

# Rhabdomyolysis due to isoniazid poisoning resulting from the use of intramuscular pyridoxine

Tuğba Eyüboğlu<sup>1</sup>, Okşan Derinöz<sup>2</sup>

<sup>1</sup>Departments of Pediatrics and <sup>2</sup>Pediatric Emergency Medicine, Gazi University Faculty of Medicine, Ankara, Turkey.  
E-mail: oderinoz@gazi.edu.tr

**SUMMARY:** Eyüboğlu T, Derinöz O. Rhabdomyolysis due to isoniazid poisoning resulting from the use of intramuscular pyridoxine. Turk J Pediatr 2013; 55: 328-330.

Isoniazid is an effective antituberculosis drug. Isoniazid poisoning produces a characteristic clinical syndrome that occurs 30 to 120 minutes after ingestion and includes seizures, metabolic acidosis, and in severe cases, coma. Rhabdomyolysis is one of the reported complications of isoniazid poisoning, but relevant data are limited. Parenteral pyridoxine is the antidote of isoniazid. In this case, a 16-year-old male patient admitted to the Pediatric Emergency Department two hours after isoniazid poisoning. For treatment, intramuscular pyridoxine was used, but he developed serious rhabdomyolysis.

**Key words:** intramuscular, isoniazid, poisoning, pyridoxine, rhabdomyolysis.

Isoniazid (INH) is an antibiotic commonly used for the prophylaxis and treatment of tuberculosis infection<sup>1</sup>. Poisoning due to INH may occur with unintentional ingestion, suicidal intent, or in patients taking extra tablets to compensate for missed doses. Acute INH poisoning frequently manifests as seizures, coma and acidosis<sup>2</sup>. One of the identified complications of INH poisoning is rhabdomyolysis, which can be due to a direct toxic effect of INH or its metabolites on the muscle or can be secondary to seizures<sup>3-5</sup>. However, severe muscle wasting can occur as a result of the use of intramuscular pyridoxine as an antidote for acute INH toxicity. Therefore, our aim was to present a case in which rhabdomyolysis developed after INH poisoning. The treatment of choice for INH poisoning, pyridoxine, may cause severe rhabdomyolysis depending on the method and route of administration.

## Case Report

A 16-year-old male patient, who was receiving INH for tuberculosis prophylaxis, was brought to the pediatric emergency department (PED) because of suicidal attempt. Two hours before admission, he had taken 20 INH tablets (300 mg each). It was learned that after drug intake, he had vomited once and had contraction of

the upper lip. On the first evaluation, Glasgow Coma Scale score was 15, vital signs were stable, and the systemic examination was normal. The amount of tablets taken was excessive and the possibility of a mass effect in the stomach was considered. Despite the arrival to the PED in the second hour of drug intake, gastric lavage was planned. During the gastric lavage, the patient had generalized tonic-clonic seizure lasting two minutes, and intravenous midazolam was performed. After gastric lavage, activated charcoal was given, and administration of intravenous pyridoxine was planned. Intramuscular pyridoxine was used because the intravenous form of pyridoxine is not available in our country. Pyridoxine ampoules in our country contain 100 mg of pyridoxine in 2 ml. The patient had ingested a 6000 mg dose of INH (120 ml). Because the required intramuscular pyridoxine could not be administered in a single dose, the total dose was planned to be given as 6 doses of 20 ml (1000 mg) at six-hour intervals until completed.

Complete blood count, blood glucose, creatine kinase (CK), and liver and kidney function tests were normal. Uric acid was 10.5 mg/dl, and 10 mg/kg allopurinol therapy was started. There was no metabolic acidosis in the blood gas analysis. However, as the patient was admitted to the PED two hours after

ingestion, had contraction of the upper lip and a seizure lasting two minutes, it was thought that the toxic effects of the drug had begun to appear. To prevent rhabdomyolysis due to INH poisoning, intravenous fluid therapy and alkalization were started. The patient was admitted to the Pediatric Intensive Care Unit (PICU) for follow-up.

The CK level began to rise on the third day of hospitalization. The fluid therapy was continued. On the fourth day of follow-up, CK had risen to 22673 U/L, and levels returned to normal on the eighth day (Table I). During follow-up in the PICU, he had no seizure. His renal function tests, urine output and vital signs were normal. He was discharged on the eighth day of hospitalization.

### Discussion

Isoniazid (INH) is an effective treatment for tuberculosis<sup>1</sup>. INH poisoning may induce a deficiency in gamma aminobutyric acid (GABA) and pyridoxine. GABA is the most important inhibitory neurotransmitter in the central nervous system. Pyridoxal-5-phosphate, which is the active form of pyridoxine, is involved as a coenzyme in the synthesis of GABA. INH causes a decrease in GABA synthesis by inhibiting the pyridoxal phosphate-dependent enzyme glutamic acid decarboxylase<sup>2</sup>. Therefore, seizures do not respond to conventional antiepileptic drugs. The best treatment option is intravenous pyridoxine to terminate seizures caused by INH and increase the concentration of GABA in the central nervous system<sup>1,2</sup>. The amount of pyridoxine used in the treatment is equal to the amount of INH taken. If the exact INH intake is unknown, 5

g of pyridoxine is given intravenously in 3-5 minutes. If seizures are resistant or repeat despite treatment, pyridoxine can be repeated in 20 minutes<sup>6</sup>. The use of benzodiazepines with pyridoxine has a synergistic effect in terms of the termination of the seizure<sup>6,7</sup>. Intoxication produces characteristic clinical findings that occur 30 to 120 minutes after ingestion. Acute INH poisoning usually manifests as altered mental status, seizure, including status epilepticus, and acidosis<sup>2</sup>. One of the identified complications of INH poisoning is rhabdomyolysis. Rhabdomyolysis is defined as damage of skeletal muscle resulting in the subsequent release of intracellular contents into the circulation, particularly myoglobin and CK<sup>8</sup>. The most common causes of rhabdomyolysis are infections, injuries, medications and toxins, muscle disease, trauma, seizure, and immobility<sup>9</sup>. INH-induced rhabdomyolysis can be due to a direct toxic effect of the INH or its metabolites on the muscle or can be secondary to seizures<sup>3-5,10</sup>. These effects could not fully explain the rhabdomyolysis. In one study, although there is a correlation between seizure duration and high CK levels, high CK levels were not correlated with the number of seizures<sup>11</sup>. In addition, intramuscular injections may cause elevation in serum muscle enzyme levels. Especially, the volume, concentration and dose of drugs used intramuscularly may increase the CK level. This situation has been reported in previous studies as a result of the use of various intramuscular drugs, such as chlorpromazine, barbiturates, atropine, diazepam, chlordiazepoxide, pralidoxime chloride, digoxin, frusemide, ampicillin, carbenicillin, and morphine<sup>12</sup>. However, it has not been reported with use of intramuscular

Table I. Laboratory Values According to Days after the Application

	1 <sup>st</sup> day	2 <sup>nd</sup> day	3 <sup>rd</sup> day	4 <sup>th</sup> day	5 <sup>th</sup> day	6 <sup>th</sup> day	7 <sup>th</sup> day	8 <sup>th</sup> day
BUN (mg/dl)	13.4	9.6	6.2	5.2	4.7	4.9	6.9	8.6
Creatinine (mg/dl)	0.79	0.74	0.74	0.69	0.66	0.63	0.66	0.74
CK (U/L)	125	164	5818	22673	20034	15868	4996	247
AST (U/L)	25.9	46	162	281	272	193	126	68
LDH (IU/L)	224	250	381	633	455	303	270	216
Uric acid (mg/dl)	10.5	9.3	5.2	4.4	3.5	3.7	3.6	3.2
Potassium (mmol/L)	4.3	4.5	3.6	3.9	4.1	4.3	4.2	

BUN: Blood urea nitrogen. CK: Creatine kinase. AST: Aspartate aminotransferase. LDH: Lactate dehydrogenase.

pyridoxine. As intravenous pyridoxine is not available in Turkey, we used intramuscular pyridoxine in the presented patient. The required dose of pyridoxine was 6000 mg (120 ml) according to the INH dose taken. Because the intramuscular drug volume was excessive for one administration, the total volume was given in six doses at six-hour intervals. Each drug volume given to the patient during intramuscular injection was 20 ml (1000 mg).

Although it is written in textbooks that intramuscular injections can increase serum CK levels, there are few or no data related to at which volume or in how many hours after drug administration serious rhabdomyolysis occurs. In one study, among patients treated with intramuscular diazepam (8/44), dipyrone (9/44), metoclopramide (14/44), pethidine/pentazoline (6/44), and penicillin (7/44), amounts ranged from 1-4.5 ml volume, and the CK level was shown to increase in only 3 patients over a 72-hour follow-up. There were no significant data showing in how many hours after injections CK levels began to rise<sup>13</sup>.

In conclusion, rhabdomyolysis is a potentially life-threatening complication of acute INH poisoning. Pyridoxine is an important antidote for INH poisoning. However, although the treatment will be used for therapeutic purposes, it should not harm the patient. It is indisputable that with an increased volume of intramuscular drug administration, there is increased risk of muscle injury. Therefore, when faced with selection of a drug that causes rhabdomyolysis as the treatment of choice, it should be noted that the method and route of administration might cause severe rhabdomyolysis.

## REFERENCES

1. Lheureux P, Penalzoa A, Gris M. Pyridoxine in clinical toxicology: a review. *Eur J Emerg Med* 2005; 12: 78-85.
2. Hoffman RS, Nelson SL, Howland MA, et al. Antituberculosis medications. In: Hoffman RS, Nelson SL, Howland MA (eds). *Goldfrank's Manual of Toxicologic Emergencies* (8th ed). USA: The McGraw-Hill Companies; 2007: 477-484.
3. Curry SC, Chang D, Connor D. Drug- and toxin-induced rhabdomyolysis. *Ann Emerg Med* 1989; 18: 1068-1084.
4. Prendergast BD, George CF. Drug-induced rhabdomyolysis - mechanism and management. *Postgrad Med J* 1993; 69: 333-336.
5. Abuelo JG. Renal failure caused by chemicals, foods, plants, animal venoms and misuse of drugs: an overview. *Arch Intern Med* 1990; 150: 505-510.
6. Minns AB. Isoniazid (INH). In: Olson KR (ed). *Poisoning & Drug Overdose* (6th ed). USA: The McGraw-Hill Companies; 2012: 249-250.
7. Chin L, Sievers ML, Laird HE, et al. Evaluation of diazepam and pyridoxine as antidotes to isoniazid intoxication in rats and dogs. *Toxicol Appl Pharmacol* 1978; 45: 713-722.
8. Koppel C. Clinical features, pathogenesis and management of drug-induced rhabdomyolysis. *Med Toxicol Adverse Drug Exper* 1989; 4: 108-126.
9. Melli G, Chaudhry V, Cornblath DR. Rhabdomyolysis: an evaluation of 475 hospitalized patients. *Medicine* 2005; 84: 377-385.
10. Blowey DL, Johnson D, Verjee Z. Isoniazid-associated rhabdomyolysis. *Am J Emerg Med* 1995; 13: 543-544.
11. Panganiban LR, Makalinao IR, Cortes-Maramba NP. Rhabdomyolysis in isoniazid poisoning. *J Toxicol Clin Toxicol* 2001; 39: 143-151.
12. Sidell FR, Culver DL, Kaminskis A. Serum creatine phosphokinase activity after intramuscular injection: the effect of dose, concentration, and volume. *JAMA* 1974; 229: 1894-1897.
13. Konikoff F, Halevy J, Theodor E. Serum creatine kinase after intramuscular injections. *Postgrad Med J* 1985; 61: 595-598.