



Monograph

N-acetylcysteine

Introduction

N-acetylcysteine (NAC) is the acetylated precursor of both the amino acid L-cysteine and reduced glutathione (GSH). Historically it has been used as a mucolytic agent in chronic respiratory illnesses as well as an antidote for hepatotoxicity due to acetaminophen overdose. More recently, animal and human studies of NAC have shown it to be a powerful antioxidant and a potential therapeutic agent in the treatment of cancer, heart disease, HIV infection, heavy metal toxicity, and other diseases characterized by free radical, oxidant damage. NAC has also been shown to be of some value in treating Sjogren's syndrome, smoking cessation, influenza, hepatitis C, and myoclonus epilepsy.

Chemistry and Pharmacokinetics

NAC is a sulfhydryl-containing compound that is rapidly absorbed into various tissues following an oral dose, is deacetylated and metabolized in the intestines and liver, and incorporated into disulfide protein peptides. Peak plasma levels of NAC occur approximately one hour after an oral dose and at 12 hours post-dose it is undetectable in plasma. Despite a relatively low bioavailability of only four to ten percent, oral administration of NAC appears to be clinically effective.¹ The biological activity of NAC is attributed to its sulfhydryl group, while its acetyl substituted amino group affords it protection against oxidative and metabolic processes.^{2,3}

Mechanisms of Action

NAC's effectiveness is primarily attributed to its ability to reduce extracellular cystine to cysteine, or to act intracellularly as a source of sulfhydryl groups. As a source of sulfhydryl groups, NAC stimulates glutathione (GSH) synthesis, enhances glutathione-S-transferase activity, promotes liver detoxification by inhibiting xenobiotic biotransformation, and is a powerful nucleophile capable of scavenging free radicals.^{4,5} NAC's effectiveness as a mucolytic agent results from its sulfhydryl group interacting with disulfide bonds in mucoprotein, with the mucus subsequently being broken into smaller, less viscous units. NAC may also act as an expectorant by stimulating both ciliary action and the gastro-pulmonary vagal reflex, thereby clearing the mucus from the airways.⁶ Studies have also shown NAC to be of benefit in heart disease by lowering homocysteine and lipoprotein(a) levels via dissociation of disulfide bonds,^{7,8} protecting against ischemic and reperfusion damage via replenishment of the glutathione redox system,⁹ as well as potentiating the activity of nitroglycerin.¹⁰

Clinical Indications

Respiratory Illness

Several animal and human studies have explored NAC's effectiveness as a therapeutic agent for various types of respiratory illness. While results varied, NAC administration resulted in decreased expectoration difficulty, cough severity,¹¹ and diaphragm fatigue.¹² A small study was conducted with 18 patients diagnosed with fibrosing alveolitis; a condition characterized by severe oxidative stress and decreased glutathione levels. NAC was administered at a dose of 600 mg three times daily for 12 weeks and improvement in both pulmonary function and glutathione levels was noted.¹³ In contrast, studies of patients with chronic bronchitis, severe airway obstruction, and cystic fibrosis showed a slight, although not statistically significant, decrease in the exacerbation rate.^{14,15}

HIV Infection

Human immunodeficiency virus (HIV)-positive individuals usually exhibit low GSH and cysteine levels, prompting studies on NAC's effectiveness as a therapeutic tool for these patients. Research suggests that NAC is capable of enhancing T cell immunity by stimulating T cell colony formation,¹⁶ and blocking NF kappa B expression.^{17,18} In a double-blind, placebo-controlled trial Akerlund et al found NAC to positively impact both plasma cysteine levels and CD4+ lymphocyte cell counts.¹⁹ More studies are needed but it appears that if given to HIV-positive patients early in the course of disease, NAC may help to prevent progression to AIDS.

Cancer/Chemoprevention

Research has shown NAC to have potential both as a chemopreventative agent and a treatment in certain types of cancer, including lung, skin, head and neck, mammary, and liver cancer.²⁰ *In vitro* studies have demonstrated NAC to be directly anti-mutagenic and anti-carcinogenic as well as inhibiting the mutagenicity of certain compounds *in vivo*.²¹ Research also indicates NAC administration in both cell cultures and animal studies selectively protects normal cells, but not malignant ones, from chemotherapy and radiation toxicity.²² Other *in vitro* studies noted NAC's effectiveness at inhibiting cell growth and proliferation in human melanoma, prostate, and astrocytoma cell lines.²³⁻²⁵

Acetaminophen and Other Poisonings

Historically the most prevalent and well-accepted use of NAC has been as an antidote for acetaminophen (Tylenol[®], paracetamol) poisoning. The resultant liver toxicity is due to an acetaminophen metabolite that depletes the hepatocytes of glutathione and causes hepatocellular damage and possibly even death. NAC administered intravenously or orally within 24 hours of overdose is effective at preventing liver toxicity; however, improvement is most notable if treatment is initiated within 8-10 hours of acetaminophen overdose. NAC's effectiveness declines when treatment is delayed beyond 10 hours and risk of mortality significantly increases.²⁶⁻²⁸ NAC has also been effective for heavy metal poisoning by gold, silver, copper, mercury, lead, and arsenic, as well as in cases of poisoning by carbon tetrachloride, acrylonitriles, halothane, paraquat, acetaldehyde, coumarin, and interferon.⁶ Studies involving these poisons are primarily animal studies or single case reports and therefore additional studies are needed to establish NAC's effectiveness in this area.

Heart Disease

Several small clinical studies have demonstrated that NAC may be an effective therapeutic agent in the management of heart disease. Wiklund et al demonstrated NAC's ability to reduce plasma homocysteine levels by 45 percent,⁸ while Gavish and Breslow demonstrated NAC (2-4 grams daily for eight weeks) was able to reduce lipoprotein(a) by 70 percent.⁷ Due to its ability to significantly increase tissue GSH, NAC may also be useful in treating the ischemia and reperfusion seen in acute myocardial infarction, and the resultant depletion in cellular sulfhydryl groups.⁹ In addition, NAC appears to potentiate nitroglycerin's coronary dilating and anti-platelet properties and therefore may be a useful combination therapy in-patients with unstable angina pectoris and myocardial infarction.^{29,30}

Other Clinical Indications

Clinical studies have also demonstrated NAC's therapeutic benefit in the treatment of Sjogren's syndrome,³¹ myoclonus epilepsy,³² influenza,³³ illness associated with cigarette smoking,³⁴ and hepatitis C.³⁵

Safety and Side-Effects

NAC is generally safe and well tolerated even at high doses. The most common side-effects associated with high oral doses are nausea, vomiting, and other gastrointestinal disturbances, and therefore oral administration is contraindicated in persons with active peptic ulcer. Infrequently, anaphylactic reactions due to histamine release occur and can consist of rash, pruritis, angioedema, bronchospasm, tachycardia and changes in blood pressure.⁶ Intravenous administration has, in rare instances, caused allergic reactions but they are generally in the form of rash or angioedema.³⁶ NAC is "Ames test" negative but animal studies on embryotoxicity are equivocal. In addition, studies in pregnant women are inadequate so NAC administration during pregnancy should be with caution and only if clearly indicated.³⁷ Oral administration of NAC and charcoal at the same time is not recommended, as charcoal may cause a reduction in the absorption of NAC.³⁸ In addition, as with any single antioxidant nutrient, NAC at therapeutic doses (even as low as 1.2 grams daily), has the potential to have pro-oxidant activity and is not recommended at these doses in the absence of significant oxidative stress.³⁹

Dosage

The typical oral dose for NAC as a mucolytic agent and for most other clinical indications is 600-1500 mg NAC daily in three divided doses. In patients with cancer or heart disease the therapeutic dosage is higher, usually in the range of two to four grams daily. For acetaminophen poisoning, NAC is usually administered orally with a loading dose of 140 mg/kg and 17 subsequent doses of 70 mg/kg every four hours. In acetaminophen poisoning, it is important to begin administering NAC within 8-10 hours of overdose to ensure effectiveness.⁶

References

1. Borgstrom L, Kagedal B, Paulsen O. Pharmacokinetics of N-acetylcysteine in man. *Eur J Clin Pharmacol* 1986;31:217-222.
2. Bonanomi L, Gazzaniga A. Toxicological, pharmacokinetic and metabolic studies on acetylcysteine. *Eur J Respir Dis* 1980;61:45-51.
3. Sjodin K, Nilsson E, Hallberg A, Tunek A. Metabolism of N-acetyl-L-cysteine. *Biochem Pharm* 1989;38:3981-3985.

4. De Vries N, De Flora S. N-Acetyl-L-Cysteine. *J Cell Biochem* 1993;17F:S270-S277.
5. De Flora S, Bennicelli C, Camoirano A, et al. In vivo effects of N-acetylcysteine on glutathione metabolism and on the biotransformation of carcinogenic and/or mutagenic compounds. *Carcinogenesis* 1985;6:1735-1745.
6. Zimet I. Acetylcysteine: A drug that is much more than a mucokinetic. *Biomed & Pharmacother* 1988;42:513-520.
7. Gavish D, Breslow JL. Lipoprotein(a) reduction by N-acetylcysteine. *Lancet* 1991;337:203-204.
8. Wiklund O, Fager G, Andersson A, et al. N-acetylcysteine treatment lowers plasma homocysteine but not serum lipoprotein(a) levels. *Atherosclerosis* 1996;119:99-106.
9. Ceconi C, Curello S, Cargnoni A, et al. The role of glutathione status in the protection against ischaemic and reperfusion damage: effects of N-acetyl cysteine. *J Mol Cell Cardiol* 1988;20:5-13.
10. Horowitz JD, Henry CA, Syrjanen ML, et al. Nitroglycerine/N-acetylcysteine in the management of unstable angina pectoris. *Eur Heart J* 1988;9:95-100.
11. Jackson IM, Barnes J, Cooksey P. Efficacy and tolerability of oral acetylcysteine (Fabrol) in chronic bronchitis: a double-blind placebo controlled study. *J Int Med Res* 1984;12:198-206.
12. Hida W, Shindo C, Satoh J, et al. N-acetylcysteine inhibits loss of diaphragm function in streptozotocin-treated rats. *Am J Respir Crit Care Med* 1996;153:1875-1879.
13. Behr J, Maier K, Degenkolb B, et al. Antioxidative and clinical effects of high-dose N-acetylcysteine in fibrosing alveolitis. Adjunctive therapy to maintenance immunosuppression. *Am J Respir Crit Care Med* 1997;156:1897-1901.
14. British Thoracic Society Research Committee. Oral N-acetylcysteine and exacerbation rates in patients with chronic bronchitis and severe airways obstructions. *Thorax* 1985;40:832-835.
15. Gotz M, Kraemer R, Kerrebijn KF, Popow C. Oral acetylcysteine in cystic fibrosis. A co-operative study. *Eur J Respir Dis* 1980;61:S122-S126.
16. Wu J, Levy M, Black PH. 2-Mercaptoethanol and n-acetylcysteine enhance T cell colony formation in AIDS and ARC. *Clin Exp Immunol* 1989;77:7-10.
17. Breithaupt TB, Vazquez A, Baez I, Eylar EH. The suppression of T cell function and NF(kappa)B expression by serine protease inhibitors is blocked by N-acetylcysteine. *Cell Immunol* 1996;173:1323-1329.
18. Droge W, Eck H-P, Mihm S. HIV-induced cysteine deficiency and T-cell dysfunction - a rationale for treatment with N-acetylcysteine. *Immun Today* 1992;13:211-214.
19. Akerlund B, Jarstrand C, Lindeke B, et al. Effect of N-acetylcysteine(NAC) treatment on HIV-1 infection: a double-blind placebo-controlled trial. *Eur J Clin Pharmacol* 1996;50:457-461.
20. De Flora S, Cesarone CF, Izzotti A, et al. N-acetylcysteine as antimutagen and anticarcinogen. *Toxicol Lett* 1992;53:Abstract W4/L2.
21. De Flora S, Rossi GA, De Flora A. Metabolic, desmutagenic and anticarcinogenic effects of N-acetylcysteine. *Respiration* 1986;50:S43-S49.
22. De Flora S, D' Agostini F, Masiello L, et al. Synergism between N-acetylcysteine and doxorubicin in the prevention of tumorigenicity and metastasis in murine models. *Int J Cancer* 1996;67:842-848.
23. Chiao JW, Chung F, Krzeminski J, et al. Modulation of growth of human prostate cancer cells by the N-acetylcysteine conjugate of phenethyl isothiocyanate. *Int J Oncol* 2000;16:1215-1219.
24. Redondo P, Badres E, Solano T, et al. Vascular endothelial growth factor (VEGF) and melanoma. N-acetylcysteine downregulates VEGF production in vitro. *Cytokine* 2000;12:374-378.
25. Arora-Kuruganti P, Lucchesi PA, Wurster RD. Proliferation of cultured human astrocytoma cells in response to an oxidant and antioxidant. *J Neurooncol* 1999;44:213-221.
26. Smilkstein MJ, Knapp GL, Kulig KW, Rumack BH. Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose. Analysis of the national multicenter study (1976 to 1985). *N Engl J Med* 1988;319:2557-2562.
27. Wang PH, Yang MJ, Lee WL, et al. Acetaminophen poisoning in late pregnancy. A case report. *J Reprod Med* 1997;42:367-371.
28. Perry HE, Shannon MW. Efficacy of oral versus intravenous N-acetylcysteine in acetaminophen overdose: results of an open-label, clinical trial. *J Pediatr* 1998;132:149-152.

29. Winniford MD, Kennedy PL, Wells PJ, Hillis LD. Potentiation of nitroglycerin-induced coronary dilatation by N-acetylcysteine. *Circulation* 1986;73:138-142.
30. Chirkov YY, Horowitz JD. N-Acetylcysteine potentiates nitroglycerin-induced reversal of platelet aggregation. *J Cardiovasc Pharmacol* 1996;28:375-380.
31. Walters MT, Rubin CE, Keightley SJ, Ward CD. A double-blind, cross-over, study of oral N-acetylcysteine in Sjogren's syndrome. *Scand J Rheumatol Suppl* 1986;61:253-258.
32. Hurd RW, Wilder BJ, Helveston WR, Uthman BM. Treatment of four siblings with progressive myoclonus epilepsy of the Unverricht-Lundborg type with N-acetylcysteine. *Neurology* 1996;47:1264-1268.
33. De Flora S, Grassi C, Carati L. Attenuation of influenza-like symptomatology and improvement of cell-mediated immunity with long-term N-acetylcysteine treatment. *Eur Respir J* 1997;10:1535-1541.
34. Rogers DF, Jeffery PK. Inhibition by oral N-acetylcysteine of cigarette smoke-induced "bronchitis" in the rat. *Exp Lung Res* 1986;10:267-283.
35. Beloqui O, Prieto J, Suarez M, et al. N-acetylcysteine enhances the response to interferon-alpha in chronic hepatitis C: a pilot study. *J Interferon Res* 1993;13:279-282.
36. Tenenbein M. Hypersensitivity-like reactions to N-acetylcysteine. *Vet Hum Toxicol* 1984;26:S3-S5.
37. Threlkeld DS, ed. *Drug Facts and Comparisons*. St Louis, Missouri: Facts and Comparisons;1997:1090-1094.
38. Klein-Schwartz W, Oderda GM. Adsorption of oral antidotes for acetaminophen poisoning (methionine and N-acetylcysteine) by activated charcoal. *Clin Toxicol* 1981;18:283-290.