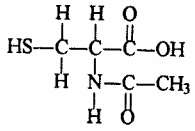
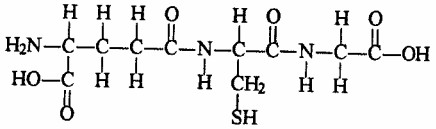
ANTIDOTES IN DEPTH

N-Acetylcysteine

Mary Ann Howland



N-acetylcysteine



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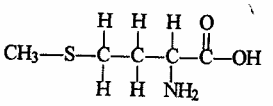
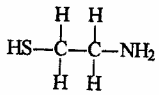


Methionine



Cysteamine

N-acetylcysteine (NAC) is the cornerstone of therapy for patients with potentially lethal acetaminophen overdose. If administered early in the course of exposure, NAC can prevent significant acetaminophen-induced toxicity. Later, it can ameliorate toxicity. NAC also has a role in limiting toxicity caused by glutathione depletion and free radical formation, such as from carbon tetrachloride, chloroform, pennyroyal oil, and possibly valproic acid.[17,25,26,93] Finally, NAC is useful in the management of fulminant hepatic failure caused by toxicologic and nontoxicologic etiologies. Its beneficial effects are also under investigation in critically ill patients with a variety of stress-induced disorders,[46,83,90] perhaps in the prevention of further renal impairment in patients with chronic renal insufficiency administered a radiographic contrast agent, and in those with hepatorenal syndrome.[32,33,76,86] Furthermore, NAC is potentially beneficial following exposure to certain metals such as cobalt.[45]

HISTORY

Shortly after the first case of acetaminophen hepatotoxicity was reported, Mitchell and coworkers described a protective effect of glutathione.[52,73] Prescott et al.[59] first suggested the use of *N*-acetylcysteine (NAC) for acetaminophen poisoning in 1974. Early experiments demonstrated that NAC could prevent acetaminophen-induced toxicity in mice when treatment was initiated within 4.5 hours of ingestion and that the oral and intravenous (IV) routes were equally efficacious when treatment was initiated within 1 hour of ingestion.[58] Mitchell et al.,[52] Prescott et al.,[59,62] and Rumack and Peterson[74] performed human research with oral and IV NAC in the 1970s. The United States Food and Drug Administration approved oral NAC in 1985 and IV NAC in 2004.

Cysteamine, methionine, and NAC, which are all glutathione precursors or substitutes, have been used successfully to prevent hepatotoxicity, but cysteamine and methionine both produce more adverse effects than does NAC therapy, and methionine is less effective than NAC. Therefore, NAC has emerged as the preferred treatment.[63,78,87]

BACKGROUND: TOXICOLOGY

Ninety percent of a therapeutic dose of acetaminophen is metabolized to nontoxic glucuronide (approximately 60%) and sulfate (approximately 30%) conjugates.[60] Only 4% is metabolized by the cytochrome P450 mixed-function oxidase system (3A4 at low doses; 2E1 predominantly at high doses)[51] to the potentially toxic reactive intermediate *N*-acetyl-*p*-benzoquinoneimine (NAPQI). This intermediate is conjugated with glutathione to form nontoxic cysteine and mercapturic acid conjugates. After acetaminophen overdose, both the fraction and the total amount of drug undergoing P450 metabolism increase, leading to glutathione depletion, binding of the highly reactive intermediate, liberation of reactive oxygen and nitrogen species, and resultant centrilobular hepatic necrosis.[18,35,64] It is postulated that the ensuing oxidative stress causes mitochondrial and other damage to cardiac, pulmonary, and hepatic tissues (Chap. 12).[9,27,64,79] NAC is a thiol-containing compound that is deacetylated to cysteine, a thiol-containing amino acid that is used intracellularly in addition to the amino acids glycine and glutamate to synthesize glutathione.[72] The availability of cysteine becomes the rate-limiting step in the synthesis of glutathione, and NAC is effective in replenishing diminished supplies of cysteine.

MECHANISM OF ACTION

When administered shortly following acetaminophen ingestion, NAC acts to prevent toxicity. Later in the clinical course, NAC modifies the subsequent xenobiotic-induced inflammatory response. NAC effectively prevents acetaminophen-induced hepatotoxicity if it is administered before glutathione stores are depleted to 30% of normal. This level of depletion occurs approximately 8 hours after toxic acetaminophen ingestion.[62,70,81] NAC acts as a precursor for the synthesis of glutathione,[41] as a substrate for sulfation,[80] as an intracellular glutathione substitute by directly binding to NAPQI,[15] and by enhancing the reduction of NAPQI to *N*-acetyl-*p*-aminophenol (APAP).[41]

After NAPQI covalently binds to hepatocytes,[70] NAC modulates the subsequent cascade of inflammatory events in a variety of ways.[29] The inflammatory damage can occur in many tissues. Antioxidants function as electron donors and are oxidized preferentially to relatively less reactive and destructive species.[9] Examples of endogenous antioxidants include vitamins C and E and reduced

glutathione. Glutathione protects cells against electrophilic compounds by acting as both a reducing agent and an antioxidant.[72] Glutathione replenishment may protect against further cell damage but is incapable of completely restoring damaged tissues. In this second stage, NAC may act directly as an antioxidant; act as a reservoir for thiol groups; increase nitric oxide synthase to improve blood flow by combining with nitric oxide to form the potent vasodilator *s*-nitrosothiol; increase formation of essential endogenous antioxidants such as glutathione; and increase substances depleted by the oxidant stress such as endothelium-derived relaxing factor.[23,29] In this manner NAC can modulate the oxidative stress and inflammatory cascade while improving oxygen delivery and extraction in extrahepatic organs such as the brain, heart, and kidney.[46,76,83]

CLINICAL USE

If the patient's history suggests an acute acetaminophen ingestion ≥150 mg/kg and the results of blood tests will not be available within 8 hours of ingestion or if the serum [APAP] falls on or above the treatment line on the Rumack-Matthews nomogram, NAC should be instituted expeditiously. Aspartate aminotransferase and APAP concentrations should be determined in adults with chronic overdoses who ingest more than the recommended maximum daily dose of 4 g or children who ingest more than 90 mg/kg/d and are at high risk (increased NAPQI formation or reduced glutathione stores). NAC should be administered when hepatotoxicity is manifest by symptoms or liver enzyme elevations (Chap. 34). Interpretation of acetaminophen concentrations in these chronic overdoses is difficult, and the acetaminophen nomogram can never be applied.

Some patients who are at increased risk for acute or chronic acetaminophen poisoning may require administration of NAC at a lower threshold. Unfortunately, this threshold is not yet defined. Glutathione-deficient patients who are malnourished, have chronic alcoholism, or are receiving CYP2E1-inducing agents such as isoniazid or ethanol may theoretically be at increased risk for acetaminophen toxicity.[12,30,42,81] However, an analysis of a small number of patients who received anticonvulsants or chronically ingested alcohol did not demonstrate these patients to be at risk independent of acetaminophen dose.[49,82] Also currently no data indicate the need to lower the threshold when evaluating a patient with hepatic enzyme abnormalities.[82]

PHARMACOKINETICS

When administered, NAC is present in plasma in the reduced or oxidized state and is either free or bound with other thiols such as NAC-cysteine. NAC is metabolized to many sulfur-containing compounds such as cysteine, glutathione, methionine, cystine, disulfides, and conjugates.[23,56,61] Thus the pharmacokinetic study of NAC is complex.

Oral NAC is rapidly absorbed, but the bioavailability is low (10–30%) because of significant first-pass metabolism.[23,61] NAC has a relatively small volume of distribution (0.5 L/kg), and protein binding is 83%. Serum concentrations after IV administration of an initial loading dose of 150 mg/kg over 15 minutes reach approximately 500 mg/L.[61] A steady-state plasma concentration of 35 mg/L (10–90 mg/L) is reached in approximately 12 hours with the standard IV protocol.[61] Its elimination half-life is 5.7 hours. Severe liver damage does not appear to affect NAC elimination.[61]

Conflicting in vitro[16,39,75] and in vivo[14,22,54,66] data regarding the concomitant use of activated charcoal suggest that the resultant bioavailability of NAC is either decreased or unchanged. This interaction is of limited importance now that IV NAC is available.

Oral NAC is being studied as a potential chemopreventive agent. Pharmacokinetics and pharmacodynamics of oral NAC were determined in a phase I trial in 26 adult volunteers at risk for development of cancer or recurrent cancer.[56] Absorption of NAC is rapid, with a mean time to maximum peak concentration of 1.4 ± 0.7 hours and a mean elimination half-life of 2.5 ± 0.6 hours that is linear with increasing dose up to 3200 mg/m^2/d given as a single daily dose. Intersubject plasma NAC concentrations vary 10-fold from a maximum concentration of 1.7–20.8 mg/L at a dose of 800 mg/m^2/d. Chronic administration leads to a decrease in plasma concentrations from a C_{max} of 8.9 mg/L at the end of 1 month to 5.1 mg/L at the end of 6 months.[56]

ORAL VERSUS INTRAVENOUS *N*-ACETYLCYSTEINE

Although these approaches have never been directly compared, they appear to confer equal protection when either is administered within 8 hours.[95]

The 20-hour IV NAC protocol is 150 mg/kg loading dose over 15 minutes, followed by an additional dose of 50 mg/kg over 4 hours and then 100 mg/kg over 16 hours for a total dose of 300 mg/kg. The 72-hour regimen is 140 mg/kg loading dose followed by 70 mg/kg for 17 additional doses for a total dose of 1330 mg/kg. Both protocols are effective in preventing hepatic damage when given within 8 hours of acetaminophen ingestion.[62] A 48-hour IV regimen studied in the United States appears to be superior to the 20-hour regimen when the first dose is delayed until 16–24 hours after ingestion.[81] The 72-hour oral NAC regimen also appears superior to the 20-hour IV NAC protocol when started 16–24 hours postingestion. Perhaps most patients who receive their first dose of NAC within 8 hours require only the short course because the inflammatory cascade is not initiated, whereas patients whose treatment is delayed benefit from a longer course of therapy and the associated benefits of the antiinflammatory/antioxidant effects of NAC. Some authors recommend a 36-hour oral course in low-risk patients with careful evaluation and follow-up, but this recommendation has not been adequately studied.

Only the IV route has been studied in hepatic failure.[28,38] The IV route achieves higher serum concentrations than the oral route. It is unclear whether oral or IV dosing results in superior drug delivery to the liver and whether the higher hepatic concentrations enhance drug efficacy.[57] The oral route often produces vomiting and requires antiemetics to complete therapy, but it is not usually associated with other serious adverse effects. Theoretically higher serum concentrations may be helpful for extrahepatic effects, whereas the oral route might provide higher intrahepatic concentrations.

We now recommend IV NAC for all adult patients without asthma[4] or other contraindication to IV NAC and in whom an anaphylactoid reaction would not be devastating. In children who do not tolerate oral NAC, IV NAC may be acceptable. However, the appropriate dilution of IV NAC in children is problematic. Currently, the package insert only provides dosing information down to a patient weight of 40 kg.[1] Hyponatremia is possible and has

been reported in a 13-kg child receiving the adult IV dosing volume (1700 mL), leading those authors to suggest a final concentration of NAC of approximately 4% in 5% dextrose in water (D_5W) to avoid the administration of excess free water and the potential for hyponatremia.[85] However, the pH of Acetadote (acetylcysteine injection, Cumberland Pharmaceuticals, Nashville, TN) is adjusted close to neutral where NAC is stable, resulting in an osmolarity of approximately 2600 mOsm/L for the 20% solution. Therefore sodium concentrations and fluid requirements must be meticulously monitored. A 2% final NAC concentration in D_5W of Acetadote is approximately 485 mOsm/L and may be more appropriate.

USE IN PREGNANCY AND NEONATES

Untreated acetaminophen toxicity is a far greater threat to the fetus than is NAC treatment.[68] The risk of not treating pregnant women almost certainly far exceeds any potential risk to the developing fetus if a toxic ingestion has occurred. Although an earlier sheep model suggested otherwise, human data demonstrate that NAC traverses the placenta and produces cord blood concentrations comparable to maternal blood concentrations.[34] NAC is Food and Drug Administration (FDA) Pregnancy Category B. Limited data exist with regard to the management of neonatal acetaminophen toxicity,[5,43,71,77] although IV and oral NAC have been used safely.[1,5] No adverse effects were observed when preterm newborns were treated with IV NAC[1] (Chaps. 30 and 34). The elimination half-life of NAC in preterm neonates was 11 hours compared to 5.6 hours in adults.[1] IV administration has the advantage of assuring adequate antidotal delivery. Oral administration in general is associated with necrotizing enterocolitis in neonates.

OTHER USES (NON–ACETAMINOPHEN)

Diverse investigations of NAC as a treatment for a number of xenobiotics associated with free radical or reactive metabolite toxicity are reported. Some of these xenobiotics include chloroform, carbon tetrachloride, 1,2-dichloropropane, acrylonitrile, doxorubicin, and cyclophosphamide.[17,23,89,93]

NAC is under study as a chemopreventive agent against amatoxins cancer, lung injury, cardiac injury, radiographic contrast exposure,[86] and malnutrition.[2,20,21,46,72,83,84] NAC has extracellular antimutagenic effects, enhances repair of nuclear DNA damaged by carcinogens, and inhibits malignant cell invasion and metastases.[21,55,65] Oral NAC added to prednisone and azathioprine preserves vital capacity in patients with idiopathic pulmonary fibrosis.[21a]

Rescue NAC therapy is being studied with high-dose acetaminophen ($\leq$20 g/m^2) in patients with advanced malignancies.[40] Use of NAC in these settings may further enhance our understanding of the beneficial effects of NAC in both the early and late phases of acetaminophen poisoning.

ADVERSE EFFECTS AND SAFETY ISSUES

Oral NAC may cause nausea, vomiting, flatus, diarrhea, gastroesophageal reflux, and dysgeusia; generalized urticaria occurs rarely. Anaphylactoid reactions described after IV NAC dosing[3,10,11,19,24,31,48,50,61,67,88,91] are not noted after oral therapy and may be related to rate, concentration, or high serum NAC concentrations.[8,91]

Administration of oral NAC via the IV route produced cutaneous reactions in 4 of 76 patients and a generalized anaphylactoid reaction in 1 patient. None of these patients developed adverse hemodynamic effects.[94]

The IV route assures delivery, but rate-related anaphylactoid reactions are possible. Although the package insert for Acetadote recommends infusing the loading dose over 15 minutes, many authors, including ourselves, believe that infusion over 1 hour reduces the potential for life-threatening anaphylactoid reactions.[48] The manufacturer categorizes the number of anaphylactoid reactions occurring in 109 patients receiving the 15-minute loading dose as mild 6%, moderate 10%, and severe 1%.[1] Although similar findings are listed for the 60-minute loading dose infusion, problems with study design cast doubt on these findings.[1,96] Of the adverse events occurring in more than 2000 patients who received IV NAC, vasodilation, rash, and pruritus account for approximately 10%, hypotension 4%, bronchospasm 6%, and angioedema 8%.[1]

If angioedema or an anaphylactoid reaction characterized by hypotension, shortness of breath, or wheezing, flushing, or erythema occurs, NAC should be stopped and standard symptomatic therapy instituted. Once the reaction resolves, NAC can be carefully readministered after 1 hour assuming NAC is still indicated. If the reaction persists or worsens, discontinue IV NAC and consider switching to oral NAC. Adverse reactions confined to flushing and erythema usually are transient, and NAC can be continued with meticulous monitoring for systemic symptoms that indicate the need to stop the NAC. Urticaria can be managed with diphenhydramine with the same precautions.[7]

Iatrogenic overdoses with IV NAC have resulted in comparable adverse events.[3,6,50] IV NAC decreases clotting factors and increases the prothrombin time in healthy volunteers and overdose patients without hepatic damage.[36,47,53,92] This effect occurs within the first hour, stabilizes after 16 hours of continuous IV NAC, and rapidly returns to normal when the infusion is stopped.[36] Because the prothrombin time is used as a marker of the severity of toxicity and is one of the criteria for transplantation, this adverse effect of NAC should always be considered when evaluating the patient's condition. An elevated prothrombin time without other indicators of hepatic damage probably is related to the NAC.

DOSING

The manufacturer recommends a loading dose of 150 mg/kg in 200 mL of D_5W (for adults) infused over 15 minutes, followed by a first maintenance dose of 50 mg/kg in 500 mL D_5W (for adults) infused over 4 hours followed by a second maintenance dose of 100 mg/kg in 1000 mL D_5W (for adults) infused over 16 hours. We recommend infusing the loading dose over 60 minutes.

The appropriate dilution of IV NAC in children is problematic. Currently, the package insert only provides dosing information down to a patient weight of 40 kg.[1] Because of issues with osmolarity, sodium concentrations, and fluid requirements, meticulous monitoring is required. A 2% final NAC concentration in D_5W is approximately 485 mOsm/L and may be acceptable until further information becomes available.

When NAC is administered orally, the patient should receive a 140-mg/kg loading dose either orally or by enteral tube. Starting 4 hours after the loading dose, 70 mg/kg should be given every 4 hours for an additional 17 doses. The solution should be diluted to 5% with a soft drink to enhance palatability. If any dose is vomited

within 1 hour of administration, the dose should be repeated[44] or IV delivery used. Antiemetics (such as metoclopramide or a serotonin antagonist) should be used to ensure absorption. If the acetaminophen concentration is above the nomogram line, the standard approach is to administer 72 hours of therapy. Shorter courses may be acceptable (Chap. 34).

If hepatic failure intervenes, IV NAC should be administered at a dose of 150 mg/kg in D_5W infused over 24 hours and continued until the patient has a normal mental status (or recovers from hepatic encephalopathy),[29] the patient's international normalized ratio (INR) becomes <2.0,[69] or the patient receives a liver transplant.[13,28,38] Before the FDA approval of Acetadote, NAC approved for oral administration was administered by the IV route, often while using a 0.22-μm filter as a delivery precaution.[37,94] We would no longer recommend this practice except under unique circumstances.

AVAILABILITY

Acetadote (NAC) is available as a 20% concentration in 30-mL single dose vials designed for dilution prior to IV administration. NAC for oral administration is available in 10-mL vials of 10% and 20% for oral administration.

ACKNOWLEDGMENT

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