Special reviews

The Use of N-Acetylcysteine in Intensive Care

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ABSTRACT

Objective: *To review the actions and clinical use of serum N-acetylcysteine in the critically ill patient.*

Data sources: *A review of articles published on the mechanisms of action and clinical use of N-acetylcysteine.*

Summary of review: *N-acetylcysteine (NAC) is an amino acid with a MW of 163.2. It acts as an antioxidant, both directly as a glutathione substitute and indirectly as a precursor for glutathione. It also causes vasodilation by increasing cyclic guanosine monophosphate levels, inhibits platelet aggregation, acts as a sulphydryl donor to regenerate endothelial-derived relaxing factor and reduces IL-8 and TNF-α production.*

While there is evidence for its effectiveness as an antidote to paracetamol poisoning, its use in other disorders has only experimental or anecdotal support. For example, in hepatic failure, there are few studies in man showing improved outcome following NAC therapy. There is also conflicting evidence for the use of NAC in sepsis or ARDS and while there is some evidence to suggest that NAC may be of benefit in acute myocardial infarction, the patient numbers are small. It may also be of use in ameliorating nitrate tolerance. It is also possible that NAC may confer benefit in reducing the risks of radiographic contrast nephropathy, although the study suggesting this was probably insufficiently powered to review all patient subsets (e.g. diabetics). N-acetylcysteine would also appear to enhance T cell function in HIV infected patients. However, the use of NAC for immunomodulation in HIV patients has not yet undergone prospective randomised controlled trials and therefore cannot be recommended as routine therapy in HIV infected, or other immune deficient, patients. There is currently insufficient evidence to propose NAC for the treatment of carbon monoxide poisoning.

Whilst there is experimental evidence for a variety of novel roles for NAC, further clinical studies are required before it can be recommended for the routine management of any disorders other than that of paracetamol poisoning.

Conclusions: *N-acetylcysteine has antioxidant properties that may be useful in many clinical conditions. Currently, however, it can only be recommended as therapy for paracetamol poisoning, in all other disorders it is still under evaluation.* (**Critical Care and Resuscitation 2002; 4: 21-27**)

Key words: N-acetylcysteine, sepsis, paracetamol poisoning, ARDS, acute coronary syndromes, carbon monoxide poisoning, HIV

N-acetylcysteine (NAC) is an amino acid with a molecular weight of 163.2 and, as with cysteine, was first used in clinical medicine in the 1960s as a mucolytic agent in aerosolised formulations.[1] Its more widespread use followed as an antidote to paracetamol poisoning, following the commercial availability of a 20% intravenous solution. Its efficacy seemed to hinge on its ability to replenish hepatic glutathione stores,

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conferring antioxidant activity. Additionally, the thiol moieties conferred direct antioxidant properties. These two mechanisms have resulted in much research into the potential benefits, which NAC could potentially confer in disorders caused by oxidative stress.

As other effects of NAC have been found, including vasodilation due to an increase in cyclic guanosine monophosphate levels, platelet aggregation inhibition, sulphydryl group donation to regenerate endothelial-derived relaxing factor and reduction in IL-8 and TNF-α production, other clinical uses have also been suggested.[2] This article explores some of these effects and the evidence for its use in clinical practice.

INDICATIONS

Mucolytic activity

The use of substances rich in cysteine for the treatment of lung conditions first occurred in ancient China with the use of compounds containing hair derivatives. Further developments led to the use of cysteine in Western medicine for suppurative lung conditions. Difficulties in administration led to the use of NAC being used in its aerosolized form for disorders of mucokinesis and subsequently bronchitis, bronchiectasis and other similar conditions.[2]

However, the 5-10% solutions of NAC initially formulated were hyperosmolar, causing secondary bronchorrhoea with a resulting increase in mucokine-sis. Moreover, the side effect of bronchospasm was also being reported, which was patient, dose, and frequency dependent. Subsequently, trials of oral preparations in Europe[3] and South America were performed which proved effective in reducing the exacerbation rate in patients with stable chronic bronchitis without the respiratory side effects noted with the aerosolized form.

Paracetamol toxicity

Paracetamol was first synthesised in the 19th century. However, its widespread clinical use did not occur until after the 1940s when its analgesic and antipyretic effects were noted. Its increasing use led to an increas-ing frequency of overdose, manifested by hepatic failure and renal dysfunction, the severity of which seemed largely dependent on dose and plasma concen-tration.

Paracetamol mostly undergoes type 2 metabolism in the liver (i.e. conjugation) with 60% excreted as the glucuronide, 35% as the sulphate and a small proportion (1% - 5%) is metabolised to an amino-benzoquinone derivative which is then dependent upon thiol conjugat-ion for excretion (Figure 1). Under normal circum-stances this requires the donation of a thiol group from glutathione. When large amounts of paracetamol are ingested, the hepatic glutathione stores are exhausted, and the benzoquinone derivative cannot be conjugated. This moiety then covalently binds to cell microsomes, resulting in hepatocellular and renal tubular damage.

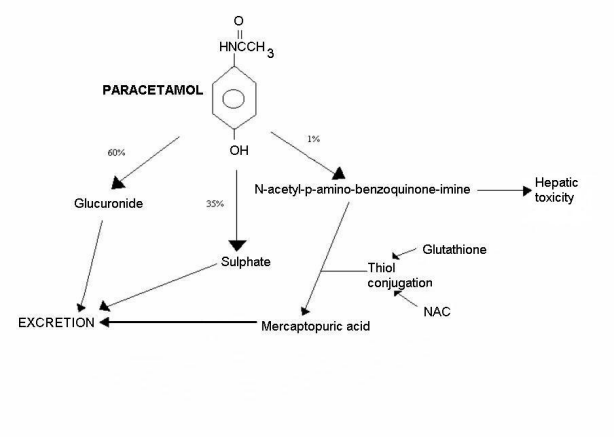

Figure 1. Metabolism of paracetamol.

The elucidation of paracetamol metabolism led to the proposal of using sulphydryl donors to prevent hepatocellular damage.[4] Prescott *et al*, described the use of cysteamine in 5 patients as a paracetamol antidote, who subsequently had a favourable outcome.[5] Patients were initially treated if serum paracetamol levels were greater than 300 mg/L at 4 hr post-ingestion, as levels higher than this had historically been observed to be associated with a poor outcome. Because of few side-effects and successful outcome in the first 2 cases, the treatment level was arbitrarily reduced to a serum paracetamol level of 250 mg/L.

Cysteamine was available as a freeze-dried powder requiring reconstitution, and had a limited shelf-life. In 1979, an 20% solution of NAC became available, and in observational studies, Prescott *et al*, reported NAC as an effective antidote in early paracetamol poisoning (i.e. when treated within 10 hr of ingestion).[6] It appeared to be more effective than cysteamine or methionine or best 'supportive' therapy when compared with historical data.[7] However, when NAC was given more than 10 hours post-ingestion, there were no differences in transaminase levels, bilirubin, or maximum INR compared with control patients, although groups were not necessarily compatible (e.g. alcohol intakes were different).

Paracetamol-induced organ damage is largely dose-dependent. However, a toxic dose may be modified by enzyme inducing agents. For example, chronic barbit-urate or ethyl alcohol ingestion induces hepatic cytochrome P 450 enzymes, resulting in lower paracet-amol doses needed to cause damage. Acute alcohol intake, paradoxically, may have an opposite effect and may afford some protection against hepatic damage.

Whilst Prescott *et al*, showed no benefit when NAC

was commenced after 10 hours (with a linear increase in those sustaining severe liver damage with increasing time from ingestion to NAC therapy), Keays *et al*,[8] suggested beneficial effects of NAC when given to patients in fulminant hepatic failure secondary to paracetamol. In an unblinded prospective study, patients admitted to a specialist liver unit more than 48 hr post overdose were allocated to receive supportive intensive care unit care (ICU) with NAC or ICU care with 5% dextrose. Forty eight per cent of those receiving NAC survived compared with 20% of controls. Harrison *et al*,[9] also suggested a lower incidence of cerebral oedema in the NAC group, though this was diagnosed on clinical grounds alone, which may not necessarily correlate with increased intracranial pressure. Both of these studies involved small numbers, and the work has not been repeated in the form of a large, prospective, randomised controlled trial.

Currently, treatment usually utilises a nomogram based on plasma paracetamol level versus time (Figure 2). As paracetamol levels may be represented by first-order kinetics, the plasma level can be characterised by an exponential decay curve with a formulae of 399 x $e^{(-0.1725x\ hr)}$ mg/L (or 2660 x $e^{(-0.1725x\ hr)}$ μmol/L).

If the blood paracetamol level is above the 'treatment' line of 200 mg/L (1300 μmol/L) or greater at 4 hr, 100 mg/L (660 μmol/L) or greater at 8 h, 50 mg/L (330 μmol/L) or greater at 12 hr, or 30 mg/L (200 μmol/L) or greater at 15 hr, then NAC is administered at 150 mg/kg (10 g/70 kg or 50 mL of a 20% solution) over 15 mins, followed by 50 mg/kg (3 g/70 kg or 15 mL of a 20% solution) over 4 hr, and completed with 100 mg/kg (7 g/70 kg or 35 mL of a 20% solution) over 16 hr. If the patient has been taking hepatic P_{450} mixed-function oxidase inducing drugs (e.g. chronic ethanol or barbiturate ingestion), or if glutathione depletion exists (e.g. malnutrition) or following starvation (which reduces paracetamol conjugation with glucuronide), then the plasma paracetamol level at which treatment with NAC is considered is halved

As has been suggested above, the treatment regime has been constructed from observational data, based on few cases. However, since many patients have subsequently been treated successfully, it is unlikely the use of NAC for paracetamol poisoning will be subjected to prospective randomised trials unless an alternative antidote, which is as cheap and devoid of side effects as NAC, is suggested.

Hepatic failure

Apart from the beneficial effect of NAC in paracetamol toxicity, few studies have reviewed the use of NAC in hepatic failure. Fernando *et al*,[10] studied the effects of partial portal vein occlusion in the rat. This resulted in a hyperdynamic circulation (i.e. an increased cardiac output and decreased systemic vascular resistance). They assessed oxidative stress by measuring the urinary prostaglandin derivative, isoprostone, which was increased six-fold in rats with portal vein ligation compared with controls. Treatment with NAC inhibited the rise in urinary isoprostone. Similar studies have not been carried out in man.

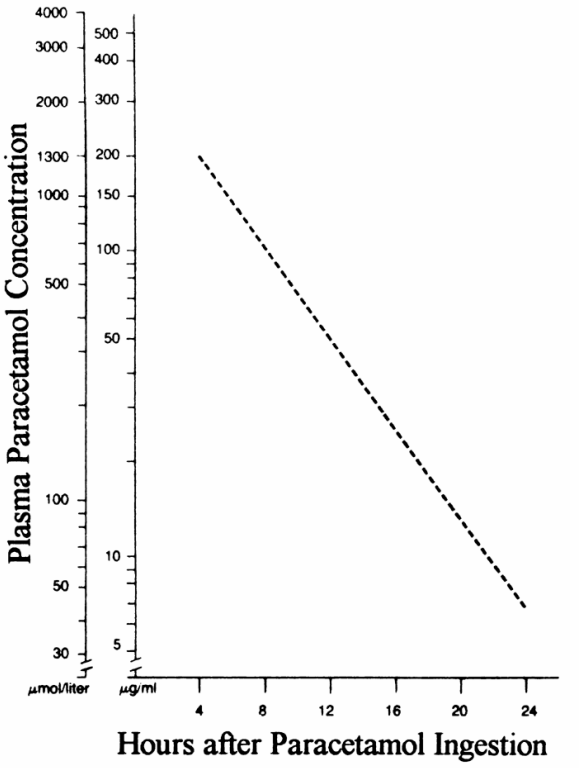

Figure 2. Plasma paracetamol 'treatment line' with values above the line requiring treatment with N-acetylcysteine.

Bromley et al,[11] reported the effects of NAC infusion during elective orthotopic liver transplantation. In this study there was no improvement in outcome with respect to morbidity, mortality or graft function. The King's group, headed by Harrison studied oxygen transport in fulminant hepatic failure.[12] The patients studied had not been previously exposed to NAC, and more than 15 hours had elapsed prior to commencing NAC infusion. They showed an increase in cardiac index, oxygen delivery and oxygen consumption. However, invasive pressure monitoring would suggest the patients were under-resuscitated prior to the NAC infusion (e.g. mean pulmonary capillary wedge pressure was 11mmHg). As NAC is hypertonic, it exerts an osmotic effect which may have increased the plasma volume and explained the improved cardiac index that was observed. As the oxygen delivery and oxygen

consumption data were measured using thermodilution cardiac output, and oxygen content measured from arterial and mixed venous blood, the conclusions may have been flawed due to the problem of mathematical coupling. To exclude this problem, Walsh *et al*,[13] measured oxygen consumption via spirometry in a similar group of patients and failed to demonstrate any improvement in oxygen delivery indices. However, in a case series of 11 patients[14] and in one case report of a pregnant patient[15] all of whom developed fulminant hepatic failure from mushroom poisoning (*Amanita phylloides*), NAC appeared to offer some benefit.

N-acetylcysteine has also been used to reduce the hepatotoxicity associated with chloroform, carbon tetrachloride and potassium permanganate.[16]

Acute lung injury and sepsis

Despite the theoretical antioxidant properties of NAC and the potential role of free radicals and oxidative stress in the pathogenesis of sepsis syndrome or acute lung injury, several studies have shown a disappointing lack of efficacy.

While Suter *et al*,[17] reported an enhanced recovery for patients with acute lung injury when treated with NAC, with a lower but not statistically significant mortality, shorter ventilation time, and increased oxygenation index; in a prospective randomised, controlled trial,[18] the same group studied NAC versus placebo in acute respiratory distress syndrome (ARDS) and found no significant difference between groups in terms of mortality (the rate was actually higher in the NAC group), oxygenation, ventilatory support, or length of unit stay.

In a prospective double blind randomised controlled trial of NAC or procysteine (an agent which is chemically very similar to NAC) versus placebo in patients with ARDS, Bernard *et al*,[19] found no difference in mortality, but did find lower acute lung injury scores in both of the treatment groups compared with the control group.

In a small double-blind randomised, controlled trial, Peake *et al*,[20] studied NAC in patients diagnosed with sepsis where the diagnosis had been made within the previous 24 hr. Following a 2 hr cardiovascular stabilisation period, patients received either NAC or 5% dextrose for 48 hr. Those receiving NAC had lower cardiac index and lower left ventricular stroke work index compared with placebo. In addition, 90% in the NAC group died, versus 50% in placebo group, though this was not statistically significant.

Spapen, *et al*,[1] in another small study of septic shock patients, suggested a shorter ventilator-dependent period and shorter ICU stay with NAC, although patients treated with NAC had a higher oxygenation index at the start of the study. Studying multi-organ failure patients, Agusti and colleagues,[21] reported the effects of NAC on haemodynamic and oxygenation indices following a randomised cross-over trial involving 10 subjects. They found an increased cardiac index and lower systemic vascular resistance with NAC. Oxygen delivery and consumption, as well as lactate were unchanged, and gastric intramucosal pH actually fell. They concluded that there were no beneficial effects of NAC.

All of these studies recruited small numbers of patients and tend to adopt the same dosage regime as that used in paracetamol poisoning (i.e. 150mg/kg over 15 min, followed by 50mg/kg over 4 hr, then 100 mg/kg over 16 hr)

Acute coronary syndromes

When perfusion is restored to ischaemic tissues, there exists a state of oxidative stress following the accumulation of toxic metabolites of anaerobic respiration. This involves the production of free radicals with strong oxidative properties, such as hydrogen peroxide and superoxide anions, which can injure tissues (e.g. cell wall lipid peroxidation). The restoration of perfusion can thus paradoxically have detrimental effects on tissues.

In the case of myocardial reperfusion, this can be evident with further ECG changes, arrhythmias, wall motion abnormalities and even enhanced cell necrosis.[22-24] NAC, with its antioxidant potential may reduce the incidence of such adverse events.

In a small study,[25] the addition of NAC was compared with the standard treatment of glyceryl-trinitate and streptokinase, in patients presenting with acute myocardial infarction (AMI). Using echocardio-graphy, cardiac index was significantly better in the NAC group. Larger studies have not been performed to confirm this finding and NAC does not feature in most treatment protocols used for patients with AMI. Sajokowsa *et al*,[26] found fewer polymorpho-nuclear infiltrates and lower, but not significant, cardiac plama hydroperoxide levels in AMI patients when treated with NAC.

NAC has also been suggested to reverse the tolerance of nitrates.[27-29] It is postulated that nitrates act by providing a precursor for nitric oxide which stimulates soluble guanylate cyclase resulting in vasodilatation.

This vasodilatation decreases with time when nitrates are given by prolonged infusion. The administration of NAC would appear to reverse the tolerance and enhance the degree of vasodilation for a given dose of nitrate. N-acetylcysteine has also been used to reduce the cardiotoxicity of doxorubicin.[16]

Renal failure

Acute renal failure can be the outcome of many physiological insults, including hypoperfusion (e.g. aortic aneurysm surgery), rhabdomyolysis, drug side-effects (e.g. non-steroidal anti-inflammatory drugs). Radiographic contrast media have also been implicated in the development of acute renal failure, particularly ionic iodinated contrast media. The incidence is higher in patients who have pre-existing renal disease, diabetes and hypovolaemia.

In a recent study of 83 patients with chronic renal insufficiency, the use of NAC as a protective agent was evaluated.[30] The patients had a mean serum creatinine of 216 μmol/L prior to being given non-ionic contrast for an elective thoracic or abdominal computerised tomogram. Patients were randomised to receive either oral NAC 600 mg, or placebo on the day prior to, and on the day of the computerised tomogram. Additionally, all patients received an intravenous infusion of 0.45% saline at 1 mL/kg/hour and were encouraged to take oral fluids *ad libitum*. In this study, 10 patients had a rise in serum creatinine; of these, 9 were in the placebo group. The mean serum creatinine rose from 212 to 226 μmol/L in the placebo group, and fell from 220 to 186 μmol/L in the NAC group. However, the standard errors of the groups were very large, and given the large disparity in creatinine at the start of the study, the study was of insufficient power to substantiate the authors conclusion that NAC may have a protective role in contrast-induced renal failure.

It has also been suggested that NAC ameliorates ischaemia/reperfusion renal injury by decreasing the induction of kinases coded by c-fos and c-jun in a rat experimental model.[31]

N-acetylcysteine has also been used to reduce haemorrhagic cystitis associated with ifosfamide and cyclophosphamide metabolites.[16]

Immune insufficiency

Glutathione has been implicated in the proliferation of T cells, in the differentiation of T and B cells, and in cytotoxic T cell and natural killer cell activity. Glutathione levels are reduced in the plasma, lung epithelium and T cells in human immunodeficiency virus (HIV) infection. Also, CD_4 and CD_8 cell sub-populations (normally rich in glutathione) are reduced in HIV patients, even when the patients are clinically well.[32] Administration of NAC improves T cell glutathione levels, though whether this improves function or outcome has not yet been elucidated, although one study has shown improved natural killer (NK) and T cell activities.[33] It has also been observed that glutathione levels decrease when inflammatory cytokine levels rise in conditions such as ARDS and multiple sclerosis.

Whilst administration of NAC to ARDS patients has resulted in little observed benefit in respiratory function or mortality, NAC significantly improves T cell function in vitro in samples from cancer patients.[34]

Carbon monoxide poisoning

Poisoning with carbon monoxide (CO) involves two distinct mechanisms. Firstly, there is mitochondrial hypoxia due to direct inhibition of cytochrome oxidase (cytochrome a3) in the mitochondrial respiratory chain. This is worsened by the high affinity of CO for haemoglobin (240 times that of oxygen), preventing O_2 from binding to haemoglobin, and thus reaching the tissues. When the exposure to CO is removed and oxygen therapy instituted, there is then secondary oxidative damage to cellular components.

Treatment for carbon monoxide poisoning classically consists of removing exposure to further CO and giving 100% oxygen to help displace CO from haemoglobin. Additionally, some advocate the use of hyperbaric oxygen therapy on the grounds that O_2 at 3 atmospheres results in sufficient oxygen dissolving in plasma to obviate the need for haemoglobin oxygen transport. There is little evidence to support this therapy over standard oxygen regimes.

In a single case report,[35] a 35 year old man exposed to CO, with an unresolving coma (5 days post-insult), was treated with NAC and allopurinol (a xanthine oxidase inhibitor) to reduce the oxidative damage. Eight hours after staring an infusion of NAC the patient spontaneously opened his eyes and tracked movements appropriately, and proceeded to make a full recovery. No larger studies have been performed.

SIDE-EFFECTS

As with any drug, NAC is not devoid of side-effects and adverse reactions. Given its high osmolality, prolonged therapy of high doses may result in osmolar effects such as confusion and disturbances in fluid and electrolyte balances. However, most adverse reactions seem to be anaphylactoid in nature, with a reported incidence of approximately 3%. This may be falsely elevated, and adverse reactions compared with sales figures of NAC shortly after its release in 1979 would put the incidence nearer 0.2%.[36]

The most common adverse events are urticarial rash and pruritis, but approximately 10% of those affected will develop bronchospasm and/or hypotension. As with all anaphylactoid or anaphylactic reactions, serious respiratory or cardiovascular effects can occur in the absence of any skin manifestations.

Treatment involves removing the causative agent, basic 'ABC' manoeuvres such as oxygen therapy, maintaining the airway and fluid therapy, as well as

administration of adrenaline, given either intramuscularly (1:1000) or intravenously (1:10 000 – 1:100 000). When giving intravenous adrenaline, ECG monitoring is obligatory. The use of corticosteroids (e.g. intra-venous hydrocortisone), antihistamines and broncho-dilators such as salbutamol, may also be considered.

Blood samples for serum tryptase and histamine, as well as urinary histamine degradation products (e.g. methylhistamine) can be taken after treatment has commenced and improvement noted. These may be performed at intervals from 1 to 24 hr after the start of the event to confirm the anaphylactic nature. Further skin testing may also be warranted.[37]

CONCLUSION

N-acetylcysteine potentially has many clinical uses in the intensive care patient. For example, it has been used to reduce the risk of hepatotoxicity associated with paracetamol, chloroform, carbon tetrachloride and potassium permanganate, nephrotoxicity caused by radiographic contrast agents, cardiotoxicity associated with doxorubicin therapy, neurological sequelae of carbon monoxide poisoning, haemorrhagic cystitis associated with ifosfamide and cyclophosphamide, as well as treatment of hepatic failure, sepsis, ARDS, acute coronary syndromes, reactivation of vascular responsiveness to glyceryl trinitrate and immunotherapy for HIV infection.

Whilst there are many patients who have been successfully treated with NAC for paracetamol poisoning (its efficacy is best if given within 10 hours after paracetamol ingestion), good data to support its use in other disorders are lacking.

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