Isoniazid

Synonym: isonicotinic acid hydrazide
CAS: 54-85-3
MF: $C_6H_7N_3O$
MW: 137.1
Solubility: 12.5 g/100 ml water, at 20°C.

Major uses
Isoniazid is a "first line" drug in the treatment of pulmonary and extrapulmonary tuberculosis (*Mycobacterium tuberculosis* and other mycobacteria). It inhibits the synthesis of mycolic acid in the mycobacterial cell wall.

Isoniazid is bactericidal to rapidly-growing mycobacteria, but is bacteriostatic if the mycobacteria are slow-growing. It is usually used in combination with other antituberculosis drugs such as rifampicin and pyrazinamide [1].

Human toxicity
The normal therapeutic dose of isoniazid is 5 mg/kg/day to a maximum of 300 mg/day. Up to 10 mg/kg/day (600 mg/day) are occasionally used in severely ill patients. The incidence of adverse effects is about 5.4%.

Isoniazid toxicity is associated with a high mortality rate. Doses of 35 to 40 mg/kg have resulted in seizures. Doses of 80 to 150 mg/kg will produce seizures and may cause death. Acute ingestion of 2 to 3 g in an adult is potentially toxic, while 10 to 15 g is frequently associated with death if untreated.

Isoniazid overdose causes seizures, generally within 1 h post-ingestion but may occur from 30 min to 5 h following ingestion. As little as 1.5 g of isoniazid ingested acutely may cause toxicity in an adult. Symptoms of severe toxicity are seizures, acidosis, tachycardia, respiratory depression, stupor and coma, and significant mortality if untreated [1].

Isoniazid blood levels higher than 10 mg/l have been associated with severe toxicity [1]. Twelve persons survived the ingestion of 2-50 g of isoniazid after developing maximal plasma concentrations of 20-143 mg/l (reviewed in [2]. Mean clinically measured acute lethal serum concentration was at the level of 77 mg/l [2, 3].

Kinetic data
Absorption: isoniazid is rapidly absorbed from the gastrointestinal tract. The absorption is reduced when isoniazid is taken with food [1].

Distribution: isoniazid readily diffuses to all body fluids and tissues, with the largest accumulation occurring in the liver [3].

Volume of distribution (V_d): 0.6 l/kg [2].

Kinetics: first-order [3].

Blood plasma protein binding: negligible (between 0 and 10%) [1, 3].

Time to peak blood concentration: within 1 to 2 h following a single 300 mg oral dose, peak plasma levels of 3 to 7 mg/l were noted [1]; 1.5-3 h at the overdose situation [3].

Passage of blood-brain barrier: free [3].

The mean elimination half-life: 0.5 to 1.6 h in rapid acetylators, and 2 to 5 h in slow acetylators [1]. See "Metabolism and excretion" below.

Metabolism and excretion

Biotransformation takes place in the liver. Isoniazid is metabolized via acetylation to acetylisoniazid; the latter metabolite is further hydrolysed to isonicotinic acid and monoacetylhydrazin. Isonicotinic acid conjugates with glycin; and monoacetylhydrazin is metabolized via acetylation to diacetylhydrazid. All these metabolites have not bacteriostatic effect and are less toxic than parental substance.

The enzyme that catalyzes the acetylation of amines is *N*-acetyl transferase, and it is located in the liver and intestinal mucosa. The polymorphism of this enzyme was reported in humans; this polymorphism is of genetic origin. Subjects are classified as "rapid" or "slow" acetylators based on their ability to acetylate isoniazid [5].

Excretion: in rapid and slow acetylators, respectively, 46% and 29% of a single dose is excreted in the 24 hour urine as acetylisoniazid, 1.8% and 2.5% as acetylhydrazine, and 23% and 49% as diacetylhydrazine (reviewed in [2]).

Toxicological mechanisms

Isoniazid has a significant effect on several biochemical pathways, among them on the metabolism of pyridoxine (vitamin B6). Pyridoxine activity is substantially reduced by isoniazid, leading to clinical pyridoxine depletion. Isoniazid is structurally related to pyridoxine.

Pyridoxine is a necessary cofactor for production of the neurotransmitter gamma-aminobutyric acid (GABA). Pyridoxine must be activated to produce GABA. Two mechanisms of pyridoxine inhibition were proposed: a) Isoniazid inhibits the enzyme pyridoxine phosphokinase, which converts pyridoxine to its active form, pyridoxal phosphate; b) Isoniazid binds to pyridoxal phosphate, forming an inactive hydrazone complex that is excreted in the urine. Inactivation of pyridoxine leads to a depletion of GABA in the brain. This reduction in GABA levels increases the susceptibility to seizures. Thus, the neurotoxic effects of isoniazid are specifically counteracted by the administration of pyridoxine.

Isoniazid is an inhibitor of several cytochrome P450-mediated functions, particularly demethylation, oxidation, and hydroxylation [4].

Target organs: CNS; liver (histopathological organ lesions) [3].

References

1. Poisindex, Thomson Micromedex (2005)
2. Baselt, R.C. & Cravey, R.H.(1995) *Disposition of Toxic Drugs and Chemicals in Man*. 4th edn., pp. 402-404. Chemical Toxicology Institute, California, USA.
3. Ekwall, B., Clemedson, C., Crafoord, B., Ekwall, Ba., Hallander, S., Walum, E., Bondesson, I. (1998) MEIC evaluation of acute systemic toxicity. Part V. Rodent and human toxicity data for the 50 reference chemicals. ATLA 26, 571-616.
4. Haddad, L.M.& Winchester, J.F. (1990) *Clinical Management of Poisoning and Drug Overdose*. 2nd ed., pp. 970-976, W.B. Saunders Company.

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