ToxTidbits

Maryland Poison Center
UNIVERSITY OF MARYLAND SCHOOL OF PHARMACY

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The Maryland Poison Center's Monthly Update: News, Advances, Information

Acute Isoniazid Toxicity

Isoniazid (INH) has been the mainstay of tuberculosis (TB) treatment and prevention for decades and is currently a first-line anti-TB agent recommended by the CDC (www.cdc.gov/tb). On September 14, 2018, the Maryland Department of Health sent a letter to health care providers in Maryland about an outbreak of a unique tuberculosis strain. In light of this alert, the Maryland Poison Center would like to remind clinicians about the severe toxicity associated with acute INH overdoses.

INH is a hydrazide derivative of isonicotinic acid. It's mechanism of action is unclear, but it may inhibit mycolic acid synthesis, resulting in disruption of the bacteria's cell wall. Familiar adverse effects with therapeutic use include peripheral neuropathy and hepatotoxicity. Acute toxic effects are due to INH inhibiting pyridoxine phosphokinase, the enzyme that converts pyridoxine (vitamin B6) to its active form, pyridoxyl 5'-phosphate. Pyridoxyl 5'-phosphate is a cofactor in the synthesis of GABA, the main inhibitory neurotransmitter in the central nervous system. In acute overdoses, INH rapidly depletes GABA, lowering the seizure threshold.

As little as 15-40 mg/kg will produce toxic effects within 0.5-2 hours. Larger doses often cause seizures, and death rapidly occurs following the ingestion of ≥80 mg/kg. After an acute overdose, nausea, vomiting, slurred speech, ataxia, drowsiness, coma, seizures, tachycardia followed by bradycardia, hypotension, respiratory depression, hyperthermia, rhabdomyolysis, and renal failure may occur. Hepatotoxicity (hepatic enzyme elevation to fulminant hepatic failure) has been reported. A severe anion gap metabolic acidosis is a result of lactic acidosis secondary to seizures.

Gastrointestinal decontamination with activated charcoal should only be attempted in the emergency department if the patient is seen immediately after the overdose and has adequate airway protection. The risk of seizures and subsequent aspiration precludes its use in most cases. Treatment of acute INH toxicity consists of supportive measures (e.g. assisted ventilation, benzodiazepines, sodium bicarbonate) and pyridoxine, a specific antidote that will likely control seizures and acidosis. Pyridoxine should be given immediately upon suspicion of an INH overdose, even if the patient is asymptomatic. Administer 5 grams pyridoxine IV if the amount of INH ingested is unknown. If the amount ingested is known, give an equivalent amount of pyridoxine in grams. The dose may be repeated if seizures continue. Co-administering benzodiazepines might help to terminate seizures. Extracorporeal (e.g. hemodialysis) removal of INH has been successful but unlikely to be needed since INH has a short half-life (0.5-5 hours) and overdoses can usually be managed successfully with supportive care and pyridoxine. INH serum concentrations are not readily available and are not useful in guiding treatment.

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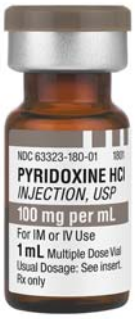

Did you know?

IV pyridoxine should be kept in stock in hospitals in enough quantities to adequately treat an INH overdose immediately.

An expert consensus panel recommends that all hospitals keep in stock a minimum of 8 grams of pyridoxine hydrochloride (100mg/mL) for intravenous use, enough to treat a 100 kg adult for the first 8 hours, or 24 grams for the first 24 hours *(Ann Emerg Med 2018;71 (30:314-25.e1).* If the IV formulation is not available, pyridoxine tablets may be crushed and administered with fluids through a nasogastric tube.

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