ToxTalks

A Bulletin for Healthcare Professionals Who Manage Poisoned Patients

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N-Acetylcysteine Dosing in Acetaminophen Toxicity

What is the role of N-acetylcysteine in acetaminophen overdose?

Acetaminophen is one of most common drugs ingested in overdose. The major risk factor for developing acute liver injury is delayed time to treatment with N-acetylcysteine (NAC). If NAC is administered within 8 hours of an acute overdose, hepatotoxicity ranges from 0-6%. After 8 hours, risk of hepatotoxicity increases from 8-50%. NAC primarily acts by providing cysteine for glutathione synthesis and forms an adduct with the toxic metabolite of acetaminophen, N-acetyl-p-benzoquinoneimine (NAPQI).

When should NAC be started?

NAC should be started in cases of suspected acetaminophen toxicity. In an acute overdose (all acetaminophen consumed within a single, one hour period), then the Rumack-Matthew nomogram can be utilized to determine if NAC should be administered. Time should be plotted from the beginning of the ingestion period, starting at a time of four hours after the ingestion. However, if there is any discrepancy in the time of ingestion, or in the case of chronic ingestion of toxic amounts of acetaminophen, the nomogram cannot be utilized. In these instances, NAC should be started if there is a detectable acetaminophen level or if there is an elevation in liver enzymes from baseline in the setting of suspected acetaminophen ingestion.

What is the recommended dosing of intravenous NAC?

In 2006, the Food and Drug Administration approved an intravenous 3 bag protocol with a loading dose of 150 mg/kg over 60 minutes, following by an infusion of 12.5 mg/kg/hour for 4 hours, followed by an infusion of 6.25 mg/kg/hour for 16 hours. In cases of large acetaminophen ingestions (e.g. 40 grams or greater), some experts have advocated for doubling the last maintenance infusion dose to 12.5 mg/kg/h for 16 hours. [1]

Many institutions utilize a single bag protocol instead of the three bag method. The single bag method uses an initial bolus of 150 mg/kg infused over 1 hour, followed by a higher maintenance dose (e.g. 12.5-14 mg/kg/h) from the

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same bag until clinic endpoints are met. The single bag method results in simplification of antidote preparation and administration. Additionally, a single bag method results in increased NAC compared to the three bag approach, and no dose adjustments are made in the event of large ingestions or if hemodialysis is performed.

When should NAC be discontinued?

End of NAC therapy should be based on clinical endpoints, not just a specified time period. NAC should be continued until acetaminophen concentration is undetectable, liver enzymes are near or at baseline, or if liver enzymes decline significantly and discontinuation of NAC is approved by a medical toxicologist. This is particularly important in individuals who present over 8 hours after ingestion, or those who present with elevated transaminases or very high acetaminophen concentrations. The pre-specified duration of therapy of 21 hours may be too short in patients with hepatic injury or those with massive ingestions and should be continued until the above clinical discontinuation criteria at met.

Are there any adverse consequences of starting NAC?

NAC is relatively inexpensive, but costs incurred include hospitalization. NAC has an unpleasant taste and smell, and can induce vomiting when given orally. While oral NAC is effective, intravenous NAC eliminates this adverse effect and results in reliable administration. With intravenous NAC, the most commonly reported adverse effects are anaphylactoid reactions. These can produce the same clinical picture as anaphylaxis (rash, pruritus, angioedema, bronchospasm, tachycardia, and hypotension), but are not IgE medicated reactions. Even in instances of severe reaction resulting in angioedema and respiratory symptoms, diphenhydramine can be given and NAC infusion can usually be resumed 1 hour after the absence of symptoms.

For guidance, call the Blue Ridge Poison Center at UVA Health: 800-222-1222 or use the healthcare professional hotline: 800-451-1428.

References available upon request.

The Blue Ridge Poison Center receives funding from University of Virginia Health, the Virginia Department of Health, and the U.S. Health Resources Services Administration (HRSA). We are accredited by the American Association of Poison Control Centers. We've been proudly serving the Commonwealth since 1978.