IOWA POISON CONTROL CENTER

Poison HOTLINE

1-800-222-1222

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Did you know .....

Benzodiazepines increase the frequency of chloride channel opening ***if*** GABA is present to activate the receptor. Barbiturates such a phenobarbital, however, have intrinsic GABA-A receptor activity (meaning barbiturates can still open chloride channels *without* GABA present) and increase the duration these chloride channels are open. This is why phenobarbital can still be used in some benzodiazepine-resistant states, such as refractory seizures from severe alcohol withdrawal or isoniazid toxicity (given with pyridoxine).

Healthcare providers can call IPCC for a 24/7 consult with a board-certified toxicologist. **1-800-222-1222**

ISONIAZID TOXICITY

Isoniazid (INH) is a prodrug that is structurally similar to nicotinic acid (a.k.a. niacin, vitamin B3) and pyridoxine (vitamin B6). INH is a key agent in the treatment of tuberculosis, where it gets activated by M. tuberculosis and irreversibly inhibits the synthesis of the cell wall.

INH is rapidly absorbed and 90% bioavailable when taken orally, with peak concentrations occurring within two hours of ingestion. Co-ingestion with food decreases both absorption and peak concentrations. It is distributed widely throughout body fluids and tissues and easily enters the CSF. INH is metabolized in the liver via acetylation, where the inactive metabolites can be renally excreted or further metabolized into additional inactive metabolites, some of which are hepatotoxic.

INH can cause life-threatening toxicity by inducing a functional pyridoxine deficiency and inhibiting the production of GABA. Normally, pyridoxine is converted into active pyridoxal-5'-phosphate, an essential cofactor in GABA synthesis, using pyridoxine phosphokinase. INH directly inhibits this enzyme, binds any available active cofactor, and increases renal elimination of pyridoxine. This results in insufficient cofactor needed for converting glutamate (excitatory neurotransmitter) into GABA (inhibitory neurotransmitter), causing refractory seizures due to an excess of glutamate and a lack of GABA. Pyridoxine is also used in catecholamine synthesis (such as norepinephrine) and important oxidation-reduction reactions throughout the body.

Acute INH toxicity begins with vomiting, dizziness, slurred speech, and tachycardia, and can progress to life-threatening symptoms. In addition to refractory seizures, patients can develop delirium, severe acidosis, rhabdomyolysis, hyperthermia, renal failure, shock, coma, and rarely, fulminant hepatic failure. Hepatotoxicity is more likely in chronic ingestions, along with most commonly peripheral neuropathy.

Pyridoxine is the antidote for INH toxicity. Consequential isoniazid toxicity is treated with IV pyridoxine to terminate any seizures, correct neurologic dysfunction, and reverse a comatose state. The initial dose should equal the amount of INH ingested in grams if known, or up to 5 grams can be given empirically if unknown. This dose can be repeated if symptoms persist. Only anti-epileptics (AEDs) with intrinsic GABAergic activity (benzos, barbiturates) can be given as adjunctive treatment with, but not instead of, pyridoxine; other AEDs are not beneficial. INH is dialyzable but often only indicated in renal failure or following massive ingestions when adequate doses of pyridoxine are not available. As always, providing excellent supportive care is a mainstay of therapy as well.

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