ToxTidbits

Maryland Poison Center
UNIVERSITY OF MARYLAND SCHOOL OF PHARMACY

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

What's New with NAC?

N-acetylcyteine (NAC) prevents hepatotoxicity from acute and chronic acetaminophen overdoses. The oral and intravenous dosing regimens vary. Many clinicians prefer the intravenous regimen which is shorter and avoids problems associated with vomiting and/or patient refusal to ingest the oral preparation for 72 hours. The FDA-approved intravenous regimen consists of three doses: a loading dose of 150 mg/kg given over one hour, a first maintenance dose of 50 mg/kg given over four hours and a second maintenance dose of 100 mg/kg given over 16 hours.

Recently, there has been debate regarding whether the standard dosing regimen is appropriate for all patients. Perhaps patients with massive overdoses need more NAC, while those with smaller overdoses or with repeated supratherapeutic ingestions need less. The majority of an acetaminophen dose is metabolized to non-toxic metabolites but a small proportion is metabolized by cytochrome 2E1 to a toxic metabolite, NAPQI, which is detoxified by glutathione. Large doses of acetaminophen result in glutathione depletion allowing NAPQI to bind covalently to liver cells with resultant cellular injury and death. The dose of NAC is estimated to correct glutathione depletion, assuming ~4% of an acetaminophen dose would be metabolized to NAPQI. However, in severely poisoned patients, up to four times as much NAPQI may be formed. Additionally, NAC dose is based on patient weight, not on acetaminophen dose or plasma acetaminophen concentration (PAC).

The risk of hepatotoxicity is higher in patients who take massive overdoses. Defining massive overdose as a dose >32 g or PAC >300 mcg/mL at 4 hours post ingestion (or extrapolated to 4 hours) on the Rumack-Matthew nomogram (used to determine treatment), Hendrickson estimated the hepatotoxicity risk increased from <1% at 150 mcg/mL to as high as 31-33% at >500 mcg/mL at 4 hours. *[Clin Toxicol 2019;57:686-91]* . He suggested that patients with massive overdoses need more NAC and recommended administering up to 4 times the second maintenance dose (6.25 to 25 mg/kg/h) depending on the acetaminophen dose and 4 hour PAC. An observational study of 200 patients with overdoses of ≥40 g of immediate release acetaminophen preparations found a significant decreased risk of hepatotoxicity in patients who received activated charcoal within 4 hours of ingestion and patients given an increased dose of NAC. *[Clin Toxicol 2017;55:1055-65.]*

On the flip side, does everyone need a full 21 hour course of NAC? A study of 100 acute overdose patients with normal initial and 12-hour ALT and 12-hour PAC <20 mcg/mL who received a 12 hour NAC course (250 mg/kg total) found no difference in ALT and INR at 20 hours compared to standard regimen. *[Hepatology 2019;69:774-784.]* In another study of 91 patients with repeated supratherapeutic ingestion, 39 patients with low PAC and normal or static ALT received an abbreviated NAC course and did not develop hepatoxicity. *[Clin Toxicol 2018;56:199-203].* However, more studies are need as neither study had sufficient numbers of patients to assess efficacy.

The take-home message: NAC regimens are evolving. Call the poison center at 800-222-1222 to find out the most up-to-date recommendations.

Did you know?

Adverse reactions to IV N-acetylcysteine are usually mild and easily managed.

Patients administered IV NAC are at risk for anaphylactoid reactions. Reactions are usually mild (e.g. rash, pruritus and flushing), usually occur during the loading dose, and are easily managed with antihistamines. In most cases, NAC does not need to be discontinued. Serious effects such as hypotension, bronchospasm, and angioedema have occurred and may require discontinuation of NAC. A history of asthma and low acetaminophen serum concentrations have been suggested as risk factors for anaphylactoid reactions.
[Br J Clin Pharmacol 2001;51:87-91; Clin Toxicol 2008,46:496-500; Clin Toxicol 2013;51:467-472].

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