N-ACETYLCYSTEINE – ANTIDOTE 2 step (dose)

Synonyms
NAC, Acetylcysteine

Common Trade Names
Mucomyst®, Parvolex®, Acetadote® (U.S.)

Action
NAC improves the outcome of **acetaminophen poisoning** by a variety of mechanisms.
Prevents hepatic injury by acting as a glutathione precursor, directly detoxifying NAPQI (the toxic N-acetyl-*p*-benzoquinoneimine metabolite of acetaminophen); acts as substrate for the nontoxic sulfate metabolites, and enhances reduction back to parent acetaminophen.
Reduces severity of hepatotoxicity by improving oxygen delivery and modifying secondary damage from inflammatory factors such as cytokines and free radicals.
See also ACETAMINOPHEN.
May act as an antioxidant and free radical scavenger and improve outcome of hepatotoxicity in poisonings from other agents (***see*** Other Indications).

Pharmacokinetics
Peak blood levels following oral administration are reached within 0.5-2 hours.
Volume of distribution is approximately 0.5 L/kg. Approximately 83% bound to plasma proteins.
Extensively metabolized to a variety of disulfides, cysteine, cystine, glutathione and other compounds. Urinary metabolites are primarily inorganic sulfates; 20-30% of an IV dose is excreted unchanged in the urine.
Elimination half-life ranges from 5-6 hours. Hepatic injury may prolong half-life; dose adjustment not required.
NAC is removed by dialysis; dose adjustment not required.

Uses and Efficacy
Acetaminophen Poisoning (acute and chronic)
Indicated when:
- Serum acetaminophen level is greater than the treatment line on nomogram in *acute* poisoning (**see** ACETAMINOPHEN), ***OR***
- Patient has signs or symptoms of hepatic injury regardless of acetaminophen level or time of ingestion, ***OR***
- Liver enzymes or serum acetaminophen levels are unavailable or will be delayed beyond 8 hours post ingestion, ***OR***
- There is a strong clinical suspicion of ≥ 30 g or ≥ 500 mg/kg of acetaminophen ingested, even prior to obtaining acetaminophen level, ***OR***
- Patient presents with early metabolic acidosis and coma following a massive overdose, even prior to obtaining acetaminophen level, ***OR***
- Following repeated supra-therapeutic ingestion (chronic excessive), in patients with either an AST or ALT that is abnormal or the serum acetaminophen level is greater than 132 µmol/L.

Most effective in preventing hepatotoxicity if treatment is initiated within 8 hours following an acute overdose, but is still effective if started later.
Improves outcome and decreases mortality even in patients presenting more than 24 hours post exposure with evidence of hepatic injury (even if acetaminophen level is low or non-detectable). In a series of 50 patients with acetaminophen-induced fulminant hepatic failure, survival was significantly higher in NAC-treated patients (48%) than in those receiving only supportive care (20%). NAC was initiated 36-80 hours after overdose and was continued until recovery or death.
For additional information regarding indications and risk assessment, **see** ACETAMINOPHEN**.**

Other Indications
NAC may reduce hepatic damage following exposure to **other toxins** or in **other types of non-acetaminophen-induced acute liver injury**. **See** IRON, MUSHROOMS-CORTINARIUS, MUSHROOMS-CYCLOPEPTIDES, AMPHETAMINES, VOLATILE OILS (pennyroyal, clove oil, citral).

Contraindications and Precautions
Caution in patients with a history of asthma or sensitivity to NAC; consider pretreatment with antihistamine; be prepared to treat anaphylactoid reactions OR consider oral administration (different dosing and schedule- **see** BELOW).

Skin flushing without pruritus or urticaria do not require treatment. If urticaria and/or pruritus occur, discontinue NAC and administer IV diphenhydramine. Once symptoms resolve, if NAC still indicated, restart at previous infusion rate. Closely monitor for systemic symptoms.

For angioedema, stridor, bronchospasm or hypotension: stop NAC and administer IM epinephrine, add nebulized epinephrine for stridor, nebulized beta-2 agonist for bronchospasm, and IV fluids for hypotension. One hour after resolution reassess the need for NAC. If NAC still indicated (based on risk/benefit) restart NAC at maintenance infusion rate of 15 mg/kg/hr. Closely monitor for recurrence of symptoms. If symptoms recur and ongoing need for NAC, consider changing to oral NAC administration (different dosing and schedule- **see** BELOW).

Use in Pregnancy

Acetaminophen and NAC cross the placenta. NAC has been administered to pregnant patients with acute acetaminophen overdose during the first, second and third trimesters with no apparent association with fetal abnormalities. NAC is indicated for potentially toxic acetaminophen overdose during any stage of pregnancy. Untreated acetaminophen toxicity or a delay in treatment in a pregnant patient can result in fetal death.

Adverse Effects

Neurologic: Massive IV NAC overdose can result in CNS toxicity and death. A 30-month-old child developed status epilepticus, intracranial hypertension and died following a massive NAC overdose of 2462 mg/kg infused over 7 hours (instead of 207.8 mg/kg). A 21-year-old developed delirium, seizures, cerebral edema and severe brain injury after receiving 100 mg/kg/**hr** IV NAC for more than 28 hours (instead of 100 mg/kg over 16 hours).
GI: Nausea and vomiting are common following oral administration.
GU: Hemolytic uremic syndrome reported in a patient who received a five-fold overdose of IV NAC.
Fluids/Lytes/Acid-Base: Dilutional hyponatremia and seizures have occurred in children after receiving IV NAC diluted in large volumes of D5W.
Blood: Clinically insignificant increase in INR within the first hour of administration, to less than 1.5 by 16 hours; rapidly returns to normal upon discontinuation.
INR greater than 2 and hemolysis have been reported following NAC overdose.
Other: *Non-allergic reactions:* Anaphylactoid reactions are likely due to dose-related (and route-related) stimulation of histamine release, rather than a true allergic response. In susceptible individuals, reactions usually occur during or shortly after the IV loading dose, particularly if infused rapidly. May be more common in patients with low serum acetaminophen levels. Rash, hives, flushing and pruritus are common. Angioedema, nausea/vomiting, tachycardia and hypotension occur infrequently. Severe reactions including respiratory arrest, cardiovascular collapse and death are rare. (see **Contraindications and Precautions** above for management). A prior anaphylactoid reaction to NAC is not a contraindication to receiving again.
Skin: see Other: *Non-allergic reactions.*
Lab: N-acetylcysteine (NAC) can interfere with some acetaminophen assays resulting in falsely low levels (greatest interference during loading dose). Clinically insignificant increase in INR may be seen within the first hour of NAC administration, stabilizing near 1.5 by 16 hours; rapidly returns to normal upon discontinuation.

Interactions

Activated Charcoal may delay absorption of *oral* NAC when given concurrently; likely not clinically significant. Does not interfere with IV NAC.

Administration and Dosage: One-concentration (1 or 2 bag), 2-Step (Dose)

Adult and Child Dose:
Step 1: Loading dose: 150 mg/kg over 60 minutes.
Step 2: Maintenance dose: 15 mg/kg/hour until discontinuation criteria are met.
Note: For patients > 100 kg, use a maximum weight of 100 kg (220 pounds) for dosing.

Administration:
Option 1 (1-concentration (**1-bag**)/2-step regimen): For institutions with programmable smart pumps (automatic switch from loading to maintenance infusion) and using single admixture preparation.

- 1-Bag: Prepare a single admixture of standard concentration of 30 mg/mL (3%) NAC in 250 mL, or 500 mL, or 1000 mL (depending on weight of patient, following your institution's guidelines) of D5W (preferred in adults), or ½ NS, or NS.
- **Step 1: Loading dose:** 150 mg/kg over 60 minutes
- **Step 2: Maintenance dose:** 15 mg/kg/hour for at least 20 hours or until discontinuation criteria are met.
- Note: For patients > 100 kg, use a maximum weight of 100 kg (220 pounds) for dosing.

Option 2 (1-concentration (**2-bag**)/2-step regimen): For institutions using separate admixture for loading dose and maintenance infusion.

- Bag 1: Prepare a single admixture of standard concentration of 30 mg/mL (3%) NAC in 100 mL, or 250 mL, or 500 mL (depending on weight of patient, following your institution's guidelines) of D5W (preferred in adults), or 1/2NS, or NS.
- Bag 2: Prepare a single admixture of standard concentration of 30 mg/mL (3%) NAC in 500 mL or 1000 mL (depending on weight of patient, following your institution's guidelines) of D5W (preferred in adults), or 1/2NS, or NS.
- **Step 1: Loading dose:** 150 mg/kg over 60 minutes. Discard remaining fluid in loading dose bag after infusion is complete.
- **Step 2: Maintenance dose:** 15 mg/kg/hour for at least 20 hours or until discontinuation criteria are met.
- Note: For patients > 100 kg, use a maximum weight of 100 kg (220 pounds) for dosing.

Preparation instructions (all methods/options):
Mixing in 100 mL bag D5W, or 1/2 NS, or NS:
Remove 15 mL from 100 mL bag
Add 15 mL of 20% IV NAC (200 mg/mL) to remaining 85 mL for final volume of 100 mL
Final concentration: 3.0 g NAC in 100 mL or 30 mg/mL (3%)

Mixing in 250 mL bag D5W (preferred in adults) or 1/2 NS or NS:
Remove 37.5 mL from 250 mL bag
Add 37.5 mL of 20% IV NAC (200 mg/mL) to remaining 212.5 mL for final volume of 250 mL
Final concentration: 7.5 g NAC in 250 mL or 30 mg/mL (3%)

Mixing in 500 mL bag D5W (preferred in adults) or 1/2 NS or NS:
Remove 75 mL from 500 mL bag
Add 75 mL of 20% IV NAC (200 mg/mL) to remaining 425 mL for final volume of 500 mL
Final concentration: 15 g NAC in 500 mL or 30 mg/mL (3%)

Mixing in 1000 mL bag D5W (preferred) or 1/2 NS or NS:
Remove 150 mL from 1000 mL bag
Add 150 mL of 20% IV NAC (200 mg/mL) to remaining 850 mL for final volume of 1000 mL
Final concentration: 30 g NAC in 1000 mL or 30 mg/mL (3%)

Dosage Adjustment:
Patient with massive ingestion, delayed presentation, or on hemodialysis or CRRT: NO dose adjustment is required.
***Patient weight > 100 kg (220 pounds)*:** A maximum weight of 100 kg (220 pounds) should be used for dosing calculations.
Renal or hepatic failure: No dose adjustment.

Oral NAC: If IV NAC cannot be used, ***oral NAC*** may be given. Oral loading dose is 140 mg/kg followed by oral maintenance doses of 70 mg/kg every 4 hours for 17 doses over 72 hours. Dilute IV NAC to a 5% concentration with juice, carbonated soft drink or water (i.e. 1 part 20% IV NAC: 3 parts juice). Contact poison centre for further information.

Discontinuation of NAC Therapy
At the end of the 21-hour infusion, N-acetylcysteine can be discontinued if:

- Serum acetaminophen level is less than 66 umol/L, **AND**
- AST and/or ALT is normal or declining (>25% decline from peak), **AND**
- INR is less than 2.0 and declining (without the influence of fresh frozen plasma), **AND**
- Patient is clinically well (no encephalopathy).
- Contact poison centre regarding discontinuation questions.

If these criteria are not met, then IV N-acetylcysteine should be continued at 15 mg/kg/hr and labs should be done every 12-24 hrs, until discontinuation criteria are met (**see** above).

Monitoring Parameters

- Near the end of the 21-hour infusion, the following lab tests should be repeated: serum acetaminophen level, AST, ALT, INR. For interpretation, **see** *Discontinuation of NAC Therapy.*
- If NAC is continued beyond 21-hour infusion, monitor acetaminophen level, AST, ALT, INR every 12-24 hours. For endpoint, **see** *Discontinuation of NAC Therapy.*

- *Note:* Clinically insignificant increase in INR may be seen within the first hour of NAC administration, stabilizing near 1.5 by 16 hours; rapidly returns to normal upon discontinuation. *Importance:* Do not confuse with liver toxicity of acetaminophen.
- Observe for hypersensitivity-like reactions, particularly during or shortly after the IV loading dose. For management, **see** *Adverse Effects: Other: Non-allergic reactions*.

Presentation
20% (200 mg/mL) sterile solution in 10 mL and 30 mL vials, designed for dilution before IV administration.