***N*-acetylcysteine in clinical practice – properties, use and adverse effects**

N-acetylocysteina w praktyce klinicznej – właściwości, zastosowanie, działania niepożądane

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Abstract

N-acetylcysteine is a simple chemical compound with antioxidant and mucolytic properties. Currently, it is the primary treatment for acetaminophen poisoning. Prior to the introduction of acetylcysteine, acetaminophen overdose was associated with high mortality due to acute liver failure. Owing to its antioxidant properties, acetylcysteine maintains appropriate levels of glutathione, thereby protecting the liver from damage by toxic metabolites of paracetamol. Acetylcysteine is also used for infections with excess respiratory secretions. The mechanism of action of cysteine derivatives involves cleavage of disulfide bonds between the macromolecules present in the mucus and, consequently, reduction of mucus viscosity. Clinical trials have shown that *N*-acetylcysteine also plays an important role in relieving cough by eliminating mucus from the airways. Owing to its antioxidant properties, it can also prevent contrast-induced nephropathy. It was shown that prophylactic doses of acetylcysteine administered the day before and at the day of contrast administration are effective in preventing contrast-induced nephropathy in patients with chronic kidney disease. The compound can also modulate pathophysiological processes involved in many mental and neurological disorders. There is also evidence supporting the efficacy of acetylcysteine in mental disorders such as autism, schizophrenia, Alzheimer's disease, psychoactive substance dependence or bipolar disorder. However, in addition to its therapeutic activity, the drug may also induce adverse effects. Adverse effects of varying severity have been reported since the introduction of acetylcysteine into clinical use.

Keywords: *N*-acetylcysteine, acetaminophen poisoning, mucolytic properties, contrast-induced nephropathy, autism, antioxidant

Streszczenie

N-acetylocysteina to prosty związek organiczny o właściwościach przeciwutleniających i mukolitycznych. Obecnie jest podstawowym lekiem stosowanym w zatruciu paracetamolem. Przed wprowadzeniem acetylocysteiny przedawkowanie paracetamolu wiązało się z wysoką śmiertelnością z powodu ostrej niewydolności wątroby. Dzięki właściwościom przeciwutleniającym acetylocysteina chroni wątrobę przed uszkodzeniem toksycznymi metabolitami paracetamolu, utrzymując odpowiednie stężenie glutationu. Acetylocysteina znajduje zastosowanie również w infekcjach z towarzyszącym nadmiarem gęstej wydzieliny w drogach oddechowych. Mechanizm działania pochodnych cysteiny polega na rozszczepianiu mostków dwusiarczkowych między makrocząsteczkami obecnymi w śluzie, co prowadzi do zmniejszenia lepkości śluzu. Badania kliniczne wykazały, że *N*-acetylocysteina odgrywa ważną rolę w łagodzeniu kaszlu przez eliminację śluzu z dróg oddechowych. Dzięki swoim właściwościom antyoksydacyjnym może również zapobiegać rozwojowi nefropatii indukowanej kontrastem. Dowiedziono, że stosowanie profilaktycznych dawek acetylocysteiny dzień przed podaniem i w dniu podania środka kontrastowego jest skutecznym sposobem zapobiegania wystąpieniu nefropatii pokontrastowej u chorych z przewlekłą niewydolnością nerek. Związek ten może także modulować procesy patofizjologiczne, które biorą udział w wielu zaburzeniach psychicznych i neurologicznych. Opisano korzystne dowody skuteczności acetylocysteiny w zaburzeniach psychicznych, takich jak autyzm, schizofrenia, choroba Alzheimera, uzależnienia od środków psychoaktywnych czy choroba afektywna dwubiegunowa. Oprócz swojego działania leczniczego może również powodować działania niepożądane. Od czasu wprowadzenia acetylocysteiny do użytku klinicznego zgłaszano występowanie skutków ubocznych o różnym stopniu nasilenia.

Słowa kluczowe: *N*-acetylocysteina, zatrucie paracetamolem, właściwości mukolityczne, nefropatia pokontrastowa, autyzm, antyoksydant

INTRODUCTION

N-acetylcysteine (NAC) is a derivative of the endogenous amino acid L-cysteine and a precursor of glutathione – one of the most important antioxidants in the human body. It is known mainly for its antioxidant and mucolytic properties, used in the treatment of acetaminophen poisoning, contrast-induced nephropathy, and conditions accompanied by difficulty expectorating thick mucous⁽¹⁾. Some reports also indicate that acetylcysteine may be used in other fields of medicine, such as mental disorders and mental illnesses⁽²⁾. However, it should be noted that NAC may also cause adverse effects⁽³⁾.

N-ACETYL-CYSTEINE AND ACETAMINOPHEN POISONING

N-acetylcysteine is an organic compound used as an antidote for the treatment of acetaminophen poisoning⁽⁴⁾. Intoxication with this drug occurs most often as a result of deliberate overdosing of oral preparations (suicidal poisoning) or accidental ingestion, especially among children. Due to the strong hepatotoxic effect (the liver is the critical organ), acetaminophen poisoning is the most common cause of acute liver failure in North America, Europe and Australia^(5,6).

Acetylcysteine reverses the toxic effects of acetaminophen. It contains thiol groups (-SH), which may participate in redox reactions, and therefore has antioxidant properties. Combined with glutamic acid and glycine, it is essential for the synthesis of glutathione, one of the most important antioxidants in the human body, which protects against free radicals, toxins, and drug metabolites. Glutathione resources may be depleted in patients with malnutrition, chronic alcoholism, and after acetaminophen overdose⁽⁴⁾.

At therapeutic doses, the half-life of paracetamol is 1.5–2.5 hours. About 95% of the compound undergoes hepatic transformation through conjugation and reduction. Conjugation produces nontoxic sulfate/glucuronide conjugates. N-acetyl-*p*-benzoquinone imine (NAPQI), which is formed as an oxidation product, is a toxic metabolite of acetaminophen. If produced in limited amounts, NAPQI is then conjugated with the sulfhydryl groups of glutathione to form a nontoxic conjugate with mercapturic acid. However, in the case of overdose, glutathione stores are depleted and NAPQI covalently binds to liver cells, leading to their necrosis^(7,8). Restoring glutathione by acetylcysteine prevents hepatocyte damage⁽⁴⁾. Additionally, the thiol (-SH) groups in acetylcysteine can directly bind to toxic NAPQI in liver cells⁽⁹⁾.

Clinical trials have shown that administration of NAC within 10 hours of acetaminophen overdose effectively prevents liver damage.

NAC is available in an oral and intravenous form. Its dose is calculated based on body weight and estimated time from acetaminophen ingestion. The Rumack–Matthew nomogram, which defines serum acetaminophen vs. time after acetaminophen ingestion, is used to estimate the likelihood of hepatic injury⁽⁴⁾.

There are two approved protocols for the treatment of acetaminophen poisoning. Intravenous NAC regimen (modified Prescott protocol) involves three different doses and infusion times. The initial dose (150 mg/kg body weight) is administered over 1 hour and is immediately followed by the second infusion (50 mg/kg of body weight) given over the next 4 hours, and the third infusion (100 mg/kg body weight) administered over the next 16 hours. The total NAC dose is 300 mg/kg body weight⁽¹⁰⁾.

It is a common practice to continue acetylcysteine therapy longer than indicated in the IV protocol (20–21 hours) if serum acetaminophen levels are still high or liver function markers are abnormal⁽¹¹⁾.

Oral NAC protocol involves the administration of a loading dose (140 mg/kg body weight), followed by treatment continuation with a maintenance dose (70 mg/kg body weight) at 4-hour intervals. The total dose of NAC in the oral protocol is 1,330 mg/kg body weight given over 72 hours⁽¹⁰⁾.

Since the 1970s, acetylcysteine has been the mainstay of treatment for acetaminophen poisoning, and has dramatically decreased the incidence of and mortality due to acute liver failure⁽¹²⁾.

N-ACETYL-CYSTEINE AS A MUCOLYTIC AGENT

Excess mucous secretion in the airways is generally seen in respiratory diseases⁽¹³⁾. N-acetylcysteine and, to a lesser extent, carbocysteine are mucolytics that are commonly used to treat chronic obstructive pulmonary disease (COPD) and bronchitis⁽¹⁴⁾.

Mucolytic agents are a class of drugs that help clear mucus from the airways. Cysteine derivatives act by cleaving the disulphide bonds between macromolecules present in the mucus, thereby reducing its viscosity⁽¹⁵⁾.

In their review, Shen et al. showed that long-term use of high NAC doses may help reduce the incidence of exacerbations in patients with COPD⁽¹⁶⁾. It was also found in one study that oral NAC administered at 200 mg twice daily led to a change in sputum composition. Patients reported reduced sputum volume, easier expectoration and reduced cough severity. Data on the efficacy of NAC and carbocysteine in the paediatric population are limited⁽¹⁷⁾.

Observational studies have shown that mucolytics play an important role in alleviating upper respiratory symptoms by facilitating mucus elimination. They ensure symptomatic relief from cough and possibly reduce the duration of symptoms⁽¹⁸⁾.

In summary, owing to its chemical properties, NAC can change the composition or volume of sputum, effectively alleviating productive cough, which is a symptom of respiratory infections. Commonly available data from randomised, placebo-controlled and observational studies suggest the usefulness of mucolytics, such as NAC, in the treatment of the following upper and lower respiratory tract infections: paranasal sinusitis, rhinitis, bronchitis and bronchiectasis, and COPD⁽¹⁹⁾.

N-ACETYL-CYSTEINE AND CONTRAST-INDUCED NEPHROPATHY

In the era of increasingly commonly used diagnostic imaging and interventional procedures using contrast agents, contrast-induced nephropathy is becoming a significant clinical problem, which may lead to temporary or permanent renal replacement therapy, prolonged hospitalisation and even death. The incidence of contrast-induced nephropathy varies, ranging from 5% in patients with mild kidney disease to 50% in patients with severe renal failure⁽²⁰⁾.

In addition to baseline estimated glomerular filtration rate (eGFR), other risk factors for contrast-induced nephropathy include diabetes mellitus, co-administration of other nephrotoxic drugs (e.g. angiotensin converting enzyme inhibitors, ACEI), dehydration as well as the dose of contrast agent administered. There is growing evidence that reactive oxygen species play a key role in contrast-induced kidney damage⁽²¹⁾. Various pharmacological agents to prevent contrast-induced nephropathy have been investigated. N-acetylcysteine, which can prevent contrast-induced nephropathy owing to its antioxidant properties, is one of these agents⁽²⁰⁾. This was shown by Tepel et al., who assessed a group of patients with chronic renal failure who underwent contrast-enhanced computed tomography (CT). After randomisation, patients were given either 600 mg oral NAC twice daily or placebo the day before the imaging and on the day of CT. Contrast-induced nephropathy occurred in 21% of patients on placebo and 2% of patients who received NAC⁽²¹⁾. The authors showed that prophylactic administration of acetylcysteine at a dose of 600 mg twice daily the day before and the day of contrast agent administration is an effective method of preventing contrast-induced nephropathy in patients with chronic kidney disease.

N-ACETYL-CYSTEINE IN PSYCHIATRY

In recent years, growing evidence has emerged for the efficacy of NAC in psychiatry. Preclinical trials suggest that NAC can modulate pathophysiological processes involved in multiple mental and neurological disorders, including oxidative stress, neurogenesis and apoptosis, mitochondrial dysfunction as well as glutamatergic and dopaminergic neurotransmission. Evidence supporting the use of NAC in

mental disorders such as autism, schizophrenia, Alzheimer's disease, addiction to psychoactive substances or bipolar disorder has been described⁽²⁾.

The use of NAC in psychiatry may become a new approach in the treatment of many mental and neurological disorders. Additionally, NAC appears to be well tolerated and safe. However, specific data are still limited in terms of the number and quality of studies. Further analyses are needed to clarify which of the mechanisms of action of NAC is most effective in the treatment of mental illnesses and disorders.

ADVERSE EFFECTS

In addition to its therapeutic activity, NAC may also induce adverse effects. Adverse effects of varying severity have been reported since the introduction of acetylcysteine into clinical use. These include nausea and vomiting, hot flushes, rash, angioedema, tachycardia, hypotension, and bronchospasm. Systemic hypersensitivity reactions are the most common complications of intravenous acetylcysteine, while vomiting and nausea are the most common complications of the oral form. Adverse effects are believed to be dependent on serum NAC levels, infusion rate and treatment duration. Higher rates of adverse effects have been reported in females and patients with a family history of allergy or asthma^(3,10).

Conflict of interest

Authors do not report any financial or personal connections with other persons or organisations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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