



IJPPR

INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH  
An official Publication of Human Journals

ISSN 2349-7203



Human Journals

**Case Report**

January 2017 Vol.:8, Issue:2

© All rights are reserved by Jaladi Himaja et al.

# Carbamazepine Induced CNS Adverse Effects: A Case Report

 **IJPPR**  
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH  
An official Publication of Human Journals

ISSN 2349-7203



**Jaladi Himaja<sup>\*1</sup>, Battu Rakesh**

*<sup>\*1</sup> Pharm.D Intern, Department of Pharmacy Practice,  
Bharathi College of Pharmacy, Bharathinagara,  
K.M.Doddi, Mandya, Karnataka, India-571422.*

**Submission:** 10 January 2017  
**Accepted:** 15 January 2017  
**Published:** 25 January 2017



HUMAN JOURNALS

[www.ijppr.humanjournals.com](http://www.ijppr.humanjournals.com)

**Keywords:** Epilepsy, Phenytoin, Partial Seizures, Generalized Tonic-Clonic Seizures, DRESS Syndrome, and Trigeminal Neuralgia.

## ABSTRACT

**Background:** Epilepsy is a chronic neurological disorder that affects people worldwide. The main goal of treatment is to achieve seizure control without adverse effects. Carbamazepine is a commonly used sedative antiepileptic medication in many countries. It is mainly indicated for the treatment of partial seizures with complex symptomatology (e.g., psychomotor, temporal lobe), generalized tonic-clonic seizures (grand mal), and mixed seizure patterns, which include the seizure types listed or other partial or generalized seizures and also for the treatment of trigeminal neuralgia. Carbamazepine is reported to cause a range of deleterious and erratic side effects at therapeutic and toxic doses. Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is an uncommon but serious hypersensitivity drug reaction most frequently associated with anti-epileptics. Common adverse effects may include drowsiness, dizziness, headaches and migraines, motor coordination impairment, nausea, vomiting, and/or constipation. Serious side effects may include skin rashes, decreased bone marrow function, suicidal thoughts, or confusion. **CASE REPORT:** We report a case of carbamazepine-induced adverse effects in 24 years young female patient who has presented with vomiting 2-3 episodes, dizziness, drowsiness and slurring of speech. Her past history revealed that she is a known case of seizure disorder since 4 years and on treatment with Tablet Phenytoin 100 mg BID and stopped taking medication. She had last episode of seizure 6 months back. Based on the presenting signs and symptoms, her condition was diagnosed as Carbamazepine-induced CNS adverse effects. The symptoms improved significantly after the offending drug was withdrawn. Alternatively, she was started on oral Phenytoin 100 mg BID. Naranjo and WHO causality assessment was done, indicating a probable relationship between the patient's symptoms and her use of carbamazepine. Patient was later managed with IV fluids, intravenous Phenytoin of 800 mg in 100 ml NS, intravenous ondansetron. After 3 days of therapy symptomatic relief was observed and patient was discharged. **CONCLUSION:** This case report highlights the adverse drug reactions of carbamazepine and the need of regular monitoring in patients on long-term therapy.

## INTRODUCTION

Epilepsy is a common neurological disorder. The main goal of treatment is to achieve seizure control without adverse effects<sup>1</sup>. Epilepsy is a relatively common condition characterized by a tendency for recurrent seizures, which is due to the disturbance of spread of electrical discharge of the cortical neurons. Up to 80% of people with epilepsy are able to control their condition with anti-epileptic drugs (AEDs). The type of drug therapy prescribed depends on the type of seizure, the underlying cause of epilepsy, age of the patient and possible side effects. Treatment usually starts with one drug at a low dose. The dose is then increased slowly. In most patients, epilepsy remits over a period of years and drug therapy may be withdrawn slowly<sup>2</sup>.

According to World Health Organization (WHO) statistics, approximately 50 million people worldwide have epilepsy. In India, the prevalence rate of epilepsy ranges between 4.15 and 7.03 per 1000 population. In newly diagnosed cases, 60% are partial and 40% generalized. Epilepsy adversely affects the psychosocial status and quality of life of patients. General approaches for epilepsy management involves identification of goals and development of care plan<sup>3</sup>.

Carbamazepine (kar" ba maz' e-peen) is an iminostilbene that is chemically related to tricyclic antidepressants and unrelated in structure to other anticonvulsants. Carbamazepine suppresses spread of seizure activity by reduction in the post-tetanic potentiation of synaptic transmission. The ultimate goal is seizures freedom without adverse effects of medication and improved quality of life. Epilepsy often requires long-term AED therapy. However, prolonged AED administration is associated with a number of problems such as behavioral and psychiatric disorders, metabolic and endocrine disorders, idiosyncratic reactions, and drug interaction effects<sup>4</sup>.

All antiepileptic drugs have a relatively high incidence of adverse reactions. They are a major cause of discontinuing treatment. Many adverse reactions are dose related and predictable and can be minimized by commencing therapy with a low dose and with gradual escalation of the dose and dose reduction if symptoms persist. With respect to carbamazepine, particularly at the start of treatment or if the initial dose is too high, the following certain types of adverse reaction can occur very commonly (>10%) or commonly (>1% to <10%).

- CNS (dizziness, ataxia, drowsiness, fatigue, headache, diplopia, accommodation disorders).
- Skin (allergic skin reactions, urticaria).
- GI Disturbances (nausea and vomiting, dry mouth).
- Blood Dyscrasias (leucopenia, thrombocytopenia).
- Liver Disturbances (elevated gamma-glutamyl transferase and alkaline phosphatase).

It is generally recommended that white blood cell counts and liver functions tests are conducted before commencing treatment and periodically thereafter.

- Endocrine System and Metabolism (edema, fluid retention, weight increase, hyponatremia).

Occurrence of CNS adverse effects may be a manifestation of relative overdosage or significant fluctuation in plasma levels. Monitoring of plasma levels may be useful as is division of the daily dosage into 3-4 doses. Idiosyncratic reactions can also occur<sup>5,6,7,8</sup>. These usually arise early in treatment but can occur at any time and are potentially serious (e.g. Stevens Johnson Syndrome, exfoliative dermatitis, hepatitis).

The toxic effects of chronic use may present with wide variety of clinical symptoms and signs. Here we report a case of Carbamazepine toxicity in an adolescent female presenting with multiple adverse drug reactions (ADRs). The objective of this report is to describe a case of CNS adverse drug reactions caused by carbamazepine and is important for the clinicians to be aware of its presentation. It is important to identify the causative agent as early as possible and withdrawal of it is necessary for critical management.

We report a case of Carbamazepine-Induced CNS adverse drug reactions induced in 24 years adult female patient who had past history of seizure disorder since 4 years and on treatment with Tablet Phenytoin 100 mg BID and stopped taking medication. She had last episode of seizure 6 months back. The following case report demonstrates the necessity of prompt recognition and initiation of appropriate therapy in preventing the potential sequelae of Carbamazepine toxicity.

## Case presentation

A 24-year adult female visited the outpatient department of general medicine unit of Mandya Institute of Medical Sciences and Teaching Hospital, Mandya, Karnataka, India. She presented with vomiting 2-3 episodes, dizziness, drowsiness and slurring of speech. She past history revealed that she is a known case of seizure disorder since 4 years and on treatment with Tablet Phenytoin 100 mg BID and stopped taking medication. She had last episode of seizure 6 months back. No other significant past medical history and drug allergies.

## Investigations

General Physical examination of the patient on day-1 examination, the patient was afebrile with a heart rate of 70 beats/minute, respiratory rate of 17 cpm and blood pressure of 120/70 mmHg. The patient was well built and nourished, irritable and appeared uncomfortable and in distress. Her abdomen was soft and non-distended with no tenderness, guarding, or hepatosplenomegaly. CNS examination—patient is drowsy, responds to verbal commands and irritable, slurring of speech, dizziness. The patient was admitted to hospital with a presumptive diagnosis of drug-induced adverse effect. At this point, the differential diagnosis included drug-induced seizures, hyponatremia and epilepsy.

Laboratory results revealed Random Blood Sugar level was 144 mg/dl, white blood cell count of 8.6 thousand/mm<sup>3</sup> (normal from 4.0 to 10.0 thousand/mm<sup>3</sup>), with 84% neutrophils, 13% lymphocytes, and 02% eosinophil's (absolute 0.32 thousand/mm<sup>3</sup>), platelet count 1.96 lakh cells/mm<sup>3</sup>. Her basic metabolic panel was within normal limits. Hepatic and Renal function tests are within normal limits. All medications were discontinued and the patient was monitored for signs of clinical recovery. On day of admission, patient condition worsened with increased irritability, drowsiness and dizziness. Thus causality assessment was shown in Table: 01.

## Treatment

The patient was managed with IV fluids. After 3 days of therapy symptomatic relief was observed and patient was discharged. On day-1 the patient was treated with following medications—IV fluids 5% dextrose with pantoprazole infusion, intravenous Phenytoin of 800 mg in 100 ml NS, intravenous ondansetron 4 mg BID, Oral Gardenal Sodium 60 mg 0-0-1 and parenteral optineuron, Parenteral Proton-Pump Inhibitor (Pantoprazole 40 mg IV OD).

The symptom has not been reduced. So the patient has been referred to take psychiatrist opinion. The psychiatrist evaluated the patient and confirmed the case as Carbamazepine-Induced CNS Adverse Drug Reactions and advised to stop Carbamazepine and use alternative anti-epileptic drug.

No fresh complaints on day-2 and patient were continued with the same medications. The common ADR's of Carbamazepine is ataxia, dizziness, somnolence, diplopia, headache, abnormal involuntary movements (e.g. tremor, asterixis, and dystonia), speech disorders (e.g. dysarthria or slurred speech) nystagmus. On day-1, the physician dechallenged the drug after that patient was recovered from the presenting symptoms and an alternative anti-epileptic agent; Tablet Phenytoin 100 mg 0-0-1 was prescribed. After 3 days of was observed and patient was discharged.

### Outcome and recovery

The patient was discharged after 3 days of stay and therapy symptomatic relief after she attained complete recovery. At discharge, only dizziness was present. During the discharge, the following medications such as oral ranitidine 150 mg BID, oral Phenytoin 100 mg 0-0-1 and Capsule B-complex OD were advised.



### ADVERSE DRUG REACTION ANALYSIS

Table 1: Causality assessment of suspected ADRs

Suspected drug	Consequence of suspected drug (ADR)	Naranjo's scale	WHO-probability scale	Karch and Lasagnas scale
Carbamazepine	Dizziness, drowsiness and slurring of speech	Possible	Probable	Probable

**Severity:** Moderate level 4b

**Predictability:** Unpredictable

**Preventability:** Probably preventable

After collecting the past and current medication history from the patient it was suspected that the patient had developed carbamazepine-induced neurotoxicity. After analyzing the ADR profiles of all the drugs that have administered to the patient, it was found that the most suspected drug for producing CNS adverse effects was Carbamazepine. We have further analyzed to establish the relationship between the drug and the observed ADRs, through causality assessment by using Naranjo's scale, WHO-UMC ADR assessing scale as well as Karch and Lasagne scale, results were shown in Table 01. The Naranjo's criteria and WHO probability scale was applied to determine the causality for suspected ADRs. The causality assessment with both scales revealed that adverse reaction due to phenytoin, in this case, was probable (Naranjo overall score: 7). The severity of ADRs was evaluated using Modified Hartwig and Siegel, based on which it was categorized as moderate level 4(b) reaction.

### **Management of adverse drug reaction**

Generally, management of ADR includes withdrawal/suspension, dose reduction of suspected drug and administration of supportive therapy. Here, in this case, report the suspected drug Carbamazepine was discontinued.

**Fate of suspected drug:** Drug withdrawn



**Treatment Given:** Specific

**Outcome:** Recovered

### **DISCUSSION**

Carbamazepine is commonly used antiepileptic agent in children with generalized and partial seizures. Carbamazepine is metabolized by cytochrome P-450 enzymes in liver and Carbamazepine 10, 11 epoxide is principal metabolite which has antiepileptic and neurotoxic property similar to Carbamazepine<sup>9</sup>. The mechanism of action of carbamazepine is to inhibit repeated cell discharges and synaptic propagation of excitatory discharge via the blockage of voltage-gated sodium channel<sup>10</sup>.

CNS ADRs like aggression, restlessness, behavioral changes; cognitive impairment by AEDs has been identified and reported in earlier studies (Lieven, 2006; Shobana *et al*, 2010; Clare *et al*, 2011; Juny *et al*, 2013; Jim *et al.*, 2013). To minimize adverse effects, carbamazepine should be initiated at low dose with a slow dosage incremental rate. Carbamazepine should

be used with caution in patients with mixed seizures which include absences, either typical or atypical. In all these conditions, carbamazepine may exacerbate seizures. Cytochrome P450 3A4 is the main enzyme catalyzing formation of carbamazepine 10, 11-epoxide. Co-administration of inhibitors of CYP3A4 may result in increased plasma concentrations which could induce adverse reaction<sup>22</sup>.

Carbamazepine toxicity may result from acute overdose or chronic therapy. Therapeutic levels are 4-12mg/L, but individual variation exists. Patients on multiple anticonvulsants may not tolerate high levels and can be maintained at 4-8 mg/L, while others can achieve levels of 8-12mg/L without adverse effects. Ataxia and nystagmus may occur at levels greater than 10mg/L. Cardiovascular effects are usually seen at levels greater than 12 mg/L. The drug interferes with action potentials in Purkinje fibers and the His bundle, which may lead to atrioventricular blocks and arrhythmias<sup>11</sup>.

Patients receiving antiepileptic medications are prone to develop significant drug interactions even in developed countries<sup>12</sup>. Problem may arise due to failure to take complete history of health professionals or withholding information or prescriptions by patients. Patient may be taking treatment from different health professionals at same time. Parents of children on long-term treatment with Carbamazepine should be well educated about importance of disclosing their drug information to treating health professionals and also about possible interaction of Carbamazepine with other drugs. Special cards or badges with written information of receiving treatment with Carbamazepine should be carried by patients. Written instructions regarding avoiding specific drugs which cause interaction with Carbamazepine may also be helpful<sup>13</sup>. In Present case, patient showed complete improvement once the drug was stopped and with the help of certain other supportive measures.

## CONCLUSION

This case report of carbamazepine toxicity helps to alert physicians about the toxic manifestations of carbamazepine in patients on long-term therapy. Long-term therapy with carbamazepine should be individualized based on the patient's clinical response, plasma drug levels and signs of toxicity. There is also need for regular follow-up to assess compliance and response to therapy. Monitoring of serum carbamazepine levels and ADRs should be done even when the seizure is under control and especially when there are doubts of early toxic effects.

This report also highlights the importance of educating patients and their caregivers about the clinical manifestations of carbamazepine toxicity, so that it can be recognized early and treated appropriately. Hence, this case report serves to alert clinicians to remain clinically vigilant for such manifestation in patients with active cognitive lifestyles who are on long-term carbamazepine therapy. Caution needs to be exercised when making dosage changes as we saw that even a small change can precipitate or mitigate the side effects. There is a need to keep in mind the erratic association of serum levels and toxic effects especially in case of carbamazepine so that the progression to such possibly hazardous behavioral changes and the dramatic consequences thereof can be prevented. Immediate withdrawal of the causative drug is mandatory to avoid a possible fatal outcome in neurotoxicity. High index of suspicion is required for antiepileptic drug toxicities when an otherwise well controlled epileptic patient develops seizures or any other symptoms especially when they are started on new drugs which can modify antiepileptic drug metabolism.

### **Conflicts of interest**

The authors declare that there are no conflicts of interest that are directly relevant to the content of the case report.



### **Funding**

Our case report did not receive any funding for the conduct and preparation of manuscript.

### **ACKNOWLEDGEMENT**

Authors would like to thank patient for her co-operation in collecting personal and medical data.

### **REFERENCES**

1. Gosavi DD, Akanksha S, Sanjay N. A case of phenytoin induced gum enlargement. *Asian J Pharm Clin Res.* 2012; 5(1): 10-1.
2. Abbashar Hussein, Amira Abdulgalil, Faroug Omer, Hassan Eltoum, Ahmed Hamad, Omer El-Adil, Bedraddin Mubarak, Mohamad Malkaldar, Iway Idris, Yasin Alwidaa, Esam Mahmoud. Correlation between Serum Level of Antiepileptic Drugs and their Side Effects. *Oman Med J*, 2010; 25(1): 17-21.
3. Soha N, Afshin BH, Iman K. Adverse Reactions to Antiepileptic Drugs in Epileptic Outpatients: A Cross-Sectional Study in Iran. *Clin Neuropharm*, 2011; 4(2): 79-83.
4. Juny S, Adepu R, Keshava BS, Harsha S. Assessment of antiepileptic drugs usage in a South Indian tertiary care teaching hospital. *Neurol Asia*, 2013; 18(2): 159-165.
5. Micromedex 2006.
6. Prodigy Guidance 2006 – Epilepsy.

7. SIGN Guidelines 2005 – Diagnosis and Management of Epilepsies in Children and Young People. A National Clinical Guideline.
8. SPC Tegretol<sup>R</sup> – Accessed October 2006 via Electronic Medicines Compendium.
9. Westphal JF. Macrolide-induced clinically relevant drug interactions with cytochrome P-450A (CYP) A4: an update focused on clarithromycin, azithromycin and dirithromycin. *Br J Clin Pharmacol* 2000; 50:285-95.
10. Apfelbaum JD, Caravati EM, Kerns WP, Bossart PJ, Larsen G. Cardiovascular effects of carbamazepine toxicity. *Ann Emerg Med.* 1995, May. 25(5):631-5.
11. Armijo JA, Shushtarian M, Valdizan EM, *et al*: Ion channels and epilepsy. *Curr Pharm Design* 2005; 11: 1975-2003
12. Novak PH, Ekins-Daukes S, Simpson CR, Milne RM, Helms P, McLay JS. Acute drug prescribing to children on chronic antiepilepsy therapy and the potential for adverse drug interactions in primary care. *Br J Clin Pharmacol* 2004; 59(6):712-7.
13. Loganathan N, Sujithkumar S, Bhuvanewari K, Thiagarajan VK. Acute Carbamazepine toxicity: A case of rare drug interaction. *Indian Journal of Pharmacy Practice* 2012; 5(2):59-60

