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Case Report

Acute isoniazid toxicity presenting with refractory seizures, severe metabolic acidosis, and rhabdomyolysis: a case report

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ABSTRACT

Isoniazid remains widely used in India due to the high burden of tuberculosis and HIV, with toxicity being an important clinical concern. While peripheral neuropathy and hepatotoxicity are common, acute overdose presenting with seizures and rhabdomyolysis is uncommon and potentially fatal. A 21-year-old male presented following intentional ingestion of approximately 9 g of isoniazid, with two episodes of generalized tonic–clonic seizures. On admission, he was drowsy but arousable (GCS 12/15). Initial management included gastric lavage and activated charcoal. Laboratory findings showed elevated creatine phosphokinase (2556 U/l) and mild metabolic acidosis. Liver enzymes rose from day 2, peaked by day 5, and normalized by day 12. CPK levels peaked on days 5–6 and declined thereafter, correlating with generalized myalgia. The patient was treated with intravenous fluids, 5 g pyridoxine, and alkaline diuresis, with gradual clinical and biochemical recovery. He was discharged on day 14 after psychiatric evaluation. This case emphasizes the need to recognize isoniazid toxicity, classically characterized by seizures, metabolic acidosis, and altered sensorium. Early administration of pyridoxine and supportive care are essential for a favorable outcome.

Keywords: Isoniazid toxicity, Pyridoxine therapy, Drug-induced seizures, High anion gap metabolic acidosis, Rhabdomyolysis

INTRODUCTION

Isoniazid (INH) is a first-line anti-tubercular drug, a core component of both intensive and continuation phases of treatment for drug-susceptible *Mycobacterium tuberculosis* (MTB) infection, and is widely used for latent tuberculosis (TB) infection and tuberculosis preventive therapy.[1,2] With the highest number of TB cases in India and widespread use of isoniazid, Indian physicians need to be aware of its potential toxicities and their management.[3]

Acute isoniazid toxicity classically presents with a triad of metabolic acidosis, seizures, and altered sensorium.[4] The seizures respond effectively to pyridoxine administration, which restores depleted pyridoxal-5-phosphate and allows normal gamma-aminobutyric acid (GABA) synthesis.[5] Other reported complications include hepatotoxicity, rhabdomyolysis, peripheral neuropathy, and rare immune-mediated effects like drug-induced lupus erythematosus.[6]

We report a rare case of intentional acute isoniazid overdose in a young male presenting with seizures, altered sensorium, and severe metabolic acidosis, who showed significant clinical improvement following pyridoxine therapy.

CASE REPORT

A 21-year-old male was brought to the emergency department with decreased responsiveness following two

episodes of generalized tonic-clonic seizures involving all four limbs associated with tongue bite and involuntary micturition. He had an alleged history of intentional ingestion of 30 tablets of isoniazid 300 mg (approximately 9 g) around two hours prior to presentation. The patient had been prescribed isoniazid prophylaxis, as a household contact was on treatment for pulmonary tuberculosis.

There was no preceding history of fever, headache, trauma, or prior seizures. He was not known to have epilepsy or any chronic medical illness, including diabetes mellitus, renal disease, or liver disease. There was no recent history of alcohol or recreational drug use.

Upon arrival, he was drowsy with a Glasgow coma scale score of 12/15. Vital signs revealed a blood pressure of 120/80 mmHg, a pulse rate of 92 beats/min, and tachypnea. Pupils were bilaterally equal at 4 mm and reactive to light. Systemic examination was otherwise unremarkable.

Initial management included airway protection with an oropharyngeal airway, insertion of a nasogastric tube, and gastric lavage. Intravenous fluids and multidose activated charcoal were given. He received 10 mg of intravenous diazepam, followed by phenytoin with a loading dose of 20 mg/kg. Despite this, he had another episode of seizures one hour later, which was treated with intravenous diazepam. Subsequently, 5 g of pyridoxine tablets were administered via the nasogastric tube, following which the patient had no further episodes of seizure.

Initial investigations revealed leukocytosis with a total leukocyte count of 15,100/mm³. Hemoglobin and platelet counts were normal. Random blood glucose was 118 mg/dl. Renal function tests and serum electrolytes were within normal limits. Urinalysis revealed no hemoglobinuria or myoglobinuria.

Arterial blood gas analysis on admission demonstrated severe high anion gap metabolic acidosis with pH 6.9, bicarbonate (HCO_3) 6 mmol/l, pCO_2 40 mmHg, and anion gap 43.8. Sodium bicarbonate therapy was initiated. Serial blood gas analyses showed a gradual correction of acidosis, as shown in Table 1. Ultrasonography of the abdomen and computed tomography (CT) of the brain did not reveal any abnormalities.

The patient's sensorium improved progressively and normalized by the third day of hospitalization. Serum aspartate aminotransferase (SGOT) and creatine phosphokinase (CPK) levels were elevated from day one, peaking between days five and six (Figures 1 and 2), accompanied by myalgia, consistent with rhabdomyolysis. Management included forced alkaline diuresis, with urine pH maintained above 6.5 and urine output above 200 ml/hour. Pyridoxine was continued at a maintenance dose of 100 mg/day. Serial monitoring demonstrated gradual normalization of SGOT and CPK levels by day twelve, with complete resolution of myalgia. The patient was discharged on day 14 after psychiatric evaluation and counselling. Follow-up visits at 30 and 60 days were uneventful, with normal biochemical parameters, indicating complete recovery. Prophylactic pyridoxine at 100 mg/day was continued.

Table 1: Serial blood gas analyses.

Day in hospital	pH	pCO_2	HCO_3	Anion gap
1	6.90	40	6.0	44
2	7.29	29	13.8	19
3	7.38	25	15.8	18
4	7.40	30	20.6	12

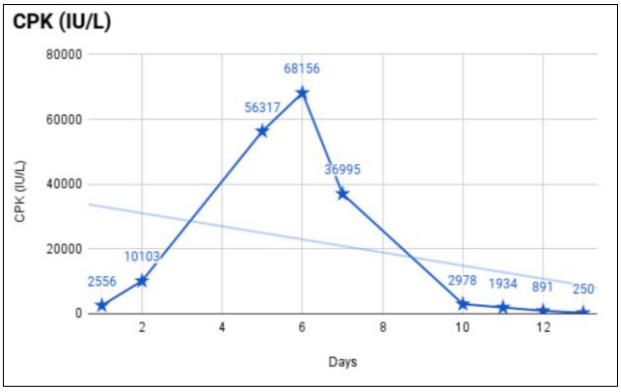

Figure 1: Serial CPK levels.

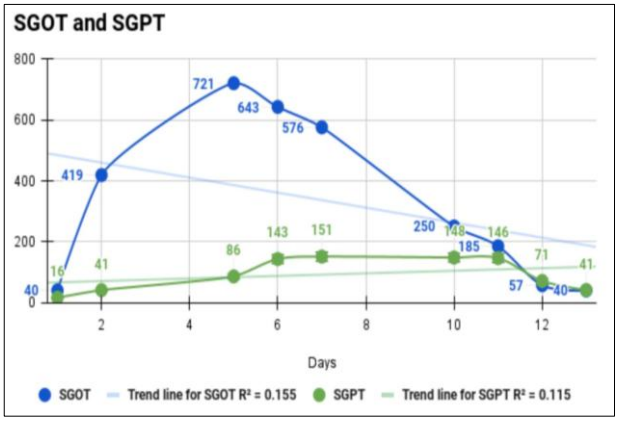

Figure 2: Serial SGOT and SGPT levels.

DISCUSSION

Role of isoniazid

The serendipitous observation that high doses of nicotinamide halted disease progression in Mycobacterium tuberculosis-infected guinea pigs prompted researchers to investigate structurally related compounds with antitubercular activity, ultimately leading Herbert Fox and colleagues to identify isoniazid as an effective antitubercular agent.[7] Isoniazid has been a cornerstone first-line drug in anti-tubercular therapy for

the past 70 years since the famous Edinburgh method by Sir John Crofton in 1952.[8]

INH, when activated in the liver, leads to the formation of several radicals and adducts with NAD, inhibiting the mycolic acid synthesis and elongation, leading to loss of cell wall integrity and death.[9] According to recent global estimates, around 4.7 million individuals received TPT in 2023, reflecting the widening adoption of INH-based preventive regimens.[10]

Toxicity of INH

INH is available as tablets (100 and 300 mg), syrup (50 mg/5 ml), and IV/IM injection (100 mg/ml). The maximum recommended dose of INH in adults is 300mg per day or up to 900 mg per day in 2 to 3 divided doses per week in intermittent regimens, while chemoprophylaxis involves 300 mg/day for 6 to 9 months.[11]

Despite its efficacy, INH has a narrow therapeutic margin and is capable of producing both acute and chronic toxicity. Clinical manifestations of acute toxicity have been reported at doses as low as 20–40 mg/kg, while ingestion exceeding 80–150 mg/kg (approximately 1.5–2 g in adults) is associated with severe toxicity and may be fatal if untreated. Acute isoniazid toxicity typically manifests at 30 minutes to 2 hours after ingestion. The drug permeates body fluids and tissues, attaining its peak concentration in the liver, causing symptoms like nausea, vomiting, dysarthria, giddiness, and urinary retention, and may progress to recurrent grand mal seizures, high anion gap acidosis, and coma. Blood levels cannot be used in the management of acute overdose.[4]

The most important dose-limiting symptoms of chronic isoniazid toxicity is hepatotoxicity.[12] Rarer adverse effects include hematological manifestations such as sideroblastic anemia; immunological reactions including drug-induced lupus erythematosus, and endocrinological presentations such as gynecomastia and pellagra-like syndrome.[13,14] Chronic toxicity is more likely with prolonged supratherapeutic exposure, particularly beyond six months, and in the absence of pyridoxine supplementation.[15] The development of chronic isoniazid toxicity is strongly influenced by host susceptibility factors, including advanced age, female sex, pregnancy or postpartum status, malnutrition, alcohol use, pre-existing liver disease such as viral hepatitis, renal impairment, diabetes mellitus, and HIV infection. Concomitant use of hepatotoxic drugs such as rifampicin, pyrazinamide, and antiepileptic medications, as well as exposure to enzyme inducers or inhibitors, further increases the risk of isoniazid-related chronic toxicity.[12,13]

According to the National Poison Data System (NPDS) of the United States, 1,373 cases of isoniazid overdose were reported, of which 40.6% occurred in individuals younger than 20 years and 16% involved children under five years of age. Serious adverse outcomes were reported in 94 cases (approximately 7%), including two fatalities. In 2020 alone, 54 cases of isoniazid toxicity were reported.[16]

Mechanisms of isoniazid toxicity

Seizures are the hallmark of acute isoniazid toxicity and typically occur at doses ≥30 mg/kg. Isoniazid interferes with pyridoxine metabolism, causing depletion of pyridoxal-5′-phosphate, an essential cofactor in gamma-aminobutyric acid (GABA) synthesis. Reduced GABA levels result in neuronal hyperexcitability and seizures. Central nervous system manifestations include confusion, drowsiness, and coma, often associated with metabolic acidosis. Pyridoxine reverses toxicity by restoring normal GABA synthesis.[4,17]

Rhabdomyolysis is a recognized complication, primarily resulting from prolonged seizure-induced muscle injury, and may lead to markedly elevated creatine kinase levels and risk of acute kidney injury.[18]

In patients presenting with seizures, altered sensorium, and high anion gap metabolic acidosis, toxicological etiologies such as methanol, ethylene glycol, salicylates, and isoniazid should be strongly considered. Important differentials also include metabolic causes (diabetic ketoacidosis, uremia), neurological conditions (status epilepticus, central nervous system infections), infectious etiologies (severe sepsis, cerebral malaria), hypoxic states, and, in children, inborn errors of metabolism. Isoniazid toxicity typically results in high anion gap metabolic acidosis due to lactate accumulation from prolonged seizures and direct mitochondrial inhibition of oxidative phosphorylation, with tissue hypoperfusion further aggravating acidosis. Sodium bicarbonate therapy is indicated in severe acidemia (pH<7.1). In the present case, metabolic acidosis improved following the timely administration of intravenous sodium bicarbonate and pyridoxine.[4]

Management of isoniazid toxicity

Management of isoniazid toxicity is primarily supportive and includes early airway protection, intravenous fluid resuscitation, and rapid control of seizures. Definitive treatment consists of prompt pyridoxine replacement, which directly reverses the underlying GABA deficiency. Gastrointestinal decontamination with gastric lavage and activated charcoal may be considered if the patient presents within one hour of ingestion. Metabolic complications, particularly high anion gap metabolic acidosis and electrolyte abnormalities, should be corrected aggressively. In cases of refractory seizures, severe acidosis, or massive ingestion, adjunctive therapies such as barbiturate infusion or hemodialysis may be required.[4,19]

Caveats

Intravenous benzodiazepines such as diazepam (5–10 mg) are recommended for initial seizure control in acute

isoniazid toxicity; however, definitive seizure termination usually requires pyridoxine administration. Pyridoxine should be administered in a dose equivalent to the estimated amount of isoniazid ingested; when the ingested dose is unknown, 5 g intravenously over 5–10 minutes is recommended, with repeat dosing if seizures or altered sensorium persist.[4]

A liberal approach to pyridoxine therapy is advised, as neurotoxicity from pyridoxine has not been reported even at very high doses (up to 50 g).[2] When intravenous preparations are unavailable, oral pyridoxine administered via crushed tablets may be used as an effective alternative.[4]

Screening patients for depression prior to initiation of isoniazid therapy is prudent, particularly in the context of expanding preventive therapy programs. High-risk individuals should receive limited medication supplies with close monitoring. All patients must be counseled regarding the toxic potential of isoniazid, pyridoxine supplementation should be routinely prescribed during long-term therapy, and strict precautions should be taken to keep medications out of children's reach.[2]

CONCLUSION

Acute isoniazid overdose is a potentially fatal but readily treatable emergency. Although its toxicity may manifest with a broad spectrum of clinical features, the presence of recurrent seizures, altered sensorium, and high anion gap metabolic acidosis should prompt early consideration of isoniazid poisoning, particularly in individuals receiving antitubercular therapy or prophylaxis. Our patient presented predominantly with recurrent seizures and demonstrated rapid clinical improvement following pyridoxine administration, highlighting the reversibility of isoniazid-induced neurotoxicity when recognized early. Prompt diagnosis, timely pyridoxine replacement, correction of metabolic derangements, and supportive care remain the cornerstones of successful management and can lead to complete recovery even after massive overdose.

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