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Case Report

A rare presentation of phenytoin toxicity triggered by isoniazid in reactivated pulmonary TB

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ABSTRACT

Phenytoin is a commonly used antiepileptic drug with a narrow therapeutic index and is susceptible to clinically significant drug–drug interactions. It is primarily metabolized by hepatic cytochrome P450 enzymes, particularly CYP2C9. Isoniazid, a first-line anti-tubercular agent, is a known inhibitor of this enzyme and may precipitate phenytoin toxicity when co-administered. We report a case of phenytoin toxicity in a patient with reactivated pulmonary tuberculosis following the initiation of isoniazid therapy. The patient experienced neurological features including dizziness, generalized weakness, involuntary movements, and MRI brain revealed multifactorial encephalopathy suggestive of phenytoin toxicity, supported by laboratory findings (serum phenytoin levels-35.2 µg/mL) and clinical evaluation. Phenytoin was discontinued and replaced with levetiracetam, along with appropriate supportive management. The patient showed gradual clinical improvement after withdrawal of phenytoin, and antitubercular therapy was continued under close monitoring. This case highlights the importance of recognizing potential drug–drug interactions between phenytoin and isoniazid, early neuroimaging and therapeutic drug monitoring in tuberculosis patients receiving long -term antiepileptic therapy.

Keywords: Phenytoin, Isoniazid, Encephalopathy, Levetiracetam, Pulmonary tuberculosis

INTRODUCTION

Phenytoin is one of the most commonly used antiepileptic drugs for the treatment of epilepsy. It acts by binding to voltage-gated sodium channels, thereby reducing high-frequency neuronal firing. Phenytoin has a narrow therapeutic index; hence, even a small change in dosage or alteration in metabolism particularly due to drug-drug interactions may lead to toxicity.[1] Concomitant use of phenytoin and antitubercular therapy (particularly isoniazid) may result in hepatic dysfunction and phenytoin intoxication. Phenytoin is primarily metabolized in the liver by the cytochrome P450 enzyme CYP2C9. Isoniazid, a first-line antitubercular drug, inhibits this enzyme, thereby reducing the metabolism of phenytoin and leading to elevated serum levels and toxicity. Accumulation of toxic levels of phenytoin may further contribute to hepatic impairment.[2]

Review articles have highlighted that drug–drug interactions are among the most frequent causes of phenytoin intoxication, especially in patients receiving long-term therapy. Therapeutic drug monitoring should be performed on regular basis in patients receiving concomitant antitubercular therapy to prevent toxicity.[3] Delayed recognition of phenytoin intoxication may lead to serious and potentially life-threatening complications. We report a case of phenytoin toxicity in a patient with reactivated pulmonary tuberculosis, emphasizing the role of drug–drug interactions and hepatic impairment in precipitating toxicity.[1-3]

CASE REPORT

Patient information

A 42-year-old female presented to the hospital with chief complaints of fever with chills, body pain, burning micturition, vomiting, loose stools, and poor appetite for 15 days. She also reported intermittent abdominal pain and unintentional weight loss for one month, along with progressive abdominal distension for the past four months.

Medical history

She had a past history of pulmonary tuberculosis diagnosed 13 years earlier, for which she had completed a full course of antitubercular therapy. She was a known case of epilepsy for the past 13 years and had been on phenytoin (100mg AM, 200mg PM) and valproic acid (300mg BD) with good seizure control and no prior adverse effects.

Clinical and diagnostic assessment

Initial laboratory investigations revealed mild hepatic enzyme elevation, Renal function tests showed urea of 12.8 mg/dL, creatinine of 0.40 mg/dL, and uric acid of 2.10 mg/dL. Anaemia with microcytic hypochromic indices, hypoalbuminemia, hyponatremia, hypochloraemia, hypocalcaemia, and elevated plasma ammonia levels. Chest radiography showed bilateral peri bronchial cuffing with patchy opacification in the left upper zone. High-resolution computed tomography (HRCT) of the chest revealed features suggestive of reactivated pulmonary tuberculosis. Interferon-gamma release assay (IGRA) was negative.

Based on radiological findings, antitubercular therapy comprising isoniazid (300 mg OD), rifampicin (300 mg OD), pyrazinamide (1000 mg OD), and ethambutol (600 mg OD) was initiated.

Clinical Course Fifteen days after initiation of antitubercular therapy, the patient developed dizziness, nausea, generalized weakness, involuntary movements, and unsteady gait. Serum phenytoin levels were markedly elevated at 35.2 µg/mL (therapeutic range: 10-20 µg/mL). MRI of the brain with contrast demonstrated features suggestive of multifactorial encephalopathy. Based on clinical findings, laboratory data, and imaging, a diagnosis of phenytoin toxicity precipitated by drug–drug interaction with isoniazid was made. Serial laboratory values are summarized in Table 1.

Based on clinical presentation, laboratory investigations, neurological evaluation and serum phenytoin levels, a diagnosis of phenytoin induced drug -drug interaction was made in the setting of reactivated pulmonary tuberculosis.

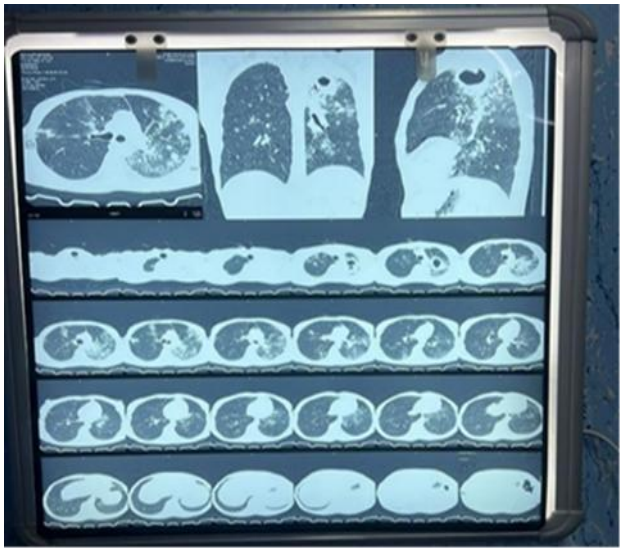

Figure 1: High-resolution computed tomography of the chest showing patchy opacities suggestive of reactivated pulmonary tuberculosis.

Management and outcome

Phenytoin was immediately discontinued and replaced with levetiracetam (500mg BD) following the detection of elevated serum phenytoin levels. The patient was managed conservatively with supportive therapy, including correction of electrolyte imbalances and close neurological monitoring. Liver function tests and serum phenytoin levels were monitored serially.

Based on HRCT findings suggestive of active pulmonary tuberculosis, anti-tubercular therapy (pyrazinamide, ethambutol, rifampicin and streptomycin) was initiated under close monitoring. Due to suspected isoniazid-induced phenytoin toxicity, isoniazid was discontinued and replaced with streptomycin (0.75gm IM) as part of the anti-tubercular regimen. The patient showed gradual improvement in gastrointestinal and neurological symptoms, including resolution of dizziness and involuntary movements. Serum phenytoin levels declined progressively, and liver enzyme levels showed improving trends.

The patient was discharged in stable condition with appropriate follow-up advice, including regular therapeutic drug monitoring and outpatient review.

Causality and severity assessment

According to the World Health Organization–Uppsala Monitoring Centre (WHO–UMC) causality assessment system, the adverse drug reaction was classified as probable, and according to the Hartwig and Siegel scale, the adverse drug interaction was classified as moderate.

Table 1: Laboratory and radiological investigations during hospital stay.

Date	Investigations	Result	Normal range
30/12/25	Serum calcium	7.6 mg/dl	8.3-10.6 mg/dl
30/12/25	IGRA	Negative	-
30/12/25	Chest radiography	Patchy opacification in left upper zone	-
30/12/25	HRCT chest (low -Dose)	Lung opacities, Suggestive of pulmonary TB	-
31/12/25	EEG	Abnormal EEG	
14/1/26	HB	11.8 g/dl	11.5-15 g/dl
14/1/26	Neutrophils	94 %	40-80%
14/1/26	Left Direct bilirubin	0.5 mg/dl	0.0-0.3 mg/dl
14/1/26	SGPT	135 u/l	Up to 41 u/l
14/1/26	SGOT	339 u/l	Up to 40 u/l
16/1/26	Serum electrolytes: sodium	127 mmol/l	135-150 mmol/l
16/1/26	Potassium	3.8 mmol/l	3.5-5.0 mmol/l
16/1/26	Chloride	86.3 mmol/l	94-110 mmol/l
16/1/26	Plasma ammonia	271.1 µg/dl	18.7-86.9 µg/dl
16/1/26	Serum phenytoin	35.2 µg/ml	10-20 µg/ml
17/1/26	MRI brain (contrast)	Features suggestive of multifactorial encephalopathy	-
17/1/26	Serum electrolytes: sodium	132 mmol/l	135-150 mmol/l
17/1/26	Potassium	3.6 mmol/l	3.5-5.0 mmol/l
17/1/26	Chloride	92.1 mmol/l	94-100 mmol/l
17/1/26	Calcium	7.8 mmol/l	8.3-10.6 mg/dl

DISCUSSION

Phenytoin is a widely used antiepileptic drug for the management of generalized, tonic-clonic and focal seizures. In the present case, a patient receiving long-term phenytoin therapy developed clinical and biochemical features of phenytoin toxicity following the initiation of anti-tubercular therapy for reactivated pulmonary tuberculosis. Phenytoin exerts its antiepileptic effect by stabilizing neuronal membranes through inhibition of voltage-gated sodium channels, thereby reducing repetitive neuronal firing. It has a narrow therapeutic index and exhibits non-linear pharmacokinetics, such that small changes in dose or alterations in hepatic metabolism may result in disproportionately elevated serum drug concentrations and toxicity.[4,5]

Phenytoin is primarily metabolized in the liver by cytochrome P450 enzymes, predominantly CYP2C9. Concomitant administration of enzyme-inhibiting drugs can significantly reduce phenytoin clearance.[2] Isoniazid, a key component of first-line anti-tubercular therapy, is a known inhibitor of CYP2C9 and has been reported to precipitate phenytoin toxicity when co administered.[6,7] In the present case, initiation of isoniazid was temporally associated with the development of neurological symptoms and a markedly elevated serum phenytoin level (35.2 µg/mL), supporting a clinically significant drug–drug interaction. In addition to pharmacokinetic interaction, underlying hepatic dysfunction may further contribute to impaired phenytoin metabolism. Patients with active tuberculosis are at increased risk of hepatic involvement, and several anti-tubercular drugs are themselves hepatotoxic.[8] The presence of deranged liver enzymes in this patient may have compounded the inhibitory effect of isoniazid, further increasing serum phenytoin concentrations and precipitating toxicity. Similar cases of phenytoin toxicity associated with anti-tubercular therapy have been reported in the literature, highlighting the clinical relevance of this interaction.[6,7] However, therapeutic drug monitoring of phenytoin is not routinely practiced in many tuberculosis endemic settings, increasing the risk of delayed recognition and adverse outcomes.[9] This case underscores the importance of close clinical and biochemical monitoring in patients receiving phenytoin concomitantly with anti-tubercular therapy. Multifactorial encephalopathy on imaging created diagnostic uncertainty between infection-related and drug-drug interaction. Early recognition of neurotoxicity, prompt measurement of serum phenytoin levels, and timely modification of antiepileptic therapy-such as switching to alternatives with fewer drug interactions like levetiracetam-are crucial to prevent serious complications.[4-9]

CONCLUSION

This case highlights the importance of recognizing the potential drug-drug interaction between phenytoin and isoniazid, resulting in phenytoin toxicity. Therapeutic drug

monitoring and considering any other antiepileptic drug is essential. Clinicians should exercise caution when prescribing phenytoin concurrently with isoniazid**.**

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