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Case Report

Phenytoin induced toxic epidermal necrolysis: a case report

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ABSTRACT

Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), are severe idiosyncratic reactions characterized by fever and mucocutaneous lesions leading to necrosis and sloughing of the epidermis. The usage of anticonvulsants like carbamazepine, phenytoin, lamotrigine, phenobarbital are associated with high risk for occurrence of TEN. We present a case of toxic epidermal necrolysis in a 30 year old female probably induced by phenytoin. A 30 year old female was admitted to the emergency medicine department of KIMS hospital, Bengaluru. Lesions over the lips and oral cavity, multiple fluid filled blisters were present diffusely all over the body. Patient had a past history of oral cavity lesions with injection phenytoin. Patient is a known epileptic of over 12 years and was on treatment. Patient had a seizure attack 3 days back and visited nearby hospital and did not inform the doctor of her allergy to phenytoin. Patient was given inj phenytoin after which she developed oral lesions and also presented with fluid filled bullae all over the body. A diagnosis of toxic epidermal necrolysis was made based on clinical history and Scoreten score and was treated with betadine wash, fluconazole and antibiotics .The lesions improved significantly with the above management and patient recovered enough to be discharged from the hospital after 5 days. Severe and serious reactions such as toxic epidermal necrolysis can be caused by commonly used drugs like phenytoin.

Keywords: Adverse drug reaction, Hartwig's severity assessment scale, Naranjo's adverse drug reaction probability scale, Phenytoin, Scoreten score, Toxic epidermal necrolysis

INTRODUCTION

Stevens Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are severe idiosyncratic reactions characterized by fever and mucocutaneous lesions leading to necrosis and sloughing of the epidermis. The percentage of epidermal detachment is the primary differentiating factor, SJS presenting with <10% epidermal detachment and TEN presenting with >30%; while cases between 10% and 30% of involvement are defined as SJS-TEN overlap. The usage of anticonvulsants like carbamazepine, phenytoin, lamotrigine, phenobarbital are associated with high risk for occurrence of TEN. Incidence rate of Phenytoin induced mucocutaneous reactions is 13.37% in India . More than 90% of SJS and TEN cases occurred in the first 63 days of anti- epileptic drug use.[1] This study present a case of toxic epidermal necrolysis in a 30 year old female probably induced by phenytoin.

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. Thus, therapeutic monitoring of a patient's phenytoin serum level is crucial to assure the safety and efficacy of phenytoin therapy.[2]

CASE REPORT

A 30 year old female was admitted to the emergency medicine department of KIMS hospital, Bengaluru. Lesions over the lips and oral cavity (Figure 1), lesions over the upper extremities (Figure 2) , multiple fluid filled blisters were present diffusely all over the body (Figure 3).

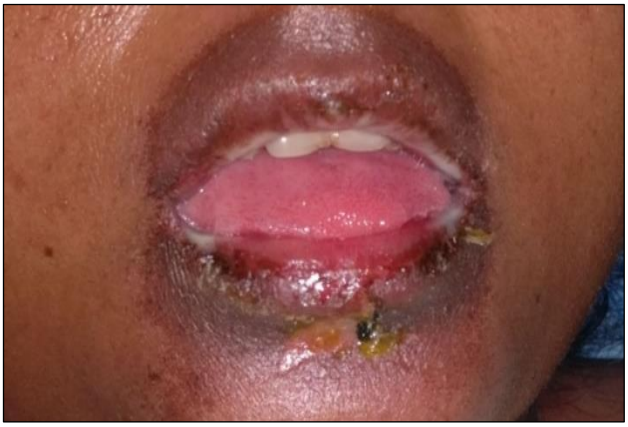

Figure 1: Lesions over the lips and oral cavity.

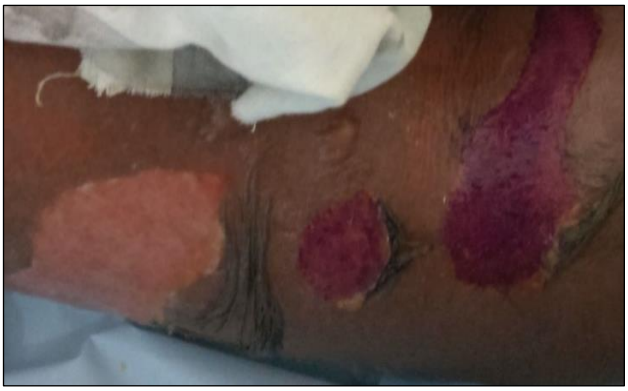

Figure 2: Lesions over upper extremities.

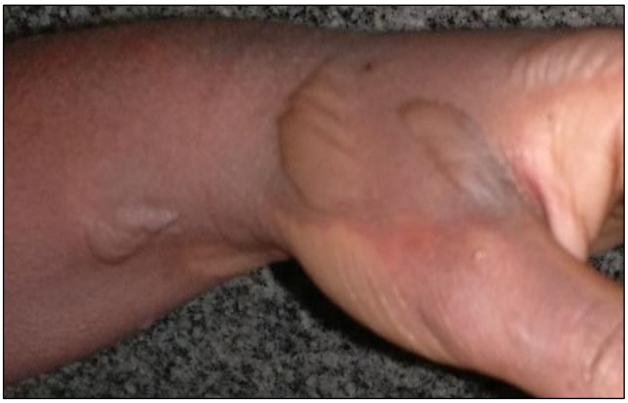

Figure 3: Fluid filled blisters over extremities.

Patient had a past history of oral cavity lesions with injection phenytoin. Patient is a known epileptic of over 12 years and was on treatment. Patient had a seizure attack 3 days back and visited nearby hospital and did not inform the doctor of her allergy to phenytoin. Patient was given inj phenytoin after which she developed oral lesions and also presented with fluid filled bullae all over the body. A diagnosis of toxic epidermal necrolysis was made based on clinical history and Scoreten score and was treated with betadine wash, fluconazole and antibiotics . The lesions improved significantly with the above management and patient recovered enough to be discharged from the hospital after 5 days.

DISCUSSION

Toxic epidermal necrolysis (TEN) and Steven Johnson Syndrome (SJS) are considered to be two ends of a spectrum of severe, life threatening epidermolytic cutaneous adverse drug reactions, differing only by their extent of skin detachment. Anticonvulsants like phenytoin are a major cause of TEN and other severe cutaneous reactions. Symptoms of toxic epidermal necrolysis are mostly cutaneous to start with and may involve mucous membranes and further body systems if not addressed. We have attempted to co-relate the findings in our patient with the available facts related to the same. In our study the Scoreten score is 2 (Table 1), Naranjo's causality assessment is probable (Table 2), WHO-UMC causality assessment is probable/likely (Table 3), Hartwig's severity assessment scale was level 5- severe (Table 4), and Schumock and Thornton preventability scale- definitely preventable (Table 5).

Table 1: Severity-of-illness score for ten.[3]

Scoreten score	Score
Age more than 40 years	0
Malignancy	0
Heart rate >120/minute	0
Initial epidermal detachment >10% of BSA	1
Serum urea level >28 mg/dl (40 mg/dl in Indian settings)	0
Serum bicarbonate levels <20 mEq/dl.	1
Serum glucose levels >250 mg/dl	0
Total score	2

The probability of death predicted by this score : 0-1 points-3%; 2 points-12%; 3 points-35%; 4 points-58%; 5 to 7 points-90%

Table 6 gives an analysis of the ADR. 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]. Thereby, it is recommended to first screen the patients for this particular allele before starting with antiepileptic drugs. 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[7]. Study conducted by Sheer et al, revealed that CYP 450 is involved in the metabolism of phenytoin and a defect in epoxide hydrolases lead to accumulation of reactive metabolites like arene oxides [8]. 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 had a known allergy to phenytoin. Such medication errors due to negligence account for about 1% of all hospital admissions which could be prevented.

Table 2: Naranjo's ADR causality assessment.[4]

Question	Yes	No	Do not know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	1
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	1
4. Did the adverse event reappear when the drug was re-administered?	+2	-1	0	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	0
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	1
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	0
Total				5

Score: ≥9=definite ADR; 5-8=probable ADR; 1-4=possible ADR; 0=doubtful AD

Table 3: WHO-UMC Causality assessment.[4]

Causality term	Assessment criteria*
Certain	Event or laboratory test abnormality, with plausible time relationship to drug intake
	Cannot be explained by disease or other drugs
	Response to withdrawal plausible (pharmacologically, pathologically
	Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon)
	Rechallenge satisfactory, if necessary
Probable/ likely	Event or laboratory test abnormality, with reasonable time relationship to drug intake
	Unlikely to be attributed to disease or other drugs
	Response to withdrawal clinically reasonable
	Rechallenge not required
Possible	Event or laboratory test abnormality, with reasonable time relationship to drug intake
	Could also be explained by disease or other drugs
	Information on drug withdrawal may be lacking or unclear
Unlikely	Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)
	Disease or other drugs provide plausible explanations
Conditional/ unclassified	Event or laboratory test abnormality
	More data for proper assessment needed, or
	Additional data under examination
Unassessable/ unclassifiable	Report suggesting an adverse reaction
	Cannot be judged because information is insufficient or contradictory
	Data cannot be supplemented or verified

Table 4: Hartwig's severity assessment scale.[5]

Level	Assessment scale
Level 1	An ADR occurred but required no change in treatment with the suspected drug.
Level 2	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment requirement was required. No increase in length of stay (LOS).
Level 3	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. AND/OR an Antidote or other treatment was required. No increase in length of stay (LOS).
Level 4	Any level 3 ADR which increases length of stay by at least 1 day (OR) The ADR was the reason for admission.
Level 5	Any level 4 ADR which requires intensive medical care.
Level 6	The adverse reaction caused permanent harm to the patient.
Level 7	The adverse reaction either directly or indirectly led to the death of the patient.

Mild = level 1 and 2; Moderate = level 3 and 4; Severe = 5, 6 and 7

Table 5: ADR preventability assessment.

Definitely preventable	
1	Was there a history of allergy or previous reactions to the drug?- YES
2	Was the drug involved inappropriate for the patient's clinical condition?
3	Was the dose, route or frequency of administration inappropriate for the patient's age, weight or disease state?
4	Was a toxic serum drug concentration (or laboratory monitoring test) documented?
5	Was there a known treatment for the adverse drug reaction?
Probably preventable	
6	Was required therapeutic drug monitoring or other necessary laboratory tests not performed?
7	Was a drug interaction involved in the ADR?
8	Was poor compliance involved in the ADR?
9	Were preventative measures not prescribed or administered to the patient?
Not preventable	
1	If all above criteria not fulfilled

Table 6: Analysis of the ADR.

Parameters	
Causality - Naranjo	Probable
Causality - WHO-UMC	Probable/likely
Severity - Hartwig	Severe
Preventability- Schumock and Thornton	Definitely preventable

CONCLUSION

TEN is a severe life threatening complication associated with use of anticonvulsants like phenytoin which may have familial tendency. As the adverse systemic reactions to antiepileptic drugs (AEDs) are rare and severe, physicians should counsel patients on the importance of notifying their physician if they develop any unusual symptoms. 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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