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Case Report

Chronic use of Phenytoin Induced Ataxia: A Case Series of Six Patients

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ABSTRACT
Phenytoin-induced ataxia increased the risk of morbidity by 10% to 50% and could be life-threatening but rarely fatal. We reported six cases of phenytoin-induced ataxia, experienced with cerebellar signs of ataxia. All study patients were found with elevated phenytoin serum concentrations (range: 30-40 mcg/ml). Assessment of SARA (Scale for the Assessment and Rating of Ataxia) scale indicated mild ataxia among all patients. Naranjo's algorithm shows 50% of patients had definite and another 50% had probable relation between phenytoin exposure and ataxia. Ataxia resulted in the withdrawal of phenytoin among five patients and dose reduction in one patient. All patients were treated with alternative anti-seizure medications along with supportive treatment and they were symptomatically better within 1-6 weeks duration of treatment. Hence, this study concluded that phenytoin-induced ataxia is common at a plasma concentration of 30 to 40 mcg/ml. Prescribers and pharmacists need to focus on monitoring phenytoin serum levels and providing appropriate counseling to prevent their toxicity.

Key words: Ataxia, Chronic use, Naranjo's algorithm, Neurotoxicity, Phenytoin, Scale for the assessment and rating of ataxia.

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INTRODUCTION

Ataxia is typically poor coordination of limbs movement and unsteadiness while performing daily tasks and caused due to cerebellum abnormalities.[1] Patient with phenytoin toxicity may be presented with drowsiness, tremor, nystagmus, dysarthria, ataxia, and cerebellar degeneration.[2] Phenytoin is an anti-epileptic drug that is widely used for the management of seizures such as generalized tonic-clonic and partial seizures.[3] It blocks the voltage-dependent sodium (Na^+) channel and slow down the epileptogenic stimuli that shoot towards the neuronal cell.[2,4] Phenytoin is a narrow therapeutic index drug and may require adequate monitoring to prevent its toxicity.[5] Phenytoin toxicity is mostly caused due to acute overdose, chronic use, drug interactions, and altered human physiology. Chronic use of phenytoin increases the risk of neurological toxicity which includes ataxia, nystagmus, slurred speech, tremor, and cerebellar hypertrophy and that is usually observed at the phenytoin serum level between 20 to 40 mcg/ml.[6] However, phenytoin-induced ataxia can be observed at a phenytoin serum level of 30 to 40 mcg/ml and that could be life-threatening as the risk of comorbidities increased by 10% to 50% but rarely fatal.[7-8] Phenytoin-induced ataxia is a rare adverse reaction and was reported previously but due to lack of adequate phenytoin serum concentration monitoring and poor awareness towards there use causing patient harm more frequently.[5] Therefore, monitoring phenytoin serum concentration, related clinical manifestations and their management become essential to prevent phenytoin-induced ataxia or related toxicities. Hence, we aimed to report of a chronic use of phenytoin induced ataxia among six patients.

CASE PRESENTATION

Case 1

A 34-year-old male patient presented with giddiness and altered sensorium. Patient had a history of cerebrovascular accident along with seizure disorder for the past 10 years. Further, patient was experienced with the last episode of seizure (generalized tonic-clonic seizure) three months back. Patient was prescribed with phenytoin (100-300 mg/day) for the past ten years and sodium valproate 200 mg for the past 2 years to treat seizure. On general examination, vital signs were normal, whereas, neurological examination revealed cerebellar signs of disorientation, confusion, and trembling walk. In this patient, serum phenytoin level was elevated 38 mcg/ml than the normal range (therapeutic range: 10-20 mcg/ml). The patient's daily activities performance was assessed by adopting a Scale for the Assessment and Rating of Ataxia (SARA) which revealed gait ataxia (gait score: 6) presented in this patient. Naranjo's causality assessment scale score was *nine*, indicating a *definite* relation between phenytoin exposure and ataxia in this patient.

Patient was advised to stop taking phenytoin and continue sodium valproate 200 mg along with phenobarbitone 60 mg, carbamazepine 200 mg, and supportive treatment. After receiving 15 days of the treatment, patient was symptomatically better and was discharged from the hospital. In the 4th week of follow-up, patient was absent with cerebellar signs and symptoms. Therefore, patient was re-administered with a low dose of phenytoin 100 mg/day along with concurrent therapy.

Case 2

A 40-years-old female patient was presented with complaints of vertigo, trembling walk, blurred vision, slurred speech, and mild headache from the past day. Patients' history revealed that the patient was diagnosed with generalized tonic-clonic seizure for the past 10 years and has been prescribed with sodium valproate 200 mg twice daily and subsequently added phenytoin 300 mg/day at past four years. The patient vital was found to be normal, whereas, neurological examination revealed that the patient was presented with drowsy, presence with bilateral cerebellar signs of ataxia and nystagmus. Laboratory examination shows elevation of phenytoin serum level of 30.4 mcg/ml (therapeutic range: 10-20 mcg/ml). Radiological examination, magnetic resonance imaging (MRI) shows the glottis area atrophy at the left temporal lobe and cerebellar atrophy. The assessment of patient's daily activity performance adopting SARA scale, that indicated ataxia (gait score: 7, stance score: 2, sitting score: 2, speech disturbance: 3, nose-finger test score: 3 and fast alternating hand movement score: 5) in this patient. The Naranjo's causality assessment scale score was eight which indicated a probable relation between phenytoin exposure and ataxia in this patient.

Patient was advised to stop phenytoin and started with levetiracetam 500 mg and clobazam 5 mg along with supportive treatment. Patient was symptomatically better after 12 days of treatment and was discharged from the hospital.

Case 3

A 32-years-old female patient was admitted with complaints of dizziness, nausea, vomiting, trembling walk, and oscillopsia from the past 3 days. The patient presented with a history of seizures from the past 10 years and was prescribed phenytoin 100 mg/day. The patient was found with normal vital signs. Neurological examinations show the presence of cerebellar signs of ataxia. Whereas, patient's serum phenytoin level was found to be elevated 30 mcg/ml (therapeutic range: 10-20 mcg/ml). MRI report shows gliosis on her left posterior parietal lobe. The daily activities of the patient's performance were assessed adopting the SARA scale, which indicated gait ataxia (gait score: 4) in this patient. The Naranjo's causality assessment scale score was eight, indicating a probable relation between phenytoin exposure and ataxia.

Patient was advised to stop phenytoin and started with the sodium valproate 500 mg and clobazam 10 mg along with supportive treatment. After 14 days of the treatment, the patient was symptomatically better and was discharged from the hospital.

Case 4

A 25-years-old female was presented with complaints of fifteen episodes of seizure (generalized tonic-clonic seizure) and experienced headache, nausea, and vomiting before the seizure episode from the past five days along with trembling walk and giddiness for 2 days. Patient history revealed that he was diagnosed with multiple tuberculomata presented in the frontal lobe (MR imaging) and experienced with seizure episodes for the past 2 years. Patient was treated with anti-tubercular drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol in a fixed-dose combination) for 6 months and stopped. Whereas, phenytoin 200 mg/daily was continued for the past 2 years. On general examination, the patient was presented with normal vital signs. Neurological examinations revealed that the patient was presented with drowsy, difficulty in holding objects, and trembling walk. In this patient, phenytoin serum level was 33.4 mcg/ml (therapeutic range: 10-20 mcg/ml) found to be elevated. The patient's performance during daily activities was assessed by SARA scale and which indicated ataxia (gait score: 5, stance score: 2, nose-finger test score: 3, and fast alternating hand movement score: 3) in this patient. The Naranjo's causality assessment scale score was *nine*, indicating a *definite* relation between phenytoin exposure and ataxia in this patient. Patient treated with a low dose of phenytoin 100 mg/day, sodium valproate 500 mg, and supportive treatment. The patient was symptomatically better on nine days of the treatment and was discharged. After four weeks of follow-up, the patient signs and symptoms were resolved.

Case 5

A 26-years-old male patient presented with complaints of trembling walk, dysarthria, and seizures (1 episode) from today morning. The patient medical history was revealed the presence of seizure disorder from the past three years and was prescribed with phenytoin 300 mg/day. Patient also provided a history of type-II diabetes mellitus from the past four years and was prescribed with anti-diabetic medications. The general examination has been shown vital signs and systemic examination was normal. In this patient, serum phenytoin level 35 mcg/ml was elevated than the normal range (therapeutic range: 10-20 mcg/ml). Radiological examination (MRI) showed the presence of gliosis in the right posterior parietal lobe. The patient's performance during daily activities was assessed by using the SARA scale indicating gait ataxia (gait score: 4). The Naranjo's causality assessment scale score was *eight*, indicating a *probable* relation between phenytoin exposure and ataxia in this patient.

Patient was advised to stop phenytoin and started with the clonazepam 0.5 mg and carbamazepine 100 mg along with supportive treatments. The patient was symptomatically better on the 7th day of treatment and was discharged. The patient was found with no cerebellar signs at 4th week of follow-up.

Case 6

A 36-years-old male patient complained of one episode of the seizure (simple partial seizure) two days back, diminished vision, behavioral abnormalities, and trembling during walking for the past one day. The patient provided a history of surgery (craniotomy) done for the removal of meningioma four months back and was prescribed phenytoin 300 mg/day. The patient vital was found to be normal. Neurological examination revealed the presence of cerebellar signs including drowsy, dilated pupils, increased tone on all four limbs, and power in all joints (4/5). Blood phenytoin level 40 mcg/ml (therapeutic range: 10-20 mcg/ml) was elevated. The patient's performance during daily activities using the SARA scale indicated ataxia (gait score: 6, sitting score: 3, nose-finger test score: 4, and fast alternating hand movement score: 4). The Naranjo's causality assessment scale score was nine, indicating a definite relation between phenytoin exposure and ataxia in this patient.

Patient was advised to stop phenytoin and treated with clonazepam 2.5 mg, carbamazepine 100 mg, clobazam 10 mg, and supportive treatment. The patient was symptomatically better after 11 days of the treatment and was discharged from the hospital. After three weeks of follow-up, patient's condition was improved and was re-administered with a low dose of phenytoin 100 mg/day along with concurrent medications.

DISCUSSION

Phenytoin is extensively used for the treatment of seizure disorders due to its easy availability and low cost. Phenytoin is well known to cause neurological toxicity on oral ingestion for chronic use or acute overdose. In this study, all six patients ingested with phenytoin (range: 100-300 mg/day) for the duration ranges from four months to ten years. Phenytoin toxicity upon chronic use can cause cerebellar abnormalities such as ataxia, slurred speech, and vision problems. Ataxia is one of the rare cerebellar signs observed at the elevated phenytoin serum concentration between 30-40 mcg/ml.,[8] In this case, series, all six patients were found

with elevated phenytoin serum concentration (range: 30-40 mcg/ml). Similar phenytoin serum concentration (41.6 mcg/ml) was reported in a study conducted by Satheesh G *et al.*[7] Another study conducted by Dasari JR *et al.*, reported a similar phenytoin serum concentration (31.4 mcg/ml).[9] In both studies, both patients' were experienced with ataxia-related signs including diminished vision, slurred speech, and trembling walk.[7,9] In this current study, all six patients were experienced trembling walk, blurred vision, and slurred speech. This indicates that phenytoin-induced ataxia and related signs are common at the phenytoin serum concentration of 30 to 40 mcg/ml. Cerebellar atrophy can be observed on the chronic use of phenytoin.[8] In this study, three patients (*Case 2, Case 3, and Case 5*) were identified with cerebellar atrophy upon radiological examination (MRI). All these three patients used phenytoin (dose range: 100-300 mg/day) orally for 3-10 years. A similar finding was observed in a study conducted by Arora M *et al.*, who reported cerebellar atrophy among all four patients who used phenytoin orally for 6-16 years.[10] This suggests that phenytoin-induced cerebellar changes could be observed at long-term use but the exact duration to develop cerebellar atrophy is still difficult to predict. This suggests that the prescriber required adequate monitoring of cerebellar health to prevent neurological complications. However, cerebellar changes could be reversible upon phenytoin withdrawal or dose alteration.[8] In this study, according to the SARA scale score, all the patients were presented with mild ataxia. A similar study conducted by Shanmugarajah P *et al.*, reported mild ataxia associated with phenytoin toxicity.[2] This indicates that the phenytoin induced ataxia is generally mild in severity but can cause significant neurological damage if left untreated for a long duration. Current study evidence can be critical for the guideline implications to detect, manage and prevent such toxicities in the future.

In the current study, causality assessment following Naranjo Adverse Drug Reaction Probability Scale shows that half of the patients (*Case 1, Case 4 and Case 6*) were found with a score of *nine* indicating *definite* and another half (*Case 2, Case 3 and Case 5) were* found with a score of *eight* indicating *probable* relation between phenytoin exposure and developed ataxia as adverse drug reaction (ADR). However, the phenytoin exposure and development of adverse reactions were always unpredictable.

The management approach of phenytoin induced ataxia and other neurological signs were depends on the cerebellar damages and the nature of symptoms. Generally, phenytoin induced ataxia is reversible upon phenytoin withdrawal, dose reduction, frequency changes and use of suitable alternatives.[8] In this study, out of six patient, in five patients phenytoin were withdrawn whereas in one patient (*Case 4*) phenytoin dose was reduced. Further, patients have prescribed alternative anti-seizure medication including phenobarbitone (*case 1*), sodium valproate (*Case 1, Case 3 and Case 4*), carbamazepine (*Case 1, Case 5 and Case 6*), clobazam (*Case 2, Case 3 and Case 6*), clonazepam (*Case 5 and Case 6*) and levetiracetam (*Case 2*), which is important to use as alternatives to the control seizure as well as improve cerebellar health. Moreover, in this study, the signs and symptoms were improved or resolved within the period of one week to six weeks of the treatment. However, an exact period to subside signs and symptoms could not be predictable because of its dependence on cerebellar health and duration of exposure. The phenytoin can be restarted as per need but need to ensure that presented neurological signs were subsided. In this current study, in two cases (*Case 1 and Case 6*) phenytoin was re-administered within 3-4 weeks. This indicates that phenytoin can be re-administered upon an estimation of risk and benefits. To prevent phenytoin induced ataxia and other related toxicities, the physician required frequent monitoring of the serum phenytoin level, neurological health status and other related adverse events. Furthermore, clinical pharmacists can play an essential role to ensure drug efficacy and safety.[11-12] Therefore, clinical pharmacists provide counseling to the patient and patients' caretakers on the preventive measures of phenytoin toxicity such as compliance towards phenytoin use, avoiding overdosing, awareness of possible adverse effects and timely notification of adverse events to treating physician, if any is essential. In this study, clinical pharmacist was counseled all six patients about preventive measures that need to be adopted to prevent phenytoin related toxicitity.

CONCLUSION

Chronic use of phenytoin increased the risk of neurological toxicity by causing cerebellar damage. This study concludes that phenytoin induced ataxia can be commonly seen at the phenytoin serum concentration of 30 to 40 mcg/ml and may result from the cerebellar damage, caused by chronic phenytoin use. Ataxia associated with phenytoin is mostly reversible and can be managed by the withdrawal or dose reduction of phenytoin and use of alternative anti-seizure medications. Hence, this study suggests that prescribers and clinical pharmacists can play an essential role in preventing phenytoin induced ataxia and other neurological toxicity by the adequate monitoring of phenytoin serum concentration, assessing cerebellar health, providing patients'counselling on possible adverse effects and importance of compliance towards phenytoin therapy.

Declaration of Patient Consent

The authors certify that informed consent was obtained from all six patients on patient consent forms before patient information collection. In the form, the patient has given their consent for publication of all the clinical information in the journal.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

SARA: Scale for the Assessment and Rating of Ataxia; **mcg/ml:** microgram per millilitre; **mg:** milligram; **MRI:** Magnetic resonance imaging; **ADR:** Adverse drug reaction.

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