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Acute Isoniazid Intoxication: Convulsion, Rhabdomyolysis and Metabolic Acidosis

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Abstract: Isoniazid is one of the most commonly used antituberculous drugs. Acute intoxication is characterized by repetitious convulsions, high anion gap metabolic acidosis and coma. The basis of therapy consists of parenteral pyridoxine administration in a dose equivalent to that of isoniazid ingested. Here we present a case of acute isoniazid intoxication presenting with convulsions and metabolic acidosis with consequent rhabdomyolysis and discuss the clinical signs and pathophysiology of isoniazid intoxication.

Key Words: Isoniazid intoxication, convulsion, acidosis, rhabdomyolysis

Akut İsoniazid İntoksikasyonu: Konvulsiyon, Rabdomiyoliz ve Metabolik Asidoz

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Özet: İsoniazid en sık kullanılan antitüberküloz ilaçlardan biridir. Akut intoksikasyonu tekrarlayan konvulsiyonlar, yüksek anyon-gap' lı metabolik asidoz ve koma ile karakterizedir. Tedavi, alınan izoniazide eşdeğer dozda piridoksinin parenteral olarak verilmesidir. Burada konvulsiyon, metabolik asidoz ve rabdomiyoliz ile başvuran bir izoniazid intoksikasyonu olgusu sunulmuş ve izoniazid intoksikasyonunun patofizyolojisi tartışılmıştır.

Anahtar Sözcükler: İsoniazid intoksikasyonu, konvulsiyon, asidoz, rabdomiyoliz

Introduction

Isoniazid is one of the most commonly used drugs in tuberculosis therapy and chemoprophylaxis. Due to increased tuberculosis prevalence in the last 20 years, the frequency of isoniazid therapy is increased. High tuberculosis prevalence is still a major concern in our country; hence, practicing physicians should be aware of the potentially fatal effects of this drug. Isoniazid taken in toxic doses can cause seizures, serious metabolic acidosis, rhabdomyolysis, coma and even death. Pyridoxine administration can potentially reverse all of the above-stated clinical and metabolic outcomes resulting from the isoniazid intoxication. In this report, we present a case of acute isoniazid intoxication and also discuss the clinical and metabolic effects of acute isoniazid overdose.

Case Report

An unconscious 18-year-old female was admitted to our emergency department with a Glasgow Coma Scale of 8/15. It was reported that she had taken an unknown amount of an unidentified drug in pill form with the intention of committing suicide. At admission her blood pressure was 120/70 mmHg and pulse was 120/min. She had spontaneous and regular respiration. Pupil diameters were 5 mm and reactive to light bilaterally. A nasogastric catheter was administered and gastric lavage was performed followed by the administration of activated charcoal. Immediately after the procedure, sudden convulsions began, which subsided within five minutes after administration of diazepam infusion. One hour after the first diazepam administration, repeating seizures occurred which gave transient responses to diazepam infusions. Serum glucose was 200 mg/dl; blood urea nitrogen, creatinine, creatine kinase (CK), liver function tests and

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electrolyte values were all within normal limits. Cranial tomography was normal. After her relatives reported that she had intentionally ingested an estimated amount of 40 isoniazid tablets (each tablet containing 100 mg isoniazid; a total of 4 g), pyridoxine (5 g) was administered parenterally. The dose was repeated twice at ten-minute intervals until the seizures subsided definitely.

Her blood gas values on admission were as follows: pH: 6.85, PO₂: 101 mmHg, PCO₂: 41 mmHg, HCO₃: 7.0 mmHg, BE: -26 mmol/L, and anion gap: 29 mmol/L. NaHCO₃ replacement therapy at appropriate dosage was promptly administered because of high anion gap metabolic acidosis. Twenty-four hours after admission she regained consciousness and consequently was transferred to internal medicine service for follow-up.

On the third day of her admission, elevated levels of serum CPK, lactate dehydrogenase (LDH) and aspartate aminotransferase (AST) values indicating rhabdomyolysis were noted, which reached peak values on the 5th day (Table). Isotonic saline, titrated to maintain a urine output of 200 cc/h, was administered along with urinary alkalinization to a pH >6.5 to prevent renal injury. Thereafter, her liver function test and CK values declined gradually and reached normal levels at the 17th day of her admission and she recovered uneventfully.

Discussion

Isoniazid toxicity has a high mortality rate. If a high dose of isoniazid is taken acutely even a dose as low as 1.5 g can cause toxicity. A dose of 30 mg/kg or higher generally causes seizures. A dose higher than 80–150 mg/kg is reported to be lethal. Acute isoniazid toxicity

presents clinically 30 minutes–2 hours after ingestion. Vomiting, rash, fever ataxia, disarticulation, peripheral neuritis, vertigo and stupor are common signs of poisoning. These signs are followed by grand-mal seizures and coma. Seizures are particularly resistant to anticonvulsants and also to barbiturates. Phenytoin should be used cautiously since isoniazid interferes with the metabolism of phenytoin. If not treated properly, respiratory depression and death eventually occur. Laboratory analysis demonstrates high anion gap metabolic acidosis, hyperglycemia, hypokalemia, glycosuria, and ketonuria. The initial presentation can easily be mistaken for a case of diabetic ketoacidosis. Serum isoniazid levels are not helpful in evaluation of isoniazid toxicity and treatment (1). Although the exact mechanism is still controversial, tissue hypoxia induced by seizures and inhibition of pyruvate conversion to lactate by interference of NAD synthesis in Krebs cycle are both reported to contribute to the lactic acidosis observed in isoniazid intoxication (2).

Acute overdose of isoniazid results in absolute pyridoxine (vitamin B6) deficiency. Pyridoxine is an essential cofactor in synthesis of gamma amino butyric acid (GABA), which is the major inhibitory neurotransmitter in the central nervous system. The antituberculous drug isoniazid reacts non-enzymatically with pyridoxal 5'-phosphate to form a metabolically inactive hydrazone, eventually interfering with GABA synthesis. Decreased levels of GABA cause a lowered seizure threshold. Therefore, pyridoxine administration can specifically prevent the neurotoxicity related to isoniazid (1,2). Whether altered mental status occurs secondary to decrease in pyridoxine levels is not clear. Several case reports in the literature describing favorable

Table. The course of biochemical parameters during the patient's hospital admission.

	DAY 3	DAY 5	DAY 7	DAY 11	DAY 15
AST (U/L)	226	443	343	136	38
ALT (U/L)	67	153	128	58	25
LDH (U/L)	887	865	700	260	200
CK (U/L)	29600	42600	27800	3200	140

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase
LDH: Lactate dehydrogenase, CK: Creatine kinase

outcome after administration of pyridoxine strongly support this view (3,4). Pyridoxine theoretically causes alteration of mental status by an additional contributing mechanism since it is an essential cofactor in the synthesis of other neurotransmitters - dopamine, serotonin and tryptamine (5).

Rhabdomyolysis is an uncommon but potentially lethal complication of acute isoniazid intoxication. The exact mechanism of rhabdomyolysis caused by isoniazid is unknown but it is thought to result from direct toxicity of either isoniazid or one of its metabolites or from severe muscle exertion due to seizures. It is stated in the literature that an amount of ingested isoniazid higher than 2.4 g is directly related to elevation in CPK levels (6).

Gastric lavage with activated charcoal theoretically decreases absorption of isoniazid; however, patients usually present several hours after ingestion. The effectiveness of these measures greatly decreases with time (7); hence, they should be considered as subsidiary procedures of decontamination. Acidosis should be treated actively. Patients with isoniazid intoxication are likely to have hypoventilation. The administration of

sodium bicarbonate under these circumstances can cause exacerbation of hypercarbia. Diazepam at a starting dose of 5-10 mg i.v. can be administered initially to control seizures, and additional doses should be administered if seizures continue. Diazepam is found to be more effective in treatment of seizures related to isoniazid intoxication compared to phenytoin and barbiturates (8). The cornerstone of therapy is the administration of pyridoxine in a dose equivalent to that of isoniazid ingested. If the amount of isoniazid taken is unknown or if there is any suspicion about whether isoniazid is responsible for the presence of metabolic acidosis and seizures, then 5 g pyridoxine should be intravenously administered within 5 to 10 minutes. Repeated doses at intervals of every 5 to 20 minutes can be necessary in the presence of repeating seizures or continuation of deep comatose state. Although no adverse effects have been reported in doses ranging from 50 to 357 mg/kg (9), pyridoxine therapy carries the potential of a transient increase in base deficit, which could be clinically relevant in the presence of metabolic acidosis (10). If conservative therapy fails or the patient has renal failure, dialysis should be considered.

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