Intensive Care Med (1995) 21:641–644

ORIGINAL

F.G. Alvarez
K.K. Guntupalli

Isoniazid overdose: four case reports and review of the literature

Abstract *Objectives:* To review the pathophysiology, presentation and treatment of isoniazid (INH) intoxication.
Data sources: Human, animal and modeling studies published since 1940 identified through MEDLINE and a review of the bibliographies of relevant articles.
Study selection and data extraction: The studies identified were reviewed with emphasis on the most recent. Earlier studies were selected for their historical value and relevance to the clinical setting.
Data synthesis: Isoniazid overdose is a potentially fatal intoxication. The incidence of tuberculosis has recently increased in the United States and therefore the frequency of INH overdose may also increase. Patients with INH overdose may present with nausea, vomiting, ataxia, symptoms reminiscent of atropine intoxication, coma and grand mal seizures. Lactic acidosis is revealed by laboratory evaluation. Treatment requires admission to the ICU for ventilatory support, and management of seizures and acid-base abnormalities. Pyridoxine, in a dose equivalent to the amount of INH ingested, is the only effective antidote.
Conclusions: INH overdose should be suspected in any patient presenting with seizures and metabolic acidosis. Prognosis is good when treatment is instituted early.

Key words Isoniazid · Overdose · Metabolic acidosis · Seizures · Pyridoxine

F.G. Alvarez · K.K. Guntupalli (✉)
Pulmonary/Critical Care Department, Medical Intensive Care Unit, Ben Taub General Hospital, 1504 Taub Loop, Houston, Texas 77030, USA

Isoniazid overdose

The number of tuberculosis cases reported to the CDC has been on the rise since 1988 following a long historical decline. In 1990, there was a 9.4% increase, which was the largest annual increase since 1952. The AIDS epidemic, homelessness, poverty, immigration from developing countries, and limited access to medical care have contributed to the resurgence of the disease in the United States. Because isoniazid (INH) is widely used in the treatment of tuberculosis (TB), accidental or intentional poisoning is expected to increase in frequency. We discuss patients with INH intoxication who were admitted to our ICU and review the literature.

Case reports

During the past year, 4 patients with INH intoxication were admitted to our ICU. All were receiving INH as preventive therapy because of positive PPD, though none had evidence of active tuberculosis. Table 1 shows demographic data and significant laboratory abnormalities. Urine and serum toxicology screens were negative and all other routine tests (hematology, urinalysis, and blood chemistry) were normal. Serum INH levels or qualitative identification in the urine was not performed in any of the patients; however, all admitted taking the drug, and empty bottles were brought in by families. All 4 patients presented with multiple generalized tonic-clonic seizures, and patients 1, 3 and 4 also had depressed mental status. All had severe metabolic acidosis with an elevated anion gap and required mechanical ventilation. They were treated with general supportive measures including airway protection, administration of

Table 1 Isoniazid overdose (P_aO_2 arterial oxygen pressure, P_aCO_2 arterial carbon dioxide pressure, HCO_3 bicarbonate, FIO_2 fractional inspired oxygen)

Patient no.	Age	Sex	Amount of INH ingested	pH	P_aO_2[a]	P_aCO_2	HCO_3	Anion gap
1	15	F	9 g	6.76	38	72	8	34
2	15	F	1.8 g	7.09	100	38	23	22
3	22	M	Unknown	6.85	325[b]	35	7	29
4	29	F	9 g	7.01	31	119	8	36

[a] $FIO_2 = 0.21$
[b] $FIO_2 = 1.0$

standard doses of naloxone, thiamine and 50% dextrose, gastric lavage and charcoal administration, and intravenous diazepam for seizures. Pyridoxine, in a dose equivalent to the amount of INH ingested, was administered as an intravenous infusion to all patients. Patient 3 received 5 g pyridoxine since the amount of INH ingested was not known. Seizures and metabolic acidosis resolved after administration of pyridoxine. Mechanical ventilation was discontinued within 24 h in all cases. There was no evidence of hepatotoxicity in any of the patients.

Discussion

General

Isoniazid (isonicotinic acid hydrazide) is an antimicrobial. INH produces peak blood levels 1–2 h after oral administration, which decline to 50% or less within 6 h. Therapeutic serum levels range from 5 to 8 μg/ml [1]. Toxic effects may be seen as early as 30 min after ingestion. INH diffuses readily to all body fluids, tissues, organs, and excreta; it passes through the placental barrier and is found in breast milk. Around 50–60% of a dose of INH is excreted in the urine in 24 h. INH is metabolized primarily by acetylation and dehydrazination.

Acute ingestion by adults of 6–10 g INH (i.e. 20–33 tablets containing 300 mg) is associated with severe toxicity and a high mortality rate [2, 3]. Even a relatively small overdose of 1.5 g INH can induce minor toxicity, and ingestion of more than 15 g is usually fatal if not adequately treated [2, 3]. Following ingestion, there is usually a latent period of 30 min to 2 h which may result in a delay in the institution of appropriate treatment [4]. Following this interval, the first signs and symptoms appear, which include nausea, vomiting, ataxia, slurred speech, dizziness and effects similar to those of atropine (mydriasis, increased visual sensitivity to light, tachycardia, retention of urine. Stupor, coma hyperreflexia, or areflexia may occur 3–4 h later, followed by grand mal or localized seizures. INH induced seizures are usually refractory to treatment with anticonvulsants, especially phenytoin and barbiturates [5]. Finally, hypotension, cyanosis, and death may occur.

Laboratory evaluation may reveal metabolic acidosis with an elevated anion gap, leukocytosis, hypokalemia, and increased urinary excretion of pyridoxine. Hyperglycemia, glycosuria, and ketonuria may confound the diagnosis by suggesting diabetic ketoacidosis [4, 6]. A transient increase in hepatic aminotransferase has also been reported, but not as a consistent finding [7]. Although death has been reported at more than 150 μg/ml, retrospective analysis of serum INH levels (20–710 μg/ml) demonstrates no correlation between the severity of intoxication and blood levels [8, 9]. Interpretation of serum INH levels is further complicated by the considerable variation of the rate of elimination from serum among individuals. In addition, if protein is not removed from the serum within 1 or 2 h after collection, INH concentration may decrease significantly. Freezing of serum may delay this process but does not prevent it [1]. Qualitative identification in the urine can be performed by reagent-impregnated paper strips sensitive to the metabolic products of INH [8].

INH toxicity should be suspected in any patient with refractory seizures and metabolic acidosis with an elevated anion gap. The differential diagnosis of acidosis with an elevated anion gap, including cases caused by poisoning, is presented in Table 2.

Pathophysiology of isoniazid poisoning

Central nervous system effects

The most consistent central nervous system (CNS) effect of toxicity associated with INH intoxication is convulsions. Human ingestion of 80 to 150 mg/kg usually

Table 2 Differential diagnosis of INH overdose metabolic acidosis with an elevated anion gap

1. Diabetic ketoacidosis
2. Lactic acidosis
3. Uremia
4. Drug intoxication
   - I. Drugs that uncouple metabolism
     - a. Salicylates
     - b. Cyanide
     - c. Carbon monoxide
   - II. Drugs that induce seizures
     - a. Tricyclics
     - b. Strychnine
     - c. Theophylline
     - d. INH
   - III. Other
     - a. Ethylene gylcol
     - b. Methanol
     - c. Paraldehyde
     - d. Iron
     - e. Phenphormin
     - f. Toluene
     - g. Alcoholic ketoacidosis

results in severe seizures and increased mortality [2, 5]. It has been postulated that the convulsant effects of INH are associated with the disruption of the glutamic acid-γ-aminobutyric acid system. In the central nervous system, γ-aminobutyric acid (GABA) inhibits synaptic transmission. Synthesis of GABA requires the L-glutamic acid decarboxylase (GAD) enzyme, and the pyridoxal 5-phosphate coenzyme (the active form of vitamin B_6). Administration of large doses of INH produces a significant increase in the urinary excretion of vitamin B_6 [10]. It has been postulated that vitamin B_6 depletion decreases the activity of the coenzyme pyridoxal 5-phosphate, which in turn impairs the synthesis of GABA and increases susceptibility to seizures. This theory is supported by the work of Rosen et al. [11] who showed that vitamin B_6 depletion decreased GAD activity, which was restored after administration of pyridoxine [11]. Furthermore, several authors have reported a protective anticonvulsant effect of pyridoxine in animals and humans after ingestion of INH [12–14]. More recently, Wason et al. successfully treated 5 patients using a single dose of pyridoxine in an amount (g) equivalent to that of INH ingested [15]. Alcohol is often ingested with INH, potentiating toxicity by increasing the degradation of phosphorylated vitamin B_6 compounds [16].

Metabolic acidosis

The mechanism of metabolic acidosis produced by INH overdose is not clear, but is most likely the result of lactic acidosis due to seizure activity [17]. Some authors have suggested that INH may block the conversion of lactate to pyruvate in Krebs' cycle, but the evidence for the latter mechanism is inconclusive [3, 18, 19].

Management of isoniazid overdose

Management of patients with INH overdose depends on the amount of drug ingested and the time elapsed prior to presentation. If it can be determined that toxicity has not occurred 4 h after ingestion of a dose of less than 20 mg/kg, only careful observation is required [4]. The management of patients presenting with evidence of significant toxicity is divided into three basic categories: (1) correction of life-threatening symptoms, (2) administration of pyridoxine, and (3) general supportive care.

1. Correction of life-threatening symptoms. The most common associated symptoms are CNS and metabolic disturbances. In sedated or otherwise unresponsive patients a secure airway should promptly be established, the vital signs assessed, and an intravenous line inserted. Diazepam has been shown to be more effective than other anticonvulsants in the treatment of INH-induced seizures; some authors suggest that this is due to an increase in GABA levels [20, 21]. Diazepam is administered at a dose of 5–10 mg IV, which may be repeated 10–20 min later, if needed. Control of seizures usually corrects metabolic acidosis. Sodium bicarbonate may be of use in severe cases.

2. Administration of pyridoxine. The data available support the use of pyridoxine in INH toxicity. The mechanism of action seems to consist of reactivation of the GAD enzyme with a subsequent increase in GABA levels, thus increasing the seizure threshold. As pointed out by Wason et al. the majority of cases reported received pyridoxine at doses of less than 10% of the amount of INH ingested [15]. Its effectiveness may thus seem questionable, but adequate doses of pyridoxine have given very encouraging results [2, 15, 22]. The dose of pyridoxine should at least be equal to the estimated maximal amount of INH ingested. Sievers et al. suggested that 5 g pyridoxine be given over 3–5 min in the event that such information were not available [4]. This dose may be repeated at 5- to 20-min intervals until seizures cease or consciousness is regained. If the estimated amount of INH ingested exceeds 200 mg/kg (about 15 g in an adult) an i.v. infusion of 5 g pyridoxine HCl in 500 ml fluid over 2 h is recommended. This infusion may be repeated if further bolus injections of pyridoxine are needed.

The outcome in 5 successfully treated patients, each of whom received a single dose of pyridoxine equal to the estimated amount of INH ingested, was compared with the results recorded in 41 well-documented literature controls [15]. Seizures did not recur in any of the patients who received adequate treatment. However, seizures recurred in 11–47% of patients treated with suboptimal doses of pyridoxine and in 60% of those who did not receive any. Repeated or higher doses of pyridoxine have been shown to awaken patients who remained comatose following INH overdose [23]. Although the incidence of pyridoxine toxicity is low, tachypnea, postural reflex abnormalities, paralysis, and convulsions have been reported [24]. Sievers and Herrier point out that only doses as high as 3–4 g/kg produce significant toxicity, and reported a patient who tolerated a dose of almost 1 g/kg without side effects [4].

3. General supportive care. After initial stabilization of life-threatening symptoms, efforts should be directed to evacuate the stomach, prevent further absorption and enhance excretion. After gastric lavage, activated charcoal, 5–10 times the estimated ingested dose, or 25–50 g in a water slurry, should be administered via a nasogastric tube [25].

Total prevention of absorption of INH was demonstrated by pharmacokinetics studies when activated charcoal and INH were administered concomitantly [26].

Forced diuresis with fluids, furosemide or mannitol have been suggested by several authors [2–4] as ways of enhancing elimination of the drug. Hemodialysis and peritoneal dialysis are seldom used although the available evidence suggests that they can be effective [27, 28].

Prognosis

Prognosis in acute INH intoxication is largely dependent on early recognition and treatment of complications. Advanced age, pre-existing seizure disorder, severe metabolic acidosis, and decreased renal function are considered poor prognostic factors [25].

Summary

Isoniazid overdose is associated with high mortality if not treated adequately. INH overdose should be suspected in: 1) any patient with access to the drug or with a history compatible with intoxication; 2) patients with intractable or new onset seizures, and 3) patients with metabolic acidosis. Treatment with IV pyridoxine in doses equal to the estimated ingested dose of INH is usually effective when combined with general supportive measures.

References

1. Yarbrough BE, Wood JP (1993) Ann Emerg Med 12:303–305
2. Brown CV (1972) Acute isoniazid poisoning. Am Rev Respir Dis 105:206
3. Terman DS, Teitelbaum DT (1970) Isoniazid self poisoning. Neurology 20:299
4. Sievers ML, Herrier RN (1970) Treatment of acute isoniazid toxicity. Am J Hosp Pharm 32:202
5. Nelson LG (1965) Grand mal seizures following overdose of isoniazid. Am Rev Respir Dis 91:600
6. Bears ES et al (1976) Suicidal ingestion of isoniazid: an uncommon cause of metabolic acidosis and seizures. South Med J 69:31–32
7. Mowry JB, Furbee RB (1991) Isoniazid. In: Rippe, Irwing, Alpert (eds) Intensive care medicine, 2nd edn. Little Brown, Boston London, pp 1297–1301
8. Moudling T, Iseman M, Sbarbaro J (1976) Prevention of isoniazid hepatotoxicity. Ann Intern Med 5:398
9. Gurnani A, Chawla R, Kundra P, Bhattacharya A (1992) Acute isoniazid poisoning. Anaesthesia 47:782–783
10. Biehl JP, Vilter RW (1954) Effects of isoniazid on pyridoxine metabolism. J Am Med Assoc 156:1549
11. Rosen F, Milholland R (1960) Effects of pyridoxine depletion on three enzymes requiring pyridoxal phosphate. Fed Proc 19:414
12. Wood JD, Peesker SJ (1972) Correlation between changes in GABA metabolism and isonicotinic acid hydrazide induced seizures. Brain Res 45:489
13. Wood JD, Peesker SJ (1972) The effect of GABA metabolism in brain of isonicotinic acid hydrazide and pyridoxine as a function of time after administration. J Neurochem 19:1527
14. Holtz P, Palm D (1964) Pharmacological aspects of vitamin B_6. Pharmacol Rev 16:113
15. Wason S, Lacouture PG, Lovejoy FH Jr (1981) Single high-dose pyridoxine treatment for isoniazid overdose. JAMA 246:1102
16. Lumeng L, Li TK (1974) Vitamin B_6 metabolism in chronic alcohol abuse. J Clin Invest 53:693
17. Chin I, Sievers ML, Laird HE et al (1979) Convulsions as the etiology of lactic acidosis in acute isoniazid toxicity in dogs. Toxicol Appl Pharmacol 49:377
18. Peters JH, Miller KS, Brown P (1975) Studies on the metabolic basis for the genetically determined capacities for isoniazid inactivation in man. J Pharmacol Exp Ther 150:298
19. Patiala J (1954) The amount of pyridine nucleotides (coenzymes I and II) in blood in experimental tuberculosis before and during isoniazid treatment. Am Rev Tuberc 70:453
20. Saad SF (1972) Effect of diazepam on gamma-aminobutyric acid (GABA) content on mouse brain. J Pharm Pharmacol 24:839
21. Saad SF, e-Masry AM, Scott PM (1972) Influence of certain anticonvulsants on the concentration of gamma-aminobutyric acid in the cerebral hemispheres of mice. Eur J Pharmacol 17:386
22. Katz G, Jobin GC (1970) Large doses of pyridoxine in the treatment of massive ingestion of isoniazid. Am Rev Respir Dis 101:991
23. Brent J, Nguyen V, Kulig K, Rumack BH (1990) Reversal of prolonged isoniazid-induced coma by pyridoxine. Arch Intern Med 150:1751–1753
24. Unna IC (1940) Studies on the toxicity and pharmacology of vitamin B_6 (2-methyl-3-hydroxy-4,5-bis-[hydroxy-methyl]-pyridine). J Pharmacol Exp Ther 70:400
25. Skoutakis VA (1972) Clinical toxicology of drugs: principles and practice. Lea & Febiger, Philadelphia
26. Siefkin AD, Albertson TE, Corbett MG (1987) Isoniazid overdose: pharmacokinetics and effects of oral charcoal in treatment. Hum Toxicol 6:497–501
27. Cocco AE, Pazourek LJ (1963) Acute isoniazid intoxication management by peritoneal dialysis. N Engl J Med 269:852
28. Schreiner G (1971) Dialysis of poisons and drugs – annual review. Drug Intell Clin Pharmacol 5:322