NCBI Bookshelf. A service of the National Library of Medicine, National Institutes of Health.

StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-.

N Acetylcysteine

Authors

Muhammed Ershad; Abdullah Naji[1]; David Vearrier[2].

Affiliations

[1] Western University of Health Sciences
[2] Drexel University College of Medicine

Last Update: June 27, 2022.

Continuing Education Activity

N-acetylcysteine (NAC) is the mainstay of therapy for acetaminophen toxicity. NAC has FDA approval for the treatment of potentially hepatotoxic doses of acetaminophen (APAP), and it is almost 100% effective if given within 8 hours post-ingestion. It is also approved for use in conditions with abnormal, viscid or inspissated mucous secretions such as pneumonia, bronchitis, tracheobronchitis, cystic fibrosis, tracheostomy patients, postoperative pulmonary complications, posttraumatic chest conditions and before diagnostic bronchoscopy to help with mucous plugging. Off-label indications include acute hepatic failure, prevention of contrast-induced nephropathy and topical treatment of keratoconjunctivitis sicca. This activity outlines the indications, mechanism of action, methods of administration, important adverse effects, contraindications, monitoring, and toxicity of NAC, so providers can direct patient therapy to optimal outcomes where NAC is indicated.

Objectives:

- Describe the mechanism of action of NAC in both acetaminophen toxicity and in conditions where mucolytic activity is beneficial.
- Review the indications for NAC use.
- Outline the administration of NAC in both APAP toxicity and in in lung conditions requiring mucolytic therapy.
- Summarize the importance of improving care coordination among the interprofessional team to enhance the delivery of care for patients who can benefit from therapy with NAC.

Access free multiple choice questions on this topic.

Indications

N-acetylcysteine (NAC) is the mainstay of therapy for acetaminophen toxicity. NAC has Federal and Drug Administration (FDA) approval for the treatment of potentially hepatotoxic doses of acetaminophen (APAP), and it is almost 100% effective if given within 8 hours post-ingestion.[1] It is also approved for use in conditions with abnormal, viscid or inspissated mucous secretions such as pneumonia, bronchitis, tracheobronchitis, cystic fibrosis, tracheostomy patients, postoperative pulmonary complications, posttraumatic chest conditions and before diagnostic bronchoscopy to help with mucous plugging. Off-label indications include acute hepatic failure, prevention of contrast-induced nephropathy, and topical treatment of keratoconjunctivitis sicca.

NAC has also been investigated for use in xenobiotics with free radical or reactive metabolite toxicity. There is good evidence to show it is of benefits in acute exposures to cyclopeptide containing mushrooms and carbon tetrachloride.[2] There are animal and human tissue studies showing its use in decreasing cisplatin-induced nephrotoxicity,[3]

although clinical evidence is minimal. NAC may also have therapeutic application in chronic valproate hepatotoxicity and acute pennyroyal or clove oil ingestion-induced hepatotoxicity[4][5]

Other potential applications, but still in the experimental stage, include NAC being used as an antineoplastic agent as well as for psychiatric conditions like schizophrenia, bipolar disorder, depression, gastrointestinal conditions like hepatorenal syndrome, Helicobacter *pylori* infections, necrotizing enterocolitis, critical care patients like lung injury, cardiac injury, multiorgan dysfunction, sepsis and hematological conditions like sickle cell disease.

There are case reports of NAC helping with improving neurological status in patients comatose with carbon monoxide poisoning.[6]

Mechanism of Action

NAC exerts its therapeutic effect in APAP overdose through several mechanisms. APAP metabolism in therapeutic dosing primarily occurs through glucuronidation and sulfation(>90%), with less than 5% being oxidized by CYP450 isoform (predominately CYP2E1) to produce a toxic metabolite called N-acetyl-p-benzoquinone imine (NAPQI), which is the precursor to cellular injury. Glutathione in the liver can normally detoxify these minuscule quantities of NAPQI and prevent tissue damage. In APAP overdose, glucuronidation and sulfation pathways are saturated, and the CYP450 pathway takes more significance, producing more toxic metabolites that deplete the glutathione reserves, leading to their accumulation and hence tissue injury by binding to cellular macromolecules.

NAC repletes glutathione reserves by providing cysteine, which is an essential precursor in glutathione production. NAC by itself also binds to the toxic metabolites and scavenges free radicals. It also increases oxygen delivery to tissues, increases mitochondrial ATP production, and alters the microvascular tone to increase the blood flow and oxygen delivery to the liver and other vital organs.

In COPD, cystic fibrosis, and other lung conditions, nebulized NAC has mucolytic, anti-inflammatory, and antioxidant properties. Studies are ongoing to understand its therapeutic efficacy, ideal dose ranges, and most effective mode of drug delivery for these indications.

Administration

The decision to give NAC in APAP overdose depends on the likelihood of hepatotoxicity in the patient. Assessment is by obtaining a thorough history, physical examination, and serum APAP and transaminase concentrations.

A detailed history including the quantity of APAP consumed is necessary. It is important to know whether consumption took place all at once or overtime. History of any other coingestants like anticholinergic medications or opioids that could cause a delayed absorption of APAP is also necessary, as is the presence of risk factors including malnutrition, alcoholism, or cirrhosis as these have associations with decreased glutathione reserves. Determination should also be made whether the APAP formulation taken is a regular or an extended-release preparation as the latter can cause a delayed peak serum concentration. Determination should also be made about the concurrent use of drugs that can induce CYP2E1 (for example, isoniazid and chronic alcohol consumption), which increases the risk of hepatotoxicity.

The Rumack-Mathew Nomogram is a useful tool to assess the risk of hepatotoxicity and hence the need for starting NAC in an acute single ingestion of APAP.[7]

If the time of ingestion of APAP is less than 4 hours, 4-hour levels of serum APAP are obtained and plotted on the nomogram. If it is above the treatment line, starting NAC should be the course of action. If it is below, the risk of hepatotoxicity is virtually nonexistent.

If the time of ingestion is between 4 and 24 hours and the time required to obtain serum APAP levels is less than 8 hours, one may wait for the APAP levels before deciding to start NAC. If the APAP levels reports are not obtainable until more than 8 hours have passed, NAC can be started empirically and stopped if the levels are below the treatment line.

If the dose ingested is unclear or if it's been more than 24 hours since ingestion, give the first dose of NAC and send APAP levels and transaminases levels. If APAP levels are more than 10 mg/L OR transaminases are elevated, NAC can be continued.

In chronic ingestion, NAC therapy should be initiated if APAP levels are more than 20 mg/L or transaminases are elevated. In pregnant women, there are no reports of fetal risk with starting NAC. Dosing for these patients can initiate according to similar protocols as in the general population.

NAC may be given either orally or intravenously with minimal differences in its effectiveness.[8] The commonest regimes used are 21-hour IV protocol and 72-hour oral dosing protocol. NAC should be started in patients at risk of hepatotoxicity and continued if hepatotoxicity develops. It may be stopped following the completion of the protocol or upon resolution of hepatotoxicity, whichever occurs last. Both oral and IV routes of administration are equally efficacious in preventing and treating APAP toxicity. The IV route has preference over the oral route in established hepatic failure and in patients who cannot tolerate oral NAC due to intractable vomiting or nausea.[9]

NAC is available as a 20% concentration in 30 ml vials that requires dilution before being given IV. Oral NAC is available in 10% and 20% vials of 10 ml each, which also requires dilution before administration.

The dosing schedule for the 21-hour IV protocol is as follows:

- Loading dose: 150mg/kg up to a maximum of 15 gm in 200 ml Dextrose 5% Water over 60 minutes.
- Second (maintenance) dose: 50mg/kg up to a maximum of 5 gm in 500 ml Dextrose 5% Water over 4 hours (12.5 mg/kg/hour).
- Third dose: 100mg/kg up to a maximum of 10 gm in 1000 ml Dextrose 5% Water over 16 hours (6.25 mg/kg/hour).

The dosing schedule for the 72-hour oral NAC protocol is as follows:

- 140 mg/kg loading dose orally.
- After 4 hours of the loading dose, 70 mg/kg should be given every 4 hours for an additional 17 doses, which is a total dose of 1330 mg/kg. The solution should be diluted to 5% and preferably mixed with a soft drink or juice to enhance palatability.
- Any vomited doses should be readministered.

NAC should be continued until APAP levels are undetectable, PT/INR is near normal, encephalopathy has resolved, and transaminases are normal or are down trending and AST < 1000 U/L. In the 21-hour IV protocol, the APAP levels and transaminases level testing should occur at 20 hours. The oral protocol requires checking at 24 hours. If APAP is undetectable and transaminase levels are normal, NAC can be discontinued at the end of the regime. If there is a detectable APAP level or AST is still elevated, restarting NAC at 6.25 mg/kg per hour (for IV protocol) or 70 mg/kg every four hours (for oral protocol) is the proper course. This can be continued until the patient returns to normal mental status and INR is below 2.0 or if the patient obtains a liver transplant.

Adverse Effects

Oral NAC may cause nausea, vomiting, diarrhea, flatus, and gastroesophageal reflux. IV NAC can cause rate related anaphylactoid reactions in up to 18% of patients,[10] which is not an issue with the oral route.

Most of the anaphylactoid reactions are mild (6%) or moderate (10%) with severe reactions like bronchospasm and hypotension rare at 1%. Interestingly, anaphylactoid reactions occur more commonly with lower APAP levels than with higher APAP levels.[11] One possible explanation is that APAP decreases the histamine release from mast cells and mononuclear cells, proportionate to the dose ingested. Bronchospasm more commonly occurs in patients with pre-existing reactive airway diseases, like asthma. Bronchodilating agents are effective in treating these patients.

When an anaphylactoid reaction occurs, NAC should be stopped immediately, and the patient treated with anti-histamine medication (e.g., diphenhydramine) and IV fluid for hypotension. Vasopressors are not typically necessary. NAC therapy may restart at a slower rate after the resolution of the reaction. If there is a persistent reaction, oral NAC should is the alternative approach.

IV NAC can cause a spurious increase in INR which normalizes once infusion stops.[12] It can also cause a false-positive result for urine ketones.[13]

Oral NAC may cause vomiting in up to 33%.[14] In patients with preexistent GI ulcers or varices, there can be concerns about inducing GI bleed with oral NAC.

Contraindications

In patients with a tendency to develop fluid overload (e.g., cardiomyopathy or congestive heart failure), the quantity of diluent fluid used in IV NAC needs to be appropriately titrated to prevent fluid overload. A pharmacist can perform this titration during the preparation of the NAC IV infusion.

Monitoring

During IV NAC administration, patients need to be monitored for manifestations of anaphylactoid reaction as described earlier.

Toxicity

Given its complicated regime, NAC has a high potential for iatrogenic errors, including overdose.[15] A 23-year-old female developed hemolysis, thrombocytopenia, metabolic acidosis and acute renal failure after NAC overdose. She erroneously received 100 gm instead of 10 gm of NAC. She then required daily hemodialysis but eventually died after developing hemolytic uremic syndrome.[16] Another case report describes a 20-year-old female, who developed hemolysis and elevated serum bilirubin. She improved with supportive measures, and her liver function tests and anemia improved within a few days.[17] Massive accidental NAC administration in the order of 100 mg/kg/hr had resulted in cerebral edema, seizures, uncal herniation, and permanent brain injury in another patient with APAP overdose.[18]

Enhancing Healthcare Team Outcomes

Managing APAP overdose with NAC requires an interprofessional team of healthcare professionals that includes the emergency physician, medical toxicologist, internist/hospitalist, nurses, pharmacists, and laboratory technologists. The decision to start NAC is usually made in the emergency department by the emergency physician in conjunction with the medical toxicologist. The preparation of NAC including calculating the dose of NAC required and the nature and quantity of the diluent should include consultation with a clinical pharmacist. The initial dose of NAC started in the ED/ICU, or floor requires close monitoring especially if given intravenously, to permit assessment for an anaphylactoid reaction which may require prompt intervention.

In patients with self-injurious APAP ingestions, once the patient has completed the course of NAC and is considered medically stable, consult with a mental health counselor or psychiatrist to assess the risk of further self-harm and the potential need for psychiatric admission.

Review Questions

- Access free multiple choice questions on this topic.
- Comment on this article.

References

1. Prescott LF, Illingworth RN, Critchley JA, Stewart MJ, Adam RD, Proudfoot AT. Intravenous N-acetylcystine: the treatment of choice for paracetamol poisoning. Br Med J. 1979 Nov 03;2(6198):1097-100. [PMC free article: PMC1597048] [PubMed: 519312]
2. Flanagan RJ, Meredith TJ. Use of N-acetylcysteine in clinical toxicology. Am J Med. 1991 Sep 30;91(3C):131S-139S. [PubMed: 1928204]
3. Nisar S, Feinfeld DA. N-acetylcysteine as salvage therapy in cisplatin nephrotoxicity. Ren Fail. 2002 Jul;24(4):529-33. [PubMed: 12212833]
4. Janes SE, Price CS, Thomas D. Essential oil poisoning: N-acetylcysteine for eugenol-induced hepatic failure and analysis of a national database. Eur J Pediatr. 2005 Aug;164(8):520-2. [PubMed: 15895251]
5. Said SA, El-Agamy DS. Prevention of sodium valproate-induced hepatotoxicity by curcumin, rosiglitazone and N-acetylcysteine in rats. Arzneimittelforschung. 2010;60(11):647-53. [PubMed: 21175036]
6. Howard RJ, Blake DR, Pall H, Williams A, Green ID. Allopurinol/N-acetylcysteine for carbon monoxide poisoning. Lancet. 1987 Sep 12;2(8559):628-9. [PubMed: 2887913]
7. Hodgman MJ, Garrard AR. A review of acetaminophen poisoning. Crit Care Clin. 2012 Oct;28(4):499-516. [PubMed: 22998987]
8. Green JL, Heard KJ, Reynolds KM, Albert D. Oral and Intravenous Acetylcysteine for Treatment of Acetaminophen Toxicity: A Systematic Review and Meta-analysis. West J Emerg Med. 2013 May;14(3):218-26. [PMC free article: PMC3656701] [PubMed: 23687539]
9. Keays R, Harrison PM, Wendon JA, Forbes A, Gove C, Alexander GJ, Williams R. Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. BMJ. 1991 Oct 26;303(6809):1026-9. [PMC free article: PMC1671790] [PubMed: 1954453]
10. Kerr F, Dawson A, Whyte IM, Buckley N, Murray L, Graudins A, Chan B, Trudinger B. The Australasian Clinical Toxicology Investigators Collaboration randomized trial of different loading infusion rates of N-acetylcysteine. Ann Emerg Med. 2005 Apr;45(4):402-8. [PubMed: 15795719]
11. Waring WS, Stephen AF, Robinson OD, Dow MA, Pettie JM. Lower incidence of anaphylactoid reactions to N-acetylcysteine in patients with high acetaminophen concentrations after overdose. Clin Toxicol (Phila). 2008 Jul;46(6):496-500. [PubMed: 18584360]
12. Jepsen S, Hansen AB. The influence of N-acetylcysteine on the measurement of prothrombin time and activated partial thromboplastin time in healthy subjects. Scand J Clin Lab Invest. 1994 Nov;54(7):543-7. [PubMed: 7863231]
13. Poon R, Hinberg I, Peterson RG. N-acetylcysteine causes false-positive ketone results with urinary dipsticks. Clin Chem. 1990 May;36(5):818-9. [PubMed: 2338001]
14. Yip L, Dart RC. A 20-hour treatment for acute acetaminophen overdose. N Engl J Med. 2003 Jun 12;348(24):2471-2. [PubMed: 12802041]
15. Hayes BD, Klein-Schwartz W, Doyon S. Frequency of medication errors with intravenous acetylcysteine for acetaminophen overdose. Ann Pharmacother. 2008 Jun;42(6):766-70. [PubMed: 18445707]
16. Mahmoudi GA, Astaraki P, Mohtashami AZ, Ahadi M. N-acetylcysteine overdose after acetaminophen

poisoning. Int Med Case Rep J. 2015;8:65-9. [PMC free article: PMC4354467] [PubMed: 25767408]

17. Srinivasan V, Corwin D, Verceles AC. An accidental overdose of N-acetylcysteine during treatment for acetaminophen toxicity. Clin Toxicol (Phila). 2015 Jun;53(5):500. [PubMed: 25881798]
18. Heard K, Schaeffer TH. Massive acetylcysteine overdose associated with cerebral edema and seizures. Clin Toxicol (Phila). 2011 Jun;49(5):423-5. [PubMed: 21740141]

Bookshelf ID: NBK537183 PMID: 30725868