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Case Report

A case of phenobarbitone induced Stevens-Johnson syndrome-toxic epidermal necrolysis along with its causality assessment

Rohit K. Singh[1]*, Rakhi Rani[1], Vikas Shankar[2], Rani I. Sinha[1]

[1]Department of Pharmacology, [2]Department of Skin and VD, Patna Medical College, Patna, Bihar, India

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***Correspondence:**
Dr. Rohit K. Singh,
Email: rohitksingh91@gmail.com

ABSTRACT

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse drug reaction, which are mainly caused by drugs; and these are usually associated with high degree of morbidity and mortality. They are characterized by mucocutaneous tenderness and typically haemorrhagic erosions, erythema and more or less severe epidermal detachment as blisters and areas of denuded skin. High risk drugs for the development of SJS-TEN include phenobarbitone, phenytoin, carbamazepine, lamotrigine, nevirapine, NSAIDs, allopurinol, and cotrimoxazole. A 33 years old female patient came to skin and venereal diseases (VD) outpatient department (OPD) with complaints of painful skin lesions. She was apparently symptom free 15 days back. Then she took tablet phenobarbitone 60 mg, BD as her anti-epileptic treatment. After 12-13 days of taking the drug, she developed erythematous papules associated with itching over her both forearm, face, chest, abdomen, back and lower limbs bilaterally which rapidly progressed to fluid-filled blisters that ruptured to form painful erosions and desquamation of skin all over the body. The patient was managed by withdrawal of phenobarbitone and conservatively, and the patient recovered successfully. The causality of phenobarbitone in this reaction was "probable" as per Naranjo scale. Seriousness of the reaction was "prolonged hospitalization". Phenobarbitone is one of the most common causative agents of SJS and TEN. The main stay of treatment is immediate withdrawal of causative agent along with supportive care.

Keywords: Phenobarbitone, Stevens-Johnson Syndrome, Toxic epidermal necrolysis, Adverse drug reaction

INTRODUCTION

Stevens-Johnson Syndrome (SJS)-toxic epidermal necrolysis (TEN) is the spectrum of severe, acute, mucocutaneous, T-cell mediated delayed type-IV hypersensitivity reaction. SJS and toxic epidermal necrolysis are mainly caused by drugs and these are associated with high degree of morbidity and mortality. SJS is characterized by involvement of <10% body surface area; SJS-TEN overlap signifies 10-30% involvement, and TEN characterizes involvement of >30% body surface area. This spectrum of disease typically appears 1-3 weeks after the beginning of therapy. More than 100 medicines have been implicated in this syndrome.[1] The incidence of TEN is 2 cases per million person per year.[2] Phenobarbitone is known to cause hypersensitivity reactions ranging from a mild to moderate rashes to life-threatening reactions such as SJS/TEN. TEN is an exfoliative disease and results in full-thickness damage to the epidermis, characterized by a widespread bullae formation with epidermal necrosis of the skin and mucous membrane. TEN mainly occurs in adults and is often attributable to drug sensitivity and considered to be a severe form of SJS.[3]

The relative risk for aromatic anti-epileptic drugs to cause Stevens-Johnson Syndrome and toxic epidermal necrolysis is 11 to 15.[4] It is also noted that more than 90% of SJS and TEN cases have occurred in the first 63 days of anti-epileptic drugs use.[5] Here I am reporting a case of phenobarbitone induced SJS-TEN overlap in a 33 years

old female patient in skin and VD department, Patna Medical College and Hospital, Patna.

CASE REPORT

A 33 years old female patient came to skin and VD OPD, Patna Medical College and Hospital, Patna on 02 August 2022 with complains of painful skin lesions as shown in Figure 1. She was apparently symptom free 15 days back, then she took tablet phenobarbitone, 60 mg, BD, as her anti-epileptic treatment. Then she developed erythematous papules associated with itching all over the body which rapidly progressed to fluid-filled blisters that ruptured to form painful erosions and desquamation of skin all over the body. Immediate withdrawal of the drug was done and the patient was admitted in intensive care unit (ICU). The patient was managed by intravenous (IV) fluids, IV antibiotics, wound care and with tapering dose of steroid. There was between 10% to 30% body surface area involvement, and so it was SJS-TEN overlap.

The causality assessment of the reaction was done by Naranjo scale.

To establish the likelihood of relationship between the drug and the SJS-TEN, Naranjo scale was used. The Naranjo algorithm or ADR probability scale is a method used to assess whether there is a causal relationship between an identified untoward clinical event and a drug using a simple questionnaire to assign probability score. The scoring by Naranjo scale is given in Table 1.

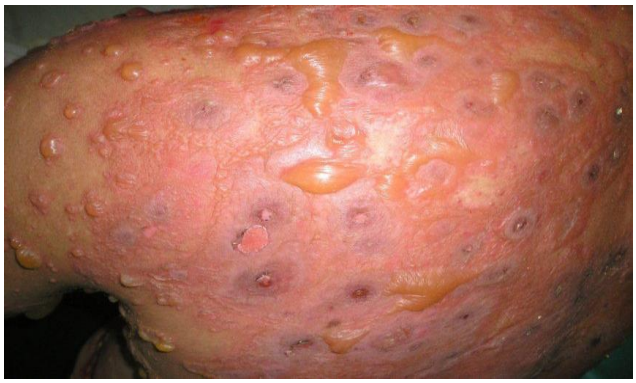

Figure 1: Stevens-Johnson syndrome- toxic epidermal necrolysis overlap.

Table 1: Scoring by Naranjo scale.

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

DNK: Do not know

Here total score is 6. Interpretation of scores in Naranjo scale- total score ≥9: definite, total score 5-8: probable, total score 1-4: possible, and total score <0: doubtful. The causality of phenobarbitone in this reaction as per Naranjo scale was "probable". Seriousness of the ADR was "prolonged hospitalization".

DISCUSSION

Phenobarbitone is used in the treatment of all types of seizures, except absence seizure. Phenobarbitone may provide a clinical advantage over carbamazepine for treating partial onset seizure. Carbamazepine may provide a clinical advantage over phenobarbitone for generalized onset tonic-clonic seizure. Sedation and hypnosis are the principal side effects of phenobarbitone. Central nervous system effects, such as dizziness, nystagmus and ataxia, are also common. In elderly patients, it may cause excitement and confusion, while in children, it may result in paradoxical hyperactivity.

Toxic epidermal necrolysis is associated with drug exposure in up to 90% of the cases. These drugs include: anti-convulsants, antibiotics, and NSAIDs.[6] In the present case, the female was started on phenobarbitone, one of the common drugs associated with SJS-TEN. Likewise, other anti-epileptic drugs (AEDs) were also incriminated with

this deadly hypersensitivity skin reaction. Few of these AEDs include phenytoin, carbamazepine, and lamotrigine.[7] Therefore, clinicians should be aware of these drugs which are highly associated with SJS-TEN and should replace with drugs associated with lower skin hypersensitivity reactions. Skin and liver are the most affected organs by TEN. However, present case had no clinical signs of liver injury.

TEN is a multi- organ disease that not only affects the skin and mucous membrane, but also several internal organs. Therefore, a multi- disciplinary approach is required. In a first step, immediate withdrawal of potentially causative agent, ideally in the early stages of the disease, is mandatory to reduce fatality in SJS-TEN. In addition, supportive cares such as fluid replacement, wound care, and nutritional support is recommended.[8] In the present case, the identified offending drug was phenobarbitone, which was immediately stopped. In addition, the patient was given fluid replacement, intravenous antibiotics, and daily wound care. The patient was recovered successfully and discharged after 10 days of admission.

CONCLUSION

SJS and toxic epidermal necrolysis are very common due to phenobarbitone and other anti-epileptic drugs containing aromatic amine group in their structure. Anti-epileptic drugs are vital in controlling the seizure attack in epileptic patients. Thus, it is important for the clinicians to be familiar with AEDs associated with highest incidence of SJS- TEN. These include carbamazepine, lamotrigine, phenobarbitone, phenytoin and valproic acid. Therefore, before prescribing these AEDs, it is important to ask history of drug allergy, atopic history, and family history of allergy to avoid occurrence of delayed hypersensitivity such as SJS- TEN.

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