

Refractory Seizures in A Young Woman

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Abstract:

The authors describe a case of Isoniazid toxicity. Causes, identification, and management are reviewed.

MeSH Words:seizures, Isoniazid toxicity, anticonvulsive treatment, pyridoxine (vit.B6)

Introduction

Seizures are a common neurological problem in the emergency department. A patient with prolonged convulsive episodes is a diagnostic and management challenge for the emergency physician.

Approximately 2-5% of the general population will experience a convulsive episode at least

once in their lives and of these, at least 50% will have additional episodes.

Seizure disorders may be divided into two main categories. The first includes those patients with strong genetic factor in the causation of their seizures. In these cases acquired focal or diffuse cerebral disease plays little or no role. These

seizures are often termed primary or idiopathic epilepsies. The second category includes those patients in whom seizures are secondary to acquired cerebral or systemic disease. Etiology also varies considerably with the age at onset of seizures.

In cases of status epilepticus the emergency physician must take into account the possibility of various systemic diseases and the possibility of poisoning or drug toxicities.

Case Presentation

A 15-year-old female of Ethiopian origin presented to the emergency department accompanied by her immediate family following a suicide attempt by ingestion of an unknown drug that had occurred approximately four hours previously.

Physical examination upon arrival: the patient was awake and without any respiratory distress. She had no obvious pallor and she had no cyanosis or jaundice. Her blood pressure was 120/60 and her pulse was regular and 125/minute. Her temperature was measured by mouth at 36.8 Celsius. Her saturation in room air was 96%. Her respiratory rate was 18/minute. Her head and neck were normal. Additionally, there were no pathological indications in her cardiac and gastrointestinal systems. The patient was alert but had very slowed responses. The ECG examination revealed a normal sinus rhythm of 125/minute with borderline QRS widening with no evidence of ischemia.

When the young woman arrived in the emergency department the "standard" procedures for treatment of suicide by ingestion of drugs in an alert patient were followed:

1. Gastric lavage was not indicated due in part to the passage of more than 4 hours after the ingestion;
2. The patient was placed on standard hemodynamic monitoring;
3. Blood tests including blood glucose, liver, kidney and coagulation profile were in normal range except for mildly elevated CPK level but later, they increased;

4. Urine test including toxicology panel was without evidence of benzodiazepines, opiates, amphetamines or other traces of substances;
5. Blood gas examinations revealed moderate metabolic acidosis (PH 7.21, bicarbonate 15 mEq/L);
6. Paracetamol level in blood was in nontoxic quantities (4 hours after possible ingestion);
7. One liter IV normal saline was administered;

The patient experienced a grand mal seizure a short time after arrival in the emergency department. Even though the patient was hemodynamically stable, sinus tachycardia was seen on the monitor. In response to the seizures, IV Valium (20 mg) was administered, but there was no cessation of convulsions. At this point, treatment with IV phenytoin loading was carefully initiated. However, the convulsions continued. At the same time, a member of the family revealed that the patient had probably been taking Isoniazid tablets for prevention of tuberculosis because of a positive PPD skin test. As a result of this new information, and within the context of refractory seizures and evidence of high anion gap metabolic acidosis, treatment was initiated with 2 ampoules of IV bicarbonate in one liter of normal saline and 5 grams IV pyridoxine (vitamin B6). It is important to point out that the patient required an extraordinary amount (50 ampoules of 100 mg) of pyridoxine to stop the seizures.

Two complications arose from the patient's condition: elevated CPK levels that peaked at 96,000 U/L and transient liver test (aminotransferase level close to 500 IU) disturbances.

After a psychiatric consultation, the patient was transferred in a hemodynamically stable condition, to the intensive care unit.

After treatment with intravenous fluids with addition of bicarbonate, the patient felt well and laboratory results were normal.

Discussion

Isonicotinic Acid Hydrazide (INH) is an antimicrobial that has been used as a first-line agent for prophylaxis and treatment of tuberculosis since 1952. Patients with a recently positive protein purified derivative (PPD) skin test and a normal chest x-ray routinely are given a 6- to 9-month course of INH. Patients with active disease are put on a regimen of INH combined with other antituberculous medications. Because of errors in dosage or intentional overdose, life-threatening toxicity may result.

Isoniazid binds to pyridoxal-5-phosphate, the active form of pyridoxine (vitamin B6), to form INH-pyridoxal hydrazones. Pyridoxal-5-phosphate is a cofactor for glutamic acid decarboxylase and GABA transaminase in the GABA synthetic pathway. INH overdose results in decreased pyridoxal-5-phosphate, decreased GABA synthesis, increased cerebral excitability and seizures.

INH undergoes N-acetylation in the liver to a variety of products that include acetylhydrazine, a potent hepatotoxin. These metabolites are excreted in the urine. With chronic administration at therapeutic doses, INH can cause clinically significant and even fatal hepatic injury in 1% of patients and elevated liver enzymes in 10-20% of patients.

The clinical triad of acute neurotoxicity consists of seizures (refractory to standard anticonvulsants), metabolic acidosis and coma. It is usually observed in ingestions of more than 200 mg/kg.

No correlation exists between serum INH levels and severity of acute intoxication. Laboratory studies generally are not helpful in diagnosis of acute INH toxicity but may identify complications, especially transient elevation of liver enzymes and elevated anion gap metabolic acidosis, as was found in our patient.

If the patient shows no signs of toxicity four hours following an ingestion of less than 20 Mg/kg, expectant management is sufficient.

Treatment of patients with evidence of toxicity involves managing immediate life threatening conditions such as refractory seizures, the

administration of pyridoxine and bicarbonate and supportive care.

Gastric lavage should be considered once the airway is secured; then activated charcoal should be administered at a dose 10 times that of the amount of ingested INH or 50 g if the ingestion is unknown.

Control of seizures will generally correct metabolic acidosis. The administration of sodium bicarbonate may be beneficial in severe cases.

While INH is dialyzable, dialysis is usually unnecessary if adequate doses of anticonvulsants and pyridoxine are administered. Hemodialysis may be indicated if the patient fails to improve with standard therapy.

Patients with clinically significant INH-associated hepatitis and progressive hepatic failure may be successfully treated with liver transplantation.

The overall mortality rate for acute INH toxicity has been estimated to be 19%. However, with current methods of supportive care, this figure may be too high.

In cases in which refractory seizures are the presenting feature, and there is suspicion of poisoning or drug intoxication, especially with high anion gap metabolic acidosis, the emergency physician must keep in mind the possibility of Isoniazid intoxication as a cause. This is important because the treatment for refractory seizures is different (pyridoxine – vitamin B6, in extremely large doses) and may be life saving.

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