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Seizures as a Manifestation of Isoniazid Intoxication: A Case Report

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ABSTRACT

Introduction: Isoniazid (INH) intoxication is a serious health problem that can be life-threatening. Acute intoxication manifests as neurological symptoms such as seizures.
Case Illustration: A woman, 27 years old, came to the emergency department with seizures after taking ten tablets (3000 milligrams) of Isoniazid. Laboratory examination showed a severe metabolic acidosis and increased liver function test. The management primarily consists of basic life support, antiseizure, and antidote.
Conclusion: Isoniazid toxicity is associated with a high mortality rate. The first signs and symptoms of isoniazid toxicity may appear within 30 minutes to two hours. Acute toxicity of Isoniazid may manifest as neurological symptoms such as seizures. Management of INH intoxication consists of controlling the life-threatening condition, administering an antidote such as pyridoxine, and symptomatic supportive therapy.

Keywords: Isoniazid, intoxication, seizures

INTRODUCTION

Isoniazid (INH) is a potent bactericidal used to treat tuberculosis (TB) infection.[1] INH intoxication is a serious health problem that can be life-threatening. Acute intoxication manifests as neurological symptoms such as seizures and loss of consciousness, whereas chronic intoxication usually causes hepatotoxicity and peripheral neuropathy.[2] INH intoxication often occurs due to inadvertent consumption, such as in children, suicide attempts, or in patients on medication who intentionally take extra tablets to compensate for being late or forgetting to take their previous medication. [3,4]

CASE ILLUSTRATION

A woman, 27 years old, came to the emergency department with the chief complaint of seizures. Seizures occur with upturned eyes, gritted teeth, and jerking of all four extremities. Seizures occurred three times, with the duration of each seizure approximately 3-5 minutes. After the seizure, the patient regained consciousness. These seizures occurred 2 hours after the patient took ten tablets (3000 milligrams) of Isoniazid as a suicide attempt. The patient had no previous history of chronic physical illness- there where no history of seizures and head trauma.

On physical examination, the patient was alert. On examination of vital signs, the patient's blood pressure was 80/50 mmHg, heart rate was 113 times/minute, respiration rate was 18-20 times/minute, and body temperature was 37.9 Celsius. Other physical examinations were within normal limits. On laboratory examination, there was severe metabolic acidosis (pH 7.16) with an anion gap of 24, and an increase in transaminase enzymes with AST 90 and ALT 112 was also found.

A loading of 1000cc of normal saline fluid was given in 30 minutes, followed by normal saline maintenance 1500cc/24 hours.

The patient was also given oral Pyridoxine 3000mg and diazepam 10 mg intravenously if seizures occurred. With a plan for monitoring the patient's complaints and vital signs and monitoring the laboratory results of blood gas analysis, liver function, and kidney function regularly.

DISCUSSION

Isoniazid has been the drug of choice for TB treatment and prevention since the 1950s.[3] INH takes 1-2 hours to reach peak plasma concentrations with a dose of 300 mg. In situations of overdose, peak plasma levels of 3–7mg/L can be achieved in 1.5–3 hours. INH then diffuses rapidly into all body fluids and tissues, accumulating mainly in the liver and undergoing a first pass effect before reaching the systemic circulation. The toxic effects of Isoniazid are dose-related. It can be an acute or chronic manifestation. Toxic doses are estimated at 35–40 mg/kg and fatal doses at 150 mg/kg. [3,4]

INH has structural similarities to pyridoxine (vitamin B6). The accumulation of INH can lead to a functional deficiency of pyridoxine. INH inhibits pyridoxine kinase, the enzyme responsible for producing pyridoxal-5'-phosphate (PLP), the active form of pyridoxine.[5] Pyridoxal phosphate is a co-factor in synthesizing gamma-aminobutyric acid (GABA), a major inhibitory neurotransmitter that can cause seizures. INH can also inhibit glutamic acid decarboxylase (GAD), which catalyzes the synthesis of GABA from glutamic acid. INH can also inhibit the enzyme lactate dehydrogenase (LDH) through its effect on the co-enzyme nicotinamide adenine dinucleotide. This can cause lactate accumulation and trigger metabolic acidosis in patients experiencing INH intoxication (Figure 1.). Metabolic acidosis is usually also exacerbated by increased lactic acid production during seizures.[3,6]

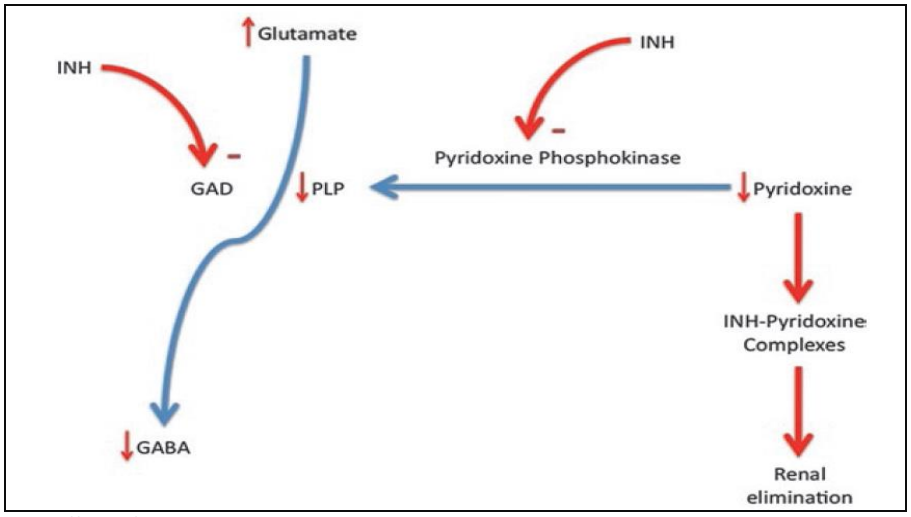

Figure 1. Effects of Isoniazid (INH) on pyridoxine metabolism and -aminobutyric acid (GABA) synthesis.[6]

INH toxicity is associated with a high mortality rate. The first signs and symptoms of isoniazid toxicity may appear within 30 minutes to two hours after taking INH and may persist for several hours. Symptoms may begin with nausea, vomiting, rash, fever, ataxia, slurred speech, peripheral neuritis, dizziness, and fainting. Grand mal seizures and coma usually follow these symptoms. Seizures are often refractory to anticonvulsants, especially phenytoin. Respiratory failure and death can occur in this phase.[7]

On laboratory examination, the patient found increased serum transaminase levels without typical clinical symptoms suspected due to INH intoxication. Hepatotoxicity is a clinical manifestation that often occurs in patients experiencing INH intoxication. However, it usually appears late, within two

weeks – 6 months after INH intoxication. It is accompanied by typical symptoms such as nausea, anorexia, fatigue, abdominal discomfort with right upper quadrant abdominal pain, general flu-like symptoms, dark urine, and jaundice.

The management of INH intoxication is generally the same as other substance intoxications. Airway management is necessary to ensure a safe airway if the patient is convulsing, comatose, or unresponsive. Installation of intravenous access and fluid administration should be done immediately to accelerate the elimination of INH.[8] Specific treatment for INH poisoning is the administration of pyridoxine. Pyridoxine is an antidote that has been shown to stop seizures and treat persistent coma in isoniazid poisoning. [9] Pyridoxine should be given in a dose equivalent to the maximum amount of Isoniazid suspected of being ingested (i.e., gram-per-gram replacement). Repeated doses may be required for persistent seizure activity and may also be used to treat deep coma.[10]

Gastric lavage is indicated if it can be performed within one hour of taking Isoniazid. Charcoal, administered within one hour of ingesting Isoniazid, is effective in preventing drug absorption. Charcoal should initially be administered as a powder with sorbitol. In this case, gastric lavage and charcoal administration were not carried out because when the patient came, it was more than an hour after taking INH, and clinical symptoms had appeared, so the effectiveness of gastric lavage and charcoal administration in this patient was low.[10]

CONCLUSION

INH is a potent antimicrobial agent that inhibits cell wall synthesis of Mycobacterium tuberculosis and is used in therapeutic and prophylactic regimens. Treatment with INH carries the risk of acute and chronic toxicity. Acute toxicity may manifest as neurological symptoms such as seizures. An important mechanism that causes these symptoms is a deficiency of GABA, which is an inhibitory neurotransmitter. Management of INH intoxication consists of controlling life-threatening conditions (airway, breathing, circulation management), administering an antidote such as pyridoxine, and symptomatic supportive therapy.

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