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CASE REPORT **OPEN ACCESS**

Drug Interaction-Induced Phenytoin Toxicity Presenting as Cerebellar Ataxia: A Case Report

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A B S T R A C T

Phenytoin, an antiepileptic drug with nonlinear pharmacokinetics, can cause toxicity, especially with drug interactions that affect its metabolism.Here, A 70-year-old man with a history of stroke and epilepsy developed worsening ataxia and falls after starting cimetidine. His serum phenytoin level was 30 mcg/ml, above the therapeutic range. MRI showed mild cerebellar degeneration. while his Phenytoin toxicity, exacerbated by cimetidine inhibiting phenytoin metabolism, leading to cerebellar dysfunction and he managed with Phenytoin was discontinued, and valproate was initiated. The patient's condition improved with supportive care. Chronic phenytoin use can cause cerebellar ataxia. Drug interactions, like with cimetidine, can increase phenytoin levels and toxicity risk. In short, Monitoring phenytoin levels and avoiding drug interactions is crucial to prevent toxicity. Switching to alternative antiepileptic drugs can improve outcomes in affected patients.

Keywords: Phenytoin Toxicity Ataxia Cimetidine Seizure Drug interaction

INTRODUCTION

Phenytoin, a hydantoin derivative (5, 5-diphenylhydantoin) is a choice of drug for the treatment of seizures. phenytoin, a commonly used antiepileptic drug, exerts its therapeutic effects primarily through modulation of sodium channels in neurons, thereby stabilizing neuronal membranes and reducing neuronal excitability. Phenytoin acts by blocking voltage-dependent sodium channels in their inactive state, thereby limiting sustained high-frequency neuronal discharges [1].

Phenytoin exhibits nonlinear pharmacokinetics due to its saturation of hepatic enzyme systems. It has a small volume of distribution (0.6 L/kg) and is highly protein-bound (90%). This binding can lead to displacement interactions with other protein-bound drugs. Phenytoin demonstrates complex pharmacokinetics characterized by saturation of

hepatic metabolism pathways, leading to dose-dependent kinetics. It follows Michaelis-Menten kinetics, where at therapeutic doses, it is metabolized primarily by hepatic enzymes, predominantly CYP2C9 [2].

However, at higher doses, it can saturate these enzymes, leading to non-linear kinetics and increased risk of toxicity. It was introduced as an antiepileptic drug in 1938. Phenytoin is commonly used to treat all types of tonic clonic and complex partial seizures, except absence seizures [3].

Phenytoin belongs to the class IB group of antiarrhythmic agents. It is occasionally used in the management of ventricular arrhythmias, particularly those associated with digoxin toxicity [4].

Phenytoin toxicity is influenced by various factors including route of administration, dosage, and duration of exposure. The main determinant of toxicity is the route of administration. The wide pharmacokinetic variability and low toxicity threshold of phenytoin can often result in its toxicity [5].

After oral administration, peak blood levels typically occur within 3-12 hours. Therapeutic levels are typically between 10-20 micrograms/ml, with toxicity occurring at levels above 20 micrograms/ml [6].

Due to its high lipophilic nature, it causes more frequent Central nervous system (CNS) related adverse drug reactions (ADR) such as muscle spasms, sedation, nystagmus, ataxia, psychosis and disturbances in the vision [7].

Non CNS related ADR of phenytoin includes gum hypertrophy, decrease in haemoglobin count, hypersensitivity syndrome, reduced serum folic acid levels [8].

Toxicity manifests predominantly as nausea, central nervous system dysfunction (particularly confusion, nystagmus, and ataxia), with depressed conscious state, coma, and seizures occurring in more severe cases. Cardiac complications such as arrhythmias and hypotension are rare in cases of phenytoin ingestion, but they may be seen in parenteral administration of phenytoin or fosphenytoin. Fosphenytoin, a prodrug of phenytoin that is administered parenterally, is believed to have fewer adverse effects than phenytoin. Toxicity in chronic therapy may be due to gradual accumulation of phenytoin over the time period as a result of non linear pharmacokinetics [9]. These effects can be reversed by withdrawing or reducing the dose of phenytoin. The mainstay of therapy for a patient with phenytoin toxicity is stopping the use and supportive care. Treatment includes attention to vital functions, and prevention of injuries due to confusion and ataxia. There is no antidote [10].

Case Presentation

A 70-year-old man came in with a 2-month period of worsening trouble walking and repeated falls, without any injuries, fever, unconsciousness, focal weaknesses, ear problems, dizziness, ringing in the ears, or headaches. The individual has a history of cardiovascular stroke and epilepsy, and has been taking phenytoin for the management of epilepsy for a decade. He is also prescribed aspirin and lovastatin to prevent cardiovascular issues. Because of stomach discomfort from phenytoin, he recently began using cimetidine, which can be bought without a prescription.

Upon evaluation, the patient showed signs of stable vital signs and was alert and aware. The neurological evaluation showed dysarthria, agitation, and chorea, along with gaze-induced nystagmus, unsteady walking, bilateral past-pointing, poor finger-nose coordination, and difficulty with the heel-shin test, indicating possible cerebellar dysfunction. The remaining part of the systemic examination showed no abnormalities.

Laboratory tests, such as full blood count, liver function tests, and electrolyte levels, were normal. Serum phenytoin level was discovered to be above the therapeutic range of 10-20 mcg/ml, measuring 30 mcg/ml. MRI screening of the brain and entire spine detected slight cerebellar degeneration, with no abnormalities found in the EEG.

DIAGNOSIS

Phenytoin toxicity manifesting as cerebellar ataxia worsened by elevated phenytoin levels caused by simultaneous cimetidine use. Cimetidine hinders the CYP2C9 enzyme that breaks down phenytoin, resulting in increased levels in the blood and causing cerebellar dysfunction as a sign of toxicity. Symptoms greatly improved after stopping phenytoin and starting a different antiepileptic drug regimen.

MANAGEMENT

Phenytoin was gradually reduced and stopped, and the patient began taking valproate to manage seizures. Supportive treatment was offered, and the patient's ability to walk and balance slowly got better after stopping the phenytoin.

DISCUSSION

In this case, chronic exposure to phenytoin resulted in cerebellar degeneration and ataxia, emphasizing the drug's potential neurotoxic effects, particularly affecting the cerebellar vermis. Even in the absence of clinical ataxia, long-term phenytoin therapy has been associated with reduced cerebellar volume [11].

The patient's phenytoin toxicity was exacerbated by the concomitant use of omeprazole, which inhibits the CYP450 enzyme responsible for metabolizing phenytoin, leading to elevated blood levels [12].

The therapeutic range for phenytoin is typically considered to be 10-20 mcg/mL. Deviations from this range can lead to varying degrees of toxicity, as summarized in Table 1 below:

Table 1: Total Phenytoin Levels (mcg/mL) and Corresponding Signs and Symptoms [13]

Total Phenytoin Level (mcg/mL)	Signs and Symptoms
Less than 10	Rare
10 - 20	Occasional mild nystagmus
20 - 30	Nystagmus
30 - 40	Ataxia, slurred speech, nausea, vomiting
40 - 50	Lethargy, confusion
Greater than 50	Coma, seizures

The clinical manifestations of gaze-evoked nystagmus, ataxic gait, past-pointing, and impaired finger-nose and heel-shin tests strongly suggested a cerebellar etiology [11]. Differential diagnoses including stroke, multiple sclerosis, paraneoplastic syndromes, and inherited ataxias were ruled out based on the patient's history, normal brain imaging, and laboratory findings. The temporal association between symptom onset and increased phenytoin levels, coupled with symptom improvement upon phenytoin discontinuation, confirmed the diagnosis of phenytoin toxicity.

Phenytoin toxicity can manifest with various neurological symptoms, including side effects such as purple toe syndrome, movement disorders like myoclonus and dystonia, and cognitive impairment [12].

Its metabolism follows dose-dependent and first-order kinetics, with toxicity risk increasing in elderly patients, neonates, those with renal impairment, hypoalbuminemia, and malignancies. Additionally, drug interactions with medications like cimetidine can exacerbate toxicity by impairing phenytoin metabolism via CYP450 inhibition [2].

Regarding differential diagnosis, alcohol ingestion can mimic symptoms; thus, blood alcohol levels should be considered. Imaging and specific markers (MRI and paraneoplastic markers) aid in ruling out other causes such as encephalitis, multiple sclerosis, and stroke. Phenytoin's widespread use as an over-the-counter household medication underscores the importance of monitoring therapeutic free phenytoin levels (1-2 micrograms/ml) to prevent toxicity [14].

CONCLUSION

This situation highlights how it is crucial to monitor serum phenytoin levels, stay alert for possible drug interactions, and educate patients on identifying symptoms of phenytoin toxicity for timely intervention and correct handling. Moreover, it highlights the importance of steering clear of OTC medications that may interact with phenytoin, potentially worsening toxicity.

In conclusion, discontinuing phenytoin promptly and starting a different antiepileptic treatment led to notable enhancement in the patient's health. This situation highlights the importance of consistent check-ins and personalized treatment plans for patients on long-term phenytoin treatment, guaranteeing the best possible results and safety for the patient.

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