

# Analysis of adverse reactions with phenytoin and carbamazepine in tertiary care hospital – A retrospective study

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## ABSTRACT

**Introduction:** Drugs used in pharmacotherapy are known to cause adverse reactions along with its useful therapeutic effects. Pharmacotherapy is the common modality of treatment for seizures and epilepsies. Despite the availability of many pharmacotherapeutic agents for the management of epilepsies, even today the broad spectrum anti-epileptic drugs like phenytoin and carbamazepine are frequently prescribed owing to their effectiveness. Here with this retrospective study an attempt has been made to understand the different adverse reactions developed especially serious reactions with the phenytoin and carbamazepine.

**Materials and Methods:** It's a retrospective study; data is collected from case sheets and adverse drug reaction reporting forms.

**Results:** In this retrospective study we noted serious reactions like Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Out of 100 reactions studied 72% are with phenytoin and 28% are with carbamazepine.

**Conclusion:** The study is intended to project the seriousness of adverse reactions with commonly prescribed anti-epileptic drugs. There is a need for further studies especially prospective safety and efficacy studies.

**Keywords:** Adverse reactions, Phenytoin, Carbamazepine, Serious reactions, SJS, TEN

## INTRODUCTION

The epilepsies are one of the common neurological disorders; more than 40 distinct types have been identified.<sup>1</sup> Millions of people are suffering from epilepsy and it has become an essential health burden. According to international league against epilepsy, epileptic seizure is defined as occurrence of signs and symptoms transiently due to excessive synchronous and abnormal neuronal activity in the brain. Conceptually epilepsy is defined as lasting predisposition to produce epileptic seizures and by psychological, cognitive,

social and neurobiological consequences. Etiologically epilepsy could be due to genetic factor, structural/metabolic abnormality factors or unknown cause. The major problem in epilepsy pharmacotherapy is of compliance as there is a need for long-term therapy together with adverse reactions to drugs.<sup>1</sup> The outcome depends on many factors one of them is adverse effects associated with treatment.

Early control of epileptic seizures is important as it allows normalization of patient's lives by reducing recurrence of seizures and also correlates with successful discontinuation of antiepileptic drug treatment after long-term seizure control.<sup>2</sup> The therapeutic approach to a patient with epilepsy depends on the type of seizure. Mechanistically, the efficacy of antiepileptic drug centers on alteration of ion channel activity.<sup>3</sup>

The drug phenytoin, first synthesized in 1908, but its anticonvulsant activity was not exploited until 1938. Phenytoin therapeutic effect is mediated by slowing of the rate of recovery of voltage-activated Na<sup>+</sup> channels from inactivation. Along with therapeutic effect it has many toxic effects.<sup>1</sup>

Carbamazepine was in use for the treatment of trigeminal neuralgia since 1960's, approved as an anti-seizure agent in 1974. Like phenytoin, carbamazepine limits the repetitive firing of action potentials. This effect appears to be mediated by slowing of the rate of recovery of voltage-activated Na<sup>+</sup> channels from inactivation.<sup>1</sup> Like any other drug carbamazepine also has adverse effects. During long-term therapy, the more frequent untoward effects seen with the drug include drowsiness, vertigo, ataxia, diplopia, and blurred vision. The frequency of seizures may increase, especially with overdose. Other adverse effects include nausea, vomiting, serious hematological toxicity and hypersensitivity reactions (like dangerous skin reactions).<sup>1</sup> There are studies showing correlation between genetic makeup and development of reactions with carbamazepine, one study confirmed observation that HLAB\* 1502 is strongly associated with CBZ-SJS/TEN.<sup>4</sup>

As the anti-seizure drugs are used for long duration and they are associated with potential adverse reactions they require a constant monitoring and detection of reactions at the earliest to prevent morbidity. Anti-epileptic drugs are frequently associated with cutaneous reactions, even severe cutaneous reactions like Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and hypersensitivity syndromes are not unusual with anti epileptic drugs.<sup>5</sup>

The present study aims at knowing the prevalence of adverse reactions especially serious ones which would help in providing information in preventing reactions and providing better therapy to patients with epilepsy.

**MATERIALS AND METHODS**

Adverse reaction reporting form, Patient case sheets, Lab reports. In this retrospective study we utilized the above materials for the collection of data. Age group between 15 – 55 years of age, both males and females and Patients prescribed anti-epileptic drugs like Phenytoin or/and Carbamazepine were included in the study and Patients on medications for other chronic diseases like diabetes mellitus, hypertension, cancer, Hepatic disorders, Renal disorders and Gastrointestinal disorders were excluded.

**Procedure**

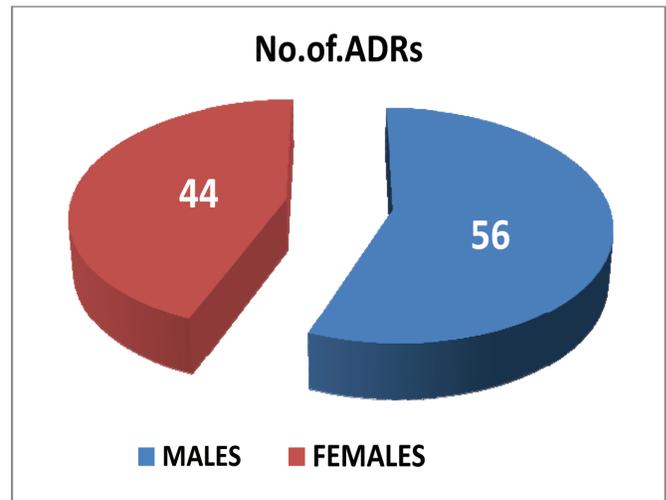
This retrospective study is planned in Gandhi Medical College/Hospital, by using data from case sheets and adverse drug reaction reporting forms. Previous case sheets and drug reaction reporting forms are screened, according to exclusion and inclusion criteria cases are selected and analysed for the presence of reaction. Demographic data, basic history and basic investigations like complete blood picture, weight of the patients are noted. The ADRs are collected in the adverse reaction reporting form and these collected variables are used for analysis. For Analysis Microsoft excel 2007 and Microsoft word 2007 is used.

**RESULTS**

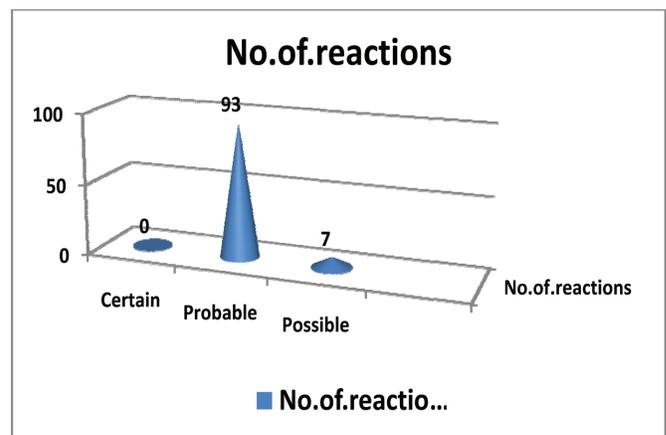
Case sheets from the medicine department were screened and depending on inclusion exclusion criteria’s cases are selected and data is collected from case sheets and adverse drug reaction reporting forms.

Out of 100 reactions studied 72% are with phenytoin and 28% are with carbamazepine. Majority of the reactions were noted in males 56% (Figure 1). The different adverse reactions noted with phenytoin and carbamazepine are represented in Table form ( Table 1, Table 2).

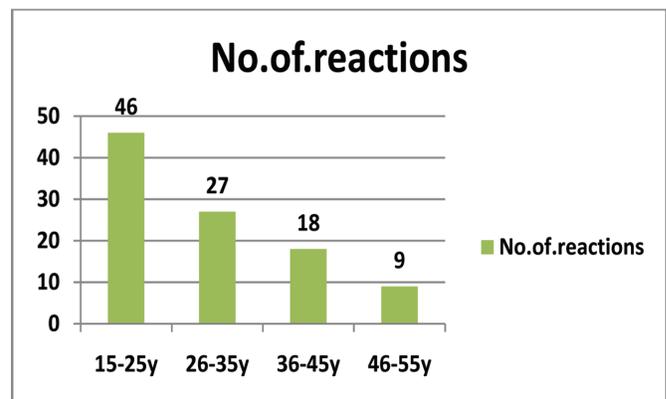
**Figure 1: Gender distribution of ADRs**



**Figure 2: Causality assessment**



**Figure 3: Age group distribution**



**Different adverse reactions based on system organ class (SOC)**

**Table 1: Adverse reactions with phenytoin**

REACTION	No.of. Reactions
<b>NERVOUS SYSTEM DISORDERS</b>	
Ataxia	13
Giddiness	05
<b>IMMUNE SYSTEM DISORDERS/ SKIN AND SUBCUTANEOUS TISSUE DISORDERS</b>	
Rash	32
<b>DRESS syndrome</b>	01
<b>Erythroderma</b>	03
Gingival Hyperplasia	02
<b>Stevens Johnson syndrome</b>	06
<b>Toxic Epidermal necrolysis</b>	03
Fixed drug eruptions	05
Lichenoid drug eruption	02

\*Reactions in bold are serious reactions

**Table 2: Adverse reactions with Carbamazepine**

REACTION	No.of. reactions
<b>IMMUNE SYSTEM DISORDERS/ SKIN AND SUBCUTANEOUS TISSUE DISORDERS</b>	
Rash	19
<b>Stevens Johnson syndrome</b>	06
<b>Toxic epidermal necrolysis</b>	01
Fixed drug eruptions	01
<b>Erythroderma</b>	01

\*Reactions in bold are serious reactions

## DISCUSSION

In the present study total of 100 adverse reactions were collected, reactions due to phenytoin and/or carbamazepine treatment. As in most of the cases of epileptic seizures phenytoin was the common antiepileptic drug prescribed, possibly explains the 72% of reactions due to phenytoin. Among the total reactions 80% reactions are related to dermatology. Of the reactions developed, 21 reactions were serious - 13 with phenytoin and 8 with carbamazepine. If we compare both drugs relatively carbamazepine is associated with more serious adverse reactions. The causality assessment and seriousness of reactions were assessed by WHO causality assessment scale and modified hartwig and siegel scale respectively, documented in adverse reaction reporting form. Of the total reactions 93 reactions were probable and 7 were possible (Figure 2).

Adverse reactions are matter of concern, considerable number of patient gets admitted due to adverse reactions and hospitalised patients receiving treatment develop one or the

other reaction.<sup>9, 10, 11</sup> Adverse drug reactions are one of the leading causes of death.<sup>12</sup> These reactions have deleterious effects on health of the patients.<sup>11,13</sup> The need for supervision and possible interventions to reduce or prevent adverse reactions is required.<sup>14,15</sup>

Treatment is intended to provide relief and improve the life style, but the reactions associated with therapeutic agents have become one of the major hurdles in providing better health service to patients. The adverse reactions can be preventable or non-preventable; it's assessed by modified schumock and thornton scale<sup>16, 17</sup>. In present study majority of the serious reactions are not preventable. Some reactions may be preventable like serious skin reactions with carbamazepine as there are studies supporting the relation between specific HLA B gene and serious reactions like Stevens Johnson syndrome, toxic epidermal necrolysis with carbamazepine in certain people.<sup>14</sup> Such knowledge helps in preventing serious reactions if treatment is preceded by screening of HLA typing.

## Limitations:

This retrospective study is based on the inpatient case sheets and adverse drug reaction reporting forms; so there is a plausible reason that many reactions are missed or under reported.

## CONCLUSION

The above study is intended to project the seriousness of adverse reactions with commonly prescribed anti-epileptic drugs, highlighting the importance of pharmacovigilance and the need for the active participation of all health care professionals to provide better health to the patients. There is a need for further studies especially prospective safety and efficacy studies, the knowledge of which helps the practitioners in providing better treatment to patients.

## ACKNOWLEDGEMENT:

I sincerely extend my gratitude to the adverse drug reaction monitoring center, Gandhi medical college, Secunderabad and the technical associate madam Venkataramana.

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**How to cite this article :** Syed Arshaduddin A, Abid Ali M, Usha Sree T S, Margaret V, Shaima Z K. Analysis of adverse reactions with phenytoin and carbamazepine in tertiary care hospital – A retrospective study. *Perspectives in Medical Research* 2019; 7(1):75-78.

**Sources of Support:** Nil, Conflict of interest: None declared.