Isoniazid Toxicity Presenting As Status Epilepticus and Severe Metabolic Acidosis

Yojana A Gokhale*, Meghna S Vaidya**, AD Mehta***, NN Rathod***

Abstract
Isoniazid (INH) is an integral component of treatment of tuberculosis. An acute overdose is potentially fatal and is characterized by the clinical triad of repetitive seizures unresponsive to the usual anticonvulsants, metabolic acidosis with a high anion gap and coma. The diagnosis of INH overdose should be considered in any patient who presents to emergency medical services (EMS) with the triad. 

We report a patient presenting with multiple generalised tonic clonic (GTC) convulsions with severe metabolic acidosis as a manifestation of INH toxicity. ©

INTRODUCTION
Peripheral neuropathy due to pyridoxine deficiency in slow acetylators on INH therapy is well known. However, INH toxicity is rarely considered in patients presenting with new onset seizures not responding to the standard line of management. The condition is easily treated with intravenous pyridoxine but if not treated in time could prove fatal.

CASE REPORT
A 30 years old married female was brought to emergency medical services of our hospital with a history of 5 episodes of GTC seizures within 4 hours. There was no history of fever, headache, vomiting or trauma. There was no history of seizures or any other medical disease in past. There was no history of substance abuse. She had two issues with uneventful obstetric history. Relatives denied the possibility of consumption of any substance with suicidal intent.

Patient had two episodes of GTC seizures in the emergency medical department. On examination, she was afebrile with pulse of 110/min, regular and good volume. BP was 120/80 mm of Hg., respiratory rate was 32/min and respiration was acidotic. The rest of general examination was unremarkable. She was post-ictal, stuporous, moving all four extremities equally on deep painful stimulus. There was no sign of meningeal irritation, tone was normal, and reflexes were brisk with bilateral flexor plantars. Respiratory system examination revealed bilateral conducted sounds and no foreign sounds. Systemic examination was normal.

An arterial blood gas analysis showed pH 6.92, HCO₃⁻ – 5.9, pO₂-98, pCO₂-20.6, O₂ saturation-98.4. Anion gap was 14 Meq. X-ray chest was normal. She was started on intravenous bicarbonate, mannitol and loaded with 500mg of phenytoin.

Patient had two more episodes of convulsion in the ward within three hours and acidosis persisted so she was empirically started on pyridoxine 5gms through Ryle’s tube as intravenous pyridoxine was not available. She had no further convulsions and acidosis responded within 24 hours. Her investigations revealed a normal haemogram, biochemistry and serum calcium. Urinary porphobilinogens were not detected.

She was asked for history of consumption of any substance. She admitted to have consumed 15 tablets of INH that her husband was taking for tuberculosis, as she was depressed. She was discharged on day 5 after psychiatry reference.

DISCUSSION
Isoniazid contains a pyridoxal nucleus and is structurally related to nicotinic acid, NAD and pyridoxine. It is rapidly absorbed from GI tract (primarily the small intestine), metabolized by acetylation by the enzyme N-acetyltransferase present in liver and intestinal mucosa.

Pyridoxine activity is decreased by INH giving rise to clinical pyridoxine depletion. This occurs by two mechanisms: 1) INH inhibition of enzyme pyridoxine phosphokinase, which converts pyridoxine to its active pyridoxal phosphate. 1 2) INH binding to pyridoxal phosphate, forming an inactive hydrazone complex that is excreted in the urine. 2

*Associate Professor; **Lecturer; ***Senior Resident; Department of Internal Medicine, Lokmanya Tilak Municipal Medical College and General Hospital, Sion, Mumbai - 400 022.
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INH doses of 35-40 mg/kg (8 tablets of 300mg INH = 2400mg) uniformly produce seizures. The acute ingestion of greater than 1.5 gm leads to minor toxicity, whereas ingestion of more than 6-10 gm (20-30 tablets of 300mg INH) is usually fatal without aggressive treatment. Severe manifestations of INH toxicity may appear as soon as 30 minutes after the ingestion. Early signs include nausea, vomiting, slurred speech, dizziness, mydriasis and tachycardia, subsequently leading to recurrent seizures, severe metabolic acidosis and coma. Seizures after INH overdose are episodic and tend to occur at regular intervals, either hyper or areflexia precedes their onset. Improvement in consciousness may occur between seizures. They are difficult to control despite anticonvulsants. Severe metabolic acidosis is another prominent feature, pH ranges from 6.8 to 7.3 are common. Various mechanisms for development of acidosis are postulated viz. 1) increase in the generation of lactic acid as a result of muscular activity and recurrent seizures. 2) generation of acidic INH metabolites. 3) increase in ketoacids due to enhanced fatty acid oxidation. 4) formation of inactive NAD leading to impairment of both glucose and fatty acid metabolites. Coma may be present after INH overdose (lasting more than 24 hours) and may continue after seizures have been controlled and metabolic acidosis has been corrected. This is attributed to CNS catecholamine depletion. Other clinical effects of acute INH intoxication are severe hypotension, hyperglycemia, acidosis, abnormal liver functions and renal failure.

The differential diagnosis of severe metabolic acidosis includes diabetic ketoacidosis, uraemia, lactic acidosis, ingestion of methanol, ethylene glycol, iron, ibuprofen and salicylates. Only INH overdose has recurrent seizures as its hallmark.

The initial management of INH intoxication requires GI decontamination with gastric lavage, stabilization of vital signs with provision of patent airway and IV soda bicarbonate, cardiovascular support with IV fluids and vasopressors. IV pyridoxine has been found to be highly effective for INH intoxication and should be administered to all symptomatic patients. The dose of pyridoxine in milligrams should equal the ingested dose of INH. Pyridoxine given as pyridoxine hydrochloride has been shown to terminate seizures, correct metabolic acidosis and abbreviate the duration of coma. If the quantity of INH ingestion is unknown, pyridoxine in the dose of 5gms can be safely administered as it tolerated without adverse effects in adults. Repeated doses of pyridoxine may be required. Forced diuresis with frusemide/mannitol enhances the elimination of INH. Hemodialysis and peritoneal dialysis are effective in the treatment of INH intoxication. Dialysis should be reserved for patients who develop INH induced renal failure.

**Conclusion**

INH toxicity should be considered in patients presenting with multiple episodes of convulsions (uncontrollable) and high anion gap metabolic acidosis.

Pyridoxine therapy should be started empirically in such patients, taking into account the low fatal dose of INH, its easy accessibility and the absence of adverse effects of high dose of pyridoxine in adults.

**References**