

ISONIAZID (INH) Fact Sheet

Isoniazid is a simple molecule related to vitamin B₃ (niacin).

- Dose:** 300 mg every, 200 mg every for adults weighing less than 100 pounds or 15 mg/kg up to 900 mg maximum dose twice or thrice weekly. A dose of 5 mg/kg produces a peak concentration of approximately 5 micrograms (mcg)/ml 1-2 hours after administration.
- Administration:** Oral on empty stomach, preferably at bedtime.
- Excretion:** 50% - 70% of a dose is excreted as unchanged drug and metabolites by the kidneys in 24 hours. Elimination is largely independent of renal function.
- Distribution:** CSF and pleural concentration similar to serum, crosses placenta and excreted in breast milk.

Adverse Reactions

Hepatotoxicity

1. Asymptomatic transaminase elevation
 - a. Very common (up to 20% of all adults taking Isoniazid)
 - b. Most common during first 2-3 months of therapy

2. Clinical Hepatitis
 - a. Difficult to attribute cause in multidrug regimens
 - b. Can occur anytime, but most common in first 2 months
 - c. Risk increases with age:
< age 20 – 0.0%; age 20-34 – 0.3%; age 35-40 – 1.2%; age 50-64 – 2.3%; and > age 64 – 3.0%.
 - d. Risk increases with alcohol intake
 - e. Risk increased in Black and Hispanic women
 - f. Case fatality estimation < 1%. In most fatal cases INH was continued after significant liver function test (LFT) abnormalities occurred or where LFT monitoring was not regularly done during INH therapy.
 - g. Similar to viral hepatitis – LFT abnormalities may be similar. Viral hepatitis does occur in patients taking INH and specific tests to evaluate for hepatitis may be indicated in some patients.

Neurotoxicity

1. Peripheral Neuritis
 - a. Mechanism: INH inhibits activation of pyridoxine to coenzymes which are essential for protein metabolism and production of certain synaptic transmitters.
 - b. Dose: Occurs very rarely with 300 mg/day or 15 mg/kg/day 2-3 times a week.
 - c. Risk: Increased risk if mildly pyridoxine deficient before INH therapy (i.e., pregnancy, cancer, malnutrition, alcoholism, or elderly).

- d. Symptoms: Stocking-glove sensation that can progress to sensory loss and nerve paralysis.
 - e. Prevention: Neurotoxicity can be prevented with as little as 6 mg/day of pyridoxine (vitamin B₆). B₆ 50 mg/day is usually given with INH to prevent neurotoxicity. If numbness or tingling occurs in a patient taking INH and B₆ 50 mg, the dose of B₆ is increased to 100 mg daily.
 - f. Treatment: Neurotoxicity can be treated with 100-200 mg/day of B₆.
2. Elevated INH concentrations may produce other CNS effects (i.e., psychosis, confusion, seizures).
 3. Usual doses have been reported to produce insomnia, muscle twitching, memory loss, restlessness, niacin deficiency and seizures in those with seizure history.

Drug Interactions

Alcohol

Daily usage may be associated with higher incidence of INH-associated hepatitis.

Aluminum Hydroxide (Antacids)

Aluminum hydroxide gel has been shown to delay and decrease gastrointestinal absorption of INH resulting in decreased serum levels of INH (20 % of control value). When both drugs are given, INH should be given at least one hour before the antacid.

Antabuse (Disulfiram)

In patients taking INH, antabuse has resulted in the occurrence of coordination difficulties and changes in affect and behavior.

Anticoagulants (Oral)

Anticoagulant activity may be enhanced by INH.

Barbiturates

Serum concentration increased by INH.

Carbamazepine (Tegretol)

Carbamazepine toxicity or INH hepatotoxicity may result from concurrent use. Monitor carbamazepine concentration and liver function.

Cycloserine

Cycloserine therapy with INH may result in increased CNS side effects particularly dizziness.

Chloramphenicol

Hematologic toxicity might occur.

Ketoconazole (Nizoral)

Serum concentration may be decreased by INH, possibly interfering with fungal disease therapy.

Levodopa (Sinemet)

There has been one case report of a patient treated with levodopa who developed agitation, flushing, and palpitation when given INH.

<u>Meperidine (Demerol)</u>	Coadministration may result in hypotension or CNS depression.
<u>Para-Aminosalicylic Acid (PAS)</u>	This interaction may increase and prolong serum levels of INH but not significantly.
<u>Phenytoin (Dilantin)</u>	INH increases phenytoin toxicity, by inhibiting the hepatic breakdown of phenytoin. Phenytoin dosage should be reduced and serum levels monitored in patients also receiving INH.
<u>Prednisolone</u>	Serum concentration decreased by INH.
<u>Pyridoxine (B₆)</u>	Isoniazid may increase the urinary excretion of B ₆ the body stores and resulting in peripheral neuritis.
<u>Rifampin</u>	INH and Rifampin coadministration may result in a higher rate of hepatotoxicity than with either agent alone. If alterations in liver function tests occur, consider discontinuation of one or both agents.
<u>Pyrazinamide</u>	Hepatotoxicity may be increased by combination with INH, but may be avoided by using lower doses of pyrazinamide (15 mg/kg).
<u>Reserpine</u>	INH inhibits reserpine.

Food Interactions

Since INH has some monoamine oxidase inhibitor activity, an interaction may occur with tyramine-containing foods (aged cheese and red wine) resulting in flushing and palpitations (swiss cheese effect).

INH may inhibit diamine oxidase causing headache, palpitations, sweating, hypotension, flushing, diarrhea, or itching to foods containing histamine (e.g., tuna, sauerkraut, yeast extract).

Monitoring

1. Patients should be followed regularly and questioned about signs and symptoms of hepatitis.
2. Liver function tests should be followed regularly in patients > 35 years of age, heavy alcohol users, and patients with a history of liver disease or taking other hepatotoxic agents.
3. Monitor monthly for the occurrence of numbness or tingling of the extremities, peripheral neuropathy.