

Acute Isoniazid poisoning

Key words: Isoniazid poisoning, status epilepticus, drug induced seizures, pyridoxine [therapeutic use].

We present the case of a 17-year-old female patient in whom a diagnosis of Isoniazid overdose was made after she presented to the Emergency Medicine department with profound alteration of mental status and status epilepticus. We review the clinical picture and the treatment of this medical emergency.

Introduction

Status epilepticus is a medical emergency. It must be managed correctly in order to avoid potentially permanent neuronal compromise (1). Acute poisoning with a wide variety of drugs or toxins may present with seizures and status epilepticus. Frequently prompt identification of the responsible agent is not possible. The standard approach to seizures is usually effective but in some instances early identification of the drug or toxin may significantly influence or modify the standard approach to seizure treatment. We present a case of intentional Isoniazid overdose, an uncommon cause of poisoning and seizures, and review the prominent clinical manifestations and cornerstones of treatment.

Case report

A 17-year-old female patient arrived at the hospital by ambulance. She was found with generalized tonic-clonic seizures after a suspected drug overdose. The pulse was 110/minute, the blood pressure 110/80 mm. Hg, O₂ saturation 90%. The patient received supplemental oxygen. An intravenous route was established and diazepam 10 mg. I.V. was given to control the seizures. The patient was transferred to our hospital. On arrival the pulse was 124/minute, the blood pressure 144/70 mm. Hg., the O₂ saturation 98%, and the rectal temperature 36°C. The skin and mucosa were normal. There were no signs of trauma or meningeal irritation. On neurological examination the patient was confused, agitated and combative. The pupils were symmetric and responsive and there were no focal deficits.. The lungs were clear. Heart sounds and abdomen were normal. Blood was drawn for laboratory tests. Shortly after arriving she had generalized tonic-clonic convulsions and an additional 10 mg. diazepam I. V. was given. A history was obtained from a friend. The patient was a new immigrant from Eastern Europe. She suffered from personality disorders; had attempted suicide twice in the past and occasionally drinks alcoholic beverages. Two months earlier because of a positive tuberculin test, with a normal chest X-ray, isoniazid was prescribed but she did not take the medication. On the day of admission she had been very distressed and ill humored. About an hour before arriving at the hospital she told her friends that something was wrong with her. Shortly thereafter she lost consciousness and had generalized convulsions.

The ECG showed sinus tachycardia with narrow QRS and normal QT interval. The laboratory results were: arterial blood gases of pH 7.1, pCO₂: 38 mm Hg., Po₂: 98 mm. Hg., bicarbonate 12 meq/lt., BE -12, O₂ saturation 97%. The blood glucose was 274-mg/dl and potassium 3.5 meq/lt.; the kidney, liver function tests and coagulation studies were within normal limits. The CPK was 802 units/lt. (normal till 170 u/lt.). The alcohol and acetaminophen levels were negligible.

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Because of recurrent seizures the patient was intubated and additional diazepam given. Gastric lavage was done and activated charcoal given by nasogastric tube. A tentative diagnosis of Isoniazide overdose was made and a consultation with the poison control center was obtained. Pyridoxine (vitamin B₆) I.V was started, and the patient was transferred to the Intensive Care Unit. A total dose of 5 gr. pyridoxine was given. The seizures did not recur and the patient returned to normal conscious state permitting extubation. She recovered without sequelae. Psychiatric consultation was obtained. She admitted attempting suicide with an Isoniazide overdose.

Discussion

Status epilepticus is defined as 30 minutes of continuous seizure activity or a series of seizures without return to full consciousness during this period. Shorter periods of seizure activity may also cause neuronal damage. Time to control of seizures is critical in preventing morbidity and mortality and an operational definition is advocated of 5 minutes of continuous seizure to start treatment as status epilepticus (2). This is a medical emergency. A systematic approach is needed as in any case of altered mental status. The goals are first to achieve stabilization including airway management, adequate oxygenation and the cessation of clinical and electrical seizure activity. Secondly, rapid determination must be sought for any potential treatable cause and the recognition and treatment of any consequences of seizure activity. Seizures may be a consequence of severe toxicity due to many drugs and toxins. In many instances prompt identification of the agent is not possible and a standard approach to seizure management is usually effective. However in some instances early identification of the causative agent may modify the standard approach as in poisoning with lithium, tricyclic antidepressants, theophylline, salicylates and isoniazid (3).

Isoniazid (INH) is used for prophylaxis and treatment of tuberculosis. Isoniazid in acute overdose may be a cause of altered mental status, seizures and status epilepticus with metabolic acidosis. Isoniazid binds to pyridoxal-5-phosphate, the active form of pyridoxine (Vitamin B₆). Pyridoxal 5-phosphate is a cofactor for enzymes involved in the gamma amino butyric acid (GABA) synthetic pathway. The reduction in GABA synthesis increases cerebral excitability and propensity to seizures. Ethanol co-ingestion may increase toxicity by enhancing degradation of pyridoxal-5-phosphate. Isoniazid also inhibits lactate dehydrogenase, an enzyme that converts lactate to pyruvate in the liver resulting in lactic acidosis. Acute ingestion of as little as 1.5 gr. can produce toxicity; 6-10 gr. may be fatal if not correctly treated. Symptoms may be seen within 45 minutes of ingestion but may be delayed up to 2 hours. The first symptoms are nonspecific: nausea, vomiting, dizziness and light sensitivity. Later slurred speech, ataxia, coma and seizures appear. Acidosis may be seen after seizures or prolonged status epilepticus from any cause. In isoniazid overdose severe anion gap metabolic acidosis often occurs after only one or two seizures due to muscle release of lactic acid and slow liver conversion of lactic acid to pyruvate as previously indicated. Hyperpyrexia, tachycardia and bleeding due to disseminated intravascular coagulation may take place and should be treated promptly. Laboratory studies may identify: elevated anion gap metabolic (lactic) acidosis, hyperglycemia, leukocytosis, and ketonemia, evidence of disseminated intravascular coagulation, glycosuria, ketonuria, and cerebrospinal pleocytosis.

Immediately after initial stabilization with airway management, oxygenation and I.V access, the patient should get I.V. pyridoxine (Vitamin B₆). This is the drug of choice for INH-induced seizures, for the metabolic acidosis and altered mental status. The dose is based on a gram-for-gram of the amount ingested. If the ingested dose is unknown, 5 gr. I.V over 3-5 minutes is given and repeated each 5-20 minutes until

seizures resolve and the patient returns to a consciousness. The dose required to induce awakening may be higher than that required to control seizures (4). Standard anticonvulsants, when used alone may be ineffective in controlling seizures. Benzodiazepines should be the first-line anticonvulsants while pyridoxine is being obtained. Phenytoin is ineffective. Barbiturates are the second-line choice until pyridoxine is available [3]. A profound metabolic acidosis is usually present. Whether this occurs before the onset of seizure or thereafter is unclear. Whether this acidosis needs to be corrected with bicarbonate is controversial. Usually pyridoxine alone corrects the metabolic acidosis.

Most of the instances of Isoniazid overdose, as in this case, occur in young female patients taking the drug for tuberculosis chemoprophylaxis (5) and most of them as a suicide attempt. Because of the potential toxicity of this drug the mental and psychosocial status of the individual should be assessed before prescribing Isoniazid (6).

Isoniazid poisoning should be suspected in any patient with acute onset of seizures, especially when accompanied by profound metabolic acidosis. In such cases it is justifiable to give empirical treatment with pyridoxine.

Every Emergency Department should have at least 10 gr. of pyridoxine in its stock of antidotes.

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