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Case Report

PHENYTOIN TOXICITY PRESENTING AS PARADOXICAL SEIZURES

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ABSTRACT - Phenytoin is a commonly used antiepileptic drug in developing countries like India. It is widely used against generalized tonic-clonic and complex partial seizures. Phenytoin is reported to cause a range of deleterious and erratic side effects even at therapeutic doses. We have come to recognize a clinical syndrome "paradoxical intoxication." This we define as the situation in which seizure frequency increases as the blood level of that anticonvulsant rises. This high drug level is accompanied by few or no toxic signs, hence the paradox. This case report highlights the adverse drug reactions of phenytoin at therapeutic doses and the need of regular monitoring in patients on long term therapy. We also stress the need to recognize toxicity of antiepileptic drugs at presentation to arrive at an early diagnosis.

Keywords: phenytoin, toxicity, paradoxical seizure

Introduction

Epilepsy is a common neurological disorder. The main goal of treatment is to achieve seizure control without adverse effects. Phenytoin (5,5- diphenyl hydantoin) is one of the most effective and widely prescribed drug for the treatment of epilepsy due to its low cost and easy availability.[1] Phenytoin toxicity is an uncommon problem seen in clinical practice. The predisposing factors for toxicity are hypo albuminemia, chronic renal failure, hepatic dysfunction and drugs which interfere with phenytoin metabolism. Common manifestations of toxicity, like confusion and ataxia, are well known. A less well known phenomenon is paradoxical seizures.

In this condition, seizures develop as the serum phenytoin level rises and decrease in frequency as levels drop.[2] It may or may not be accompanied by other features of toxicity. We present one patient with paradoxical seizures with serum phenytoin level >40mcg/ml in the absence of gingival or gum hypertrophy, hirsutism, or skin manifestations.

Case Report- A 42-year-old male belonging to the middle socio-economic level was referred to the outpatient (OP) department with three episodes of generalized tonic clonic seizures, and had one episode in OP so shifted to causality and loaded with intravenous levetiracetam.

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In past history, relatives revealed that he had road traffic accident with moderate head injury, underwent surgery in December 2012. He was put on antiseizure medication phenytoin 300mg/day and levetiracetam 1g/day for post traumatic seizures and has been regularly taking the medicines. It was noticed that he had swaying while walking, vomiting, headache and vertigo since1week.

On clinical examination, he was in altered mental status, confused, occasional irritability, and drowsiness with a Glasgow coma scale of 10 on day 1. Day 2 of admission showed bilateral horizontal and vertical nystagmus, diplopia, impaired tandem walking with bilateral finger to nose and finger to finger incoordination, intention tremor and gait ataxia. Clinical examination were mimicking posterior circulation stroke, but imaging was normal. It was noticed that his symptoms like confusion, vomiting and giddiness were progressively increasing despite antiplatelets, antiepileptic and antivertigo medications.

On further history taking, his brother gave history of giddiness since 2months with recurrent falls, forgetfulness, forgetting ways to his house, confused behavior for 1 month. Phenytoin toxicity was suspected. There was no gingival hypertrophy with bleeding gums, hirsutism or skin manifestations like nodular changes. Phenytoin was stopped and blood was sent for analysis.

On evaluation, serum phenytoin levels were >40mcg/ml .The Naranjo's criteria and WHO probability scale were applied to determine the causality for suspected adverse reactions (ADRs). The causality assessment with both scales revealed that adverse reaction due to phenytoin in this case was probable (Naranjo overall score: 6) after withdrawal of Phenytoen vomitinh, giddiness subsided, ataxia reduced and sensoriumi mproved.

Discussion

The possibility of a paradoxical increase in seizure frequency as a manifestation of intoxication has been recognized in this case. Phenytoin (PHT) appears to be implicated most frequently in reports of paradoxical intoxication.[3] In some cases an increase in seizure frequency may be the only presenting symptom of drug intoxication as noted in our case.

Phenytoin has a narrow therapeutic range of 10-20 mcg/ml. At plasma concentrations below 10 mcg/ mL, elimination follows first order.[1] However, at higher concentrations, including those in the therapeutic range (10-20 mcg/mL), the metabolic pathway becomes saturated and elimination shifts to zero order. Half-life of Phenytoin varies between six and twenty-four hours at plasma concentrations less than 10 mcg/ml, but increases with higher concentrations. The toxic effects seen with chronic treatment are primarily dose related Cerebellar-vestibular effects. It may also cause other central nervous system effects, behavioral changes, increased seizure activity, gastrointestinal symptoms, hirsutism, gingival hyperplasia, osteomalacia and megaloblastic anaemia.

Our patient presented with seizure, vertigo, ataxia and behavioral changes. Our case did not show classical signs like gum hypertrophy, hirsutism or skin changes.

Chronic Phenytoin ingestion leads to its accumulation in the cerebellar cortex, resulting in atrophy of cerebellum, causing ataxia and nystagmus. Gingival hypertrophy may be attributed to altered collagen metabolism. Altered metabolism of sex steroid hormones by Phenytoin can induce hyper androgenic symptoms like hirsutism and nodular skin lesions. Signs of Phenytoin toxicity usually manifest at Phenytoin levels above 15 mcg/mL. Serum Phenytoin levels were >40mcg/ mL in our patient. Toxic effects may develop at therapeutic concentrations in some patients. This may be attributed to the unpredictable relationship between serum levels of Phenytoin and their side effects.[4]

This case report of Phenytoin toxicity helps to alert physicians about the toxic manifestations of Phenytoin in patients on long term therapy. There is also need for regular follow up to assess compliance and response to therapy. [5]Monitoring of serum Phenytoin levels and ADRs should be done even when the seizure is under control and especially when there are doubts of early toxic effects. This report also highlights the importance of educating patients and their caregivers about the clinical manifestations of Phenytoin toxicity, so that it can be recognized early and treated appropriately.

Conclusion

Clinician should keep in mind that phenytoin toxicity itself c an cause seizure without the commonly known manifestation. Early stoppage of drug appropriately might prevent dreadful complications. Long term therapy with Phenytoin should be individualized based on the patient's clinical response, plasma drug levels and signs of toxicity.

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