5:39.

List of abbreviation:
BP – Blood Pressure.

Inj – Injection

Tab – Tablet

Lot – Lotion

mg – milligram

kg – kilogram

od – once in a day

bid – bis-in-die (two times a day)

pc – post cibos (after meal)

hs – horra somni (at bed time)

D25 – Dextrose 25%

DNS – Dextrose Normal Saline

RL – Ringer's Lactate 25%

APCHE - Acute Physiology and Chronic Health Evaluation

Conflict of Interest Reported: Nil; Source of Funding: None Reported