

Two-bag Acetylcysteine: Simpler and Safer

Acetaminophen overdose is a common call to U.S. poison centers and is the most common cause of acute liver failure in the U.S. We have been studying acetaminophen for years and seem to know a lot about management and prognosis. Truth be told, acetaminophen is one of the few ingestions for which we have a true antidote: N-acetylcysteine, or more commonly, NAC. NAC is very effective and confers close to 100% protection if started within 8-10 hours after a single acute ingestion of acetaminophen. While NAC is an effective antidote, it is not without its flaws. Here, we'll discuss the two main flaws of intravenous (IV) NAC and one method that has been proposed to fix both.

The first issue with IV NAC is that the dosing regimen is horribly complex. The original investigators aimed for a level of NAC to achieve steady-state rapidly, then dosing to continue to provide a constant maintenance dose. Unfortunately, this was originally performed by giving a bolus of $\frac{1}{2}$ of the total dose (150 mg/kg) over 15 minutes, then 50 mg/kg over 4 hours, then 100 mg/kg over 16 hours; a 20.25-hour protocol. Subsequently the dosing was changed to infuse the first bag over 1 hour rather than 15 minutes, a 21-hour protocol which is the approved dose in the U.S. This is fraught with errors including delays in dosing, wrong rates and wrong bag orders. In a study by Hayes et al, there was a 33% rate of errors with IV NAC (*Ann Pharmacother* 2008;42:766-70. PMID: 18445707). Since there is a high rate of errors, individual toxicologists and poison centers recommend re-loading patients if there are delays between bags. However, there is inadequate data to support re-load recommendations.

The second issue with IV NAC is that there is approximately a 12% chance of anaphylactoid reactions (*Clin Toxicol* 2018;56:618-21. PMID: 29219630). While not terribly difficult to manage, anaphylactoid reactions are uncomfortable and they can cause delays in therapy when the IV NAC needs to be discontinued and the anaphylactoid reaction is managed.

Fortunately, researchers in other countries have come up with a possible solution for both errors and anaphylactoid reactions: combine the first and second NAC doses and give it over 4 hours (200 mg/kg over 4 hours). Two studies have evaluated the risk of anaphylactoid reactions using this modified two-bag protocol (*Clin Toxicol* 2018;56:618-21. PMID: 29219630. *Clin Toxicol* 2016;5:115-9. PMID: 26594846). Both studies found that the rate of anaphylactoid reactions is reduced to about 4.6% with no increase risk of liver toxicity. That equates to one fewer reaction for every 13.3 patients treated with a simpler protocol that requires fewer bags.

The potential benefits of the two-bag method of administering NAC include fewer errors and less risk of anaphylactoid reactions, both of which are improvements in care. However, it is important to note that it is not yet approved for use in the U.S. by the FDA nor is it considered the standard of care.



Did you know?

Anaphylactoid reactions are the most common adverse event associated with IV NAC but are usually mild and easily manageable.

Authors have attempted to identify what puts patients at risk for anaphylactoid reactions. Asthma and rate of infusion have been identified as possible risk factors. The 15-minute first bag infusion might be associated with a higher rate of anaphylactoid reactions vs the currently recommended loading dose given over 1 hour, but data are inconclusive. (*Ann Emerg Med* 2005;45:402-8. PMID 15795719). In at least two studies, high acetaminophen levels were protective against anaphylactoid reactions (*Clin Toxicol* 2013;51:467-72. PMID: 23697458; *J Med Toxicol* 2018;14:120-7. PMID: 29423816).

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