Isoniazid: A Review with Emphasis on Adverse Effects

Allan L. Goldman, CPT, MC,* and Sidney S. Braman, MAJ, MC**

A review of the adverse effects of isoniazid (INH) was undertaken and it was found that these effects could be divided into: (1) toxic, (2) idiosyncratic and (3) hypersensitivity reactions. Major toxic reactions are peripheral neuropathies at conventional dosage and seizures from overdosage. Pyridoxine is of benefit in these disorders. Other presumed toxic reactions are autonomic neuropathy, psychosisis, optic atrophy, and pyridoxine responsive anemia. Idiosyncratic reactions are INH-induced lupus erythematosus, rheumatic-like syndromes and various hematologic disorders. These respond promptly to withdrawal of the drug. Hypersensitivity reactions to INH include hepatitis, dermatitis, fever, anginitis and hemolytic anemia. These reactions promptly subside with withdrawal of the drug although in mild reactions this may not be necessary. Corticosteroid therapy or desensitization can be used if INH needs to be readministered.

Isoniazid (INH) is one of the primary drugs used in the treatment of tuberculosis and is of definite value in preventive therapy (chemoprophylaxis). There has been no comprehensive review of the multisystem adverse effects of this drug in recent years. It is with this in mind that the following is presented, as we can expect to see more of these effects and perhaps new ones in the future.

Pharmacology

Isonicotinic acid hydrazide (isoniazid) is rapidly absorbed both orally and parenterally so that the peak plasma level occurs one to two hours after an oral dose. The drug is distributed to all organs and can be recovered from ascitic, pleural, and cerebrospinal fluid as well as from caseous material. INH is both bacteriostatic and bactericidal to susceptible strains of Mycobacterium tuberculosis, but the exact mode of action is unknown.

INH is metabolized in the liver by an acetylation process which is under genetic control. Plasma levels of isoniazid six hours after an oral dose are bimodal. “Slow” inactivation of isoniazid is probably an autosomal recessive trait and people with this have higher blood levels of the free compound than autosomal dominant “rapid” inactivators. Paraaminosalicylic acid (PAS) and severe liver disease also reduce the acetylation of INH. INH is excreted primarily in the urine in both the free and acetylated form. Consequently, the dosage of INH may need to be reduced in uremia.

Untoward effects of INH are dose related: about 1 percent to 2 percent occurring at conventional low dose therapy (3 to 5 mg/kg/day) and 15 percent at 10 mg/kg/day. The adverse effects of INH can be roughly divided into:

1. Side Effect—an undesirable pharmacologic action experienced by some people, such as epigastric distress.

2. Idiosyncrasy—an individual genetic defect that causes a qualitative abnormal response, such as the lupus phenomenon.

3. Toxicity—an effect which is an expected pharmacologic action that will occur in a majority of patients at a given dose, such as the neurologic effects of INH.
4. Allergic Reaction—an immunologic response such as drug fever, dermatitis, and hepatitis.

Other untoward effects, such as some hematologic abnormalities and diphenylhydantoin intoxication do not conveniently fit into the above schema.

INH-INDUCED NEUROLOGIC SYNDROMES

The earliest known and most widely recognized untoward effects of INH are the neurologic syndromes. Foremost among these is peripheral neuropathy. In the fully developed syndrome, the patient first complains of numbness or tingling of the feet. If the drug is withdrawn at this point, the symptoms will abate. However, with continuation of the drug, these paresthesias will spread up the legs to the knees and possibly even develop in the hands or fingers in a typical bilateral stocking-glove distribution. Frequently these symptoms are accompanied by muscle aching, which is made worse by activity. While sensory complaints dominate, weakness is a minor component, but muscle atrophy and fasciculation can be observed late in the course. Other findings can include a decrease or absence of the achilles reflex and a hyper- or hypoactive patellar reflex. Muscle weakness is a minor component, but muscle atrophy and fasciculation can be observed late in the course. Unless the syndrome has progressed to obvious muscle weakness, all findings are reversible within a few weeks after withdrawal of the drug. If despite the appearance of symptoms, therapy is continued for more than a few weeks, residual difficulties may persist for a year or more.

This syndrome is dose related and susceptibility is highest in chronic alcoholics, individuals with malnutrition and "slow" inactivators. With the commonly employed dose of 300 mg/day (3 to 5 mg/kg), an incidence of up to 2 percent of patients should be expected. The time of onset of symptoms after the institution of INH therapy varies roughly with the dosage. With high doses of INH, symptoms often appear within three to five weeks. In patients receiving conventional low dose INH therapy, symptoms usually do not appear until six months. Pyridoxine, 50 mg daily, can prevent the occurrence of peripheral neuropathy in the high susceptibility groups.

Symptoms of pellagra, including skin lesions, cheilosis, watery stools, and mental changes may occur following the administration of INH and are responsive to the administration of nicotinamide.

There was early recognition of autonomic dysfunction following therapy with INH. Symptoms of dry mouth, difficulties in visual accommodation, constipation, frequent erection, nocturnal emission, frequency of urination, difficulty in micturition, and frank urinary obstruction were noted with low-dosage INH therapy. Reversal of symptoms on withdrawal of the drug is to be expected. Symptoms of vasomotor instability such as flushing of the face and Raynaud's phenomenon rarely occur.

Central nervous system stimulation due to INH can cause irritability, euphoria, restlessness, insomnia, and headache. Central nervous system depression causing lethargy and drowsiness also occurs. Psychological effects from INH are not uncommon. Patients may complain of depression, unbalanced state of mind, or impairment of memory. In a prospective study, special memory tests showed a statistically significant impairment of memory after several months of ambulatory treatment. Symptoms disappeared a few months after treatment had been stopped.1

In a recent report, seven alcoholic patients who were treated with conventional low dosage INH for 30 days without complications developed changes in their effect or behavior when begun on disulfiram (antabuse) therapy.2 These changes were not seen in comparable patients on disulfiram who were not put on INH therapy. It was felt that both disulfiram and INH interfered with the metabolism of biologic amines in the central nervous system and in combination caused mental changes. With time, other drugs will probably be shown to interact with the biologic effects of INH.

The appearance of acute psychosis following administration of INH is most often seen in those who have an antecedent history of unstable personality, although it can occur in otherwise normal people. Weidorn and Ervin3 reported on five cases of INH-induced acute psychosis. They noted increased psychomotor activity about one month prior to the onset of the acute psychosis. These changes consisted of restlessness, irritability, and a heightened awareness of surrounding visual and auditory stimuli. None of the patients had any awareness of these new symptoms. During the acute phase, purposeless, poorly coordinated muscle activity and gross muscle jerking were frequently noted. In addition, disorientation to time, place and person, and hallucinatory experiences, usually persecutory in content, were noted. Withdrawal of INH will usually lead to a reversal of psychosis; however, this is not invariable.

Although INH has no definite effect on EEG tracings, it should be used with caution in those...
with known seizure history or with previous head trauma. Death or prolonged coma from persistent seizure activity can follow the administration of conventional low dosage INH to patients with known seizure history. Anticonvulsants, especially phenobarbital, usually are effective in preventing these seizures.

It has long been recognized that diphenylhydantoin (Dilantin, DPH) intoxication occurs at the commonly prescribed dose of 300 mg per day when INH is given concomitantly. Kutt and co-workers described 11 percent DPH intolerance in 72 patients taking concomitant INH. There was no correlation with hepatic function tests, nor any age or sex predilection. They confirmed that this occurred only in slow inactivators, and in vitro studies revealed INH to be a strong noncompetitive inhibitor of DPH metabolism. PAS potentiated this inhibition of DPH metabolism by INH.

Treatment of DPH intoxication in a patient receiving INH consists of discontinuing DPH for five to ten days and then restarting it at 100 to 200 mg per day.

Other rare but serious neurologic complications of INH therapy are toxic myelopathy, encephalopathy, and optic neuritis. These may or may not respond to withdrawal of INH. Pyridoxine and steroids may be beneficial.

OVERDOSE

With widespread use of INH, it was inevitable that both accidental and intentional overdosages would occur.

Terman and Teitelbaum reported four patients treated for INH “self poisoning.” The clinical syndrome consisted of:
1. Coma developing one to three hours after ingestion often with respiratory depression.
2. Status epilepticus
3. Severe metabolic acidosis
4. Hyperglycemia and acetonuria
5. Occasionally hyperpyrexia

Treatment of INH overdosage is similar to other intoxications. In four severely ill patients, Terman successfully treated two with hemodialysis, one with peritoneal dialysis, and one with forced diuresis. The rates of recovery of INH were not cited.

Treatment of seizures associated with INH overdosage has been controversial. Standard anticonvulsants have been used. Katz and Jobin at the Alaska Native Medical Center treated 22 INH ingestions with up to 10 gm of intravenous pyridoxine with prompt termination of seizures and without any evidence of pyridoxine toxicity. Among Terman’s patients, some took INH-pyridoxine combination tablets and they did not find additional intravenous pyridoxine useful. They found the seizures unresponsive to anticonvulsants until the metabolic acidosis was corrected by bicarbonate.

INH-INDUCED RHEUMATIC SYNDROMES

The association of INH and rheumatic syndromes has recently been discussed by Good. Typically, the patients experienced sudden onset of joint pain, tenderness, and morning stiffness in the hands, especially the proximal interphalangeal joints. This occurred from five days to 20 weeks after institution of INH. Other joints affected include the metacarpal-phalangeals, elbows, wrists, shoulders, hips and spine. Within a few days, some developed marked limitation of motion leading to complications such as frozen shoulder and tendon contractures in the hands. There was no evidence of synovial effusions although diffuse swelling of the fingers was sometimes seen. No evidence for an underlying rheumatic disease could be detected. Negative findings included antistreptolysin 0 titers, LE cell preparations, serum uric acid levels, rheumatoid factors, and roentgenograms of involved joints. Ethionamide, a drug similar in structure to INH, has also been thought to produce rheumatic symptoms in tuberculosis patients.

The association of INH and this rheumatic syndrome is based purely on the temporal relation of the appearance of the symptoms and the administration of the drug. This syndrome in well-nourished, mobile individuals on conventional low dosage INH should not be a frequent finding. Although some patients in whom INH is not discontinued will demonstrate slow improvement with salicylates and physical therapy, the rapid improvement on withdrawal of the drug and severe disability that could result from long-term administration of INH make it mandatory that this syndrome be recognized.

INH-INDUCED LUPUS SYNDROMES

Since the advent of the lupus erythematosus cell phenomenon, a growing list of drugs known to induce the lupus erythematosus syndrome (LE) has been compiled. These drugs fall into two categories: (1) those that bring about the lupus syndrome by eliciting an allergic reaction such as penicillin, sulfonylides, tetracycline, oral contraceptives, propylthiouracil, reserpine, and methyl-dopa and (2) those that induce LE by having some specific pharmacologic property such as hydralazine, anticonvulsants, procainamide hydrochloride, and INH.

The drug-induced syndromes closely resemble
those of the spontaneously occurring types. Drug-induced lupus shows a predominance of cases in women as does the idiopathic form. Although there is a predominance of Negroes in spontaneous LE, no racial predilection was found for the drug-induced forms.

Although over 20 cases of suspected INH-induced LE have been reported in the literature, there has not been enough clinical information given about most of the cases to determine whether any distinct clinical pattern will appear. A few distinct differences have been apparent with the other drug-induced forms, such as the predominance of pleuropulmonary symptoms in procainamide lupus, the paucity of anemia and leukopenia in both hydralazine and procainamide lupus, and the lower incidence of renal manifestations in all of the drug-induced forms.

The first case of INH-induced lupus syndrome was reported in 1966 by Zingale and co-workers in a patient who had received approximately two months of antituberculosis therapy including 400 mg of INH daily. The patient developed fever, arthritis, bilateral pleural effusions and electrocardiographic evidence of evolving pericarditis. Laboratory findings included a relative leukopenia and many strongly positive LE cells. Serum protein electrophoresis demonstrated elevated alpha 2 and beta globulin fractions, and a positive antinuclear antibody (ANA) was found. The patient clinically improved after INH was discontinued and prednisone begun. Several months after discontinuing INH, LE cell tests and ANA tests were negative.

The drug-induced form of LE is usually reversible on withdrawal of the precipitating agent. However in some cases, clinical manifestations and positive ANA tests have persisted for years.

Strong evidence supporting the LE cell inducing ability of INH has been obtained from serologic studies in tuberculosis patients. Cannat and Seligmann found the incidence of ANA significantly higher in tuberculosis patients after prolonged therapy with INH (19 percent) than in untreated patients or healthy controls (2 percent) matched for sex and age. Some patients were followed from a pretreatment ANA negative status to an ANA positive status three to six months after treatment was begun, although no clinical manifestations of LE appeared. Mice studies have emphasized the importance of age, sex and strain on the experimental induction of ANA, suggesting that genetic factors play a major role in addition to environmental factors in the drug-induced lupus cell phenomenon. The genetic influences may be weak, requiring environmental influences to bring about either clinically silent or overt LE. A genetically predisposed individual who takes INH, a relatively weak LE-inducer, may reach a clinically silent stage manifested only by serologic abnormality; or, the same individual if exposed to hydralazine or procainamide, two stronger LE inducers, may develop the full-blown clinical syndrome. An individual with strong genetic predisposition may reach the second or symptomatic-stage with little or no environmental stimulation. Alarcón-Segovia likens these two stages to those of prediabetes and diabetes. The clinical spectrum results from the interplay between genetic predisposition and the strength of environmental factors.

The mechanism by which any drug may activate the LE syndrome is to date unknown. Recently, however, there has been some interesting experimental work that may shed light on a possible mechanism for INH, hydralazine and possibly other drugs. Both INH and hydralazine are acetylated in the liver by the hepatic enzyme acetyl transferase. Perry and associates found that as with INH, there were fast and slow acetylators of hydralazine and that the induction of ANA by this drug was related to both the rate of acetylation and the total intake of drug. Few fast acetylators had a positive ANA after 400 to 1200 gm of hydralazine. Of those who developed the LE syndrome, all were slow acetylators. Whether only slow acetylators of INH will develop the lupus syndrome remains to be determined.

The evidence for the relationship between INH and overt LE or the prelupus state manifested only by serologic abnormalities seems quite strong at this time. Clinical recognition of the syndrome followed by the quick withdrawal of the drug should lead to prompt remission in most cases. What the far-reaching clinical implications are of such variables as rapid and slow INH acetylation, family predisposition to LE, and high and low dose regimen, remains to be worked out.

HEMATOLOGY

Isoniazid has been associated with a variety of hematologic abnormalities; however, in most cases, other antituberculosis drugs were given concomitantly and a cause and effect relationship is hard to establish. Those abnormalities with which INH has been associated are: hemolytic anemia, pyridoxine-responsive anemia, agranulocytosis and red cell aplasia.

Hemolytic anemia due to INH has recently been reported. A three and one-half year-old Negro boy was treated with INH 15 mg/kg per day for
one year at which time he developed fever, abdominal pain, and hemoglobinuria. Laboratory examination revealed a Coombs'-positive hemolytic anemia. Discontinuation of INH and institution of prednisone reversed the hemolysis.

The pathogenesis of isoniazid induced pyridoxine-responsive anemia is unclear. The anemia is usually seen in patients who have developed fever, abdominal pain, and hemoglobinuria. Laboratory examination reveals a reticulocytosis and rise in hemoglobin, but the response is usually incomplete. Red cell morphology often returns to normal, and the anemia is usually shown to be normoblastic. Bone marrow examinations have shown normoblastic hyperplasia with maturation arrest of red cells. McCurdy and Donohoe described three patients who also had target cells in their blood smears. Two of these also demonstrated low erythrocyte GOT and two demonstrated Howell-Jolly bodies. Two of their three cases following parenteral pyridoxine treatment were associated with hypergammaglobulinemia, and one-half-year-old child with tuberculous meningitis was treated initially with INH, PAS, and streptomycin for 18 days, then INH alone at a dose of 8 mg/kg per day. After ten weeks, she developed a skin infection treated with penicillin. Two weeks later the skin infection recurred at which time a complete blood count (CBC) was normal. The infection cleared spontaneously but two weeks later recurred and a CBC revealed white blood cell count of 4900 with 1 percent polymorphonuclear leukocytes (PMN's), normal hematocrit, and normal platelet count. Penicillin and aureomycin were administered and INH was discontinued. Two days later bone marrow examination revealed active granulopoiesis and three days later the CBC revealed 6698 PMN's per mm².

Hypersensitivity

Isoniazid, like other antituberculosis drugs, causes a significant number of hypersensitivity (allergic) reactions. This reaction may be manifested by fever, rash, arthralgias, angitis, hepatitis, adenopathy, eosinophilia, or leukopenia.

The incidence of this response is hard to determine because in most studies INH was given with other drugs which can elicit hypersensitivity, and once hypersensitivity develops the patient often will become hypersensitive to all drugs given.

In a retrospective study of 1744 patients hospitalized for treatment of tuberculosis, "drug intolerance" developed in 11.1 percent; streptomycin intolerance occurred in 10.3 percent of 400 patients, PAS intolerance in 8.8 percent of 1698 patients, and INH intolerance in 1.3 percent of 1724 patients. Of 792 patients taking high dose INH (usually 16 mg/kg), 20 developed intolerance, whereas only two of 932 patients who received 100 mg tid developed intolerance. Of the reactions attributed to INH, fever accounted for 13, dermatologic manifestations for nine, hepatitis for six (four of the six had fever and rash concomitantly), leukopenia for two and arthralgia for one. These reactions generally occurred during the first 60 days of treatment. Desensitization was successful in all 12 in whom it was used.

Liver

Liver abnormalities may be caused by tuberculous granulomatous hepatitis or by a hypersensitivity response to one or several drugs. Tuberculous granulomas are commonly found in liver biopsy in both acute and chronic tuberculosis, presumably from hematogenous seeding. They are most common in miliary tuberculosis, but rarely cause clinical jaundice. In patients with chronic pulmonary tuberculosis without clinical evidence of extrapulmonary disease, hepatic function tests including bilirubin,
SGOT and SGPT are usually normal although liver biopsy is often abnormal.

Drug-induced hepatic injury may be caused by 1) a direct hepatotoxin, ie CCL₄ which is a protoplasmic poison, its toxicity is dose related, and after a brief interval produces a characteristic lesion on liver biopsy, 2) an indirect hepatotoxin which inhibits essential metabolites, and 3) a hypersensitivity reaction which has a low incidence, is not dose related, and follows a sensitization period (usually one to four weeks). This hypersensitivity reaction tends to recur promptly on readministration of small doses and is frequently accompanied by fever, rash, urticaria, eosinophilia, and sometimes blood dyscrasias. The liver involvement may be hepatocellular or cholestatic.

Several antituberculosis drugs are known to cause hepatotoxicity: INH, PAS, pyrazinamide and ethionamide. INH causes a hepatocellular type of hypersensitivity reaction and histologically may be indistinguishable from viral hepatitis. Cohen and coworkers in 1961, reviewed all six previous cases of supposed INH induced jaundice and found that five of them had also received PAS. Jaundice occurred nine days to seven weeks after starting treatment. In addition, they reported a case of a 50-year-old man with sarcoidosis who received INH, NPH insulin, and methylprednisolone (Medrol). He developed a rise in SGOT and INH was withheld. SGOT returned to normal in two weeks, but later INH was restarted by mistake and he developed “hepatitis” and lapsed into hepatic coma and died. Autopsy revealed “acute massive necrosis of the liver,” and no evidence of hepatic sarcoid was found.

Sharer and Smith, in part of a prospective study, noted that in 90 employees given chemoprophylaxis with INH, 11 (12.2 percent) developed SGOT and SGPT levels greater than 50 in the first two months, nine of whom were asymptomatic. This occurred from 14 to 60 days after beginning INH (average of 37 days) and the SGOT ranged from 65 to 160, SGPT from 76 to 500. Bilirubin and alkaline phosphatase levels when measured were normal. In two of nine asymptomatic patients, INH was discontinued because of marked enzyme elevations and the SGOT returned to normal in 14 and 60 days. In the other asymptomatic cases, INH was continued and the SGOT returned to normal in 14 to 120 days (average 50 days). In part of the same study among 77 hospitalized patients being treated for tuberculosis, INH was felt to be the cause of transaminase elevations in seven, and was discontinued. In one of those cases, the SGOT was 600 and the SGPT 900. Desensitization with small progressing doses was no more successful in preventing enzyme changes than readministration of full dosage. INH was restarted without further enzyme rises after as many as four trials.

After an outbreak of tuberculosis early in 1970 on Capitol Hill, 2,321 people with positive tuberculin tests were placed on INH chemoprophylaxis. On November 19, 1970, the deaths of two INH recipients from liver disease were reported. Further studies identified 17 others who had a history of jaundice or dark urine without known exposure to needles, blood products, raw clams, or raw oysters. These cases were noted throughout the nine-month period of therapy. Six cases had negative tests for Australian antigen. Whether or not INH can be incriminated is conjectural at this point, but this report raises the question whether INH induced hepatitis can occur after the three month interval commonly cited.

A very interesting recent report describes a 42-year-old man being treated with INH, PAS, and streptomycin who, after one month, developed fever, rash, eosinophilia and adenopathy, and subsequently jaundice shortly after the drugs were discontinued. Skin tests with INH and PAS were unreactive as were antigen induced leukocyte histamine release and serum reagins. INH however caused a positive lymphocyte transformation test with increased incorporation of radioactive thymidine. Streptomycin caused less transformation and PAS caused an insignificant amount. After desensitization, there was no transformation with INH. The patient's son who also had INH allergy manifested by fever and rash without hepatitis had a negative lymphocyte stimulation test. This report supports the view that INH induced hepatitis in the full blown allergic syndrome is due to a delayed type of hypersensitivity. Further studies need to be carried out with patients who develop asymptomatic SGOT elevations to see if the same mechanism is operative.

Conclusions

Isoniazid is presently in widespread usage. The adverse effects may be generally divided into 1) toxic effects which are dose related and 2) idiosyncratic and allergic reactions which are not dose related.

Toxic effects are predisposed to by liver disease, PAS and genetically “slow” acetylation which by reducing the metabolism of INH raise the serum level. Uremia, by reducing excretion of INH, raises the serum level. Alcoholism, malnutrition and pyridoxine deficiency also seem to predispose to INH toxicity.
Foremost among the toxic effects of INH are the neurologic syndromes. Peripheral neuropathy is definitely dose related: rare in conventional low dosage INH therapy except in alcoholic or severely malnourished patients and of considerably higher frequency in high dosage INH therapy. Although the mechanism of this neuropathy is unknown, pyridoxine administration will prevent or treat it. Consequently, patients on high dosage INH and alcoholic or malnourished patients on low dosage INH should receive pyridoxine 10 mg per 100 mg INH.

Seizures also are dose related. This is dramatically seen in INH overdosage. Known epileptics should be maintained on anticonvulsant medications especially phenobarbital even when given low dosage INH therapy. One must be alert to the possibility of diphenylhydantoin intoxication and reduce the dosage accordingly.

Encephalopathy, psychosis, memory impairment, central stimulation and depression, autonomic dysfunction and optic atrophy are believed to be toxicities of INH although there is no evidence to show they are definitely dose related. Pyridoxine has been used in the treatment of optic neuritis. Pyridoxine seems to have no effect in preventing psychosis, encephalopathy, dizziness, or ataxia.

Pyridoxine-responsive anemia, although not proved to be dose related, would seem to be a toxic effect. The interactions of INH and pyridoxine remain to be fully discovered. The anemia simulates iron deficiency, but serum iron is normal and marrow iron plentiful. Treatment consists of adding pyridoxine 10 to 100 mg per day and, in those few cases that are megaloblastic, folic acid appears to be beneficial.

Idiosyncratic and hypersensitivity reactions are not dose related. Those that seem to be idiosyncratic reactions are the lupus syndrome, rheumatologic abnormalities, agranulocytosis, and red cell aplasia. Because of the severity of these reactions and the availability of other antituberculosis drugs, INH should be discontinued in these circumstances.

Hypersensitivity reactions include fever, rash, eosinophilia, hemolytic anemia, angitis, and hepatitis. It is important to recognize that these may occur singly or in combination, and treatment depends on the severity of the reaction. In some cases, the drug may be continued and the reaction may spontaneously subside as in INH induced asymptomatic hepatitis. In more severe reactions, such as florid hepatitis, hemolysis, angitis or severe skin reactions, the drug should be discontinued and antihistamines or steroids may be given. Depending on the indications for INH, the severity of the reaction and the availability of other effective antituberculous agents, a decision should be reached whether to desensitize the patient or administer other agents. After discontinuation of INH so that fever, rash, etc have subsided, desensitization consists of administering small progressive amounts of INH until the therapeutic dose is reached or the reaction recurs. Densensitization may require several attempts before being successful. Steroids may be given concomitantly for rapid desensitization.

REFERENCES