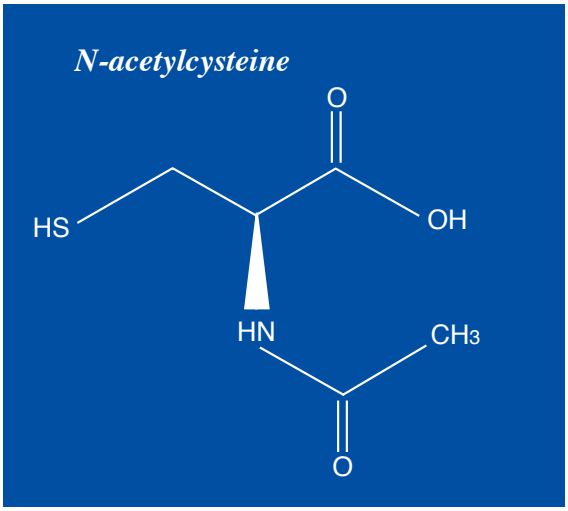

N-acetylcysteine

Introduction

N-acetylcysteine (NAC) is the acetylated derivative of the amino acid L-cysteine. Historically NAC 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 have shown NAC to be a powerful antioxidant and potential therapeutic agent in the treatment of cancer, heart disease, HIV infection, heavy metal toxicity, and other diseases characterized by oxidative damage. NAC has also been shown to be of value in Sjogren's syndrome, influenza, hepatitis C, and myoclonus epilepsy.

Biochemistry and Pharmacokinetics

NAC is a sulfhydryl-containing compound rapidly absorbed into various tissues following an oral dose, deacetylated and metabolized in the intestines and liver, and its metabolites incorporated into proteins and peptides. Peak plasma levels of NAC occur approximately one hour after an oral dose; at 12 hours post-dose it is undetectable in plasma. Despite a relatively low bioavailability of only 4-10 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] NAC administration is an effective method of increasing plasma glutathione (GSH) levels, as incorporation of cysteine into GSH appears to be the rate-limiting step in GSH synthesis.

Mechanisms of Action

NAC's effectiveness is primarily attributed to its ability to reduce extracellular cystine to cysteine, and as a source of sulfhydryl groups. NAC stimulates glutathione 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 mucoproteins, with mucus subsequently being broken into smaller, less viscous units.

NAC may also act as an expectorant by stimulating ciliary action and the gastro-pulmonary vagal reflex, thereby clearing 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 ischemia 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 vary, NAC administration has resulted in improved expectoration, with decreased cough severity[11] and diaphragm fatigue.[12] In a small study of 18 patients with fibrosing alveolitis – a condition characterized by severe oxidative stress and decreased glutathione levels – NAC 600 mg three times daily for 12 weeks resulted in improvement in pulmonary function and glutathione levels.[13] Studies of patients with chronic bronchitis, severe airway obstruction, and cystic fibrosis showed a slight, although not statistically significant, decrease in exacerbations.[14,15]

HIV Infection

Human immunodeficiency virus (HIV)-positive individuals usually exhibit low GSH and cysteine levels, which has prompted studies on NAC's effectiveness as a therapeutic tool for these patients. Research suggests 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, NAC positively impacted plasma cysteine levels and CD4+ lymphocyte cell counts.[19] More studies are needed, but it appears NAC may help prevent progression to AIDS when given to HIV-positive patients early in the course of disease.

Cancer/Chemoprevention

Research has shown NAC to have potential as a chemopreventive agent and as a treatment in certain types of cancer, including lung, skin, head and neck, breast, and liver cancer.[20] *In vitro* studies have demonstrated NAC to be directly anti-mutagenic and anti-carcinogenic. NAC also inhibits the mutagenicity of certain compounds *in vivo*.[21] NAC administration in cell cultures and animal studies selectively protects normal cells, but not malignant ones, from chemotherapy and radiation toxicity.[22] Other *in vitro* studies note NAC's inhibition of 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 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, at which time the 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] Information involving these substances is primarily from animal studies or single case reports; therefore, additional studies are needed to establish NAC's effectiveness in this area.

Viral Hepatitis

The standard therapy for chronic hepatitis C (CHC) involves the usage of interferon-alpha (IFN); however, many patients are either resistant to IFN therapy or they become resistant after a period of time. A pilot study found six-month NAC supplementation (600 mg three times daily) enhanced the response to IFN therapy in chronic hepatitis C patients resistant to IFN, with normalization of serum alanine aminotransferase (ALT) in 41 percent of patients.[29] In a subsequent study of 147 CHC patients, 1,800 mg per day NAC plus IFN for six months resulted in a small increase in sustained virological response – 5.5 percent versus 4.1 percent on IFN alone.[30] Significant improvements were seen in ALT, viral load, and redox balance in 77 patients on NAC plus IFN, compared to IFN alone, in a more recent study.[31]

Heart Disease

Several small clinical studies have demonstrated NAC may be an effective therapeutic agent in the management of heart disease. Wiklund et al found NAC reduced plasma homocysteine levels by 45 percent,[8] while Gavish and Breslow demonstrated NAC's (2-4 grams daily for eight weeks) ability to decrease lipoprotein(a) by 70 percent.[7] Due to its ability to significantly increase tissue GSH, NAC may also be useful in treating 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.[32,33]

Other Clinical Indications

Clinical studies have also demonstrated NAC's therapeutic benefit in the treatment of Sjogren's syndrome,[34] myoclonus epilepsy,[35] influenza,[36] and illness associated with cigarette smoking.[37]

Side Effects and Toxicity

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; 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 generally in the form of rash or angioedema.[38] NAC is "Ames test" negative, but animal studies on embryotoxicity are equivocal. In addition, studies in pregnant women are inadequate; therefore, NAC should be used with caution during pregnancy, and only if clearly indicated.[39] Oral administration of NAC and charcoal at the same time is not recommended, as charcoal may cause a reduction in the absorption of NAC.[40] 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.[41]

Dosage

The typical oral dose for NAC as a mucolytic agent and for most other clinical indications is 600-1,500 mg daily in three divided doses. In patients with cancer or heart disease the therapeutic dosage is higher, usually in the range of 2-4 grams daily. For acetaminophen poisoning, NAC is 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]

Warnings and Contraindications

NAC may have a protective effect on normal tissue in individuals utilizing many cancer chemotherapeutic agents;[42-47] however, two studies noted that NAC inhibits cytotoxicity of the cancer chemotherapy drug cisplatin,[48,49] and an animal study suggests NAC might reduce the anti-neoplastic action of doxorubicin. These combinations should be avoided unless further information recommends otherwise.[50]

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