INTENTIONAL OVERDOSAGE WITH ISONIAZID: CASE REPORT AND REVIEW OF LITERATURE

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ABSTRACT

Isoniazid (INH) is widely used in most prophylactic and therapeutic anti-tuberculosis regimens because of its effectiveness and low cost. Yet, INH poisoning appears to be rare. We report the first case of intentional INH overdosage in Singapore. A 26-year-old Filipino male presented with mental obtundation, recurrent seizures, metabolic acidosis and hepatic dysfunction. He was successfully treated with large doses of pyridoxine (vitamin B_6). Recommendations for the management of acute INH toxicity are highlighted.

Keywords: acute isoniazid poisoning, pyridoxine (vitamin B_6), recurrent seizures, metabolic acidosis, hepatic dysfunction

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INTRODUCTION

Accidental or intentional isoniazid (INH) poisoning is not common[1-3]. Not many cases have been reported worldwide although tuberculosis (TB) is endemic in many developing countries and has gained prominence in areas where the human immunodeficiency virus infection has escalated tremendously. No case of INH poisoning has been reported in Singapore over the last three decades even though TB is so common locally. The number of new cases of TB notified in Singapore in 1993 was 1,939 (1,576 residents and 363 non-residents)[4]. In the same year, there was a total of 248 relapsed cases of TB. The resident population of Singapore, comprising citizens and permanent residents, was about 2.7 million in 1990[5].

A 30-month study among south western American Indians revealed that the frequency of INH overdosage was proportional to the extent of INH usage in each tribe[6]. However, this is not the experience here.

Two previous papers identified the Southeast Asian refugees as the sub-population at risk for intentional INH overdosage. Nolan et al[7] reported 6 cases of intentional INH overdosage during preventive therapy of young Southeast Asian refugee women during a two-year period from January 1984 through December 1985. Two of these patients had major depression; two, adjustment disorders with depressed mood; and two, no psychiatric illness but overdosed themselves immediately following family disputes.

Blanchard et al[8] described eight cases of suicidal INH overdosage by Cambodian refugees in Minnesota. In contrast to the previous study, psychiatric evaluation of all the patients was normal.

In both these studies, all the patients presented with generalised seizures and metabolic acidosis. There were no deaths. However, acute INH intoxication has its mortality[9-13].

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Specific therapy with high dose pyridoxine should be instituted promptly to reduce the mortality and morbidity associated with INH poisoning.

We present an adult with INH overdosage who was successfully treated, and a brief review of the literature.

CASE REPORT

A 26-year-old Filipino man was admitted in January 1994 following intentional ingestion of 20 tablets of Trisofort 400. Each Trisofort 400 tablet contains 400 mg of INH and 25 mg of pyridoxine. He had past history of pulmonary TB 2 years ago in the Philippines and was treated for 6 months. He came to Singapore 9 months ago to work as a designer. He obtained the Trisofort tablets from his friend who has TB.

He developed a grand mal seizure 20 minutes after ingestion. Over the next 2 hours, he threw another 4 generalised seizures. This was followed by 2 other generalised seizures in the emergency room (2½ hours after ingestion) and the ward on admission. Both fits were aborted with intravenous (IV) diazepam 10 mg.

Clinical examination revealed a drowsy patient with stable vital signs and no focal neurological deficits.

Arterial blood gases analysis showed metabolic acidosis with pH 7.33, standard bicarbonate 16.4 mmol/L, base excess -9.7 mmol/L and PCO_2 26.5 mmHg. The calculated anion gap was 39 mmol/L on admission and the serum salicylate was less than 0.3 mg%. The prothrombin time (PT) was 15 seconds (normal: 11-14) and the partial thromboplastin time (PTT) was 35 seconds (normal: 20-38). His blood sugar was 5.1 mmol/L. His renal function was normal.

Gastric lavage was performed after endotracheal intubation to protect the airway. Activated charcoal was given.

IV pyridoxine 3.6 gm was given 8 hours after ingestion. An additional 5 gm of IV pyridoxine was given only another 8 hours later when the supply was available. There was no more recurrence of fit subsequently. The metabolic acidosis was corrected and the PT and PTT improved to 12.5 and 31 seconds respectively the next day. He was extubated within 24 hours after admission.

Toxicology studies revealed the presence of 1.7 mg of INH per total gastric washout of 120 mL. Urine analysis also showed the presence of INH but a quantitative blood analysis was not available in Singapore.

Serial liver function tests (Table I) were suggestive of INH induced hepatitis.

He had no clinical evidence of hepatic failure and he continued to improve with supportive therapy and oral pyridoxine 100 mg om.

He was referred to the psychiatrist who diagnosed him to

Table I – Serial liver function tests on the respective days of suicidal attempt

		Day 1	Day 4	Day 6
Total bilirubin	(3-24μmol/L)	6.9	20.9	9
SAP	(32-103 μ/L)	131	93	72
ALT (GPT)	(7-36 μ/L)	64	443	898
AST (GOT)	(15-33 μ/L)	81	301	526
GGT	(11-50 μ/L)	76	57	51

have paranoid psychosis with delusional jealousy about his wife. He was discharged to the care of his doctor in the Philippines on day 8 of his suicidal attempt with oral anti-psychotic drug and pyridoxine.

DISCUSSION

Acute toxicity from ingestion of INH is characterised by rapid onset of seizures, prolonged obtundation and metabolic acidosis unresponsive to conventional therapy[9,10,14-16]. High-dose pyridoxine treatment has been well documented in the literature to reverse the adverse effects of INH overdose[9,10,14-25].

Ingestion of more than 80 mg/kg body weight produces severe central system symptoms[16] and a dose of 125 mg/kg is potentially lethal[26] if not promptly treated. In the literature, two papers[2,27] have documented INH overdosage as high as 12 gm (40 tablets) and one paper reported an overdosage of 15 gm[10]. All these patients survived with effective treatment. In adult humans, acute ingestion of 2 to 3 gm (35 to 40 mg/kg) is potentially toxic while 10-15 gm, if untreated, is frequently associated with fatalities[28].

IV pyridoxine should be administered in amounts equal to the estimated quantity of INH ingested, even in an asymptomatic patient[18,23,24,29]. Large doses of pyridoxine have been shown to prevent the seizures and metabolic acidosis caused by ingestion of more than 2 to 3 gm of INH[18]. The earlier pyridoxine is given, the fewer the complications[30].

If the amount of INH ingested is unknown, pyridoxine 5 gm can safely be given diluted in 50 mL of dextrose 5% drip over 30 minutes[10,17,18,23,28]. The dose can be repeated if seizures recur.

If the amount of INH ingested is known, the remainder may be given by IV drip in 500 to 1000 cc of dextrose 5% over the next one to two hours[17].

Seizures are treated with IV diazepam, and IV pyridoxine recommended as above. In adult, 5 to 10 mg diazepam initially is given and repeated if necessary. In a child, 0.1 to 0.4 mg/kg up to 10 mg/dose is given. If the seizures are refractory to these measures, IV phenobarbital (15 to 20 mg/kg in 60 mL of 0.9% saline over 15 minutes) or general anaesthesia with thiopental or halothane are recommended[31]. Electroencephalogram should be monitored to ensure cessation of cerebral seizure activity. Severe metabolic acidosis should be corrected with IV sodium bicarbonate first to a pH of at least 7.2[24,31,32].

INH overdosage can be complicated by cerebellar ataxia[32] and peripheral neuropathy[33-35] which were absent in this patient. INH has also been reported to result in severe foetal deformities when ingested excessively in early pregnancy[36].

Acute metabolic acidosis in INH intoxication is most likely due to the production of lactic acid secondary to INH induced seizures[23] and metabolic reactions in which INH interferes with metabolism of pyridoxine and also the conversion of lactate to pyruvate[31]. Association of beta hydroxybutyric acidosis with INH intoxication has been reported[37]. Hence, control of seizures with IV pyridoxine and diazepam may resolve the acidosis without the use of IV sodium bicarbonate, though severe acidosis should be corrected as mentioned earlier.

Serum INH levels do not play an important role in the acute management of INH intoxication because serum INH determinations are not available in many hospitals and have not been shown to correlate closely with symptomatology[33] and liver injury[38]. Serum INH results are also subject to variability owing to sampling procedures (serum protein must be removed within 2 hours of sampling)[23].

INH poisoning can also cause hepatotoxicity[2,38-40] which was manifested in this patient. Elevation in serum levels of glutamic oxaloacetic transaminase and lactic acid dehydrogenase[2], initial fall of prothrombin and a prolonged fall of clotting factor VII[38] have been documented. The rest of the coagulation factors as well as the inhibitory activity were unaffected. Bear et al[2] observed that the liver-dependent clotting factors occurred immediately after ingestion and hence the apparently rare INH induced liver injury is considered as dose-dependent. On the other hand, there appears to be no correlation between liver injury and INH plasma levels as the serum half-life of INH amounted to 2.98 hours but the decrease of factor VII persisted over 46 hours. This may be explained by the fact that only the acetylated intermediates of INH may be hepatotoxic[38].

Forced diuresis is not indicated in the patient who responds to adequate doses of IV pyridoxine and diazepam as only 4 to 27% of INH is eliminated as free drug in the urine[31].

Peritoneal dialysis[41] and haemodialysis[26,42] have been used successfully in the management of INH overdose. Exchange transfusion has also been performed in a 19-month-old 11 kg child following ingestion of about 900 mg INH[43]. These extraordinary measures should be reserved for those patients with persistent coma or refractory seizures due to the associated complications inherent in these procedures and the generally favourable outcome with the use of adequate doses of pyridoxine, diazepam and bicarbonate.

Measures to remove any unabsorbed drug from the stomach should be considered after control of seizures. These include emesis, gastric lavage and activated charcoal/cathartic.

Emesis may be induced unless the patient is mentally obtunded or at risk of convulsing. Seizures usually occur within 1 to 3 hours after ingestion and less commonly between 30 and 60 minutes[31]. In the presence of any of these contraindications, cuffed endotracheal intubation to protect the airway should precede gastric lavage with a large-bore tube (adult: 36 to 42 French; child: 24 to 32 French).

In children over 5 years or adults, lavage with 150 to 200 mL lukewarm tap water or saline per wash. In young children 50 to 100 mL of normal saline per wash is used. Volume of lavage return should approximate the volume given to avoid fluid-electrolyte imbalance[31].

Siefkin et al[29] found that oral activated charcoal taken immediately after therapeutic INH ingestion totally prevented the absorption of INH in 3 volunteers. Scolding et al[44] however found that the area under the concentration-time curve and the half-life were not significantly changed when activated charcoal was given one hour after therapeutic INH ingestion in 6 volunteers.

The charcoal is administered as slurry. The Food and Drug Administration suggests a minimum of 240 mL of diluent per 30 gm of charcoal[31]. The optimum dose of charcoal is not known. The usual charcoal dose is 30 to 100 gm in adults and 15 to 30 gm in children; some suggest using 1 to 2 gm per kg as a rough guide, particularly in infants[31]. Charcoal slurry may be given separately in the aqueous form, or mixed with saline cathartics or sorbitol.

The recommended dosages of saline cathartic or sorbitol are as follows[31]:

i) Magnesium or sodium sulfate
   a) Adult: 20 to 30 gm/dose
   b) Child: 250 mg/kg/dose

ii) Magnesium citrate
   a) Adult and child: 4 mL/kg/dose up to 300 mL/dose

iii) Sorbitol
   a) Adult: 1-2 gm/kg/dose up to 150 gm/dose
   b) Child (> 1 yr) : 1-15 gm/kg/dose as a 35% solution up to a maximum of 50 gm/dose

Administration of cathartics should be stopped when a charcoal stool appears. The safety of more than one dose of a cathartic has not been established and repeated dosing should be done with extreme caution, if at all. Hypermagnesemia has been reported after repeated administration of magnesium containing cathartics even in patients with normal renal function. In patients with impaired renal function, saline cathartics should not be used. Cathartics are contraindicated in patients who have ileus.

CONCLUSION

INH poisoning, although rare, is extremely dangerous. Prompt recognition and specific therapy is crucial to prevent mortality. When a history of drug ingestion is not available, physicians should consider the possibility of INH overdose in patients with an unexplained severe metabolic acidosis and seizures. In the light of experience from this case, all hospitals in Singapore should have enough IV pyridoxine stocked up at least for one patient should the need arise. Additional supply can be obtained from other hospitals if more than one patient is admitted for acute INH poisoning. Careful selection of patients for anti-TB prophylaxis or treatment, dispensing of small amounts of the drugs at short intervals and the close monitoring of patient compliance with the prescribed drug regimen are recommended[6]. In addition, the combination of INH and pyridoxine within the same tablet should be preferred. Each 100 mg of INH should be supplemented with 10 mg of pyridoxine[10]. To prevent accidental ingestion in children, INH should be kept in child-resistant containers.

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