AKADEMİK ACİL TIP OLGU SUNUMLARI DERGİSİ

AKATOS 2011;2(4):45-47 JAEMCR 2011;2(4):45-47
doi: 10.5505/jaemcr.2011.82905

Status epileptikus, hiperglisemi, ciddi metabolik asidoz ve hepatotoksisite ile prezente olan izoniazid intoksikasyonu

Isoniazid intoxication presenting as status epilepticus, hyperglycemia, severe metabolic acidosis and hepatotoxicity

Evrim ÇAKIR[1], Murat ÇINARSOY[2], Selma KARAAHMETOĞLU[2], Erdal ESKİOĞLU[2]

1 Department of Endocrinology, Diskapi Yildirim Beyazit Training and Research Hospital, Ankara
2 Department of Internal Medicine, Numune Training and Research Hospital, Ankara

ABSTRACT

Isoniazid (isonicotinic acid hydrazide [INH]) is an antimicrobial that has been used as a firstline agent for prophylaxis and treatment of tuberculosis. Since isoniazid is increasingly being used to control the spread of tuberculosis, physicians must be aware of its potentially fatal effects. An acute overdose is potentially fatal and is characterized by the clinical triad of repetitive seizures unresponsive to the usual anticonvulsants, metabolic acidosis with a high anion gap and coma. The diagnosis of INH overdose should be considered in any patient who presents to emergency medical services with the triad. We report a patient presenting with multiple generalized tonic clonic convulsions with severe metabolic acidosis and hyperglycemia as a manifestation of INH toxicity.

Keywords: *isoniazid, intoxication, tonic clonic convulsion, metabolic acidosis, hepatotoxicity*

Received : 17.01.2011 ***Accepted:*** 15.02.2011

ÖZET

İzoniazid (izonikotinik asit hidrazid [INH]) bir antimikrobiyal olup tüberküloz profilaksi ve tedavisinde ilk seçenek ajan olarak kullanılmaktadır. Tüberkülozun yayılımını kontrol altına almada İzoniazid'in artan kullanımından dolayı klinisyen ilacın potansiyel fatal etkilerinin farkında olmalıdır. Akut yüksek doz antikonvulzanlara cevap vermeyen tekrarlayıcı nöbetler, yüksek anyon gapli metabolik asidoz ve koma ile seyreden triad ile karakterizedir ve potansiyel fatal olabilir. Izoniazid yüksek doz alımı acil servise bu triadla gelen her hastada düşünülmelidir. Biz de burada multipl, jeneralize, tonik-klonik nöbet, ciddi metabolik asidoz ve hiperglisemi ile prezente olan INH toksikasyonu vakasını sunduk.

Anahtar Sözcükler:*izoniazid, intoksikasyon, tonik klonik konvulzyon, metabolik asidoz, hepatotoksisite*

Başvuru Tarihi : 17.01.2011 ***Kabul Tarihi***: 15.02.2011

Yazışma Adresi/Corresponding to:
Evrim Çakır
Diskapi Yildirim Beyazit Training and Research Hospital
Department of Endocrinology, Ankara-Turkey
GSM: 0 505 269 24 68
e-mail: evrimcakir@mynet.com

doi: 10.5505/jaemcr.2011.82905

INTRODUCTION

Isoniazid (isonicotinic acid hydrazide [INH]) is an antimicrobial that has been used as a first-line agent for prophylaxis and treatment of tuberculosis.[1] Since isoniazid is increasingly being used to control the spread of tuberculosis, physicians must be aware of its potentially fatal effects.[2] An acute overdose is potentially fatal and is characterized by the clinical triad of repetitive seizures unresponsive to the usual anticonvulsants, metabolic acidosis with a high anion gap and coma.[3] If isoniazid is taken acutely, as little as 1.5 g (five 300-mg tablets) can cause toxicity. Doses larger than 30 mg per kg often produce seizures. Ingestion of the drug in amounts greater than 80 to 150 mg per kg can rapidly lead to death.[4] The diagnosis of INH overdose should be considered in any patient who presents to emergency medical services with the triad.[3]

We report a patient presenting with multiple generalised tonic clonic convulsions with severe metabolic acidosis as a manifestation of INH toxicity.

CASE REPORT

A 22 years old girl was admitted to emergency medical services in an unconscious state. After 20 minutes of her hospitalization she had generalized seizures of tonic-clonic type. Examination revealed comatose subject, with a blood pressure of 120/83 mm Hg, a pulse rate of 86 beats per minute, a respiratory rate of 17 breaths per minute, an oral temperature of 36.5°C and absent deep tendon jerks. Pupils were dilated with sluggish light reflex and fundus was normal. A bad smell was sensed from her exhaled air. Other systems were essentially normal. Initial laboratory studies revealed a high anion gap metabolic acidosis (arterial ph 7.01, arterial po2: 106 mmHg pco2:25 mmHg, serum bicarbonate 3.7 mmol/L, serum anion gap 29) and hyperglycemia (serum glucose 296 mg/dL). The patient was found to have leukocytosis (white blood cell:33600/ml, polymorph nuclear cell percent:%76). In urinalysis glucosuria was positive but ketonuria was not seen. Serum LDH and creatinin kinase(CPK) levels were 577 IU/L (100-245),192 IU/L(40-226) respectively. Initial liver function tests, electrocardiogram, plain chest radiography and a computed tomographic scan of the brain were normal. Diabetic ketoacidosis, ethanol ingestion, drug or other toxic exposure was suspected. Acute emergency department management for an unknown toxic ingestion was initiated. Due to,unconscious state of patient gastric lavage could not be applied. Because of bad smell of her breath ethanol ingestion was considered and pyridoxine (vitamin B6) was given 15 miligram. Isotonic saline infusion, bicarbonate replacement and parenteral diazapam were ordered to control the seizures. But her repetitive seizures were unresponsive to diazepam, so phenytoin infusion was started. Although we had reached to maximum dose therapy her generalized tonic clonic seizures had continued for seven hours.

After eight hours of her hospitalization it was learned that the patient had ingested 6 g (130 mg per kg) isoniazid (her father was a patient of pulmonary tuberculosis but he did not say this at initial history). At the same time she became awake, alert and responsive. Pyridoxine (vitamin B6) infusion was administered. Repeat arterial blood gas measurements revealed correction of the metabolic acidosis. She remained alert and oriented, with slightly slurred speech. She exhibited mild ataxia, a positive Romberg sign and nystagmus, but these problems resolved over the next few days.Following day serum CPK level had increased. Third day serum transaminase level had increased. After one month serum levels of hepatic enzymes and CPK had decreased to normal limits (Table 1).

	GLU mg/dL	UREA mg/dL	CRE mg/dL	AST IU/L	ALT IU/L	LDH IU/L	CPK IU/L
INITIAL DAY	296	17	1	34	12	577	192
SECOND DAY	76	5	0,7	87	21	377	71500
FOURTH DAY	90	80	0,6	493	140	1480	48800
FIRST MONTH	78	14	0,7	50	75	190	50

DISCUSSION

We presented a case of isoniazid intoxication with hyperglycemia, metabolic asidosis and seizures resistant to medication. Labarotory analysis revealed a multisystemic effect of intoxication including nervous, musculoskeletal and hepatobiliary system resulted in coma, metabolic acidosis, toxic hepatitis and hyperglycemia. Hyperglycemia is also one of the side effects of isoniazid administration.[5] As we had experienced in this case a satisfactory history of drug ingestion could not be taken from patient or her relatives. After initial evaluation emergent attempts including airway, breathing and circulation should be provided. Valuable and rapid labarotory analysis like complete blood count, biochemical, urine and blood gas analysis should be ordered. Odour of the breath in patients with acidosis is critical to reach a diagnosis and initial management. This patient's history of drug ingestion was taken after a waste of some time, fortunately every possible diagnosis of high anion gap metabolic acidosis had been considered and managements were planned according to differential diagnosis (uremia/kidney failure, alcoholic ketoacidosis, diabetic ketoacidosis, starvation ketoacidosis, drug ingestions) and coming labaratory results with time. Here we want to emphasize the critical effect of 6 gr of isoniazide resulted in seizures resistant to medication. In this case we saw that major toxicity of isoniazid is observed in nervous system resulted in seizures for hours and after resolution of seizure toxicity effect was seen as nystagmus and other nervous system abnormalities. As the laboratory analysis had shown hepatic and skeletal system toxicity was seen after days of ingestion without any sequela and lethal effect.

In this case we have experienced that isoniazid intoxication effects mainly nervous system and management should be concentrated on this abnormalities immediately. And second important point that should be handled is the acidosis.

doi: 10.5505/jaemcr.2011.82905

In our case high dose isoniazid caused hyperglycemia and challenged the differential diagnosis. As we have mentioned rapid laboratory analysis of urine for ketone can eliminate diabetic ketoasidosis. Hyperglycemia was improved after saline infusion. Diagnosis of uremic acidosis was considered until serum analysis of urea and creatinin were found to be normal. As we had wasted time to reach the certain diagnosis, initially diagnosis was considered to be alcohol intoxication so we ınfused only 15 mg of pyridoxin. Even with low doses of pyridoxin infusion seizures had stopped within eight hours. The first signs and symptoms of isoniazid toxicity may appear 30 minutes to two hours after ingestion and include nausea, vomiting, rash, fever, ataxia, slurring of speech, peripheral neuritis, dizziness and stupor. These symptoms are usually followed by grand mal seizures and coma and the seizures are often refractory to anticonvulsant therapy.[6] Pyridoxine should be administered in a dose equivalent to the suspected maximum amount of isoniazid ingested (i.e., gram-per-gram replacement). If the amount of ingested isoniazid is unknown, 5 g of pyridoxine is given intravenously over five to 10 minutes. Repeat dosing may be needed for persistent seizure activity and may also be used to reverse deep coma.[7] In this case patient had been infused only 15 mg pyridoxin before we learned 6 gr INH ingestion for eight hours after acute intoxication. But seizures stopped this low dose pyridoxin, hydration, bicarbonate replacement and anticonvulsant therapy.

Isoniazid toxicity should be suspected in any patient who presents with refractory seizures, hyperglycemia and metabolic acidosis. As we had not known INH ingestion seizures were accepted to be status epilepticus so the first choice drug was diazepam and the second choice was fenitoin after unresponsiveness to diazepam. But it is known that phenytoin increases hepatotoxicity effect of INH. Hepatotoxicity after three days of INH intoxication can be due to phenytoin intoxication or INH itself and improved without any sequela and lethal effect.

REFERENCES

1. Mechem CC, Toxicity, Isoniazid. E Medicine Specialties-Emergency Medicine-Toxicology. Updated: Mar 21, 2009.
2. Romero JA, Kuczler FJ. Isoniazid overdose: recognition and management. Am Fam Physician 1998;57(4):749-52.
3. Gokhale YA, Vaidya MS, Mehta AD, Rathod NN. Isoniazid toxicity presenting as status epilepticus and severe metabolic acidosis. J Assoc Physicians India. 2009;57:70-1.
4. Shannon MW, Lovejoy FH Jr. Isoniazid. In: Haddad LM, Winchester JF, eds. Clinical management of poisoning and drug overdose. 2d ed. Philadelphia: Saunders, 1990:970-5.
5. Mandell GL, Sande MA. Antimicrobial agents, drugs used in chemotherapy of tuberculosis and leprosy In: Goodman Gilman A, Goodman LS, Rall TW, et al. The Pharmacological Basis of Therapeutics. 8th ed, New York. Mc Millan 1991.
6. Alvarez FG, Guntupalli KK. Isoniazid overdose: four case reports and review of the literature. Intensive Care Med 1995;21:641-4.
7. Yarbrough BE, Wood JP. Isoniazid overdose treated with high-dose pyridoxine. Ann Emerg Med 1983;12:303-5.