CASE STUDY

Phenytoin Toxicity: A Comprehensive Case Report Highlighting Clinical Manifestations, Therapeutic Drug Monitoring, and Management Strategies

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Abstract

Phenytoin, a widely used antiepileptic drug, in a loading dose of 15–20 mg/kg, followed by a maintenance dose of 4–7 mg/kg/day in divided doses, can lead to toxicity if the dose is exceeded, causing adverse neurological and systemic effects. This case report provides a concise overview of phenytoin toxicity, encompassing its mechanisms, clinical manifestations, and management. Common symptoms include ataxia, nystagmus, and altered mental status, while severe cases may involve cardiovascular and hematological complications. Monitoring serum levels, prompt recognition, and appropriate dose adjustments are crucial in preventing toxicity. Clinicians must maintain a high index of suspicion, as early intervention significantly impacts patient outcomes. This case report underscores the importance of vigilance and tailored interventions to mitigate the risks associated with phenytoin toxicity.

Key words: Adverse drug reaction, dose adjustments, phenytoin, therapeutic drug monitoring, toxicity

INTRODUCTION

Antiepileptic drug phenytoin, which is frequently used, has entirely revolutionized how different seizure disorders are treated.[1]

The main conditions for which phenytoin are prescribed include status epilepticus, focal seizures, and generalised tonic-clonic seizures. The usual dosage schedule changes according to the indication:

- Seizure prophylaxis and epilepsy: Initial oral loading dose of 15–20 mg/kg, followed by a maintenance dose of 4–7 mg/kg/day in divided doses.
- Status epilepticus: Intravenous loading dose of 15–20 mg/kg at a rate of ≤50 mg/min, followed by a maintenance infusion or oral dose of 4–6 mg/kg/day.[2]

It does, however, have possible hazards and negative consequences, much like any powerful medication. When the drug's concentration in the bloodstream exceeds therapeutic limits, it can cause phenytoin toxicity, which can result in a variety of alarming signs and problems.[3] In order to ensure patients receive the most benefits from phenytoin while reducing the risk of negative effects, this condition requires close attention and monitoring. In order to raise awareness and improve patient outcomes, we will delve into the intricacies of phenytoin toxicity. As a specific sodium channel blocker, the antiepileptic drug phenytoin stabilizes neuronal membranes and lowers excitability. It is frequently employed to manage different types of seizure. However, cautious administration and monitoring are essential to prevent toxicity due to its limited therapeutic index and nonlinear pharmacokinetics.[4] Adverse effects from phenytoin intoxication can include ataxia, nystagmus, and

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gingival hyperplasia.[5] Prompt recognition and appropriate management are vital for optimizing treatment outcomes while mitigating the risk of harmful consequences. The dose range of phenytoin can vary significantly depending on the patient's age, weight, individual response to the medication, and the condition being treated. Generally, the usual adult maintenance dose for phenytoin is between 200 and 400 mg/day, divided into two to three equally spaced doses.[6] It is important to note that phenytoin has nonlinear pharmacokinetics, meaning that its metabolism can be unpredictable and not directly proportional to the dose administered.[7] Therefore, close monitoring of blood levels is essential to ensure that the drug remains within the therapeutic range and to avoid toxicity. Individualized dosing and careful adjustments are necessary to achieve optimal treatment outcomes while minimizing the risk of adverse effects.[8]

CASE DESCRIPTION

A 48-year-old male presented to the general medicine with the chief complaints of decreased vision in both eyes for 2 days, fever since 15 days, generalized weakness, headache, ataxia, and difficulty in walking since 15 days, constipation, nausea, vomiting, forget fullness, and irrelevant talking for 4 days.

On inquiring about the past history, it was found that the patient was a known case of diabetes mellitus-II (DM) and hypertension (HTN) for past 15 years and was on GLIMISON MR (2/500, 1-0-1) and Tablet. ARKAMINE (0.1 mg, 1-1-1), Tablet. CILACAR TC (40/10/12.5 1-0-0) for DM-II and HTN, respectively. He had cerebrovascular infarct – left posterior cerebellar artery infarct 3 years back and was on ECOSPIRIN AV (150/75 0-0-1). He had seizure, a year back-1st episode last year and 4 episodes this year, he was previously prescribed with EPTOIN 300 mg at bed time, but after that seizure, the dose was increased from 300 mg to 600 mg from some other hospital.

On examination, it was found that the blood pressure was 170/100 mmHg. The patient was confused, drowsy, and disoriented to place, and the Glassgow coma scale was $E_4V_5M_6$.

The patient was admitted and was provided combined care from the general medicine and neurology department.

The laboratory tests-complete blood count, electrolytes, urine test, renal function test, liver function test, lipid profile, hemoglobin A1c, thyroid stimulating hormone, hepatitis C virus, and HbAg and human immunodeficiency virus were performed, they revealed that the urea and bilirubin were elevated. Ultrasound abdomen and pelvis revealed 2 renal calculi with mild two side hypronephrosis with subtle cortical irregularity suggestive of renal parenchymal disease. CT KUB was done, which revealed left renal pelvic calculus of 23 × 30 × 50 mm, left sided mild hydronephrosis with gross lower pole calyectasis, bilateral perinephric, and periuretric fat stranding.

Magnetic resonance imaging (MRI) was also planned, but the patient had claustrophobia and was not giving consent for it. The relative provided consent, but due to patient motion artifacts and it was scheduled on the next day. On the following day, oxygen saturation was decreased during MRI, and so it was not completed.

Ophthalmology reference was done in view of papilloedema and DM/HTN retinopathy. The fundus examination revealed no papilloedema, but the patient had grade-1 hypertensive retinopathy in both eyes.

Therapeutic drug monitoring (TDM)

The TDM was done, and the blood sample was collected for evaluation of serum phenytoin level. It was 40 mcg/mL, a lot higher than the normal value (10–20 mcg/mL).

Adverse drug reaction assessment

The table 1 summarizes the evaluation of an adverse drug reaction (ADR) using standardized pharmacovigilance tools. According to the WHO-UMC scale, the reaction is deemed probable, indicating a likely causal relationship with the drug. The Karch–Lasagna and Hartwig's scales both classify the reaction as severe, with Hartwig's level 5 suggesting hospitalization or extended care. The Naranjo algorithm rates the causality as definite, confirming a strong association with the suspected drug. Additionally, the reaction was considered predictable based on the drug's known profile and definitely preventable, implying that proper precautions or monitoring could have averted the event.

Management

Phenytoin tapering was started. Patient was given 400 mg on 1st day, then 200 mg on 2nd, and on 3rd day after admission.

Table 1: ADR assessment

Scales and criteria	Assessment
WHO-UMC causality assessment scale	Probable
Karch-Lasagna's scale	Severe
Hartwig's severity assessment scale	Level -5 (severe)
Naranjo's algorithm	Definite
Predictability	Predictable
Preventability	Definitely preventable

WHO-UMC: World health organization-Uppsala monitoring center, ADR: Adverse drug reaction

Table 2: Treatment management

Generic name	Dose	Frequency	Indication
Tab. amlodipine	5 mg	1-0-1	Hypertension
IVF NS/RL+2 ampoule optineuron	500 mL+2 mL	80 cc/h	Electrolyte replenishment
Inj. pantoprazole	40 mg	24 hourly	Acidity
Inj. on dansetron	4 mg	8 hourly	Vomiting
Tab. Glimiperide+metformin	2/500 mg	1-0-1	For diabetes
Tab. Telmiride+cilnidipine+chlorthalidone	40/10/12.5 mg	1-0-1	For hypertension
SYP. lactulose	30 mL with half glass water	H.S	Constipation
Aspirin+Atorvastatin	75/10 mg	0-0-1	For CVA protection

CVA: Cerebrovascular accident

And gradually phenytoin was stopped [Table 2].

Levetiracetam 500 mg 0-0-1 was started. All the other medications were continued.

Nephrolithotomy was not possible because the patient was not completely stable for surgery. It was planned on a follow-up.

DISCUSSION

Our patient presented with generalized weakness, difficulty in walking, vomiting, and constipation the similar complaints are seen in a case report done by Menon *et al*. Their patient was taking 200 mg phenytoin for the past 5 years and had normal ranges for biochemical reports, but the serum phenytoin level was 21.6 mcg/mL. By considering all clinical signs and serum phenytoin level, it was diagnosed a case of phenytoin toxicity. Similar investigations are found in our case. The biochemical reports are normal, but the serum phenytoin level was increased, 46 mcg/mL.[9]

Our patient had headache, dizziness, and ataxia. Similar complaints such as involuntary movements, ataxia, generalized weakness, and ataxia due to phenytoin toxicity were found in a case report done by Juhi *et al*.[10]

The therapeutic range for phenytoin is only 10–20 mcg/mL. First-order elimination occurs at plasma concentrations <10 mcg/mL. At higher dosages, particularly those greater than the therapeutic range (10–20 mcg/mL), the metabolic pathway becomes saturated, and elimination shifts to zero order. At plasma concentrations below 10 mcg/mL, the half-life of phenytoin ranges from 6 to 24 h, while it is prolonged at higher doses. As a result, the plasma concentration rises disproportionately even with a tiny dose. In general, toxicity and rising plasma levels are correlated. The lengthened duration of toxic effects can also be caused by the extended half-life brought on by zero order pharmacokinetics.[9] Overdosing on phenytoin increases the risk of toxicity; signs of phenytoin toxicity include coma, trouble speaking clearly, involuntary eye movements, poor coordination of the muscles, hypotension, nausea, sluggishness, slurred speech, tremors, and vomiting. For the best dosing regimen, it is important to therapeutically monitor the plasma levels of phenytoin.[10] In our case, patient came with phenytoin toxicity symptoms such as weakness, nystagmus, irritability, irrelevant talking, headache, and dizziness.

Considering the size of kidney stone (23 × 30 × 50 mm), the recommended first-line treatment plan is nephrolithotomy. In an article by Skolarikos *et al*., nephrolithotomy possesses advantages in removing large stones and decreases morbidity.[11]

CONCLUSION

This case report highlights phenytoin toxicity. Phenytoin is a common drug with numerous side effects. It is important to consider symptomatic phenytoin toxicity. This case supports the need for free phenytoin concentration monitoring in specific cases where there is clinical suspicion. This case highlights the need and importance of proper patient counseling as well as proper dosing regimen by the physician.

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DECLARATION OF PATIENT CONSENT

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) have given their consent for his/her images and other clinical information to be reported in the journal. The patients understand that his/her name and initial will not be published and due efforts will be made to conceal his/her identity.

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