
Urgent Hemodialysis for the Treatment of Isoniazid Overdose

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Abstract

Isoniazid (isonicotinyl hydrazine; INH) overdose is associated with a high rate of death, especially in discrete communities at high risk of tuberculosis. Thus, its early and appropriate treatment is very important. The aim of this report was to describe two patients with neurotoxic complications of INH overdose that were treated effectively with emergency hemodialysis and to discuss the advantages of this novel method. The patients, both female, had ingested more than 80 mg/kg INH and presented with the typical clinical triad of coma, seizures, and acidosis. Hemodialysis was started when the seizures failed to respond to intravenous pyridoxine and diazepam within the first hour of pyridoxine treatment. The seizures terminated completely after one hour of hemodialysis, and the arterial gas findings normalized after 5 hours. The patients were discharged home in good condition after 3 and 9 days. These cases indicate that urgent hemodialysis effectively and rapidly improves metabolic acidosis complicating INH overdose and leads to satisfactory clinical improvement. We suggest that it be considered in cases of INH overdose when coma and seizures are not adequately controlled by standard second-line treatment or INH levels are extremely high (more than 30 µg/ml).

MeSH Words: Isoniazid, Overdose, Urgent hemodialysis

Introduction

Isoniazid, also called isonicotynil hydrazine (INH), is the standard antimicrobial treatment for active and latent tuberculosis (TB) [1]. The United States government screens all refugees for TB and treats those with active disease and positive skin test [2]. Previous reports have described INH poisoning in discrete communities at high risk of TB [2-5]. Nolan and co-workers [4] estimated an extraordinary 4.2% risk of isoniazid overdose among South Asian refugee women aged 25 to 34 years being treated for TB. In a study of Arizonian Native Americans, Sieverrs and colleagues [5] noted an

annual suicide attempt rate of 447 per 100,000; INH was implicated in 8% of cases. The rate of death from INH overdose was 8.3%. Young women were at particular risk. All deaths were associated with ingestion of more than 15 g of INH and a delay of more than 4 hours in seeking medical attention [5].

According to the Annual Report of the National Poison Data System (NPDS) of the American Association of Poison Control Centers, there were 350 cases of INH overdose in 2006, of which 266 involved a single exposure. Three persons died: two ingested INH with additional drugs (acetaminophen+diphenhydramine and

fluoxetine), and one, only INH. Ninety-five of the overdoses following isolated exposure were suicide attempts [6].

These high reported rates make the appropriate and early management of INH overdose very important. At present, the standard treatment is supportive only. The aim of this study was to describe two patients in whom hemodialysis proved an effective alternative to third-line treatment with phenobarbital and propofol and to discuss the advantages of this novel therapeutic mode.

Case report

Case 1

A 19 year-old woman weighing about 65 kg attempted suicide by ingestion of 30 tablets of INH (300 mg per tablet; 138 mg/kg) prescribed for her father for treatment of TB. Other than major depression, there was no history of serious underlying disease, such as diabetes or hypertension. One hour after ingestion of the tablets, the patient was taken to a local state hospital where she was treated with gastric lavage and activated charcoal. However, she failed to regain consciousness. Four hours after onset of treatment, tonic-clonic seizures developed, and the patient was transferred to the Dicle University Medical School Hospital.

On physical examination, the patient was comatose, with seizure activity. Arterial blood pressure measured 110/70 mmHg and pulse 104 bpm; breathing was rapid (26 breaths/min). The arterial blood gas findings are shown in Table 1. The anion gap was calculated as 20 meq/L. Other laboratory values, including complete blood cell count, blood glucose level, electrolytes, and liver enzymes were within normal range.

Treatment consisted of 5 g pyridoxine and 10 mg diazepam via separate intravenous lines. Diazepam was administered 3 times at 5-minute intervals. When the seizures failed to respond, intravenous 10 mg benzodiazepine was added to the regimen.

However, owing to the continued seizures combined with the presence of acidosis, we decided to treat the patient with hemodialysis instead of the standard propofol. An 11 F central venous catheter was inserted into the [subclavian](#)

vein. Hemodialysis was started 6 hours after INH ingestion and within the first hour of pyridoxine treatment. The seizures stopped after the first hour of dialysis, and arterial blood gas findings normalized after 5 hours of hemodialysis. The patient was discharged home 3 days later.

Case 2

A 28 year-old woman weighing about 50 kg attempted suicide by ingestion of 15 tablets of INH (300 mg per tablet; 90 mg/kg) that had been prescribed for treatment of TB. She was brought by her family to our emergency department because of seizures. The time of tablet ingestion was unclear. The patient had no history of psychiatric or other chronic disorders except TB. On physical examination, the patient was unconscious, with continual seizures. Arterial blood pressure was 110/60 mmHg, pulse 92 bpm, respiratory rate 28 breaths/min.

The arterial blood gas determinations are shown in Table 1. The anion gap was calculated as 18 meq/L. There was a minimal increase in liver enzyme levels. Blood cell count, blood glucose level, and electrolyte levels were within normal range.

Treatment consisted of 5 g pyridoxine and 10 mg diazepam via separate intravenous lines. Diazepam was administered 3 times at 5-minute intervals. Owing to the failure of the seizures to respond and the concurrent acidosis, we opted for hemodialysis instead of phenobarbital and propofol. Hemodialysis was started in the first hour of pyridoxine treatment and was continued for 5 hours. The seizures ceased in the first hour of dialysis and clinical stabilization was noted after 5 hours. The acidosis disappeared. The patient was discharged home 9 days later.

Discussion

INH is reportedly one of the 5 major causes of seizures associated with poisoning and drug overdose [7]. Emergency department staff should be made aware of the increasing use of INH chemoprophylaxis, particularly among young persons [8].

Acute ingestion by adults of as little as 1.5 g (5 tablets) INH can produce signs of mild toxicity: nausea, vomiting, fever, dizziness, light sensitivity, ataxia, slurring of speech, peripheral

Table 1: Laboratory findings before and after hemodialysis

Patient	pH	HCO ₃ (mol/L)	pO ₂ (mmHg)	pCO ₂ (mmHg)	Lactate (mg/dl)
Pt. 1					
At presentation	7.012	9.1	98	36	116
After hemodialysis	7.442	23.3	91.3	32.2	21
Pt. 2					
At presentation	7.005	10.2	102	48	103
After hemodialysis	7.380	22	97	44	29

neuritis, and stupor [9]. At doses of 30 mg/kg or more, INH can cause abrupt, generalized tonic-clonic seizures, and at doses of 80 to 150 mg/kg, it causes severe central nervous system symptoms [10]. The clinical triad of acute INH neurotoxicity consists of recurrent seizures, metabolic acidosis, and coma. Doses exceeding 200 mg/kg can rapidly progress to death [10]. The immediate causes of death are acute respiratory failure or hypotension [11].

Patients exposed to an overdose of INH may become symptomatic within 30 to 45 minutes of ingestion, or symptoms may be delayed for up to 2 hours, when blood levels peak [9,10]. The drug readily diffuses to all body fluids and tissues, with the largest concentration in the liver [12]. The plasma half-life in patients with normal renal and hepatic function is 1 to 4 hours; the plasma half-life may be prolonged in acute overdose [11]. Blood levels are not helpful in managing an acute isoniazid overdose.

In both cases reported here, the ingested INH dose was more than 80 mg/kg. Both patients presented with the classic clinical triad of INH overdose. Vital signs were stable.

Unconscious patients with known or suspected INH overdose should undergo gastric lavage via a large-bore gastric tube to remove any remaining drug from the stomach [13], followed by intravenous infusion of 5% dextrose in normal saline solution at rates determined by the clinical setting. Vasopressors (dopamine, epinephrine) are occasionally required [14].

Pyridoxine is the specific antidote for INH overdose [14]. Pyridoxine is a necessary co-factor for the production of the neurotransmitter gamma-aminobutyric acid (GABA), and it must be activated to produce GABA. In isoniazid overdose, the susceptibility to seizures is induced by isoniazid binding to endogenous pyridoxine, rendering it inactive and resulting in a depletion

of GABA in the brain. Therefore, the administration of exogenous pyridoxine directly counteracts this neurotoxic effect [15].

If the amount of INH ingested is unknown, 70 mg/kg pyridoxine (up to 5g) should be administered. If the amount is known, the first dose of pyridoxine (5-10% solution) should match the INH dose ingested (up to 5 g). Pyridoxine is administered over a 5-15 minute period via an intravenous line separate from the one being used for administration of other anticonvulsants [16]. Pyridoxine alone is effective for the treatment and prophylaxis of seizures in most cases of INH overdose. However, if the seizures prove resistant, diazepam should be infused after adequate airway control is established. Phenobarbital or propofol also may be used, but phenytoin is not effective. Pyridoxine is acidic and should not be mixed with bicarbonate [14]. However, its simultaneous administration with benzodiazepine has a synergistic effect in terminating seizures [16]. Our patients received intravenous pyridoxine immediately on presentation, but it failed to alleviate the seizures.

The continuing refractoriness of the seizures in our patients prompted our decision to attempt hemodialysis. Hemodialysis is generally reserved for specific toxins that must be both potentially life-threatening and amenable to removal by this method. Accordingly, INH is a small, water soluble molecule which is poorly protein bound and distributes in a small volume (0.6 l/kg) [11]. Hemodialysis is advantageous in this setting because it removes toxins that are already absorbed from the gut lumen in addition to substances that do not adhere to activated charcoal, and it removes both the parent compound and the active toxic metabolites [17]. It should be considered when coma and seizures are not adequately controlled with pyridoxine or when INH levels are extremely high (over 30

µg/ml). Its use is not necessary in mild cases of INH overdose [18]. Orłowski et al. [19] described a 7-year-old child who ingested 125 mg/kg of INH and showed persistent metabolic acidosis and coma after administration 6 g of pyridoxine. Hemodialysis was initiated 11.5 hours after ingestion. After the 5-hour session, the patient was fully conscious and free of seizure activity. In our patients, too, one session of hemodialysis was applied to control INH-induced seizures and metabolic acidosis, and it led to improvement in the acidosis, the electrolyte and acid-base disturbances, and the clinical symptoms. The seizures were eliminated completely.

Our patient 2 was a chronic user of INH, and she presented with a minimal increase in liver enzyme levels. Therefore, she required a relatively long hospitalization time (9 days) until we were able to stabilize her liver function and reconstitute her anti-tuberculosis treatment. By contrast, patient 1, who was not a chronic INH user and presented with normal range liver enzyme levels, was hospitalized for only 3 days. Although chronic use of INH at therapeutic doses has been associated with hepatotoxicity and peripheral neuritis, severe INH overdoses are characterized by neurotoxic effects [10].

It should be noted that we did not evaluate serum levels of INH or other toxic agents such as alcohol in our patients because our laboratory facilities were not equipped to conduct these tests.

In conclusion, INH toxicity should be suspected in any patient who presents at the emergency department with refractory seizures and metabolic acidosis [10]. INH has been implicated in a high rate (8%) of suicide attempts [5]. Given that the incidence of TB is increasing, we may expect even more suicide attempts related to INH overdose. Our report shows that urgent hemodialysis treatment not only corrects the metabolic acidosis characteristic of INH overdose, but also leads to more rapid clinical improvement than standard methods. We suggest that urgent hemodialysis be considered for use in the presence of extremely high INH blood levels. It is not necessary in cases of mild INH toxicity. Further studies are needed to compare the effectiveness and rate of action of hemodialysis with other treatments in alleviating INH neurotoxicity.

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Murat Orak: preparing case data and writing of manuscript
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