ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

https://ijmsweb.com

Indian Journal of Medical Sciences


*Case Report*

# Phenytoin-induced aplastic anemia in generalized tonic clonic seizures patient: A case report

P. Hima Bindu, S. Vinod Naik, Paruvelli Krishnaveni, Gundapaneni Paparayudu, Varun Lal

Department of Pharmacy Practice, TVM College of Pharmacy, Ballari, Karnataka, India.

***Corresponding author:**
Dr. Varun Lal,
Department of Pharmacy Practice, TVM College of Pharmacy, Ballari - 583 103, Karnataka, India.

varunlal50@gmail.com

Received : 21 December 19
Accepted : 28 January 20
Published : 02 April 20

**DOI**
10.25259/IJMS_23_2019

**Quick Response Code:**

## ABSTRACT

Aplastic anemia is a hematopoietic stem cell disorder characterized by pancytopenia of the peripheral blood and hypocellular bone marrow. Phenytoin is the most commonly and most widely used anticonvulsant, which is used for the prevention and treatment of generalized seizures, partial seizures, and status epileptics. The main aim of the study is to enlighten the drug-related problem and address such problems to prevent the occurrence of adverse event and optimizing drug therapy. Here, we present a case of a 35-year-old female patient who was admitted with complaints of fever, breathlessness, and lower limb swelling. She is a known case of hypertension and generalized tonic clonic seizures for which was taking tablet amlodipine and tablet phenytoin from 5 and 2 years, respectively, after which the patient developed aplastic anemia.

**Keywords:** Aplastic anemia, Phenytoin, Anticonvulsant, Generalized tonic clonic seizures

## INTRODUCTION

Aplastic anemia is a hematopoietic stem cell disorder characterized by pancytopenia of the peripheral blood and hypocellular bone marrow.[1,2] Aplastic anemia is idiosyncratic complication of the drug treatment. Phenytoin is the most commonly and most widely used anticonvulsant, which is used for the prevention and treatment of generalized seizures, partial seizures, and status epileptics.[3] Hematological problems are rare with phenytoin which includes macrocytosis, agranulocytosis, granulocytopenia, leukopenia, and pancytopenia.[4,5] The effect produced by phenytoin is dose-dependent. The etiology of drug-induced aplastic anemia remains obscure, toxic, reactive metabolites of a variety of compounds which may play a crucial role. Covalent binding of the intermediates to cell macromolecules results in formation of electrophilic metabolite leading to bone marrow toxicity through variety of potential mechanism.[6,7] Direct hematopoietic stem cell toxicity or mutation or immunologic processes involving formation of haptens or damage to lymphocytes with critical function in hematopoiesis can occur. Aplastic anemia is classified into nonsevere, moderately severe, severe, and very severe based on the degree of bone marrow cellularity and peripheral neutrophils, platelets, and reticulocyte count.[7] In this case, the patient is having moderate aplastic anemia.

### Aim

The main aim of the study is to enlighten the drug-related problem and address such problem to prevent the occurrence of adverse event and optimizing drug therapy.

## CASE REPORT

A 35-year-old female patient was presented with complaints of fever, fatigue, breathlessness, and lower limb swelling for 10 days. The patient is known case of generalized tonic-clonic seizures for 2 years and hypertension for 5 years and was on regular medication, i.e., tablet amlodipine 5 mg o.d. and tablet phenytoin 100 mg b.i.d. On examination, blood pressure was normal and pulse rate was elevated 120 bpm.

### Lab investigations

#### *Hematology*

Hemoglobin: 7.1 g/dl, red blood cell (RBC): 1.3 million/$mm^3$, white blood cell: 1100 cells/cumm, and platelets: 12,000 lacs/cumm, bone marrow biopsy shows hypocellular bone marrow. Renal function test, liver function test, electrolytes were normal.

#### *Treatment*

During Hospitalization the following medications were prescribed (1) Injection pantoprazole 40 mg intravenous (IV) b.i.d. (2) Injection ceftriaxone 1 g IV t.i.d. (3) injection Vitamin $B_1$, $B_6$, $B_{12}$ IV o.d. (4) Tablet ferrous fumarate + folic acid 325 mg + 1500 mcg PO o.d. (5) Tablet amlodipine 5 mg PO o.d. (6) Tablet sodium valproate 200 mg PO b.i.d. (7) 1 pint packed RBCs IV o.d. The patient experienced aplastic anemia secondary to phenytoin therapy. Primary treatment for drug-induced condition is to remove offending agent and hence phenytoin was on hold. To treat severe anemia packed RBC transfusion, iron and Vitamin B supplements were prescribed. Injection ceftriaxone is prescribed to prevent infection and tablet sodium valproate is give as alternative therapy for seizures.

#### *Discharge medication*

The Patient was discharged with the following Tablet ferrous fumarate + folic acid 325 mg + 1500 mg PO o.d. Tablet amlodipine 5 mg PO o.d. Tablet sodium valproate 200 mg PO b.i.d. Tablet pantoprazole 40 mg PO b.i.d. After discontinuing phenytoin, the hematological parameters which were too low became almost normal. Moreover, signs and symptoms were relieved.

## DISCUSSION

The patient appeared with complaints of fever, fatigue, breathlessness, and lower limb swelling for 10 days. Patient was taking phenytoin since 2 years which induced aplastic anemia. Patient was not consuming any other medication that causes the above condition. The use of phenytoin is associated with 3.5 fold increased risk of aplastic anemia.[8] In this case, a Narinjo adverse drug reaction (ADR) probability scale was applied for causality assessment and the score was 9 (definite) and Hartwig's Severity Assessment Scale was used to classify severity of aplastic anemia, which was level 4b (the ADR is reason for admission).

## CONCLUSION

Phenytoin is frequently used anticonvulsant, rarely it may be related to serious complication such as aplastic anemia.[9] Routine monitoring of complete blood count helps to identify these complications. Therefore, it is important to educate patient regarding the offending agent and to avoid further exposure.[10] Clinicians and clinical pharmacist should have adequate knowledge regarding such reactions and they must give careful attention to such patients. The patient developed aplastic anemia after 2 years use of phenytoin. This condition is reversible when the drug is withdrawn within 1–2 weeks, but in some patient, it takes as long as 2–3 months.

### Therapeutic intervention

During hospitalization, phenytoin was withheld and alternative drug sodium valproate was prescribed. Idiosyncratic aplastic anemia is listed as possibly associated with cell major anticonvulsant except gabapentin (specifically, felbamate, carbamazepine, phenytoin, valproate, etc.).[1,4] The alternative drug prescribed was sodium valproate that is also known to cause the aplastic anemia. Since the patient is having generalized tonic-clonic seizures, gabapentin is not the drug of choice instead of phenobarbital, clonazepam can be given.[1]

### Statement of human and animal rights

All procedures performed in human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

### Acknowledgment

We want to thank our Principal Prof. Dr. Manjunath V. Jali and HOD of Pharmacy Practice Prof. Dr. H. N. Girish for their guidance and support.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

## REFERENCES


1. DiPiro DD, Joseph T. In: Pharmacotherapy: A Pathophysiologic Approach. New York: McGraw-Hill Medical; 2008. p. 1702-5.
2. Gerson WT, Fine DG, Spielberg SP, Sensenbrenner LL. Anticonvulsant-induced aplastic anemia: Increased susceptibility to toxic drug metabolites *in vitro*. Blood 1983;61:889-93.
3. Golan DE. In: Golan DE, Tashjian AH, Armstrong EJ, editors. Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy. Baltimore: Lippincott Williams and Wilkins; 2005. p. 236.
4. Foye WO, Williams DA, Lemke TL. Foye's Principles of Medicinal Chemistry. 5th ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2002. p. 392.
5. Verrotti A, Scaparrotta A, Grosso S, Chiarelli F, Coppola G. Anticonvulsant drugs and hematological disease. Neurol Sci 2014;35:983-93.
6. Handoko KB, Souverein PC, van Staa TP, Meyboom RH, Leufkens HG, Egberts TC, *et al*. Risk of aplastic anemia in patients using antiepileptic drugs. Epilepsia 2006;47:1232-6.
7. Qahtani SA. Drug-induced megaloblastic, aplastic, and hemolytic anemias: Current concepts of pathophysiology and treatment. Int J Clin Exp Med 2018;11:5501-12.
9. Tomita S, Kurokawa T, Ueda K, Higuchi S. Aplastic anaemia induced by intravenous phenytoin and lidocaine administration. Eur J Pediatr 1985;144:207-8.
8. Alvaro SV. Phenytoin induced rash and aplastic anemia: A case report. Rev Chil Neuro Psiquiatria 2011;49:171-6.
10. Robins MM. A plastic anemia secondary to anticonvulsant. Am J Dis Child 2015;104:614-24.


**How to cite this article:** Bindu PH, Naik SV, Krishnaveni P, Paparayudu G, Lal V. Phenytoin-induced aplastic anemia in generalized tonic clonic seizures patient: A case report. Indian J Med Sci 2019;71(3):127-9.