Isoniazid

Brand Name: Nydrazid

Drug Description

Isoniazid is a synthetic isonicotinic acid-derivative antitubercular agent. [1]

HIV/AIDS-Related Uses

Isoniazid is approved by the FDA for use in latent tuberculosis treatment or preventive treatment of clinical tuberculosis in HIV patients. HIV infected people with a positive tuberculin skin test (PPD) and people who have close contact with people with infectious tuberculosis, regardless of skin test results, age, or prior courses of chemoprophylaxis, are recommended to use isoniazid prophylaxis. Isoniazid is also indicated in combination with other antitubercular agents in the treatment of all forms of tuberculosis, including tuberculous meningitis. Isoniazid use in the treatment of atypical opportunistic infections, such as Mycobacterium avium complex (MAC), should be avoided, however, because of its weak activity.[2]

Non-HIV/AIDS-Related Uses

Isoniazid is indicated in the prophylaxis of tuberculosis in certain patients with a positive PPD, including household members and other close contacts of people with recently diagnosed tuberculosis; adults taking immunosuppressives or prolonged therapy with corticosteroids; adults with hematologic disease, reticuloendothelial disease, diabetes mellitus, silicosis, or gastrectomy; children up to 4 years of age; and recent converters (those with PPD significant increases).[3]

Isoniazid is also indicated in combination with other antitubercular agents in the treatment of all forms of tuberculosis, including tuberculous meningitis.[4]

Pharmacology

Isoniazid displays highly specific activity against organisms of the genus Mycobacterium, with in vitro and in vivo activity against M. tuberculosis and M. bovis.[5] The exact mechanism of isoniazid's antitubercular action is unknown, but it may involve inhibition of mycolic acid synthesis and disruption of the cell wall in susceptible organisms.[6] Isoniazid may be bacteriostatic or bactericidal in action, depending on the concentration of the drug attained at the site of infection and the susceptibility of the infecting organism. The drug is active against susceptible bacteria only during bacterial cell division.[7]

Isoniazid is readily absorbed from the gastrointestinal (GI) tract after oral administration and from intramuscular injection sites.[8] Both absorption and bioavailability are reduced when isoniazid is administered with food.[9] Following oral administration, peak plasma concentrations occur within 1 to 2 hours.[10]

Isoniazid distributes readily into all body fluids and tissues, including cerebrospinal (CSF) fluid, pleural and ascitic fluids, skin, sputum, saliva, lungs, muscle, and caseous tissue.[11] CSF concentrations are reported to be 90% to 100% of concurrent plasma concentrations.[12]

Protein binding of isoniazid is very low (0% to 10%).[13] The plasma half-life of isoniazid ranges from 1 to 4 hours, depending on rate of metabolism in a given individual. Impaired hepatic function or severe renal impairment will prolong the plasma half-life. Isoniazid may undergo significant first-pass hepatic metabolism following oral administration. Isoniazid is inactivated in the liver by acetylation and dehydrazination; inactive metabolites may also undergo hydroxylation by the cytochrome P450 oxidase system. The rate of isoniazid acetylation is genetically determined and is subject to individual variation; however, it is usually constant for each person. The rate of acetylation does not appear to alter efficacy when the drug is administered daily or 2 to 3 times weekly, but it has been noted that rapid inactivation relates to poor therapeutic response in once-weekly intermittent regimens. Isoniazid is excreted as unchanged drug and metabolites primarily by the kidneys (75% to 96%) within 24 hours of administration. It can be removed by hemodialysis or peritoneal dialysis.[14]

Isoniazid is in FDA Pregnancy Category C. Isoniazid crosses the placenta, resulting in fetal

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Pharmacology (cont.)

plasma concentrations approximately equal to or exceeding maternal plasma concentrations. It is also distributed in milk, possibly resulting in infant plasma concentrations similar to maternal concentrations. Isoniazid has not been shown to be teratogenic in mice, rats, or rabbits.[15] No isoniazid-related congenital abnormalities have been observed in mammalian reproductive studies, but it has been reported that isoniazid may exert an embryocidal effect when the drug is administered orally in pregnant rats and rabbits. Although safe use of the drug during pregnancy has not been definitely established, isoniazid (combined with rifampin and/or ethambutol) has been used to treat clinical tuberculosis in pregnant women. The potential benefits of isoniazid therapy for latent tuberculosis infection during pregnancy should be weighed against the possible risks to the fetus. Neonates and breast-fed infants of isoniazid-treated mothers should be carefully observed for evidence of adverse effects.[16]

Natural and acquired resistance to isoniazid has been demonstrated in vitro and in vivo in strains of M. tuberculosis. The mechanism of resistance may be related to the failure of the drug to penetrate or be taken up by the resistant bacteria. Resistant strains develop rapidly if isoniazid is used alone in the treatment of clinical tuberculosis; however, development of resistance does not appear to be a major problem when the drug is used alone in preventive therapy. Further, when isoniazid is combined with other antitubercular agents in the treatment of clinical tuberculosis, emergence of resistant strains may be delayed or prevented.[17]

Adverse Events/Toxicity

Peripheral neuritis, characterized by clumsiness, unsteadiness, and burning or paresthesia of the hands and feet, is one of the most common adverse effects of isoniazid; it occurs more frequently in malnourished patients and those predisposed to neuritis, such as HIV infected individuals, diabetics, and alcoholics. Rarely, other adverse nervous system effects, including seizures, euphoria, memory impairment, dizziness, and toxic psychosis, have been reported. Neurotoxic effects may be prevented or treated by the administration of pyridoxine daily during isoniazid therapy, especially in children, adolescents, breast-feeding infants and their mothers, and pregnant women.[18] [19]

Isoniazid has been reported to cause mild and transient elevations in serum AST (SGOT), ALT (SGPT), and bilirubin concentrations in 10% to 20% of patients, usually during the first 4 to 6 months of therapy. Laboratory values usually return to pretreatment levels with continued use of the drug; however, progressive liver damage, bilirubinemia, jaundice, and severe and sometimes fatal hepatitis have occurred rarely. Hepatitis and hepatitis prodromal symptoms (e.g., persistent fatigue, weakness, or fever exceeding 3 days; malaise; nausea; vomiting; or unexplained anorexia) have been observed with the use of isoniazid. The incidence of isoniazid-associated hepatitis is lowest in those younger than 20 years of age and highest in daily users of alcohol and in patients 35 years of age or older. Liver function tests should be performed periodically and patients should be carefully observed for any of the prodromal symptoms of hepatitis.[20]

Hypersensitivity reactions, including fever, skin eruptions, lymphadenopathy, vasculitis, and hypotension, have occurred rarely with isoniazid, generally 3 to 7 weeks after the start of treatment. Other adverse effects requiring medical attention include optic neuritis, characterized by a sometimes painful blurring or loss of vision, and hematologic abnormalities, such as agranulocytosis, eosinophilia, thrombocytopenia, methemoglobinemia, and hemolytic, sideroblastic, or aplastic anemia.[21]

GI disturbances (abdominal pain, diarrhea, nausea, and vomiting), dryness of the mouth, hyperglycemia, pyridoxine deficiency, pellagra, metabolic acidosis, urinary retention, and gynecomastia in males have also been reported with isoniazid use. Irritation at the site of injection has occurred during intramuscular administration of isoniazid.[22]

Drug and Food Interactions

The absorption and bioavailability of isoniazid are reduced when administered with food.[23]

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Drug and Food Interactions (cont.)

Fixed-dose combination products containing isoniazid should be administered either 1 hour before or 2 hours after a meal.[24]

Concurrent use of alcohol, alfentanil, disulfiram, and other hepatotoxic medications with isoniazid may increase the potential for hepatotoxicity and should be avoided. Concurrent use of rifampin with isoniazid also may increase the potential for hepatotoxicity, requiring additional monitoring of liver enzymes and clinical symptoms.[25] Some evidence suggests that adverse nervous system effects may be additive if antitubercular agents are taken concurrently; isoniazid should be used with caution in patients receiving cycloserine and ethionamide. Isoniazid inhibits the multiplication of bacille Calmette-Guérin (BCG); the BCG vaccine may not be effective if adminstered during isoniazid therapy.[26]

Concurrent use of ketoconazole with isoniazid has been reported to decrease serum concentrations of ketoconazole.[27] Concurrent administration of isoniazid with carbamazepine has resulted in increased serum concentrations of the anticonvulsant and caused symptoms of carbamazepine toxicity, including ataxia, headache, vomiting, blurred vision, drowsiness, and confusion. This interaction is believed to occur because isoniazid inhibits hepatic metabolism of carbamazepine; the symptoms of toxicity subside when carbamazepine dosage is decreased or when the antitubercular agent is discontinued. Isoniazid also inhibits the hepatic metabolism of phenytoin, resulting in increased plasma phenytoin concentrations and toxicity in some patients. Patients should be closely monitored for any evidence of toxicity, and anticonvulsant doses should be reduced accordingly.[28]

Isoniazid may have MAO-inhibiting activity, so there is a slight risk of serotonin syndrome when isoniazid is given in combination with selective serotonin-reuptake inhibitors (SSRIs) or other serotonergic medications. Aluminum hydroxide-containing antacids decrease GI absorption of isoniazid, so isoniazid should be administered at least 1 hour before the antacid.[29]

Contraindications

Isoniazid is contraindicated in patients with a hypersensitivity to isoniazid. Patients hypersensitive to ethionamide, pyrazinamide, niacin (nicotinic acid), or other chemically related medications may show cross-sensitivity to isoniazid.[30]

Isoniazid is also contraindicated in patients with acute liver disease or a history of previous isoniazid-associated hepatic injury.[31]

Clinical Trials

For information on clinical trials that involve Isoniazid, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Isoniazid AND HIV Infections.

Dosing Information

Mode of Delivery: Oral (tablet and syrup; fixed combination regimens in capsule and tablet); intramuscular.[32]

Dosage Form: Isoniazid tablets containing 50 mg, 100 mg, and 300 mg; isoniazid syrup containing 50 mg isoniazid per 5 ml in 70% sorbitol.[33] [34]

Isoniazid injection for intramuscular administration containing 100 mg/ml with preservative.[35] [36]

Fixed combination capsules with rifampin (isoniazid 150 mg and rifampin 300 mg per capsule).[37]

Fixed combination tablets with rifampin and pyrazinamide (isoniazid 50 mg, rifampin 120 mg, and pyrazinamide 300 mg per tablet).[38]

Storage: Oral and injectable isoniazid should be stored at temperatures below 40 C (104 F), preferably between 15 C and 30 C (59 F and 86 F). Tablets and syrup should be stored in well-closed, light-resistant containers. The injection form should be protected from light. The syrup and injection forms should be protected from freezing.[39] [40]

Isoniazid

Chemistry

CAS Name: 4-Pyridinecarboxylic acid, hydrazide[41]

CAS Number: 54-85-3[42]

Molecular formula: C6-H7-N3-O[43]

C52.55%, H5.14%, N30.64%, O11.67%[44]

Molecular weight: 137.14[45]

Melting point: 171.4 C (crystals from alcohol)[46]

Physical Description: Colorless or white crystal or crystalline powder (oral).[47]

Clear, colorless to faintly greenish-yellow liquid (injection).[48]

Stability: Crystallization of isoniazid in solution may occur at low temperatures. The injection should be warmed to room temperature to redissolve any crystals prior to use.[49]

Solubility: At a temperature of 25 C (77 F), isoniazid is soluble in water at approximately 125 mg/ml and in alcohol at 20 mg/ml.[50] At a temperature of 40 C (104 F), isoniazid is approximately 26% soluble in water, and it is approximately 10% soluble in boiling alcohol.[51]

Other Names

INH[52]

Isonicotinic acid hydrazide[53]

Tubazide[54]

Ftivazide[55]

Phthivazide[56]

Isoniazida[57]

Laniazid[58]

Further Reading

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Manufacturer Information

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(800) 526-6367

Nydrazid
Sandoz Inc
506 Carnegie Center Drive
Suite 400
Princeton, NJ 08540
(609) 627-8500

Isoniazid

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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