IOWA POISON CONTROL CENTER

Poison HOTLINE

1-800-222-1222

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Did you know ……

Acetaminophen (APAP) is normally metabolized in the liver by sulfation and glucuronidation to nontoxic metabolites. A small percent is normally metabolized by the CYP-450 system to a highly reactive metabolite called N-acetyl-p-benzoquinone-imine (NAPQI). NAPQI is detoxified by binding with glutathione. In large overdoses, the sulfation and glucuronidation pathways are saturated and more APAP is metabolized to NAPQI. As glutathione stores are depleted, NAPQI begins to covalently bond to proteins in the liver cells resulting in cell death and liver failure.

N-acetylcysteine (NAC) treats APAP overdoses by replenishing glutathione and also by directly binding to NAPQI. NAC can be given orally or intravenously.

Call the IPCC at **1-800-222-1222** for assistance with APAP and NAC cases.

Fomepizole in Acetaminophen Overdose

Acetaminophen (APAP) ingestion is one of the most common calls to the poison center. In overdose, APAP can result in liver injury and even failure. The US Acute Liver Failure Study Group registry found 42% of all cases of acute liver failure in the United States are attributed to APAP overdose. The mainstay of treatment for APAP toxicity is N-acetylcysteine (NAC). This is the only FDA approved antidote for acetaminophen toxicity.

While NAC remains the standard of care for APAP toxicity, fomepizole has emerged as potential adjunctive treatment. Fomepizole is more well known as an antidote for toxic alcohols due to its ability to block alcohol dehydrogenase. More recently, fomepizole has emerged as a potential adjunctive treatment in acetaminophen overdose. Most APAP overdoses can be effectively treated with NAC and supportive care. Two situations in which patients may develop hepatic injury or even failure despite treatment with NAC are massive overdose and late presentation.

In massive overdoses, NAPQI may be generated at quantities and rates too high for NAC infusions to keep up with. Fomepizole is well known to block alcohol dehydrogenase but also appears to be a potent inhibitor of CYP2E1, the enzyme responsible for metabolizing APAP to NAPQI. By blocking CYP2E1 and slowing the rate of NAPQI formation, fomepizole may help shunt APAP to non-toxic metabolic pathways and help NAC infusions keep up with the rate of NAPQI formation.

In late presentations, NAPQI has already had a chance to form and cause hepatic damage and mitochondrial dysfunction. Very limited research suggests fomepizole may help reverse some of the downstream damage caused to liver cells by NAPQI.

There are no widely accepted guidelines for when to use fomepizole and clinical research is currently limited. Despite this, fomepizole is sometimes used as an off label adjunctive treatment in select cases of APAP overdose particularly in massive overdoses and late presenting cases. We recommend involving a toxicologist in the decision to use fomepizole to treat a patient with APAP overdose. Call IPCC at **1-800-222-1222** for a consult.

Janet Gray, RN, BSN, CSPI
Certified Specialist in Poison Information

POISON HELP™ 1-800-222-1222

Hotline Editor: Bryan Wilson, MD

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