Acute isoniazid neurotoxicity in childhood

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Acute isoniazid (INH) poisoning is uncommon in children. Although most physicians are aware of INH hepatotoxicity, acute INH poisoning and its treatment are not well recognized. INH is increasingly being used to control the spread of tuberculosis, and physicians should know its potentially fatal effects. INH overdose is known to result in rapid onset of seizures, metabolic acidosis and prolonged obtundation. We report two cases of obtundation secondary to INH overdose that was immediately reversed by pyridoxine. Parenteral pyridoxine administration is an effective method in INH intoxication. The intravenous form of pyridoxine must be available in the emergency care units, and INH toxicity should be suspected in any patient with refractory seizures and metabolic acidosis.

Key words: isoniazid neurotoxicity, pyridoxine.

The incidence of tuberculosis has increased dramatically in the world over the past decade as a consequence of poverty, immigration from high prevalence countries, the HIV epidemic, and limitations in health care services to high-risk populations[1]. Since introduced in 1952, isoniazid (INH) still remains as a first line agent in the treatment and prophylaxis of tuberculosis. INH-related acute poisoning, either intentional or accidental, can be fatal if not diagnosed and treated properly[2-6].

Most physicians are aware of the INH hepatotoxicity and the importance of liver function tests. However, acute INH poisoning and treatment are not very well known. The clinical triad of acute neurotoxicity includes seizures resistant to anticonvulsants, metabolic acidosis, and coma[1,3-8]. Although INH-related neurotoxicity is usually seen in ingestion of doses greater than 200 mg/kg, a less than 40 mg/kg dosage of INH may be symptomatic[4,7,8].

In this article, our experience with two INH intoxication cases is presented, and the treatment is discussed.

Case Reports

Case 1

A previously healthy 14-year-old girl with generalized seizures lasting 15-20 seconds presented to the nearest hospital, where she was given 10 mg of diazepam intravenously, due to repeated generalized seizures. Upon cessation of seizures, she was transported to our pediatric emergency department with the diagnosis of acute encephalitis.

Her history was unremarkable, with no previous seizures and no medication use. However, her sister had been receiving isoniazid for tuberculosis lymphadenitis for the last three months.

At admission to our pediatric emergency department, she was found to be lethargic. Neurologic examination showed no lateralizing signs. Her pulse rate was 104 beats/minute, and respiratory rate was 20 breaths/minute. Other vital signs were in normal limits.

Laboratory findings on arrival were as follows: WBC: 28,200/mm^3, Hb: 128 g/dl, Htc 39%, PLT: 309,000/mm^3, glucose 181 mg/dl, sodium 138 mmol/L, potassium 3.6 mmol/L, urea 14 mg/dl, SGOT 26 IU/L, SGPT 14 IU/L, pH: 7.40, pCO_2 34 mmHg, pO_2 74 mmHg, and HCO_3 21.6 mmol/L. Chest roentgenogram, computerized cranial tomography, and electroencephalographic investigations were all normal.

It was learned that the patient had ingested 2 g of her sister's isoniazid (30 mg/kg) after a dispute between them. She was treated with

multiple doses of activated charcoal and received 2 of pyridoxine intramuscularly (equivalent to the amount of isoniazid ingested) eight hours after INH ingestion. Since the intravenous form was not available, we used the intramuscular form of pyridoxine. Full conciousness was noted after six hours of the therapy. She did not become lethargic again or require further pyridoxine. After the resolution of intoxication, a psychiatric consultation was obtained.

The following hospital course was complicated by transaminase elevation on the 4th day after INH ingestion, measured as SGOT: 331 IU/L and SGPT: 114 IU/L. Other laboratory findings (GGT, NH_3, PT, PTT) were normal.

After SGOT and SGPT levels had dropped below 100 IU/L, the patient was discharged on the 7th day, with follow-up planned by our pediatric gastroenterohepatology and psychiatry outpatient clinics.

Case 2

A 20-month-old boy weighing 10 kg was well until two hours prior to admission when he became somnolent and developed generalized tonic-clonic seizures. He was brought to the nearest hospital where 5 mg rectal diazepam was administered. He was then transferred to our hospital with the diagnosis of acute encephalitis.

At admission to the pediatric emergency department, he was comatose, afebrile, and breathing spontaneously. Neurologic examination revealed generalized hypertonicity of the extremities, and hyperactive deep tendon reflexes. The heart rate varied between 100-120 beats/minute, respiratory rate was 28 breaths/minute, and blood pressure was 100/60 mmHg. The pupils were myotic and responded to light. Meningeal signs were negative, and there were no findings suggesting trauma.

Results of initial laboratory studies included the following: WBC: 20,700/mm^3, Hb: 11.5 g/dl, Htc 34%, PLT: 221,000/mm^3, glucose 119 mg/dl, sodium 139 mmol/L, potassium 4.0 mmol/L, urea 17 mg/dl, SGOT 31 IU/L, SGPT 16 IU/L, pH: 7.14, pCO_2 28 mmHg, pO_2 80 mmHg, HCO_3 9 mmol/L, and ABE-18 mmol/L.

One hour after arrival he developed clonic seizures marked on the right arm and right side of his face. Seizure activity stopped in a minute without any medication, but 10 minutes later a generalized seizure activity was observed which was treated with phenobarbital (10 mg/kg) intravenously. His cerebrospinal fluid examination, EEG, and cranial computerized tomography (CT) findings were normal. A review of his history revealed that he had been playing with his father's INH bottle 30 minutes before the seizures. INH toxicity was suspected. The patient's father checked the bottle and remarked that three tablets of INH were absent. After intravenous administration of 1 g pyridoxine [4 hours after INH ingestion, equal to the amount of isoniazid ingested (100 mg/kg)], no further seizure occurred.

Additionally, gastric lavage was performed, and activated charcoal and sodium bicarbonate were administered. He was also given 20 mmols sodium bicarbonate. After the therapy, his blood gas results were as follows: pH: 7.37, pCO_2 31 mmHg, Hg, pO_2 84 mmHg, Hg, HCO_3 28.0 mmol/L, and ABE-6 mmol/L.

Six hours after pyridoxine ingestion the patient was fully alert with no further seizure activity. He was followed for possible transaminase elevations. On the 4th day after INH ingestion, he was discharged and no enzyme elevation was observed.

Discussion

Isoniazid is widely used in the management and prophylaxis of tuberculosis. INH intoxication can occur either as an accident or with the intent to commit suicide, and is not frequent in childhood. The signs of intoxication can be observed if INH is consumed in doses of more than 1.5 g at once, or 30 mg/kg[4,7,8].

Isoniazid is rapidly absorbed following oral ingestion, and the first signs of intoxication can occur 30-45 minutes after ingestion[4,7], although this period is sometimes prolonged to two hours. In our first case, the first sign was observed within two hours, and in the second case this period was 30 minutes. The intoxication symptoms are nausea, vomiting skin rashes, fever, ataxia, speech disorders, peripheral neuritis, and alterations in consciousness. These symptoms are usually followed by seizures and coma. The seizures are often refractory to anticonvulsants. Rerspiratory failure and death can follow. The mortality rate due to INH intoxication is significantly high if it is not treated. Death occurs rapidly if the amount of ingestion is approximately 80-150 mg/kg[4,7-12]. In

our first case INH was consumed at a dose of 30 mg/kg, and in our second case the total amount of ingested INH was 100 mg/kg. The laboratory findings of acute INH intoxication were elevated anion gap, metabolic acidosis, hypokalemia, hyperglycemia, ketonemia, transient elevation of liver enzymes, leukocytosis, positive disseminated intravascular coagulation panel, glucosuria, ketonuria and cerebrospinal fluid pleocytosis[2,6,8,9,11,12].

Pyridoxine (B_6) has a significant role in the function of more than 60 enzymes. One of these important roles is the synthesis of γ-amino-butyric acid (GABA), a significant inhibitory neurotransmitter in the brain. The active form of pyridoxine, pyridoxine 5 phosphate, is the cofactor of the two enzymes that are responsible for the degradation and the synthesis of GAB INH binds with the active form of pyridoxine to produce INH pyridoxal hydrasone. This molecule is excreted in the urine and results in the pyridoxine decrease. Due to the decrease in GABA synthesis, seizures can occur. As seen in our cases, these seizures are usually resistant to anticonvulsive agents[1,2,5,6,11,12].

Altered consciousness observed in INH toxicity has a wide range, from lethargy to coma. The etiology is thought to be multifactorial. The use of anticonvulsive agents and the postictal period are generally blamed. In our cases, acute alternations in consciousness were observed and this led us to believe that there might be other responsible factors.

Wason et al.[5] and Brent et al.[13] observed an early recovery in altered consciousness following the administration of pyridoxine. In our cases, consciousness improved rapidly after pyridoxine administration. In our first case, altered consciousness totally recovered six hours after pyridoxine administration; in our second case this period lasted three hours.

Severe metabolic acidosis can occur in INH intoxication[2,3,6,8,11-14]. Lactic acidosis due to resistant seizures and inhibition of lactate dehydrogenase results in metabolic acidosis. Generally it is not necessary to manage this condition with sodium bicarbonate treatment, but severe acidosis is an exception[7,8,12-14]. In our second case we observed severe metabolic acidosis which was responsive to sodium bicarbonate.

In 1963, Starke and Williams[11] suggested that high-dose pyridoxine administration is an effective therapy in INH intoxication. The authors observed that the administration of pyridoxine equal in dose to the ingested INH might be more effective in controlling seizure activity and improving clinical prognosis[5,12]. Due to the similarity of pyridoxine and INH molecules, the "gram for gram" principle has taken its place in the management of INH intoxication[5]. Brown[12] and Katz et al.[15] noted that if the dose of INH ingestion was unknown, 5 g of pyridoxine should be administered. In our cases, data about INH ingestion was collected from the parents. Pyridoxine was administered with an equal dose to INH, and no seizure activity was observed following treatment.

In the literature, intravenous administration is usually recommended, but it can be given orally if the intravenous form is not available[2-5,7,8]. In our first case, the intramuscular form of pyridoxine was used as the intravenous form was not available, and this treatment was also effective. In our second case, the intravenous form of pyridoxine was administered.

Due to high-dose pyridoxine, side effects such as tachypnea, postural reflex disorders, paralysis and seizure can be observed. A peripheral neuropathy has also been noted. However, there have been several cases with no side effects, even with the administration of 52 g pyridoxine[3-5,8,15-18].

It is suggested that repeating pyridoxine might be useful if the seizure activity continues after the first administration. In our cases, there was no need for a second administration[3,7,8].

In Turkey, and in the world at large, tuberculosis is still an important health problem. INH is the most frequently used agent in the treatment. Therefore, physicians should be aware of the management of INH intoxication and of the side effects of INH.

In conclusion, parenteral pyridoxine administration is an effective method in INH intoxication, so the intravenous form must be available in emergency care units. The toxic effect of INH should be explained to all patients. Keeping the drug away from children must be stressed, and manufacturers should be encouraged to imprave the packaging and labelling of their products.

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