



N-acetylcysteine: The multiuse antioxidant

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Abstract:

N-acetylcysteine is an acetylated L-cysteine amino acid, it is an effective antidote capable of enhancing cell defense against oxidative stress by restoring the diminished intracellular glutathione pool as an antioxidant, often depleted due to increased oxidative stress and inflammatory status. It has diminishing and antioxidant features, working as a direct ROS (reactive oxygen species) scavenger. NAC is used for various indications in different dosage forms. Other NAC applications have been shown by several studies, such as mucolytic action that is helpful in obstructive airways, diseases of nasal sinus as it liquefies bacterial biofilms (antibacterial action), decreases kidney disease caused by radio contrast, treatment by core pathways of many neuropsychiatric disorders such as Alzheimer's disease, bipolar disorder, major depressive disorder, obsessive compulsive disorder, schizophrenia, particular drug addictions (cocaine) and a certain type of epilepsy (progressive myoclonic) and enhanced fertility outcomes in both men and women.

Abbreviations: NAC (N-acetylcysteine), ROS (reactive oxygen species), COPD (chronic obstructive pulmonary disease), GSSG (oxidized glutathione), GSNO (S-nitrosoglutathione).

Key words: N-acetylcysteine, Reactive oxygen species, Biologic antioxidant, Glutathione.

Introduction:

N-acetylcysteine is a medication sometimes referred to as acetylcysteine that is used in peoples suffering from cystic fibrosis or chronic obstructive pulmonary disease (COPD) to loosen thick mucus and regulate the toxicity of paracetamol (acetaminophen). It can be administered orally, inhaled like a mist or intravenously. NAC is used by certain

people as a dietary supplement (1).

NAC was first discovered in 1960 and in 1968 it was approved for use. It is one of the potent and safe substances needed in the system of health and is a major drug on the list of the World

Health Organization. It is accessible as a generic drug and it is inexpensive (2).

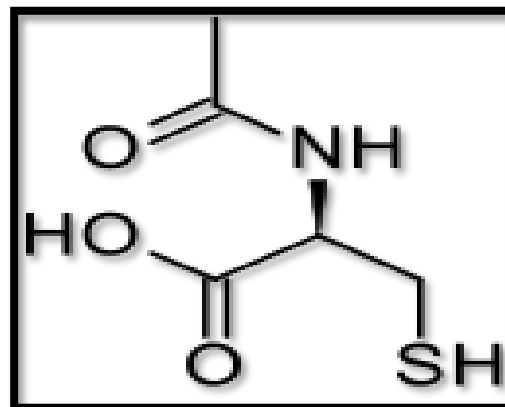


Figure (1): Chemical structure of NAC (2)

Dosage forms:

For different indications, NAC is available in various dosage forms: (8)

- Inhalation solution (Mucomyst, Mucosil, Assist) - used for mucolytic therapy).
- Intravenous (Parvolex, Acetadote, Assist) for paracetamol overdose.
- Oral solution.
- Effervescent tablets.
- Ocular solution.
- Capsules.
- Tablets or sustained release formula as a nutritional supplement.

Therapeutic uses:

1- Paracetamol overdose

For treatment of paracetamol toxicity, intravenous and oral acetylcysteine formulations are accessible.

N-acetyl - p-benzoquinone imine (NAPQI) accumulates inside the body

when paracetamol is taken in significant amounts. It is usually conjugated with glutathione, but glutathione stores in the body are not sufficient to inactivate the toxic amount of NAPQI when ingested at higher doses.

That metabolite is then able to react freely with the main liver enzymes, causing liver cell damage.

This can result in serious damage to the liver and even death from acute liver failure (9, 10).

A recent study recorded that when NAC is taken within 10 hours of overdose, the liver toxicity rate is about 3 % (8). In treatment of paracetamol overdose, NAC maintains or replenishes depleted glutathione reserves in liver and enhances non-toxic metabolism of acetaminophen. Such steps are used to protect the cells of liver from toxicity with NAPQI. When administered within 8-10 hours after overdose, it is most helpful in preventing or minimizing liver damage. (7, 8, 9).

There is low toleration of oral administration because high oral doses is ne-

eded due to decreased oral bioavailability, unpleasant odour and taste and adverse effects, particularly vomiting and nausea (7).

Oral NAC is similar to cysteine precursors in bioavailability.

However, a severe anaphylaxis like allergic reaction, involving intense breathing difficulty (due to bronchospasm), hypotension, rash, angioedema, nausea and vomiting is experienced by 3 to 6 percent of people given intravenous NAC (9, 11).

Anaphylaxis-like reaction mostly occur in persons given intravenous NAC despite serum levels of paracetamol may not so increased to be considered toxic (12, 13).

NAC functions as an antioxidant by preserving the reservoir of intracellular decreased glutathione, which is frequently depleted as a result of inflammation and increased oxidative stress.

In addition, NAC has antioxidant and reducing properties, acting as a direct scavenger of ROS.

It has been used as a chelator of heavy metal to

protect against oxidative stress and escape cell damage (14, 15, 16).

The metabolism of xenobiotics takes place in the liver to a large degree.

Sometimes, byproducts of that metabolism are more harmful than the original drug as NAPQI which is the toxic byproduct of paracetamol and more toxic than paracetamol itself leading to liver damage and the onset of liver diseases (17).

2- Mucolytic therapy

In addition to therapies for respiratory problems associated with excessive or thick mucus development, inhaled NAC is used for mucolytic therapy.

As a diagnostic aid and in tracheotomy treatment, NAC is used post-operatively and may be ineffective in cystic fibrosis (18).

3- Kidney disease

Some studies have shown that prior NAC administration decrease kidney disease caused by radio contrast, although others have found uncertain results (19).

4- Hemorrhagic cystitis

NAC is used for hemorrhagic cystitis caused by cyclophosphamide, other therapies are favoured due to NAC's ability to decrease the efficacy of Cyclophosphamide (20).

5- Psychiatry

For different mental conditions, NAC has been successfully tried as a therapy. There is clear evidence of NAC effectiveness in treatment of Alzheimer's disorder, schizophrenia, bipolar or major depressive disorder, obsessive-compulsive disorder, particular drug addictions (cocaine) and a specific type of epilepsy (progressive myoclonic) in a systematic analysis from 2015 and several earlier studies (6).

Via its regulation of dopamine and glutamate neurotransmission and its antioxidant effects, NAC has been hypothesized to exert beneficial effects (21).

6- Microbiological use

NAC can be used in the Petroff process of sputum liquefaction and decontamination in preparation for mycobacterium recovery. Important antiviral activity against influenza A viruses is also shown (22).

NAC has bactericidal capabilities and breaks down clinically important pathogens from bacterial biofilms including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Staphylococcus epidermidis*, *Enterococcus faecalis* and *Klebsiella pneumoniae* (23).

Additional uses

The advantages of NAC for fertility of men and women have been shown by

several studies. NAC has been shown to increase the quality of sperm in males. It has been shown to improve ovulation by 52 percent in women. Also, endometrial thickness increased substantially (24, 25).

Side effects:

Itching, rash and urticaria may be caused by NAC intravenous formulations. Anaphylaxis reactions, characterized by rash, wheezing, shortness of breath and/or hypotension, have been reported in up to 18 percent of patients. With slower rates of infusion, lower rates of anaphylactoid reactions have been recorded (26).

Nausea, vomiting, rhinorrhea, fever, sleepiness, stomatitis, clamminess, chest tightness and bronchoconstriction are the side effects of NAC inhalational formulations. Nausea, vomiting, fever and rash have been reported as adverse effects on oral NAC formulations (3, 26).

Conclusion:

N-acetyl cysteine is an important antioxidant with many uses and few side effects in several diseases, so further research should be conducted to test its effects against other oxidants and diseases.

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