PRESCRIBING INFORMATION

Pr

Dom-Isoniazid

Isoniazid tablets USP 300 mg

Tuberculosis Therapy

Antimycobacterial

Dominion Pharmacal
Montreal, Canada

Date of preparation
June 29, 1995

PHARMACOLOGY:

Isoniazid is a bactericidal agent active only against organisms of the genus Mycobacterium, specifically, M. tuberculosis, M. avium intracellulare, M.bovis and some strains of M. kansasii. It is a highly specific agent, ineffective against other microorganisms. The mode of action is unknown but the drug is firmly bound to actively growing, sensitive, tubercle bacilli and does not affect these organisms when they are in the metabolic resting state.

When used alone in the treatment of tuberculosis, resistant strains emerge very rapidly; when combined with other tuberculostatic drugs, the emergence of resistant strains may be delayed or prevented. When isoniazid is used alone in the prophylaxis of tuberculosis, the development of resistance does not appear to be a major problem.

Pharmacokinetics: Isoniazid is rapidly and almost completely absorbed, when administered either orally or i.m., and peak blood levels are reached in about 1 to 2 hours. Bioavailabilty is reduced when isoniazid is administered with food. It diffuses readily into all body fluids (including cerebrospinal, pleural, and ascitic), tissues, organs and excreta (saliva, sputum and feces). The drug also passes through the placental barrier and into milk in concentrations comparable to those in the plasma. Isoniazid is < 10% bound to plasma proteins.

Isoniazid is metabolized by the liver mainly by acetylation and dehydrazination. The N-acetylhydrazine metabolite is believed to be responsible for the hepatotoxic effects seen in patients treated with isoniazid. The rate of acetylation is genetically determined. Approximately 50% of Blacks and Caucasians are slow inactivators; the majority of Eskimos and Orientals are rapid inactivators. The half-life in fast acetylators is 1 to 2 hours while in slow acetylators it is 2 to 5 hours. Elimination is largely independent of renal function, however the half-life may be prolonged in liver disease. The rate of acetylation has not been shown to significantly alter the effectiveness of isoniazid. However, slow acetylation may lead to higher blood concentrations with chronic administration of the drug and thus, to an increase in toxic reactions. Isoniazid and its metabolites are excreted in the urine with 75 to 95% of the dose excreted in 24 hours. Small amounts are also excreted in saliva, sputum and feces. Isoniazid is removed by hemodialysis and peritoneal dialysis.

INDICATIONS:

Used in conjunction with other antituberculosis drugs in the treatment of pulmonary and extrapulmonary tuberculosis and alone in the prophylaxis of tuberculosis.

CONTRAINDICATIONS:

Patients who develop severe hypersensitivity reactions to isoniazid, included drug induced hepatitis; acute liver disease of any etiology.

WARNINGS:

severe and sometimes fatal hepatitis associated with isoniazid therapy may occur and may develop even after months of treatment. Serum AST levels become elevated in about 10 to 20% of patients, usually during the first few months of therapy, but it can occur at any time. Usually enzyme levels return to normal despite continuance of the drug, but in some cases progressive liver dysfunction occurs. The risk of developing hepatitis is increased with preexisting liver disease, increasing age, concurrent use of other hepatotoxic medications and excessive or chronic use of alcohol. Patients given isoniazid should be carefully monitored and interviewed regularly. Patients should be instructed to report immediately any of the prodomal symptoms of hepatitis, such as fatigue, weakness, malaise, anorexia, nausea or vomiting. If symptoms and signs suggestive of hepatic damage are detected, discontinue the drug promptly and follow the patient closely. An alternative agent should be used since continued use of Isoniazid in these patients may cause a more severe form of liver damage. Defer preventive treatment in individuals with acute hepatic diseases. If isoniazid must be reinstituted, this should be done only after symptoms and laboratory abnormalities have cleared. Restart in very small and gradually increasing doses, and withdraw immediately if there is any indication of recurrent liver involvement.

PRECAUTIONS:

Stop all drugs at the first sign of a hypersensitivity reaction. If isoniazid is reinstituted, it should be given in very small and gradually increasing doses to determine whether the manifestations are drug induced.

Use of isoniazid should be carefully monitored in patients with convulsive disorders (see Drug Interactions), preexisting hepatic diseases, or severe renal dysfunction.

Optic neuritis has been reported as a rare complication. Periodic ophthalmoscopic examinations during isoniazid therapy are recommended when visual symptoms occur.

It is believed that isoniazid competes with pyridoxyl phosphate for the enzyme apotryptophanase which may lead to symptoms of pyridoxine (vitamin B6) deficiency. Pyridoxine administration can prevent and reverse peripheral neuropathy complicating isoniazid use.

Drug Interactions: Since the chemotherapy of tuberculosis involves the use of at least 2 drugs, the possible adverse reactions of each drug should be borne in mind as well as a possible interaction when used concomitantly.

Anticonvulsants: Isoniazid inhibits hepatic metabolism of carbamazepine and phenytoin, resulting in increased anticonvulsant concentrations and toxicity in some patients. If isoniazid and carbamazepine or phenytoin are administered concurrently, serum concentrations of the anticonvulsant should be monitored, the patient observed for evidence of toxicity and the dosage of the anticonvulsant should be reduced accordingly.

Aluminum Hydroxide Gel: Decreases gastrointestinal absorption of isoniazid; isoniazid should be administered at least 1 hour before the antacid.

Cycloserine: in combination with isoniazid may result in increased cycloserine CNS side effects such as dizziness or drowsiness.

Disulfiram: Coordination difficulties and psychotic episodes have occurred in patients receiving isoniazid and disulfiram; concurrent administration of the drugs should be avoided.

Rifampin: Hepatotoxicity has been reported to occur more frequently when rifampin and isoniazid are given concurrently. The incidence may be higher in slow isoniazid acetylators, those receiving high doses of isoniazid or those with preexisting liver disease.

Ketoconazole: Concentrations may be decreased by isoniazid, possibly decreasing the antifungal effect.

Others: In addition, isoniazid may cause inhibition of metabolism of the following: acetaminophen, corticosteroids, diazepam, oral anticoagulants, primidone and theophyllines. The patient should be observed for increased effect or toxicity of these agents.

P^regnancy: Although safe use of isoniazid during pregnancy has not been definitely established, isoniazid has been used to treat clinical tuberculosis in pregnant women. Isoniazid is considered part of the treatment of choice for tuberculosis occurring during pregnancy, as the risk to the mother and fetus of untreated tuberculosis is far greater than treatment of the disease. Prophylactic therapy is best postponed until after delivery, unless the woman is positive for HIV infection and has evidence of tuberculosis infection.

Lactation: No adverse effects have been reported, but there is a potential risk of peripheral neuritis or hepatic damage. Breast-fed infants should be carefully observed for evidence of adverse effects.

ADVERSE EFFECTS:

Toxic effects are usually encountered only with higher doses of isoniazid, and their incidence is reportedly higher in slow inactivators. The incidence of adverse effects at a dose level of 10 mg/kg has been reported to be 15%.

CNS: peripheral neuropathy (occurs most often in the malnourished and is usually preceded by paresthesias of the feet and hands) is the most common (see Precautions). Convulsions, toxic encephalopathy, optic neuritis and atrophy, and toxic psychosis may occur rarely.

Gastrointestinal: nausea, vomiting, epigastric distress.

Hepatic: elevated serum transaminases (ALT, AST) and bilirubin concentrations (10 to 20%), hepatitis with or without jaundice. Isoniazid associated, occasionally severe and sometimes fatal hepatitis is generally considered an unpredictable hypersensitivity reaction (see Warnings).

Hematologic: agranulocytosis, hemolytic, sideroblastic or aplastic anemia; thrombocytopenia; eosinophilia.

Hypersensitivity: fever, skin eruptions (morbilliform, maculopapular, purpuric, or exfoliative), lymphadenopathy, vasculitis. Hypersensitivity reactions usually occur in the first 6 to 7 weeks of therapy (see Precautions).

Metabolic and Endocrine: pyridoxine deficiency, pellagra, hyperglycemia, metabolic acidosis, gynecomastia.

Miscellaneous: rheumatic syndrome and systemic lupus erythematosus like syndrome.

OVERDOSE: SYMPTOMS:

Manifestations of isoniazid overdosage are apparent within 30 minutes to 3 hours. Nausea, vomiting, dizziness, slurring of speech, blurring of vision and visual hallucinations (including bright colors and strange designs), are among the early manifestations. With marked overdosage, respiratory distress and CNS depression, progressing rapidly from stupor to profound coma, are to be expected, along with severe, intractable seizures. Severe metabolic acidosis, acetonuria and hyperglycemia are typical laboratory findings.

TREATMENT:

Treatment of overdosage consists of careful emesis and lavage usually following intubation, correction of any acidosis with sodium bicarbonate, administration of i.v. anticonvulsants and the i.v. injection of large doses of pyridoxine (e.g., a gram-for-gram dose equivalent to the amount of isoniazid ingested). See Vitamin B6 General Monograph. Forced diuresis may be tried and hemodialysis or peritoneal dialysis has been used.

DOSAGE:

Orally, as a single daily dose, preferably on an empty stomach. Absorption may be reduced with food but isoniazid may be taken with meals if gastrointestinal irritation occurs. Treatment of Active Tuberculosis (in conjunction with other antitubercular agents): Adults: 5 mg/kg once daily (maximum 300 mg); Children: 10 to 20 mg/kg once daily (maximum 300 mg). Therapy should be continued for 6 to 9 months, or longer. Twice weekly dose (following 2 months of daily dosing): Adults: 15 mg/kg (maximum 900 mg); children: 20 to 40 mg/kg (maximum 900 mg).

Prophylaxis of Tuberculosis: for 6 to 12 months: Adults: 300 mg once daily; Children: 10 mg/kg once daily (maximum 300 mg).

SUPPLIED:

in bottles of 100 and 1000