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Case Report

Phenytoin-induced cerebellar symptoms – A case report

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ABSTRACT

Phenytoin, a hydantoin derivative, is an effective anticonvulsant drug widely used to treat seizure disorder. The wide pharmacokinetic variability and low toxicity threshold of phenytoin often contribute to its toxicity. We now report the case of a 43-year-old woman who was hospitalized with ataxia, nystagmus, external ophthalmoplegia, drowsiness, gingival hypertrophy, vomiting, and generalized weakness for 10 days while she was on treatment with T. phenytoin 200 mg/day for the past 6 months for seizure disorder. Two days before the onset of these symptoms, the dose of T. phenytoin was increased from 200 mg/day to 300 mg/day. Based on her signs, symptoms, and laboratory tests, she was diagnosed with phenytoin-induced poisoning. After stopping the medication, the symptoms improved. She started using oral levetiracetam instead. Based on the Naranjo and the World Health Organization, a causal analysis of the relationship between the patient's symptoms and phenytoin use was done. The severity of this adverse drug reaction is moderate at level 4 on the Hartwig severity rating scale. These data highlight the adverse effects of phenytoin and the importance of clinical monitoring for a drug with a narrow therapeutic index.

Keywords: Phenytoin, Seizure, Ophthalmoplegia, Nystagmus

INTRODUCTION

Phenytoin, a hydantoin derivative discovered in 1908, is an effective anticonvulsant drug that is used to treat many varieties of seizure disorders, such as generalized tonic-clonic seizures, complex focal seizures, and status epilepticus without neurological deficit.[1] Despite its narrow therapeutic index, it is one of the most widely used anticonvulsants, listed on the World Health Organization (WHO) list of essential medicines.[2] Phenytoin inhibits the reactivation of action potentials induced by excitatory depolarization in preserved rat spinal cord neurons *in vitro*.[3] Phenytoin blocks the voltage-gated Na^+ channel that limits the repetitive firing of the action potential by delaying the rate of recovery of the Sodium (Na) channel.[4] Phenytoin is 90% bound to plasma protein and metabolized by cytochrome P (CYP) enzymes, which contribute to various drug interactions and adverse effects.[1,4] Phenytoin's low toxicity threshold and broad pharmacokinetic variability can frequently lead to intoxication. Nystagmus, ataxia, decreased coordination, hyperreflexia, slurred speech, diplopia, confusion, lethargy, and coma are the common adverse effects caused which are concentration-dependent.[5] Hereby, we report a case of a middle-aged female with phenytoin-induced cerebellar symptoms and gum hypertrophy.

CASE REPORT

A 43-year-old woman presented to the outpatient department of Sri Manakula Vinayagar Medical College and Hospital, Madagadipet, Puducherry, with a history of vomiting, drowsiness,

nystagmus [Video 1], external ophthalmoplegia [Video 2], gingival hypertrophy, and generalized weakness with difficulty in walking for the past 10 days which was sudden in onset. Further, she revealed that she had a known case of seizure disorder, taking Tab. phenytoin 200 mg/day for the past 6 months. She had complaints of giddiness 12 days back, for which she visited a private clinic where the dose of T. phenytoin was increased from 200 mg/day to 300 mg/day.

The patient was not a known case of diabetes mellitus, systemic hypertension, and thyroid disorders. On examination, the patient was oriented and afebrile. Her vitals were stable and on systemic examinations, no abnormality was detected. On oral cavity examination, gingival hypertrophy was present. Her laboratory investigations revealed phenytoin toxicity with serum phenytoin level of 47.8 mcg/mL, aspartate aminotransferase: 44 IU/L, gamma-glutamyl transferase: 151 U/L, total protein: 5.9 g/dL (albumin - 3.9 g/dL), urine sugar: +++, random blood sugar: 206 mg/dL, and lymphocytes: 15.4%. Other biochemical parameters were all within normal limits. Her echocardiogram report was normal with an ejection fraction of 60%, and magnetic resonance imaging (MRI) brain imaging showed chronic infarct of the left corona radiata and age-related mild cerebral atrophy with periventricular leukoaraiosis. The diagnosis of phenytoin-induced toxicity was determined based on the patient's clinical appearance, laboratory test, and prior medication history, and Tab. phenytoin was replaced by T. levetiracetam 500 mg twice daily, after which the patient started to recover. Within a week, external ophthalmoplegia, vomiting, and ataxia resolved completely, and nystagmus improved slightly as soon as the drug was withdrawn. Nystagmus and gum hypertrophy resolved significantly within the next 3 months.

Naranjo's criteria and the WHO's risk assessment were used to determine the cause of suspected adverse drug reactions (ADRs). Causality analysis of the two indicators showed that the adverse event in this case was mainly due to phenytoin (Naranjo total score: 8). The severity of this ADR was moderate, level 4 on the Hartwig severity rating scale.

DISCUSSION

Epilepsy is one of the most common neurological diseases in India.[6] Phenytoin, 5,5-diphenylhydantoin, is a potent non-sedative anticonvulsant used to treat and prevent a wide range of seizure disorders. The therapeutic range is narrow and is between 10 mg/L and 20 mg/L, which limits the use of phenytoin.[7] Phenytoin is available in both oral and parenteral formulations; in oral, they are available in both rapid-release and extended-release forms. Extended-release forms make it possible for a once-daily dose. Hence, there may be confusion in dosing phenytoin due to the availability of different formulations, such as phenytoin and phenytoin sodium; therefore, phenytoin equivalents can be considered. Therefore, to ensure therapeutic safety serum-level monitoring is necessary.[1,4] Phenytoin is metabolized predominantly by cytochrome enzymes (CYP2C9 and CYP 2C19) to inactive metabolites, and it induces CYP3A4, which accounts for many of its drug interactions. Elimination follows first-order kinetics when plasma concentration is below 10 mg/L; following the increase in concentration, elimination changes to zero-order kinetics, and the average half-life of 22 h can become prolonged with marked overdose. Overdose of phenytoin in oral formulation mainly causes neurotoxicity, and in parenteral formulation causes cardiotoxicity. The neurotoxic effects of phenytoin are largely concentration-dependent and are nystagmus, ataxia, slurred speech, vomiting, lethargy, and finally, coma and death. Paradoxically, at very high concentrations, it can cause seizures.[1,2] It can also manifest gastrointestinal symptoms, hirsutism, gingival hyperplasia, osteomalacia, megaloblastic anemia, hyperglycemia, and glycosuria.[4,8]

The following is a link between total plasma phenytoin concentrations and adverse effects:

- Less than 10 mg/L: Infrequent adverse events
- 10–20 mg/L: Mild horizontal nystagmus on lateral gaze may occasionally occur
- 20–30 mg/L: Nystagmus
- Ataxia, slurred speech, tremor, nausea, and vomiting at doses of 30–40 mg/L

Video 1: Nystagmus.

Video 2: Ophthalmoplegia.

- 40–50 mg/L: Lethargy, confusion, hyperactivity
- More than 50 mg/L: Seizures and coma[2]
- The blood levels for ophthalmoplegia varied from 36 mg/L to 55 mg/L.[9]

Our patient presented with giddiness, external ophthalmoplegia, vomiting, gingival hyperplasia, ataxia, nystagmus hyperglycemia, and glycosuria. There are reports that suggest ataxia, nystagmus, external ophthalmoplegia, gingival hyperplasia, hyperglycemia, and glycosuria are caused due to phenytoin toxicity.[8,10-12] Phenytoin potentiates gamma aminobutyric acid (GABA)-mediated inhibitory synapse in the vestibulo-ocular pathway leading to ophthalmoplegia.[9] Gingival hyperplasia due to phenytoin is multifactorial but mainly due to disturbance in the gingival fibroblast.[12] Chronic phenytoin ingestion leads to its accumulation in the cerebral cortex, causing atrophy of the cerebellum, resulting in ataxia.[11] Phenytoin causes insulin insensitivity by inhibiting insulin release, causing hyperglycemia and glycosuria.[12] The signs and symptoms presented by the patient can be explained in terms of complex pharmacokinetics, individual variation in metabolism and elimination of phenytoin, and narrow therapeutic index.[1,2] Symptoms of phenytoin poisoning usually occur when the phenytoin concentration is above 25 mcg/mL. This patient's blood phenytoin concentration was 47.8 mcg/mL. The toxic effects of phenytoin can be avoided with regular monitoring of serum phenytoin level, especially when altering the dose. Since phenytoin has non-linear pharmacokinetics, there may be gradual accumulation over a period of time, and a small increase in dose may lead to toxicity. These effects may be reversed by discontinuing the drug or reducing the phenytoin dose.[13]

CONCLUSION

This case report highlights the blood level-related adverse effects of phenytoin and alerts the treating physician of the importance of therapeutic monitoring of drugs that have a narrow therapeutic index, especially when escalating the dose of such drugs. There is a need to create awareness among physicians about the therapeutic drug monitoring when patients are on long-term drug therapy on drugs with a narrow therapeutic index and educate the patient and caregiver about regular follow-up and signs and symptoms of such toxicities to detect and treat as early as possible.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

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

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript, and no images were manipulated using AI.

REFERENCES

1. Gupta M, Tripp J. Phenytoin. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK551520 [Last accessed on 2024 Jul 16].
2. Iorga A, Horowitz BZ. Phenytoin toxicity. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2021.
3. McLean MJ, Macdonald RL. Sodium valproate, but not ethosuximide, produces use- and voltage-dependent limitation of high frequency repetitive firing of action potentials of mouse central neurons in cell culture. J Pharmacol Exp Ther 1986;237:1001-11.
4. Thakral A, Shenoy R, Deleu D. Acute visual dysfunction following phenytoin-induced toxicity. Acta Neurol Belg 2003;103:218-20.
5. Larsen JR, Larsen LS. Clinical features and management of poisoning due to phenytoin. Med Toxicol Adverse Drug Exp 1989;4:229-45.
6. Nadig R, Namapally US, Sarma GR, Mathew T. Outpatient burden of neurological disorders: A prospective evaluation of 1500 patients. Neurol India 2019;67:708-13.
7. National Library of Medicine (US), National Center for biotechnology information. Compound summary for CID 1775, phenytoin. Bethesda, MD; 2004. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Phenytoin [Last accessed on 2022 Jan 29].
8. Menon V, Kurian J, Undela K, Ramesh M, Gowdappa H. Phenytoin toxicity: A case report. J Young Pharm 2015;7:272-5.
9. Spector RH, Davidoff RA, Schwartzman RJ. Phenytoin-induced ophthalmoplegia. Neurology 1976;26:1031-4.
10. Singh J, Tyagi SS, Singh JM, Muhammed R, Manik C, Tripathi RK. Ataxia, manifestation of phenytoin toxicity: A case report. J Young Pharm 2019;11:112.
11. Chacko LN, Abraham S. Phenytoin-induced gingival enlargement. BMJ Case Rep 2014;2014:bcr2014204670.
12. Al-Rubeaan K, Ryan EA. Phenytoin-induced insulin insensitivity. Diabet Med 1991;8:968-70.
13. Stensrud PA, Palmer H. Serum phenytoin determinations in epileptics. Epilepsia 1964;5:364-70.

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