1: Free Radic Res. 2009 Jul;43(7):691-6.

Potentially detrimental effects of N-acetylcysteine on renal function in knee arthroplasty.

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Ischaemia/reperfusion induces systemic inflammation and oxidative stress and thereby remote organ injury in the kidney. In a double-blind, placebo-controlled clinical trial of 30 patients undergoing knee arthroplasty with tourniquet, this study evaluated the effect of N-acetylcysteine (NAC) infusion on renal function by measuring urine alpha-1-microglobulin, N-acetyl-beta-D-glucosaminidase (NAG), glutathione-S-transferase-alpha and -phi and serum creatinine and cystatin C concentrations up to 24 h post-operatively. Compared to the baseline, urine alpha-1-microglobulin/creatinine increased in both groups and was higher in the NAC group than in the placebo group at tourniquet deflation and at 3 h thereafter. Urine NAG/creatinine increased at deflation and at 3 h thereafter in the NAC group and the ratio was higher than in the placebo group. The two sensitive indicators of proximal tubular damage and function used in the present study suggest that use of NAC in clinical setting of ischaemia/reperfusion injury may increase the risk of remote kidney injury.

PMID: 19526394 [PubMed - indexed for MEDLINE

Crit Care Med. 2009 Jun;37(6):1929-34.

N-acetylcysteine is associated with increased blood loss and blood product utilization during cardiac surgery.

Wijeysundera DN, **Karkouti K**, **Rao V**, **Granton JT**, **Chan CT**, **Raban R**, **Carroll J**, **Poonawala H**, **Beattie WS**.

Clin Toxicol (Phila). 2009 Feb;47(2):81-8.

Adverse reactions associated with acetylcysteine.

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INTRODUCTION: Paracetamol (acetaminophen) is one of the most common agents deliberately ingested in self-poisoning episodes and a leading cause of acute liver failure in the western world. Acetylcysteine is widely acknowledged as the antidote of choice for paracetamol poisoning, but its use is not without risk. Adverse reactions, often leading to treatment delay, are frequently associated with both intravenous and oral acetylcysteine and are a common source of concern among treating physicians. METHODS: A systematic literature review investigating the incidence, clinical features, and mechanisms of adverse effects associated with acetylcysteine. RESULTS: A variety of adverse reactions to acetylcysteine have been described ranging from nausea to death, most of the latter due to incorrect dosing. The pattern of reactions differs with oral and intravenous dosing, but reported frequency is at least as high with oral as intravenous. The reactions to the intravenous preparation result in similar clinical features to true anaphylaxis, including rash, pruritus, angioedema, bronchospasm, and rarely hypotension, but are caused by nonimmunological mechanisms. The precise nature of this reaction remains unclear. Histamine now seems to be an important mediator of the response, and there is evidence of variability in patient susceptibility, with females, and those with a history of asthma or atopy

are particularly susceptible. Quantity of paracetamol ingestion, measured through serum paracetamol concentration, is also important as higher paracetamol concentrations protect patients against anaphylactoid effects. Most anaphylactoid reactions occur at the start of acetylcysteine treatment when concentrations are highest. Acetylcysteine also affects clotting factor activity, and this affects the interpretation of minor disturbances in the International Normalized Ratio in the context of paracetamol overdose. CONCLUSION: This review discusses the incidence, clinical features, underlying pathophysiological mechanisms, and treatment of adverse reactions to acetylcysteine and identifies particular "at-risk" patient groups. Given the commonality of adverse reactions associated with acetylcysteine, it is important to ensure that any adverse event does not preclude patients from receiving maximal hepatic protection, particularly in the context of significant paracetamol ingestion. Further work on mechanisms should allow specific therapies to be developed.

PMID: 19280424 [PubMed - indexed for MEDLINE]

Emerg Med J. 2002 Nov;19(6):594-5.

Fatal anaphylactoid reaction to N-acetylcysteine: caution in patients with asthma.

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Paracetamol overdose is a common reason for presentation to the emergency department and N-acetylcysteine is frequently used in the treatment of toxic paracetamol ingestions. Adverse reactions to N-acetylcysteine are common though usually mild and easily treated. Serious reactions to N-acetylcysteine however, are rare and there have been no previous reported fatalities with its therapeutic use. This report describes the case of a 40 year old brittle asthmatic patient who died after treatment with intravenous N-acetylcysteine. Asthma is a risk factor for adverse reactions to N-acetylcysteine and special caution should be exercised in its use in brittle asthmatic patients.

PMID: 12421803 [PubMed - indexed for MEDLINE]

Clin Toxicol (Phila). 2008 Nov;46(9):921

Cardiac arrest following therapeutic administration of N-acetylcysteine for paracetamol overdose.

Cassidy N, **Tracey JA**, **Drew SA**.

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Tidsskr Nor Laegeforen. 1997 May 30;117(14):2038-9.

[Anaphylactic reaction to N-acetylcysteine after poisoning with paracetamol]

[Article in Norwegian]

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Paracetamol is among the most common substances consumed in self-poisoning attempts. The recommended treatment is intravenous N-acetylcysteine. Adverse reactions to this treatment are relatively common, but are rarely serious. The article reports and discusses a patient who had an anaphylactoid reaction to N-acetylcysteine after an overdose of paracetamol. This reaction was most probably an acute toxic effect of N-acetylcysteine, and not a result of an immunologic hypersensitivity reaction. Reducing the infusion rate of the initial loading dose might reduce the risk of adverse reactions. Recent guidelines recommend giving the loading dose over 60 minutes, instead of 15 minutes.

PMID: 9235683 [PubMed - indexed for MEDLINE]

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S-nitrosothiols signal hypoxia-mimetic vascular pathology.

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Abstract

NO transfer reactions between protein and peptide cysteines have been proposed to represent regulated signaling processes. We used the pharmaceutical antioxidant N-acetylcysteine (NAC) as a bait reactant to measure NO transfer reactions in blood and to study the vascular effects of these reactions in vivo. NAC was converted to S-nitroso-N-acetylcysteine (SNOAC), decreasing erythrocytic S-nitrosothiol content, both during whole-blood deoxygenation ex vivo and during a 3-week protocol in which mice received high-dose NAC in vivo. Strikingly, the NAC-treated mice developedpulmonary arterial hypertension (PAH) that mimicked the effects of chronic hypoxia. Moreover, systemic SNOAC administration recapitulated effects of both NAC and hypoxia. eNOS-deficient mice were protected from the effects of NAC but not SNOAC, suggesting that conversion of NAC to SNOAC was necessary for the development of PAH. These data reveal an unanticipated adverse effect of chronic NAC administration and introduce a new animal model of PAH. Moreover, evidence that conversion of NAC to SNOAC during blood deoxygenation is necessary for the development of PAH in this model challenges conventional views of oxygen sensing and of NO signaling.

WHAT THE ABOVE STUDY, published in J.Clin.Invest. 2007, IS SAYING, IN LAYMAN'S TERMS:

Researchers at the University of Virginia Health System have discovered troubling side effects of N-acetylcysteine (NAC), a common antioxidant used in nutritional and bodybuilding supplements.

NAC can form a red blood cell-derived molecule called nitrosothiol that fools your body into thinking there's an oxygen shortage, which can lead to pulmonary arterial hypertension (PAH).

PAH is a serious condition, where the arteries in the lungs narrow, increasing the blood pressure in your lungs, causing the right side of your heart to swell.

Lead researcher Dr. Ben Gaston, noted that this is an entirely new understanding of how oxygen is sensed by the body. As it turns out, your body responds to the nitrosothiols, which are created when a decreased amount of oxygen is carried by red blood cells -- not to the amount of oxygen dissolved in the blood.

So far, studies have only been performed on mice. **The next step is to determine the threshold at which the antioxidant becomes detrimental to heart and lung function in humans.**

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