Case Report: Acute isoniazid intoxication after intentional ingestion

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Abstract
Isoniazid is an anti-tuberculosis medication that is extensively used for treatment and prevention of tuberculosis. Acute isoniazid poisoning is characterized by a clinical triad of recurrent seizures, raised anion gap metabolic acidosis and coma. The seizures are unresponsive to standard anticonvulsant drugs, instead requiring pyridoxine administered in a dose equal to the amount of isoniazid consumed. Due to the high incidence of tuberculosis in low-income countries like Nepal, isoniazid intoxication should be considered in any patient who present with such unresponsive seizures and coma. We report a case of a 31 years old woman from Nepal, who intentionally ingested 12 grams of isoniazid and presented with generalized tonic-clonic seizures. She was successfully managed with 10 grams of pyridoxine along with other supportive management, including sodium bicarbonate for metabolic acidosis and mechanical ventilation.

Doctors working in low-income countries, like Nepal, where tuberculosis is endemic, should be well acquainted with presentations and management of isoniazid intoxication.

Keywords
Isoniazid, seizure, metabolic acidosis, coma, pyridoxine
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**Introduction**

Isoniazid (INH), a bactericidal antimicrobial that has been the mainstay of tuberculosis (TB) treatment and prevention since the 1950s. In recent years, TB has remained a severe worldwide health problem in low and middle-income countries. Nepal is one of the countries with the highest TB burden as of 2021, with a growing prevalence of cases. The use of INH preventive therapy (IPT) for HIV-positive individuals has grown as well. Because of its widespread usage in TB prevention and treatment, accidental or intentional poisoning is anticipated to become more common. INH dosages as low as 1.5 g have been recorded to induce mild toxicity, doses of 6–10 g have been known to cause severe toxicity, and doses greater than 15 g have been documented to be deadly. Acute INH toxicity results in a clinical triad of recurrent seizures, metabolic acidosis and coma. Seizures can progress to status epilepticus, which is resistant to benzodiazepines and antiepileptic drugs. INH poisoning is thought to be responsible for 6% of all drug-induced seizures. We report a case of a patient who intentionally ingested a lethal dose of INH, presenting with refractory status epilepticus, metabolic acidosis and coma.

**Case report**

A 31-year-old Nepalese woman, homemaker, with no previous medical history presented to the emergency room (ER) of a nearby hospital with the complaints of irregular body movement, tongue biting, and urinary incontinence, all of which were consistent with generalized tonic-clonic seizure (GTCS). One hour prior to the presentation, she had consumed 12 grams of INH (40 tablets, each containing a dose of 300 mg). Her husband mentioned that he had been diagnosed with HIV/AIDS and Hepatitis C and was taking INH as a prophylaxis for tuberculosis. He also stated that they had an argument shortly before she ingested INH tablets. No prior efforts at self-harm had been made.

On examination in the ER, the patient was unconscious (GCS: 10/15, E2 V4 M4), foaming, and clenching her teeth. Her vital signs were unstable [blood pressure: 82/52 (normal 90–120/60–80) mm Hg, oxygen saturation: 89% (normal >94%) in room air, heart rate: 163 (normal 60–100) beats per minute]. The patient was resuscitated with IV fluid and oxygen administered via a face mask at a rate of 6 liters per minute. She had another episode of GTCS minutes after arriving at the ER. Subsequently, 10 mg of intravenous diazepam and phenytoin at a dose of 20mg/kg body weight were administered. In addition, a nasogastric (NG) tube was placed, and a gastric lavage with 1.5 liters of normal saline was performed. In addition, 5 grams of pyridoxine tablets were administered via an NG tube.

The patient further developed five more episodes of GTCS before regaining consciousness in the ER, for which she received subsequent doses of 10 mg of diazepam. An additional 5 gm of pyridoxine was provided, following which the seizure was controlled. Arterial blood gas (ABG) analysis revealed severe metabolic acidosis with raised lactate [pH: 6.789 (normal 7.35–7.45), pCO₂: 40.1 (normal 35–45) mm Hg, pO₂: 68.7 (normal 80–100) mm Hg, HCO₃⁻: 6.1 (normal 22–26) mmol/L, Lactate: 18.8 (normal <2) mmol/L]. Thus, a bolus of 100 mEq sodium bicarbonate was given over 2 minutes, followed by a continuous sodium bicarbonate infusion of 100 mEq in 1 L over 4 hours. The patient was promptly referred to our center’s intensive care unit (ICU). On examination in the ICU, her GCS was 4/15 (E1V1M2). Her vital signs were unstable (blood pressure: 70/50 mm Hg, respiration rate: 26 breaths per minute, heart rate: 120 beats per minute, temperature: 98°F, oxygen saturation: 98% with high flow oxygen via face mask). Her pupils were 4 mm in diameter bilaterally and reactive. Deep tendon (+++) and plantar reflexes were normal. Respiratory, cardiovascular and abdominal examinations were normal. An endotracheal tube was placed to protect the patient’s airway and she was kept on mechanical ventilation in AC/VC (assist control/volume control) mode. Additionally, a central venous catheter was placed, and inotropic support was initiated.

The initial laboratory investigation revealed an elevated total blood count (32,800/mm³; reference range, 4000–11000/mm³) with neutrophilic predominance (95%). Renal function test (RFT) revealed normal urea (7 mg/dl; reference range: 10–45 mg/dl) and creatinine (0.6 mg/dl; reference range: 0.5–1.2 mg/dl) levels. Serum electrolytes including sodium (145 mEq/L; reference range: 135–145mEq/L), potassium (4.1 mEq/L; reference range: 3.5–4.5 mEq/L) were normal; however, the patient’s calcium (7.2 mg/dl; reference range: 8.5–10.5 mg/dl) and magnesium (0.8 mg/dl; reference range: 1.7–2.2 mg/dl) were low. Liver function test (LFT) revealed normal total bilirubin (0.4 mg/dl; reference range: 0.4–1.2 mg/dl), direct bilirubin (0.1 mg/dl; reference range: 0.1–0.4 mg/dl), alanine transaminase (93 U/L; reference range: 35–110 U/L). However, her creatinine phosphokinase level was elevated (36415 U/L; reference range: 24–195 U/L).

The patient’s total blood count, liver enzymes, RFT and ABG analyses were monitored daily. The liver enzymes were found to be elevated on the second day, peaked on the fourth day, and then returned to normal on the seventh day with conservative management (Figure 1). Her acid-base analysis returned to normal on the third day of admission with sodium bicarbonate supplementation (Table 1). Lactate was also persistently high until the third day (up to 36 hours after last episode of seizure) (Figure 2).

The patient regained consciousness 36 hours after her admission, and was weaned off the ventilator and extubated. She showed no signs or symptoms of neurological damage after being extubated. The patient was discharged on the eighth day of hospital admission. On follow up a week later, she denied new complaints and was feeling better. A psychiatry review did not reveal any underlying disorder leading to self-harm and she was managed with psychosocial counselling alone.
Figure 1. Trend of liver enzymes level (U/L) following isoniazid ingestion.

Table 1. Acid base analysis following isoniazid ingestion.

<table>
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<tr>
<th>Day of admission</th>
<th>pH</th>
<th>pCO2</th>
<th>HCO3</th>
<th>Anion gap</th>
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<tr>
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<td>7.445</td>
<td>29.2</td>
<td>19.6</td>
<td>10</td>
<td>99</td>
</tr>
</tbody>
</table>

Figure 2. Trend of serum lactate levels (mg/dl) following INH ingestion.
Discussion
Isoniazid is a bactericidal antimicrobial that has been used as a first-line drug for treatment of TB for over 70 years. It prevents the synthesis of lipids and DNA of Mycobacterium tuberculosis, halting their cell wall synthesis and development. INH is also used as IPT for people living with HIV who do not have active TB symptoms.

INH toxicity may occur with doses as low as 10–30 mg/kg. The first indications of toxicity appear 30–120 minutes after intake in most cases. Initial symptoms of acute overdose include nausea, vomiting, slurred speech and ataxia. Stupor and coma ensue in rapid succession, followed by seizure at doses over 30 mg/kg. Severe toxicity is characterized by the clinical triad of coma, recurrent seizures, and metabolic acidosis. The seizures are usually generalized tonic-clonic in nature and resistant to anticonvulsants such as phenytoin and barbiturates and begin within the first two hours after the overdose. INH causes seizure by lowering pyridoxal 5-phosphate in the brain, which is the active form of vitamin B6 (pyridoxine) and a necessary cofactor for the enzyme glutamic acid decarboxylase. Synthesis of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, in the central nervous system (CNS) are reduced as a result of this. Lower levels of the GABA in the CNS result in unrestrained electric activity, which manifests as seizures. Pyridoxine deficiency is most likely to be responsible for the loss of consciousness and coma, as supplementation of adequate amounts of pyridoxine causes a rapid recovery of consciousness. After only one or two seizures, profound anion gap metabolic acidosis (pH 6.8–6.7) is common, and it is most likely caused by lactic acidosis due to seizure activity. INH may also prevent lactate from being converted to pyruvate in the liver, worsening lactic acidosis caused by seizures.

Even when seizure activity is under control, lactate usually clears slowly.

Our patient ingested 12 grams (240 mg/kg) of INH, which is a deadly dose. Her husband was HIV-positive and was taking INH for tuberculosis prevention. Our patient presented one hour later with seizure as her primary symptom. Benzodiazepines and antiepileptics were not effective in controlling her seizure. In addition, she exhibited a severe metabolic acidosis with a large anion gap and raised lactate level.

Liver injury is a potential complication of acute INH poisoning, which can take several days to manifest. Increased synthesis of acetylhydrazine, an INH metabolite, can cause hepatic dysfunction. Our patient’s liver enzymes were initially normal, but they began to rise on the second day and peaked on the fourth day. Her LFT steadily improved and normalized with conservative management by the seventh day. Another complication of INH poisoning is rhabdomyolysis, indicated by elevated creatinine phosphokinase as in our case. Rhabdomyolysis can be secondary to seizures or can be due to a direct toxic effect of the drug or its metabolites on the muscles. Kidney failure, hyperglycaemia, and hyperthermia are other complications of acute INH poisoning. Fortunately, our patient did not exhibit these complications.

Management of INH toxicity consists of correction of life-threatening symptoms, administration of the antidote pyridoxine and supportive management to improve elimination of INH. Resuscitative management of airway, breathing and circulation should be done. Intubation is necessary when consciousness is strongly depressed. For patients with seizure, diazepam should be administered intravenously or intrarectally in a dose of 5 to 10 mg, dose should be repeated if necessary after 10 to 20 minutes. The seizures in INH poisoning are often refractory to anticonvulsants such as phenytoin and barbiturates.

Pyridoxine is the antidote of choice for the treatment for INH-induced seizure. It should be given in doses equivalent to the quantity of INH consumed. If the amount of INH consumed is uncertain, a dose of parenteral pyridoxine of 5g or 70 mg/kg to a maximum of 5g in a child can be given. The doses can be repeated every 5 to 20 minutes until the seizures stop or the patient regains consciousness. If intravenous pyridoxine is not available, an equivalent amount can also be administered via an enteral tube or orally. For the treatment of severe metabolic acidosis (pH 7.1 or less), sodium bicarbonate is useful. Treatment with pyridoxine also expedites the resolution of metabolic acidosis. After life-threatening symptoms have been stabilized, gastric lavage and gastrointestinal decontamination with activated charcoal should be undertaken to prevent additional absorption of INH. Because INH is rapidly absorbed from the gastrointestinal tract, these procedures are only effective if administered within an hour. In our patient, we could not administer activated charcoal because she presented after the time frame of one hour.

Our patient had seven episodes of GTCS that were not responsive to diazepam and phenytoin. Seizure subsided after she received 10 grams of pyridoxine via NG tube, 5 grams each time given 10 minutes apart. She had severe metabolic acidosis, for which she was provided sodium bicarbonate infusion. She remained comatose following seizure activities, thus an endotracheal tube was placed to protect her airway and she was subsequently kept on mechanical ventilation. She was weaned off the ventilator and extubated 36 hours later when she recovered consciousness. Despite our patient consuming a lethal dose of isoniazid and presenting to us with severe symptoms, she received timely medical intervention including pyridoxine that helped her condition improve swiftly. In addition, the inter-disciplinary team (ER team, ICU team, psychiatrist, psychotherapist, physiotherapist) approach to provide optimal medical care to the patient led to improved patient outcome.

Prognostic factors include advanced age, pre-existing seizure disorder, severe metabolic acidosis, and impaired renal function. However, treatment with pyridoxine intravenously in dosages equivalent to the predicted consumed dose of INH...
when paired with general supportive measures, has shown beneficial impacts.\textsuperscript{10,16}

Conclusion

Due to the high incidence of tuberculosis and HIV in our part of the world, INH intoxication should be considered in any patient presenting with metabolic acidosis, seizures, especially if they are resistant to standard anticonvulsants, and coma. Pyridoxine (vitamin B6) is the cornerstone of treatment, and the dose should be equivalent to the quantity of INH consumed. Prognosis is primarily determined by early diagnosis and treatment.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Consent

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient.

References