

Commentary

***N*-acetylcysteine in clinical sepsis: a difficult marriage**

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Related to *Research* by Emet *et al.*, see page 292

Abstract

The high morbidity and mortality of severe sepsis and septic shock fosters a continuous search for novel therapies that go beyond pure correction of oxygenation and hemodynamics. Within this scope, *N*-acetylcysteine shows great promise. Beside proven anti-oxidant, anti-inflammatory and cyto-protective effects, *N*-acetylcysteine does also ensure endothelial protection and enhances micro-vascular blood flow. Studies that put these highly favourable properties to the clinical test remain scarce but are definitely needed to determine whether *N*-acetylcysteine has a place in our therapeutic armamentarium against sepsis.

Keywords *N*-acetylcysteine, organ failure, oxidative stress, sepsis

Lipid peroxidation of cell membranes stands out as an important mechanism underlying endothelial cell damage, myocardial dysfunction and organ failure during severe sepsis and septic shock. Injurious oxidation originates from sepsis-induced hyperproduction of reactive oxygen species that overwhelm and exhaust endogenous antioxidant (e.g. intracellular glutathione) defence mechanisms [1]. Hence, adding antioxidants to standard treatment holds evident promise for controlling organ failure in sepsis.

N-acetylcysteine (NAC) is one of the most extensively studied antioxidants. NAC is a safe drug with a wide toxic–therapeutic window, as documented by years of clinical experience in patients with liver failure due to paracetamol overdose [2]. Many potentially beneficial and protective effects of NAC have been demonstrated in experimental endotoxic and septic conditions. As a thiol-containing compound, NAC scavenges free oxygen radicals and replenishes depleted body glutathione stores. NAC also suppresses the activation of neutrophils and macrophages [3], attenuates leukocyte–endothelial cell adhesion and capillary leakage [4], and blocks the release of tumour necrosis factor alpha and IL-8, probably by modulating gene expression of these mediators at the transcriptional level [5].

Only few clinical trials have investigated NAC as an adjuvant treatment in human sepsis. In this context, the study of Emet and colleagues is welcomed. These authors found that early infusion of NAC in severe septic patients did not affect cytokine levels, gastric intramucosal pH, oxygenation/haemodynamic variables and outcome [6]. The results of this ‘negative’ clinical trial are in line with those of a recently published study in animals. Vassilev and colleagues administered NAC (150 mg/kg bolus, followed by 20 mg/kg per hour for 11 hours) after 12 hours of endotoxaemia in volume-resuscitated pigs. NAC significantly elevated glutathione concentrations but failed to improve gas exchange, metabolism and any systemic, pulmonary or hepatosplanchnic parameter [7]. The reason(s) why these investigators failed to reproduce or confirm the more favourable results from previous animal and human studies are not easily clarified. Nevertheless, the timing and dosing of the NAC infusion appear to be of vital importance.

Most of the animal data were obtained in pretreatment or early post-treatment studies. In that way, they are of limited relevance to the clinical setting. Clinical studies produced controversial results. NAC treatment during the first hours of severe clinical sepsis and septic shock decreased peroxidative

stress [8], enhanced cardiac output and tissue oxygenation [9], and improved hepatic function [10] and respiratory function [11]. Delayed administration, however, failed to improve tissue oxygenation [12] and adversely affected survival in critically ill patients with established organ failure [13].

The dose of NAC in sepsis is based upon the administration protocol in patients treated for paracetamol poisoning. However, the rationale for using this dose in critically ill septic patients has never been questioned or challenged. A significant increase in cardiac output along with a systemic vasodilatation is commonly described when a high dose of NAC is infused over a short period [9,10]. These haemodynamic changes appear to be short lived, however, and they probably merely reflect the volume effect and the high plasma concentrations that are obtained after administration of the 150 mg/kg bolus dose [14]. Of more concern is the worsening of organ failure, and particularly cardiovascular failure, that has been described when NAC infusion was continued beyond 24 hours. Peake and colleagues demonstrated that administration of NAC in septic shock caused depression of cardiovascular performance, as indicated by a decrease in the cardiac output and the mean arterial pressure [15]. This finding was corroborated by Molnar and colleagues, who observed a higher need for inotropic support in a cohort of critically ill patients treated with NAC for longer than 24 hours [13].

Many issues regarding the use of NAC in septic patients have received remarkably poor attention or remain unresolved. The pharmacokinetics and pharmacodynamics of the drug are virtually unknown. It remains to be determined whether and how NAC influences basic cellular processes such as bacterial clearance, neutrophil–endothelial cell interplay and apoptosis. Finally, more information is needed about possible drug interactions and toxic effects of NAC or its metabolites.

In summary, as indicated by the study of Emet and colleagues [6], any clinical benefit of NAC in sepsis remains to be proven. The timing and dosing of NAC in relation with onset, evolution and probably even severity of sepsis seem to be crucial determinants of its *in vivo* activity. Surviving sepsis requires rapid and sustained haemodynamic stabilisation and containment of organ failure. Any drug that does not attain or even jeopardises these goals should be avoided. We definitely need a large trial using well-defined endpoints to consider the real value of NAC as an adjuvant treatment in sepsis.

Competing interests

None declared.

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