INTERNATIONAL RESEARCH JOURNAL OF PHARMACY

www.irjponline.com

ISSN 2230 – 8407

Research Article

PHENYTOIN INDUCED MYELOSUPPRESSION IN AN ADULT EPILEPSY PATIENT : A CASE REPORT

Nina K Mathew [1], Keerthana Chandrasekar [2]*

[1]Department of Pharmacy Practice, JSS College of Pharmacy, Udhagamandalam - 643001, The Nilgiris, Tamil Nadu. JSS Academy of Higher Education & Research, Mysuru, Karnataka, India

[2]Resident, Department of Pharmacy Practice, JSS College of Pharmacy, Udhagamandalam - 643001, The Nilgiris, Tamil Nadu. JSS Academy of Higher Education & Research, Mysuru, Karnataka, India

*Corresponding Author Email: keerthana@jssuni.edu.in

Article Received on: 12/10/18 Approved for publication: 23/11/18

DOI: 10.7897/2230-8407.0912307

ABSTRACT

Phenytoin is one of the most common and widely used anticonvulsant drug. The present case report explains the rare adverse effect of long term phenytoin treatment induced myelosuppression in a secondary care public hospital, Udhagamandalam, India. We report a case of 25 year old patient who was a known case of seizure for past 10 years. The patient was presented with complaints of two episodes of seizure, fever and abdominal pain to the intensive care unit. The patient was treated with intravenous fluids- dextrose normal saline and ringer lactate, intravenous routes of phenytoin, ciprofloxacin, metronidazole, ranitidine and tablet zinc. The patient's vital signs and blood parameters were monitored on a regular basis. The patient's blood pressure was fluctuating and blood parameters were found to be drastically reducing during the course of treatment with phenytoin. Blood transfusion was initiated in this patient for the treatment of myelosuppression due to which the blood parameters were seen normal during the discharge. In any patient presented with suspected drug induced myelosuppression, early diagnosis of cytopenia with a complete blood count is crucial. In such cases, appropriate symptomatic management along with timely withdrawal of drug remains the best option in current scenario. Being considered a classic antiepileptic, these kinds of serious haematological adverse effects of phenytoin on long term use is often overlooked. Reporting of these types of rare but potential adverse effects is necessary to create awareness among more clinicians.

Keywords: Phenytoin, Myelosuppression, Management, Intensive Care Unit, Secondary Care Hospital.

INTRODUCTION

Phenytoin is a hydantoin anticonvulsant and is used in the treatment of a wide variety of seizure disorders[1]. It was first synthesized in 1902 by Heinrich Biltz, but didn't gain much recognition, until its usefulness to treat and prevent seizures, without any sedation effects unlike phenobarbital was discovered in 1938. Phenytoin is one of the foremost studied and most used anticonvulsant agent, but various insidious and severe untoward effects have been associated with its long term use. These adverse effects can be idiosyncratic or dose related. Some of the idiosyncratic adverse effects include skin rashes (5-10%), gingival hyperplasia (40-50%)[3], agranulocytosis (0.0003%), bone marrow suppression etc[2]. The therapeutic plasma levels of phenytoin are 10-20 mcg/ml, although in some patients, it could be 5 to 10 mcg/ml. Some of the dose dependant side effects of phenytoin are often translated clinically into lethargy that may appear at 20 mcg/dl, ataxia(30 mcg/dl),nystagmus and dysarthria over 40mcg/dl etc[4]. However, such dose-related side effects show marked variation among different patients[5].

Myelosuppression is a very common and anticipated adverse effect of cytotoxic chemotherapy. Conversely, drug-induced myelosuppression due to non-cytotoxic agents such as phenytoin is very rare, unpredictable and potentially life threatening. It is possibly because of the increased risk of infection and bleeding complications such as neutropenia and thrombocytopenia associated with it[6,7].

There are only very few reports and limited data established on non-cytotoxic drug induced myelosuppression worldwide and in India. This study reports a rare case of myelosuppression associated with long term phenytoin use.

CASE REPORT

A 25 year old male patient was admitted to the intensive care unit of a secondary care public hospital, Udhagamandalam on 23rd April 2016 with chief complaints of two episodes of seizure since after noon, fever and abdominal pain. Patient is a known case of seizure for 10 years and was on medication: Tab. Phenobarbitone 30mg PO OD, Tab. Phenytoin 100 mg PO TID, and Tab. Sodium valproate 200mg PO TID. On examination, there was no loss of consciousness, no chest pain, no palpitation, but decreased urine output was found in this patient. The patient was not a known case of diabetes mellitus/ hypertension /bronchial asthma/ tuberculosis/ epilepsy. On examination the patient was found to be conscious, oriented, afebrile and vitals were found to be normal. On the first day, the patient was prescribed with Intravenous fluids: DNS and RL 1pint each and then Inj.Phenytoin-600mg in normal saline IV followed by injection phenytoin-100mg IV TDS, Inj. Rantidine-50mg IV BID, Tab. Sodium valproate 200mg TID, and Inj.Vitamin B-complex OD. The altered laboratory parameters throughout the hospital admission is represented in Table 1. On second day, the patients had chief complaints of fever, not passing urine and had no new episode of seizures . On examination the patient was found to be conscious and disoriented, CVS and RS : NAD and per abdomen soft. The patient was given with NS and DNS 1 pint each, RL- 2 pint, Tab. Paracetamol- TID, Inj. Cefotaxime 1g IV BD and tepid sponging. On the 3rd day the patient had no new chief complaints, Temperature observed 98.4°F, Blood pressure: 100/50mmhg and the same medication was continued. On next day the patient's

temperature was 98.4, blood pressure 110/ 70mmhg, bloody Peri-rectal and a case of loose stool blood. GC was fair. The patient was administered with IVF RL- 2 pint, Inj. Ciprofloxacin-200mg IV BD, Inj. Metronidazole 500mg IV TDS, Tab. Zinc-1 OD. On the next day , patient was diagnosed with fever, and his vitals were recorded as PR 86 beats/mins, RR 20 cycles/mints, Blood pressure 110/60mmHg and was still a case of loose stool since 2 days. On examination the patient was found to be conscious, oriented, severe pallor(+), periorbital oedema, facial puffiness, B/L pitting oedema, CVS-S1S2+, RS -BAE (+), P/A- disoriented and was suspected of having dilated basal loops and paralytic ileus, P/R-no mass / no bleeding. He was also diagnosed with anaemia, congestive cardiac failure, and suspected with paralytic ileus. The patient was prescribed with soft diet, IVF RL -2 pint, Inj. Ciprofloxacin-200mg IVBD, Inj.Metronidazole-500mg IVBD, and Inj. Ranitidine- 50 mg IVBD. On the same day , patient was seen by the physician and noted that the patient was a known case of seizure disorder and a case of bleeding Peri-Rectal (loose stools) at present; on examination the patient was afebrile, cardiovascular and respiratory sounds was clear. The doctor prescribed Tab. Sodium valproate- 200mg BID, Tab. Phenytoin – 100mg BID, Inj. Diazepam-2.5mg IVBD. The patient's electrolyte levels were also monitored and his potassium level was found to be low. On 28/4/16 the patient had complaints of giddiness; on examination the patient was found to be conscious, oriented, pallor+, P/A- distended, no mass and the patient was transferred from Intensive Care Unit to General Ward. The physician ordered for blood transfusion because the patient's haemoglobin was dropped to 3.9gm/dl and platelets-52x $10^3/mm^3$. On the next day, blood pressure was found to be 130/80mmhgand blood transfusion was carried out, after monitoring the necessary vitals. The temperature was observed to be 100^0F, on examination. After blood transfusion, the patient was conscious, oriented and vitals were stable. On 30/4/16, blood pressure was 120/80mmhg. By that day afternoon, the patient was breathless; the blood pressure dropped to 90/60mmhg and the patient was administered with IVF NS -1 pint. On 1/5/16 the patient had chief complaints of abdominal distress, urine output (N), on examination the patient's general condition was fair, and the same medication was continued. The patient was advised to seek the advice of a haematologist and was discharged on 1/5/16 with following medications: Tab. Sodium valproate - 200mg BD, Tab. Phenytoin 100mg BD and blood transfusion with required units of O^+ blood.

TABLE 1: SUMMARY OF LABORATORY INVESTIGATIONS

LAB PARAMETERS	DAY 1	DAY 2	DAY 5	DAY 8	NORMAL RANGE
White blood cells	$1.0x10^3$cells/mm^3	$1.0x10^3$cells/ mm^3	-	$19.3x10^3$cells/ mm^3	$4.5\text{-}11x10^3$cells/ mm^3
Platelet count	$72x10^3$ cells/mm^3	$72x10^3$ cells/mm^3	$52x10^3$ cells /mm^3	$52x10^3$ cells /mm^3	130-400 $x10^3$cells /mm^3
Red blood cells	-	$1.77x10^6$cells/mm^3	-	-	$3.5\text{-}5.0x10^6$cells/mm^3
Haemoglobin	-	5.6g/dL	3.9g/dL	3.9g/dL	14-18g/dL

DISCUSSION

Phenytoin is extensively prescribed for prophylaxis and rapid control of generalized tonic clonic, complex partial and psychomotor seizures by physicians. Non cytotoxic agent such as phenytoin rarely causes myelosuppression. Such peripheral blood cytopenias are generally not anticipated ,are idiosyncratic (type B) and calls for more attention , unlike the cytotoxic chemotherapeutic agents that produce predictable, dose-dependent myelosuppression (type A) that is usually reversible at clinical dosages. Early recognition of cytopenia with a complete blood count is crucial in any patient presented with suspected drug-induced myelosuppression either type A or B. At the first indication of idiopathic myelosuppression, treatment with all potentially implicated drugs has to be intervened; switching to another agent from the same drug class may be considered. Providing the patient with early supportive care is also important to limit the potential major risks associated with myelosuppression.

Empirical therapy with a broad spectrum antibiotic intravenous agent should be given to neutropenic patients with fever or other signs of infection. If patient doesn't improve despite first- and second-line antimicrobial therapy, intravenous amphotericin B may be considered. But antibacterial therapy is rarely recommended as a prophylaxis for neutropenic patients in the absence of any signs of infection. If platelet count is $<10 \times 10^9$/L due to myelosuppression, prophylactic administration of platelet concentrate may be considered. Anaemia resulting from drug-induced myelosuppression may be corrected by allogeneic red blood cell transfusion to maintain normal haemoglobin range[6,7,8]. A few case studies suggests the potential use of G-CSF agents in drug induced agranulocytosis [9,10].For prolonged drug induced myelosuppression even after discontinuation of drug, treatment options may include immunosuppressive therapies such as high dose corticosteroids, cyclosporine or bone marrow transplantation[6,7].

In this case, the patient was treated with phenytoin for past 9 days, during the time of treatment, the blood parameters of the patient reduced drastically and his blood pressure was fluctuating which strongly indicated myelosuppression associated with long term phenytoin use. The patient was treated for myelosuppression with transfusion of blood due to which the blood parameters were found to be normal. He was also administered with empiric antibiotic therapy based on local bacterial prevalence and antibacterial resistance. The early detection and withdrawal of the drug will help the patient improve his condition.

CONCLUSION

Even though phenytoin is a classic antiepileptic drug, it is crucial to keep in mind about its potential but rare immunological and haematological adverse effects including myelosuppression in a clinical setting. Early diagnosis, timely discontinuation of drug and appropriate management remains the mainstay in drug induced myelosuppression. Suspected instances of drug-induced myelosuppression, particularly of type B reactions to novel drugs, should be considered to be reported to regulatory authorities to create vigilance among more clinicians.

ACKNOWLEDGEMENT

The authors would like to acknowledge the support provided by the Government District Headquarters Hospital, Ooty, Tamilnadu, India.

ABBREVIATIONS

1. NS- Normal saline
2. RL- Ringer lactate
3. DNS- Dextrose normal saline
4. CVS- Cardiovascular system
5. RS- Respiratory system
6. OD- Omni die (Once Daily)
7. BD- Bis die (twice daily)

8. TID-Thrice Daily
9. BP- Blood pressure
10. PR- Pulse rate
11. RR- Respiratory rate
12. P/A- Per abdomen
13. NAD- No abnormalities detected
14. IVF- Intravenous fluids
15. PO- Per oral
16. IV- Intravenous

REFERENCES

1. Thomas A Ban, Max Fink. An Oral History of Neuropsychopharmacology. USA: ANCP;2011.
2. Dilantin[monograph on the Internet]. New York: Parke-Davis (Division of Pfizer Inc);2015[cited 2015 Jul 14].Available from:https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/084349Orig1s074lbl.pdf.
3. Kriti Garg, Vishal Mehrotra, Garima Singh, Rohini Singh. Phenytoin induced gingival enlargement: a case report. International Journal of Contemporary Medicine Surgery and Radiology. 2016;1(1):19-20.
4. Anup Jagarlamudi, Asma Begum, Nazmeen Saba, Mahalakshmi Teegala. Phenytoin Induced Truncal Ataxia: Need For TDM. Indian Journal of Pharmacy Practice. 2016;9(1):60-62.
5. Jyothsna Rani Dasari, Sangram Vurumadla, Om Prakash Prasad. A Case Report on Phenytoin Induced Ataxia. Asian J Pharm Clin Res. 2016; 9(4):5-6.
6. Carey PJ. Drug-induced myelosuppression: diagnosis and management. Drug Saf. 2003;26(10):691-706.
7. Drug-induced myelosuppression requires early recognition, accurate diagnosis and supportive treatment. Drugs Ther. Perspect. 2004; 20(10):23-6.
8. Livanainen M, Savolainen H. Side effects of phenobarbital and phenytoin during long-term treatment of epilepsy. Acta Neurol Scand Suppl. 1983;97:49-67.
9. Rawanduzy A, Sarkis A, Rovit RL. Severe phenytoin-induced bone marrow depression and agranulocytosis treated with human recombinant granulocyte-macrophage colony-stimulating factor: Case report. J Neurosurg. 1993;79(1):121-4.
10. Dona S Raju, Christeena George, Renoy A Henry, Naveen Kumar Panicker. A Case Report on Phenytoin Induced Agranulocytosis and Rash. J. Pharm. Sci &Res. 2017;9(12):2434-6.

Cite this article as:

Nina K Mathew and Keerthana Chandrasekar. Phenytoin induced myelosuppression in an adult epilepsy patient : A case report. Int. Res. J. Pharm. 2018;9(12):140-142 http://dx.doi.org/10.7897/2230-8407.0912307

Source of support: Nil, Conflict of interest: None Declared