Pharmacology, Formulations, and Adverse Effects

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21.1 Introduction

Besides understanding the effectiveness of N-Acetylcysteine (NAC) for the treatment of disease and the positive effect on physiological systems, other considerations of NAC are important, including the pharmacology, formulations, and adverse effects of NAC. This chapter will review these important aspects of NAC.

21.2 Methods

A systematic online literature search was performed to identify all clinical trials using NAC using the filters "human" and "clinical trials." From these the author reviewer screened titles and abstracts of all potentially relevant publications and high-quality studies were selected which discussed the pharmacology, formulations and adverse effects of NAC.

21.3 Pharmacological Studies of NAC

Studies have shown that a single oral dose of 200 mg NAC increased endogenous levels of NAC about 20-fold (Gabard and Mascher 1991). One study investigated the pharmacokinetics of three oral doses of NAC, 200, 600, and 1200 mg, in healthy individuals. Although the maximal plasma concentration increased with dose, the 200 mg dose was significantly lower than the 600 and 1200 mg dose, but the 600 and 1200 mg doses were not statistically significantly different from each other (Borgstrom and Kagedal 1990). There was no difference in the pharmacokinetic parameters if 600 mg NAC was given once or twice a day (Borgstrom and Kagedal

1990). Sustained-release oral NAC was compared between 600 mg and 1200 mg. Dose-related increases in plasma concentrations were observed; a doubling of the dose resulted in a doubling of the area under the curve without a change in clearance (Nolin et al. 2010). One study compared intravenous (IV) NAC 200 mg and oral 400 mg, finding that the half-life was 5.6 h with IV NAC and 6.3 h with oral NAC. Oral bioavailability of total NAC was 9.1% (Olsson et al. 1988).

Changes in pharmacokinetics have been studied in some specific physiological conditions. One study demonstrated that chronic liver disease altered the pharmacokinetics of IV NAC. The area under the curve was increased by 50%, and clearance was decreased by about 30% in patients with biopsy-proven cirrhosis as compared to healthy patients (Jones et al. 1997). NAC clearance was reduced by 90% in end-stage renal disease (ESRD) patients (Nolin et al. 2010). Another study demonstrated that dialysis increased clearance by over 400% (Soldini et al. 2005). In premature neonates the plasma clearance and volume of distribution of IV NAC correlated with weight and gestational age (Ahola et al. 1999). Vigorous cycling exercise reduced the whole-body clearance of IV NAC by about 25% (Brown et al. 2004).

Lastly, clinical studies have demonstrated that NAC can be administered with antibiotics amoxicillin, cefadroxil, cefpodoxime, doxycycline, erythromycin, loracarbef, and thiamphenicol without significant change in concentration (Barkworth et al. 1991; Kees et al. 1996; Roller et al. 1992).

21.4 NAC formulations

The best known NAC formulation in the United States (US), Mucomyst™ (or the generic version thereof), is available as a 10% or 20% solution of NAC sodium salt that is typically administered orally for treatment of acetaminophen (APAP) overdose. Since Mucomyst™ has a strong, disagreeable flavor, it is usually mixed with fruit juice or a soft drink before consumption. Still, as many physicians can attest, patients commonly find it very difficult to tolerate orally, thereby requiring administration via nasogastric tube. Mucomyst™ is also administered IV in some settings, particularly when patients are unconscious or unable to retain the orally administered drug.

To overcome problems with oral administration, European manufacturers produce NAC in pill and capsule formulations. It is also produced and packaged in a variety of effervescent formulations ("fizzy tabs") that can be dissolved in water, juice, or carbonated drinks to create a pleasant tasting, readily tolerated beverage. Formulations produced under European Good Manufacturing Practice (GMP) standards are designed to minimize NAC oxidation to its dimeric form ("di-NAC"), which is pharmacologically active at very low concentrations with immunologic effects opposite to those of NAC (Sandstrom et al. 1998). In general, di-NAC constitutes less than 0.1% of the European GMP NAC formulations, which are intended for oral administration and have qualified for health insurance reimbursement (Grandjean et al. 2000).

Several US nutraceutical dealers manufacture and sell unbuffered (acidic) NAC. Since the Food and Drug Administration (FDA) does not tightly regulate the production and packaging of nutraceutical products in the United States, neither the

content nor the purity of the NAC formulations currently produced and marketed in the US can be reliably judged. Manufacturing methods for these NAC preparations may not prevent formation of NAC by-products (e.g., di-NAC) and may not have been validated for stability during storage. The authors are concerned that some of the variability in clinical trials is due to the formulation of NAC as many non-GMP products have been used in various clinical trials (e.g., Weisbord et al., 2018).

21.5 Potential Adverse Effects of NAC

NAC is the clinically accepted cysteine source used to treat GSH deficiency due to APAP overdose and can be administered by IV, enteral, and rectal routes. Oral NAC dosages for APAP overdose start with a loading dose of 140 mg/kg body weight followed by doses of 70 mg/kg body weight administered every 4 h over a period of 3 days (Miller and Rumack 1983). Smaller dosages (600 mg to 8 g daily) have been administered for substantially longer periods in many clinical trials.

Although NAC has been administered orally at quite high dosages, little if any toxicity has been associated with NAC ingestion. In one study with a particular high long-term NAC dosage (an average of 6.9 g/day administered in three to four divided doses) administered to 60 HIV-infected subjects for 8 weeks and to over 50 subjects for up to 6 months in an open-label continuation, no adverse events (AEs) requiring physician intervention were observed (Herzenberg et al. 1997). Current evidence suggests that 600–900 mg/day, the common daily dosage in Europe for cough and cold relief, may be a reasonable maximum dose for healthy individuals who wish to routinely take NAC.

21.5.1 Symptomatic Adverse Effects

21.5.1.1 Gastrointestinal Discomfort

In another study of patients being treated for APAP overdose, the incidence of emesis from 33 to 51%, and diarrhea from 0 to 44% with treatment of 30 g of oral NAC daily for 3 days with the incidence of these AEs proportional to the total dose given (Miller and Rumack 1983). In one study that used high doses of oral NAC, gastric distress was not infrequently reported similar to that reported elsewhere (De Rosa et al. 2000; Herzenberg et al. 1997). However, half of these subjects were in the placebo arm, suggesting that the distress was related to ingestion of the excipient that may have contained significant amounts of lactose. Thus, gastrointestinal AEs are not uncommon with NAC treatment, particularly with high oral doses of NAC, but could be related to the additives or vehicle in which the NAC is formulated.

21.5.1.2 Headache

NAC has been shown to potentiate nitroglycerin-induced headache in two studies, one in healthy volunteers (Iversen 1992) and one study in patients with unstable angina

(Ardissino et al. 1997). In the former study, it was suggested that the headache was caused by prolonged dilation of the temporal artery (Iversen 1992).

21.5.1.3 Allergic Reaction

There are several reports of anaphylactoid and allergic responses in response to IV NAC (Schmidt and Dalhoff 1999; Walton et al. 1979; Vale and Wheeler 1982; Flanagan and Meredith 1991; Bonfiglio et al. 1992; Stavem 1997; Bailey and McGuigan 1998; Huitema et al. 1998; Bateman et al. 1984). These AEs may in part be explained by findings from preclinical studies demonstrating inflammatory-type responses in animals treated with the oxidized (di-NAC) form of NAC (Sandstrom et al. 1998) which can contaminate NAC preparations that have not been protected against oxidation. In any event, the anaphylactoid reactions to IV NAC are easily treated (Bailey and McGuigan 1998).

21.5.1.4 Delirium

In a large open-label study of patients undergoing liver resection, NAC did not change the incidence of AEs or liver failure but was associated with a higher incidence of delirium (2.7 and 9.8%), resulting in early trial termination. A multivariate analysis suggested an association between NAC and postoperative complications (Grendar et al. 2016).

21.5.2 Adverse Physiological Effects

21.5.2.1 Renal Function

Although dozens of studies demonstrate that NAC improves or at least does not worsen indices of kidney function in populations with various disorders and studies performed on healthy humans demonstrate that it improves kidney function (Hoffmann et al. 2004), there is one study that suggests that NAC worsened a measure of proximal tubular damage. In a small study of patients undergoing tourniquet-induced ischemia during knee arthroplasty, NAC was found to be associated with an increase in the urine N-acetyl-beta-D-glucosaminidase to creatinine ratio at reperfusion suggesting an increase in proximal tubular damage with NAC treatment (Laisalmi-Kokki et al. 2009).

21.5.2.2 Coagulation

In a triple-blind trial high-dose study, intracoronary NAC did not reduce the level of platelet activation biomarkers in patients undergoing percutaneous coronary intervention (Eshraghi et al. 2016). However, NAC was associated with decreased prothrombin time and adenosine diphosphate-induced platelet aggregation in patients undergoing abdominal aortic reconstruction (Niemi et al. 2006), and in a large cardiac surgery study, IV NAC resulted in increased chest tube blood loss and a greater transfusion volume (Wijeysundera et al. 2009). However, several other studies in which NAC was used in surgery have not reported increased bleeding, blood loss, or need for transfusion.

21.5.2.3 Hypotension

In patients with severe drug-resistant unstable angina pectoris, 5 g IV NAC reduced the incidence of acute myocardial infarction but increased the incidence of symptomatic hypotension when added to IV nitroglycerin in a small study (Horowitz et al. 1988). In rodent studies, NAC significantly reduced the pressor effect of angiotensin and reduced angiotensin converting enzyme activity (Boesgaard et al. 1993).

21.5.2.4 Hepatic Protein Catabolism

Caution may be indicated concerning the routine consumption of NAC and other sulfur-containing amino acid (SAA) precursors in the absence of diseases or conditions leading to cysteine/GSH deficiency, particularly in the American populations in which the intake of animal protein tends to be high and individuals may be ingesting two to three times the recommended daily allowance for SAAs on a daily basis.

However, recent observational studies showing that colonic hydrogen sulfide production increases in proportion to consumption of animal protein raises questions (Magee et al. 2000). Since the long-term effects of SAAs are not known, it is important to consider this in individuals with high animal protein intake.

In a small controlled study, NAC was found to reduce amino acid loss and increased urea nitrogen release from the liver graft. These findings are believed to signal increased net protein catabolism in the liver, possibly suggesting increase of the energy and oxygen demand of the liver, potentially putting the liver under increased metabolic stress because of increased amino acid metabolism (Taut et al. 2001).

21.5.2.5 Endothelial Damage

Although several studies suggest that NAC improves endothelial function (Scholze et al. 2004; Sahin et al. 2007; Wittstock et al. 2009; Swarnalatha et al. 2010), a medium-sized randomized placebo-controlled trial in the intensive care unit of patient with organ dysfunction in severe clinical sepsis found that NAC treatment was associated with worsening of the cardiovascular sequential organ failure assessment score, leading the authors to conclude that NAC did not attenuate endothelial damage in this specific patient population (Spapen et al. 2005).

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