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Original Article

Dermatology Section

# Morphological Pattern of Cutaneous Adverse Drug Reactions due to Antiepileptic Drugs in Eastern India

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## ABSTRACT

**Introduction:** Cutaneous manifestations of adverse drug reactions are a common occurrence and need to be differentiated from other causes of similar manifestations. Antiepileptic drugs (AED) usually are responsible for severe cutaneous adverse drug reactions (CADR) like Stevens-Johnson Syndrome/Toxic epidermal necrolysis (SJS/TEN) and drug rash with eosinophillia and systemic symptoms (DRESS). There is paucity of published research regarding morphological pattern of CADR due to various antiepileptic drugs AED.

**Objective:** To study the morphological patterns of CADR due to AED and common anticonvulsant drugs implicated particularly in severe CADR such as SJS/TEN and DRESS in a tertiary care teaching hospital in eastern India.

**Materials and Methods:** A prospective, observational study was conducted over a period of 4 years from August 2009 to July 2013 after the approval of the Institutional Ethics Committee using self-reporting method for selection of cases.

**Settings:** All patients with CADR after AED consumption for various conditions presenting to the Dermatology outpatient department (OPD) and Pediatric OPD and Indoor patients of a tertiary care teaching hospital located in Rohtas district of Bihar were included in this study.

**Results:** During the study period, 64 cases of severe CADRs were included in this study. Out of 64 patients, 28 were male and 36 were female with mean age 36.1 years (range 6 years to 72 years). Most common AED implicated for CADR was Phenytoin. Maculopapular rash was the most common cutaneous manifestation of ADRs (42.85%). Serious CADR like TEN and SSJS were more likely in patients prescribed Phenytoin and Carbemazepine simultaneously.

**Conclusion:** CADRs are a common occurrence and awareness about the same is essential for diagnosis and prevention. This study identified combined use of phenytoin and carbamezepine as a most important risk factor for serious CADR like SJS and TEN.


**Keywords:** Stevens-Johnson Syndrome/Toxic epidermal necrolysis, Maculopapular rash

## INTRODUCTION

CADR is an unexpected, undesired, and unintended or a toxic consequence of drug administration. CADRs are common comprising 10-30% of all reported ADRs [1,2] and its incidence in hospitalized patients is estimated to be 2-3 % [3]. Cutaneous ADRs (CADRs) are among the most frequent ADRs. Studies have found the incidence of CADRs in developed countries as 1–3%, while the incidence in developing countries is supposed to be higher between 2 and 5% [4,5]. Certain patient groups like patients on anti epileptic drugs seem to be at increased risk of developing a cutaneous drug reaction. The incidence of developing a cutaneous reaction increases with the number of the drugs taken [6].

The pattern of CADR and their causative anticonvulsant drugs vary greatly among the different populations previously studied in Europe, Israel and Asia [2-9]. Although the majority of CADR are mild and self limiting, severe CADR such as SJS/TEN and DRESS are associated with significant mordality and mortality [10].

There are paucity of published research from developing countries like India regarding morphological pattern of CADR due to various AED. We conducted this study to know the morphological patterns of CADR due to AED and common anticonvulsant drugs implicated particularly in severe CADR such as SJS/TEN and DRESS in a tertiary care teaching hospital in eastern India. Safe use of the drugs is the responsibility of health care professional and a proper knowledge of adverse cutaneous drug reaction related information may be helpful in prevention of it.

## MATERIALS AND METHODS

This prospective, observational study was conducted over a period of four years from August 2009 to July 2013 after the approval of the Institutional Ethics Committee at a tertiary care teaching hospital located in Rohtas district of Bihar, Eastern India using self-reporting method for selection of cases.

Sixty Four (64) patients with CADR after AED consumption for various conditions presented to the Dermatology OPD and Pediatric OPD and Indoor patients of a tertiary care teaching hospital located in Rohtas district of Bihar, Eastern India were included in this study.

### Inclusion Criteria

Only those patients with some CADR who was taking Anti epileptic drugs like phenytoin, carbamazepine, sodium valproate either alone or in combination.

### Exclusion Criteria

Patients with CADRs due to other drugs.

## STATISTICAL ANALYSIS

The mean age expressed in mean (range). Data were analysed using Open Epi free statistical software version 2.3.1.

Drug reactions due to different drugs involve different organs including skin. Sometime acute drug reaction may occur as anaphylactic shock leads to death, where as only mild skin lesion with itching, therefore extent of severity vary with different drugs

and individuals. One drug may cause urticaria in one person and may cause SJS in another person. It is very unpredictable to say that, which drug causes what type of reaction. In a case of CADR, through history and clinical examination is an essential part to reach a diagnosis. Today anti epileptic drugs used not only by neuro-physician but general physician and untrained persons in remote areas without knowing adverse effects.

Exact pathophysiology responsible CADR not known but following are some of the most likely probable pathogenesis responsible for CADR:

1. It is in genetically suscitable patients, immunologically mediated. It has HLA association (HLA 1502 particularly in Chinese peoples and Indian also).
2. It is also found in glutathion depleted keratinocytes (genetically determined).Therefore pattern of cutaneous manifestation depends on drug bioactivity and detoxification capacity.
3. Hydroxylamine – Keratinocytes adducts can trigger MCH dependent clonal proliferation of T- cell lymphocytes.

AED – Oxidation by cytochrome p-450 Reactive arene oxide metabolites.

Epoxide hydrolase detoxified metabolites - Deficiency of enzyme-Loss of detoxification - Accumulation of reactive metabolites - T cells are target of these metabolites & Trigger cellular injury in genetically susceptible patients- inflammatory mediators including interleukins & TNF – alfa- Epidermal keratinocytes & mucosal cell injuries leads to cutaneous manifestations develop.

**AED associated with following specific morphological patterns:**

(1) Exanthematous (morbiliform), (2) Erythema multiforme, (3) Photosensitivity, (4) Urticaria, (5) Erythroderma, (6) SJS, (7) Toxic epidermal necrolysis, (8) Hyperpigmentation, (9) Vasculitis.

## RESULTS

During the study period, 64 cases of severe CADRs were included in this study. Out of 64 patients, 28 were male and 36 were female with mean age 36.1 years (range from 6 years to 72 years). Characteristics of the all 64 patients with severe CADR. In this study most common cause for AED use was generalized/ Idiopathic seizure in 31 patient (48.4%), as shown in [Table/Fig-1].

Specific clinical pattern due to anti epileptic drugs SJS found in 34% of total patients. Maculopapular rash and TEN in 25% of total patients. Urticaria, erythema and photosensitivity in 3.2% each in total patients. Vasulitis found in 6.4% of total patients as shown in [Table/Fig-2].

Phenytoin caused severe CADRs like SJS/TEN in 8 patients out of 22 patients in own group and 5.12% of total patients as shown in [Table/Fig-3]. Patients with CADR used only Carbamazepine as AED cause SJS, TEN, maculopapular rash, urticaria, and vasculitis in 6, 4, 2, 2, and 2 patients respectively out of 18 patients. Carbamazepine alone produce SJS in 6 patients (33%) only and TEN in 4 (28%) patients out of 16 patients. Sodium Valproate alone causes maculopapular rash and SJS in 2 patients each.

Combination of cabamazepine and phenytoin produces more frequent and severe reaction. SJS/TEN found in 9 patients (75 %) out of 12 patients as shown in [Table/Fig-4]. Combination of Phenytoin and sodium valproate caused SJS in 50% patients with severe CADR (4 /8) and maculopapular rash in one patient with CADR (1/8).

| Conditions | Numbers |
|---|---|
| Generalized seizure | 31 |
| Post traumatic/Post neurosurgery | 11 |
| Complex partial seizure | 4 |
| Trigeminal neuralgia | 08 |
| Post herpetic neuralgia | 06 |
| Migraine | 04 |

**[Table/Fig-1]:** Diseases for which drugs uses

| Sl No. | Specific Clinical Pattern | No. | Percentage |
|---|---|---|---|
| 1 | Steven Johnson Syndrome | 22 | 34% |
| 2 | Maculopapular rash | 16 | 25% |
| 3 | Toxic epidermal necrolysis | 16 | 25% |
| 4 | Urticaria | 02 | 3.2% |
| 5 | Erythroderma | 02 | 3.2% |
| 6 | Photosensitivity | 02 | 3.2% |
| 7 | Vasculitis | 04 | 6.4% |

**[Table/Fig-2]:** Specific clinical patterns

| Drugs | No. of patients |
|---|---|
| Phenytoin | 22 |
| Carbamazepine | 18 |
| Sodium valproate | 04 |
| Phenytoin and carbamazepine | 12 |
| Phenytoin sodium and valproate | 08 |

**[Table/Fig-3]:** Antiepileptic drugs used

| Specific Pattern | Phenytoin (N= 22) | Phenytoin + Carbamazepine ( N= 12) |
|---|---|---|
| Maculopapular rash | 10 | 0 |
| Erythroderma | 02 | 02 |
| Stevens –Johnson's syndrome | 06 | 03 |
| Photosensitivity | 02 | 0 |
| Toxic epidermal necrolysis | 02 | 06 |
| Vasculitis | 0 | 01 |

**[Table/Fig-4]:** Phenytoin and combined phenytoin and carbamazepine induced specific clinical pattern

## DISCUSSION

The frequency of CADR due to antileptic drugs more common in Indian population influenced by the drug utilization habit, reaction rates of favorite drugs and pharmacogenetic trials of the population studies. Most epidemiological studies analysed the occurrence of CADR in inpatients and revealed a wide variation in the prevalence rate which range from 0.36% to 12.2% [5-9,11]. Few studies explored the rate of CADRs seen by a hospital dermatology department; CADRs accounted for 1.38% of all referrals to university hospital department of dermatology in Denmark and 1.5 % of total dermatology consultations seen at a hospital in Tunisia [7,12]. HLA-B 1502 a known genetic marker for both carbamazepine and phenytoin induced CADR was reported to be present in 47 of 300 (15.7%) normal Malay controls, 5.7% of 300 normal chinese controls and in none of the 100 normal Indian controls, in a study of 21 carbamazepine induced TEN/ SJS in Malaysia [9,10].

These AED are commonly used in the management of different neuro– medical and neurosurgical problems as prophylactic as well as therapeutic agents. Specific clinical pattern due to anti epileptic drugs, SJS found in 34% of total patients,maculopapular rash and TEN in 25% of total patients. urticaria, erythema and photosensitivity in 3.2% each in total patients. Vasulitis found in 6.4% of total patients. Phenytoin produces severe CADRs like SJS/TEN in 8 patients out of 22 patients in own group and 5.12% of total patients. In our study we found that carbamazepine alone was used in 18 (28.1 %) patients and in combination 30 (46.9%), which was similar to other indian study in which, Devi et al., found that Carbamazepine is a

widely prescribed antiepileptic in India and is found to be the most commonly implicated drug responsible for SJS/TEN among Indians [13]. Carbamazepine alone produce SJS in six patients (3.4%) only and TEN in 4 patients out of 16 patients.

The mechanism by which CBZ causes ACDR is not well understood. Potential defects in the enzymes responsible for bioactivation and detoxification of CBZ have been proposed [14]. CBZ is bioactivated by hepatic cytochrome P450 enzymes, which generate various potentially reactive metabolites, such as CBZ 10, 11-epoxide, 3-hydroxy CBZ, 2- hydroxy CBZ, and CBZ 2,3-epoxide 51-52. Most of the reactive epoxides are detoxified to nontoxic dihydrodiols by liver microsomal epoxide hydrolase 1 (EPHX1) or to glutathione conjugates by glutathione transferase [15,16].

Combination of cabamazepine and phenytoin produces more frequent and severe reaction. SJS/TEN found in 12 patients out of 16 patients i.e. more than 7.68% of total patients develop severe reactions. Combination of Carbamazepine and phenytoin cause more severe form of CADR and more frequently, most likely due interaction between these two anti epileptic drugs and simultaneoushly Phenytoin also reduces glutathione reductase significantly and also produces several kind of free radical. In one study, the lavels of serum copper, Zinc, copper-zinc superoxide dismutase, and malondialdehyde were significantly increased, but the glutatione reductase level was significantly decreased, in epileptic patients using phenytoin monotherapy compared with those of the controls [17].

HLA-B*1502 as a marker for carbamazepine-induced SJS is well established in the Han Chinese by different studies [1,10]. In a study from India, Mehta et al., found that six out of eight patients had HLA-B*1502 while none of the 10 controls were found to be positive. This clearly indicates a significant association between carbamazepine-induced SJS and HLA-B*1502 among Indians. To prevent the severe form of CADR, HLA-B*1502 testing before initiating carbamazepine drug therapy in Indians can be a reasonable option [18].

## CONCLUSION

CADR are a common occurrence and awareness about the same is essential for diagnosis and prevention. This study identified combined use of phenytoin and carbamezepine as a most important risk factor for serious CADR like SJS and TEN. We suggest to avoid the combination of phenytoin and carbamazepine in any patient with epilepsy.

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