Abstract

Isoniazid neurotoxicity has been well studied. The classic clinical triad of acute isoniazid neurotoxicity which includes seizures, metabolic acidosis, and coma is well recognised. We report a case of attempted suicide by isoniazid ingestion that resulted in seizures and coma. The neurological toxicity resolved after pyridoxine administration. Clinicians should be aware that acute isoniazid neurotoxicity may potentially present with classical neurological signs and symptoms which can be effectively treated with pyridoxine administration.

Case report

A 22 year old female patient was a known case of pulmonary tuberculosis on isoniazid and rifampicin. She presented with history of ingestion of 20 tablets of isoniazid (300 mg each) which was followed by vomiting. Within one-and-a-half hour of ingestion, the patient developed generalised tonic-clonic convulsions followed by loss of consciousness. There was no history of fever, trauma, headache, or convulsions in past.

On examination:
Pulse: 96/min; blood pressure: 130/80 mmHg. General examination was normal, icterus was absent. On central nervous system examination, the patient was stuporous, responding to deep painful stimuli; there was generalised hypotonia; pupils were bilaterally equal, reacting to light; both plantar reflexes were absent. There was no focal neurological deficit, and no signs of meningeal irritation were present. Examination of other systems was unremarkable.

Investigations:
 CBC, S. bilirubin, S. alkaline phosphatase, random blood sugar, blood urea, S. creatinine, and S. electrolytes were in normal range. SGPT was 151 IU. Chest X-ray showed left upper zone fibrosis. CT-scan of brain was normal. Arterial blood gas analysis was normal and oxygen saturation was 94% on room air.

Treatment:
After securing i.v. line, thorough oropharyngeal suction was done followed by inj. diazepam i.v. 5 mg, broad spectrum antibiotics, and i.v., fluids. Gastric lavage was performed till the aspirate was clear. Since plain injectable preparation of pyridoxine was not available, the preparation optineuron (contents: vitamine B₆ 100 mg with B₁, B₂, B₃, B₅, B₁₂) having highest concentration of B₆ was selected. The patient was given 10 ampoules of inj. optineuron dissolved in one pint of dextrose-normal-saline, infused over one hour. Five such cycles of infusion were given each followed by inj. frusemide 40 mg i.v. to prevent volume overload. Within four hours of initiation of therapy, patient regained consciousness and improved remarkably. Over the next 24 hours, the patient was given intravenous infusion of a total of 15 ampoules of inj. optineuron rendering the patient to be completely stable and neurologically normal. After referring the patient to a psychiatrist she was discharged on oral pyridoxine and anti-depressant drugs. The follow-up was uneventful.

Discussion

Acute overdoses of isoniazid have been identified with a classical triad of symptoms including seizures refractory to standard anticonvulsants, metabolic acidosis, and coma. If isoniazid is taken acutely, as little as 1.5 g (five 300-mg tablets) can cause toxicity. Doses larger than 30 mg per kg often produce seizures. Ingestion of the drug in amounts greater than 80 to 150 mg per kg can rapidly lead to death. Peak blood levels of isoniazid are reached one to two hours after ingestion, although toxic effects can begin to appear much sooner. The drug readily diffuses into all body fluids and tissues, with the largest concentration occurring in the liver. Approximately 75-95% of the drug is metabolised and excreted in the urine within 24 hours.
The first signs and symptoms of isoniazid toxicity may appear within 30 minutes to two hours after ingestion and may include nausea, vomiting, rash, fever, ataxia, slurring of speech, peripheral neuritis, dizziness, and stupor. These symptoms are usually followed by grandmal seizures and coma. Respiratory failure and death could follow. Laboratory studies may show an elevated anion gap and metabolic acidosis, hyperglycaemia, hypokalaemia, glucosuria, and ketonuria. Blood levels are not helpful in managing an acute isoniazid overdose.

Chronic therapy leads to peripheral neuropathy, toxic encephalopathy, ataxia, stupor, memory impairment, toxic psychosis, optic neuritis, and optic atrophy.

The mechanism of isoniazid toxicity involves pyridoxine metabolism. Isoniazid depletes systemic pyridoxine levels. Three mechanisms responsible for interfering with the function and supply of pyridoxine are:

1. Isoniazid binds directly with pyridoxine to form isonicotinylhydrazide.
2. Isoniazid is dehydrised to its hydrazones; which block pyridoxine phosphokinase, thus preventing conversion of pyridoxine to its active form, pyridoxal 5' phosphate.
3. Isoniazid hydrazides inactivate pyridoxal 5' phosphate, which is essential for the formation of gamma amino-butyric acid from glutamic acid. Lack of GABA formation, and the accumulation of glutamic acid leads to CNS excitation and seizures.

Management of acute isoniazid toxicity

The three mechanisms described above demonstrate how isoniazid can deplete the body of pyridoxine. Pyridoxine is thus an antidote. In acute toxicity, pyridoxine has been shown to halt seizures, correct metabolic acidosis and shorten coma duration. The following step-care approach may be of help:

1. Secure the airway.
2. Obtain intravenous access, and administer intravenous fluids.
3. For seizures: In adults, administer diazepam intravenously in a dose of 5 to 10 mg, and repeat the dose if necessary. In children, administer diazepam intravenously in a dose of 0.25 to 0.40 mg per kg, up to 10 mg per dose. The dose can be repeated if necessary.
4. Obtain arterial blood gases. If the pH is 7.1 or less, give sodium bicarbonate, 1 to 3 mEq per kg intravenously.
5. Replace pyridoxine: If the amount of ingested isoniazid is known, administer a gram-per-gram dose of pyridoxine (diluted to a concentration of 50 ml per g) intravenously over five to 10 minutes. The pyridoxine dose may be repeated every five to 20 minutes until the seizures stop, or the patient regains consciousness. Pyridoxine can also be given to resolve residual neurologic defects. If the amount of ingested isoniazid is unknown, give 5 g of pyridoxine (diluted to 50 ml per g) intravenously over five to 10 minutes. If the intravenous form of pyridoxine is not available, the drug can be given as a slurry, using crushed tablets in a similar gram-per-gram replacement dose.
6. Perform gastric lavage if within one hour of isoniazid ingestion. Remember to protect the airway: use an endotracheal tube with the cuff inflated, or place the patient in the Trendelenburg and left lateral decubitus position.
7. Administer charcoal and sorbitol (within one hour of isoniazid ingestion).
8. If the above methods fail to control seizures, consider haemodialysis or the administration of thiopental by an anaesthesiologist.
9. If the patient remains symptomatic, obtain a complete blood count, urinalysis and measurements of electrolytes, blood urea nitrogen, creatinine, glucose, creatinine kinase and liver enzymes. If the patient has liver damage, monitor the prothrombin time or the International Normalised Ratio.

Conclusion

With increasing tuberculosis incidence and, consequently, increased isoniazid use, there needs to be an increased awareness of isoniazid side effects,
neurotoxicity, and potential ocular toxicity. Poisoning, whether intentional or accidental, is not uncommon because the drug is widely used in the treatment and prophylaxis of TB. Symptoms of isoniazid neurotoxicity may present as acute or chronic toxicity. Acute overdoses of isoniazid have been identified with a classical triad of symptoms including seizures refractory to standard anticonvulsants, metabolic acidosis, and coma. Chronic therapy leads to peripheral neuropathies, toxic encephalopathy, ataxia, stupor, memory impairment, toxic psychosis, optic neuritis and optic atrophy. Treatment is aimed at prompt replacement of pyridoxine which usually cures the patient.

References