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Mini Review

Isoniazid Toxicity

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Abstract

Pharmacokinetic characteristics of INH are presented. Adverse effects and toxicity caused by INH has been reviewed under the headings of neuropathy and seizures, hepatotoxicity, rhabdomyolysis, agranulocytosis, acidosis and other adverse drug reactions. Cases of poisoning by INH have been mentioned independently. Few case reports indicating symptoms of intoxication and the mechanism of toxicity have been described. Relevant treatment for INH toxicity has been indicated. Due to structural similarity, pyridoxine is the only antidote for INH toxicity. References indicating use of pyridoxine in the treatment of INH toxicity have been mentioned.

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ABBREVIATIONS

INH: Isoniazid; GABA: Gamma-Amino -Butyric Acid; LFT: Liver Function Test; CYP: Cytochrome P450 enzyme; NAT: N-Acetyl Transferase enzyme; HIV: Human Immunodeficiency Virus; HAART: Highly Active Anti-Retroviral Therapy; ALT: Alanine Transferase enzyme; CK: Creatine Kinase; NAD: Nicotinamide Adenine Dinuleotide; IV: Intra Venous; GIT: Gastro Intestinal Tract; V_d: Volume of Distribution; CNS: Central Nervous System; WBC: White Blood Cells.

INTRODUCTION

Isoniazid (INH) is also known as Isonicotinyl hydrazide. It is an antibiotic used for treatment of tuberculosis. For active tuberculosis, INH is used along with Rifampicin, Pyrazinamide and Ethambutol. It is usually taken by mouth but may be used by injection into muscle.

INH has following pharmacokinetic characteristics:

- Absorption: INH is rapidly absorbed from GIT. The absorption is reduced when INH is taken with food.
- Distribution: INH rapidly diffuses to all body fluids and tissues with the largest accumulation in the liver.
- Volume of distribution (V_d): 0.6 l/kg
- Kinetics: first order.
- Blood plasma protein binding: negligible (0-10%)
- Time to peak blood concentration: within 1-2 hours following a single 300mg oral dose.
- Peak plasma level of 3-7 mg/l
- 1.5-3 hours at the overdose situation.

A summary of toxic effects caused by INH is presented here. Fortunately, pyridoxine (vitamin B6) works as an antidote to treat poisoning by INH.

Neuropathy and seizures [1-21]

Neuropathy [1-15]: Following characteristics of neuropathy are observed:

- INH inhibits activation of pyridoxine to coenzymes which are essential for protein metabolism and production of some neurotransmitters.
- Neuropathy occurs very rarely with a dose of 300mg per day or 15mg/kg/day 2-3 times a week.
- There is increased risk of peripheral neuritis if there is mild pyridoxine deficiency before INH therapy, i e in pregnancy, cancer, malnutrition, alcoholism or elderly.
- Symptoms can progress to sensory loss and nerve paralysis.
- Elevated INH concentrations can produce psychosis, confusion and seizures.
- Usual doses have been reported to produce insomnia, muscle twitching, memory loss, restlessness, niacin deficiency and seizures in patients with history of seizures.

The incidence of INH -induced neuropathy ranges from 0.2-2% in general population [6]. This susceptibility is highest in the elderly, during pregnancy and lactation, in chronic alcoholics, malnourished, HIV infected individuals, diabetic patients, chronic renal failure and patients with slow acetylator genotype. Patients taking medications which antagonize B6 effects like hydralazine, cycloserine, penicillamine and anti-retro viral drugs are at higher risk of neuropathy due to INH [10].

Following drugs are known to increase toxicity of INH [22]

- Daily use of alcohol increases incidence of INH-associated hepatitis.

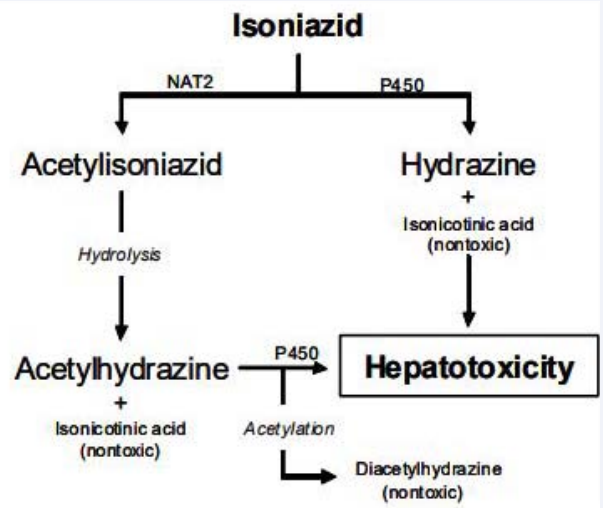

Figure 1 Mechanism of INH Hepatotoxicity.

- Barbiturates increase serum concentrations of INH.
- Concurrent use of carbamazepine can increase INH hepatotoxicity.
- Cycloserine therapy with INH can result in increased CNS side effects, particularly dizziness.
- Co-administration of Meperidine can result in hypotension or CNS depression.
- Co-administration with Rifampin may result in higher rate of hepatotoxicity.
- Pyrazinamide is also known to increase hepatotoxicity, when used with INH.

Few adverse interactions of INH with food are of clinical importance [22]

- INH has some monoamine oxidase inhibitor activity. Hence tyramine-containing foods like aged cheese and red wine can result in flushing and palpitations when taken along with INH.
- INH inhibits diamine oxidase causing headache, palpitations, sweating, hypotension, flushing, diarrhoea or itching when taken along with foods containing histamine; e g tuna, sauerkraut, yeast extract.

Seizures [16-21]: A case report indicating status epilepticus due to isoniazid toxicity has been reported [18]. An acute overdose of INH is potentially fatal and is characterized by repetitive seizures, unresponsive to usual anti-convulsants, metabolic acidosis with a high anion gap and coma. The patient had consumed 15 tablets of 300mg INH. It is indicated that a dose of 35-40mg/kg (8 tablets of 300mg INH) uniformly produce seizures. A dose of more than 6 to 10grams of INH can be fatal, if it is not aggressively treated [8]. Severe manifestations of INH toxicity may appear within 30 minutes of ingestion [8,71]. Early signs of toxicity include nausea, vomiting, slurred speech, diziness, mydriasis, tachycardia followed by recurrent seizures, severe metabolic acidosis and coma.

In yet another case of INH toxicity, presence of epidural hematoma along with INH poisoning made it difficult to discriminate the cause of seizure [21]. There was acidosis, hyperglycemia and seizures. The patient had consumed 7.5gms of INH. Following gastric lavage, the patient was administered 1g/kg oral doses of activated charcoal. The seizures were controlled by phenytoin 18mg/kg and IV 10mg diazepam.

There is one more case report of status epilepticus caused by overdose of INH [94]. It was a case of suicidal attempt. Gastric lavage was done and activated charcoal was given by nasogastric tube. Pyridoxine was given by IV route. In addition to pyridoxine, IV diazepam was also given. The patient recovered without sequelae.

Hepatotoxicity [22-46]

Following features of hepatotoxicity are observed [22]

- It is common. It is observed in about 20% of adults taking isoniazid.
- It is most common during first 2-3 months of therapy.
- The risk increases with age: 20-34- 0.3%; 35-40: 1.2%; 50-64: 2.3%; and >64: 3%.
- The risk increases with intake of alcohol.
- There is increased risk in Black and Hispanic women.
- Estimation of fatality of cases is < 1%.
- In most fatal cases, INH was continued even after significant abnormalities in liver function tests (LFT).
- Viral hepatitis does occur in patients taking INH. The cause for change in LFT should be investigated.
- Hepatotoxicity by INH appears to be an idiosyncratic response.
- INH is metabolized to monoacetyl hydrazine, which is further metabolized to a toxic product by cytochrome P_{450} leading to hepatotoxicity.
- CYP2E1 is involved in hepatotoxicity related to INH [33].
- INH has an inhibiting effect on CYP1A2, 2A6, 2C19 and 3A4 activity. CYP1A2 is involved in hydrazine detoxification [41].
- INH can induce its own toxicity, possibly by the induction or inhibition of related enzymes [26,41].

Mechanism of hepatotoxicity by INH: The primary means of INH metabolism is through acetylation by N-acetyl transferase (NAT-2) in the liver generating acetylisoniazid. Acetylisoniazid can undergo hydrolysis to form acetylhydrazine and non-toxic isonicotinic acid. Polymorphism of NAT-2 divides human beings into either rapid or slow acetylators. Slow acetylators shunt some of the INH to a secondary metabolic pathway via Cytochrome P450, producing hydrazine. It appears that both acetylhydrazine and hydrazine, generated by rapid and slow acetylators respectively, are capable of generating oxidative stress. Hydrazine may induce CYP2E1, increasing production of additional toxic metabolite. Thus hepatotoxicity may occur both in rapid and slow acetylators due to different reasons [30].

Surveillance for INH hepatotoxicity: American thoracic society [42] has given following recommendations for surveillance of INH hepatotoxicity:

- Baseline and follow up serum ALT and bilirubin are recommended for patients with a possible liver disorder: history of chronic liver disease (hepatitis B/C. alcoholic cirrhosis), chronic alcohol use, HIV patients receiving HAART, pregnant women and women up to 3 months post-partum should be carefully monitored.
- Baseline and follow up ALT concentrations for patients > 35 years old at an interval of monthly, bimonthly or at 1,3,6 months depending on perceived risk and ALT stability should be monitored.
- ALT is the preferred laboratory test for detecting and tracking hepatotoxicity.

Rhabdomyolysis [47-54]

Rhabdomyolysis is defined as damage of skeletal muscle resulting in the subsequent release of intracellular contents in to the circulation, particularly myoglobin and creatine kinase (CK) [54]. 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 [47,48,49]. In the referred case of rhabdomyolysis [50], pyridoxine was given by intramuscular route. Intramuscular injections may cause elevation in serum muscle enzyme levels. The volume, concentration and dose of drugs used intramuscularly are known to increase CK level. This situation is reported in case of various drugs given intramuscularly. Some of the drugs are barbiturates, ampicillin, digoxin, morphine [54]. In the referred case [50], the cause of rhabdomyolysis was intramuscular pyridoxine.

Agranulocytosis [55-60]

Agranulocytosis is an acute condition involving a severe leucopenia I e lower WBC count, most commonly of neutrophils causing neutropenia in the circulating blood. It is also called as agranulosis or granulopenia. Agranulocytosis is a serious idiosyncratic drug reaction and a very rare side effect of INH or rifampicin (R). A case report is mentioned in the literature [55]. In the reported case the patient recovered within 5 days after stopping rifampicin and INH. If left untreated and unrecognized, benign agranulocytosis can be fatal. Discontinuation of the offending drug can reverse neutropenia.

Acidosis [61,62]

Severe metabolic acidosis is another prominent feature of INH toxicity [61]. pH ranges from 6.8 to 7.3 are common. Following mechanisms are responsible for acidosis:

- Increase in the generation of lactic acid due to muscular activity and recurrent seizures if they exist.
- Generation of acidic INH metabolites
- Increase in keto acids due to enhanced fatty acid oxidation.
- Formation of inactive NAD leading to impairment of both glucose and fatty acid metabolites.

Other ADRs [63-71]

In addition to the adverse reactions mentioned earlier, Pancreatitis [63,67], febrile reactions [64-66], and dermatitis [68,69] are additional ADRs observed with INH. It is also suggested that INH should be used cautiously in case of geriatric cases [70,71] because of possibility of increased ADRs.

Poisoning [72-123]

Acute toxicity from ingestion of INH is characterized by rapid onset of seizures, prolonged obtundation and metabolic acidosis unresponsive to conventional therapy [78,81,118,122,123].

Ingestion of more than 80mg/kg INH produces several CNS symptoms [122] and a dose of 125mg/ kg is potentially lethal [103] if not promptly treated. Two papers [76,86] reported 12gm and one paper [81] reported 15gm ingestion of INH. All these patients survived with effective treatment. 10-15gms of INH, if untreated is associated with fatality [114].

INH over-dosage can be complicated by cerebellar ataxia [79] and peripheral neuropathy [87] INH has also been reported to result in severe foetal deformities when ingested excessively in early pregnancy [95].

Acute metabolic acidosis in INH intoxication is most likely due to the production of lactic acid secondary to INH-induced seizures [106]. Causes of lactic acidosis are production of lactic acid during seizure activity and INH's interference with NAD, which is cofactor in the reaction which converts lactate back to pyruvate [130].

INH poisoning can cause hepatotoxicity [5,76] Mild elevation in serum levels of glutamic oxaloacetate transaminase and lactic acid dehydrogenase [76], initial fall of prothrombin and a prolonged fall of clotting factor VII [109] have been documented. INH-induced liver injury appears to be dose dependent; however there is no correlation between liver injury and plasma INH levels. Half life of INH is 2.98 hours while decrease of factor VII persists for 46 hours. It may be due to hepatotoxicity of acetylated intermediates of INH.

Clinical signs of toxic intake of INH begin within 30 minutes to 2 hours. The main side effects are nausea, vomiting, rash, fever, ataxia, slurred speech, visual disturbances, dizziness, stupor, peripheral neuritis, hypotension, tachyarrhythmia, bradycardia, tachypnea and hyporeflexia [21]. The most common laboratory findings are metabolic acidosis due to lactic acidosis, hyperglycemia, leucocytosis and abnormal liver functions [21]. The classical triads of high dosage INH poisoning are recurrent seizures, lactic acidosis and coma [131]. Life threatening symptoms are recurrent seizures, respiratory failure, renal failure and coma, particularly at high doses of administration [16].

Intentional ingestion of more than 50 INH tablets (100mg each) has been reported. Within half to 3 hours seizure, acidosis and coma was reported [93]. Five cases of INH toxicity have been reported along with a review of another 41 cases [132]. All the reported patients had seizures, coma and acidosis. All patients had vertigo and different stages of coma I to III. Death has been reported with consumption of 0.5gram INH [107]. Serious ill effects have been observed after 0.6 gm of INH [75].

A case report of ingestion of 20 tablets of INH (300mg each) has been reported [82]. It was a case of attempted suicide. The clinical signs of seizures, metabolic acidosis and coma were recognized.

Three mechanisms have been suggested to be responsible for interfering with functions and supply of Pyridoxine by INH: [114]

- INH binds directly with Pyridoxine to form isonicotinyl hydrazide.
- INH is dehydrised to hydrazones; which block pyridoxine phosphokinase, thus preventing conversion of pyridoxine to its active form, pyridoxal 5′ phosphate
- INH hydrazides inactive pyridoxal 5′ phosphate, which is essential for formation of gamma amino-butyric acid (GABA) from glutamic acid. Lack of GABA formation, and accumulation of glutamic acid leads to CNS excitation and seizures.

The author [114] has suggested a stepwise approach for the treatment of INH toxicity securing airway, administration of IV diazepam, checking blood p H and administering sodium bicarbonate if needed, administration of IV pyridoxine, gastric lavage, administration of activated charcoal and sorbitol are some of the important measures to limit INH toxicity.

A case of persisting dementia after INH overdose has been reported [99]. The patient consumed 9-12gms of INH with an attempt of suicide. The patient developed acute toxic encephalopathy. The patient had dilated pupils and decerebrate posturing. After treatment patient recovered but he had significant persistent deficits, specially retrograde amnesia for one to one and half years, anterograde learning difficulties, apraxia and personality change in the form of a newly acquired passivity. Repeated interviews and neuropsychological testing did not support diagnosis of a major depressive disorder. After 20 days on the in-patient psychiatric service and two months of out-patient cognitive rehabilitation, the patient regained function to the point that he can live with family. One year after the overdose, he continued to have cognitive difficulties and had not returned to baseline. It is suggested that long term neuropsychiatric screening is warranted in patients who have experienced significant INH overdose.

Another case of suicidal psychosis secondary to INH has been reported [88]. The case strongly suggests an association of toxic psychosis with INH, even in therapeutic doses. There exists a wide variation both in latency from initiation to onset of psychiatric symptoms and interval from discontinuation of INH to clinical improvement. Most cases of psychosis either resolve or dramatically improve upon withdrawal of INH. The author has reviewed cases of INH- induced psychosis. In one case, a 64-year old man developed dramatic onset of visual hallucinations and disruptive behavior 12 days after INH therapy. The patient's symptoms resolved completely after discontinuation of INH [89]. In yet another case a 31 year old woman developed paranoid delusions after 8 weeks of INH. In this case, symptoms abated only minimally after discontinuation of INH. The patient was symptom free after anti-psychotic treatment [73].

Cerebellar ataxia has been reported in a child with INH toxicity [96]. A 10 year old girl experienced INH toxicity after one year prophylactic regimen of 300mg INH. The patient experienced marked nystagmus along with involuntary gyrating movements of her head. With finger-to-nose and heel-toe-shin tests she showed lack of co-ordination. Diagnosis of cerebellar ataxia was made. The patient recovered six months after stopping INH. It is recommended that maintenance therapy of pyridoxine 15-50mg be made in patients showing INH toxicity.

Two cases of INH over-dose and successful management of the case is reported [129]. In first case, an 8 year old girl had consumed 20 tablets of INH (100mg) and 4-5 capsules of rifampicin (150mg), 2 hours prior to admission. On admission, the child was drowsy and had slurred speech. Metabolic acidosis with pH of 7.15, pCO_2 30.4 mm, pO_2 110 mm was reported. Gastric lavage was done immediately. It was followed by pyridoxine by intravenous route. In the second case, a 3 year old child consumed 10 tablets of INH (100mg). Metabolic acidosis was reported. Gastric lavage was done and IV pyridoxine was given. In both the cases, earliest manifestations included nausea, vomiting, blurred vision, increased visual sensitivity and slurred speech. In absence of adequate treatment stupor, respiratory distress, coma and seizures quickly ensue. IV pyridoxine and correction of metabolic acidosis by administration of bicarbonate is suggested.

Thus cases of INH poisoning show a mixture of most of the major toxicities referred earlier i.e. Hepatotoxicity, Neuropathy, Seizures, Acidosis. If pyridoxine in intravenous form is given at an appropriate time, the patient can survive. Recovery of CNS symptoms may take a longer time.

Treatment and use of pyridoxine [123-133]

INH toxicity is treated with Pyridoxine because it is a specific antidote with structural similarity. There are several clinical observations to justify utility of Pyridoxine for treatment of INH toxicity [123-133].

DISCUSSION

INH has structural similarity with pyridoxine (vitamin B6). Accumulation of INH causes functional deficiency of pyridoxine. As a result, metabolic functions dependent on pyridoxine are adversely affected. Neuropathic symptoms including seizures are caused due to deficient pyridoxine; this is one of the major adverse reaction with INH. Acidosis contributes to neuropathic symptoms due to anion gap and increased accumulation of acidic metabolites of INH. Rhabdomyolysis, which is a complication of INH toxicity, is caused by direct damage to muscles by INH or its metabolites or as a consequence of seizures. Agranulocytosis is probably a idiosyncratic adverse reaction to INH.

Metabolism of INH occurs by acetylation. Genetically, slow and fast acetylators are observed as two sub-groups. In both sub-groups hydrazine metabolites are responsible for hepatotoxicity. Abnormalities in liver function tests, especially elevation of ALT is indicative of hepatotoxicity.

Several cases of poisoning due to INH have been reviewed. Signs of INH toxicity are a mixture of various adverse effects on CNS, liver, muscles and acidosis. Fortunately pyridoxine is a specific antidote for INH toxicity. Slow intravenous administration of pyridoxine can be a life- saving in case of INH toxicity.

Since functional deficiency of pyridoxine is the basic cause of INH toxicity, symptoms of INH poisoning can offer a clue to physiological role of pyridoxine.

CONCLUSION

Ready availability of intravenous pyridoxine in every hospital can be life-saving in case of INH toxicity.

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