

EMPHYSEMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Nacystelyn, a novel lysine salt of N-acetylcysteine, to augment cellular antioxidant defence in vitro.

Respir Med (ENGLAND) Mar 1997, 91 (3) p159-68

Nacystelyn (NAL), a recently-developed lysine salt of N-acetylcysteine (NAC), and NAG, both known to have excellent mucolytic capabilities, were tested for their ability to enhance cellular antioxidant defence mechanisms. To accomplish this, both drugs were tested in vitro for their capacity: (1) to inhibit O₂⁻ and H₂O₂ in cell-free assay systems; (2) to reduce O₂⁻ and H₂O₂ released by polymorphonuclear leukocytes (PMN); and (3) for their cellular glutathione (GSH) precursor effect. In comparison with GSH, NAL and NAC inhibited H₂O₂, but not O₂⁻, in cell-free, in vitro test systems in a similar manner. The anti-H₂O₂ effect of these drugs was as potent as that of GSH, an important antioxidant in mammalian cells. To enhance cellular GSH levels, increasing concentrations (0.2 x 10⁻⁴ mol l⁻¹) of both substances were added to a transformed alveolar cell line (A549 cells). After NAC administration (2 x 10⁻⁴ mol l⁻¹), total intracellular GSH (GSH + 2GSSG) levels reached 4.5 +/- 1.1 x 10⁻⁶ mol per 10⁶ cells, whereas NAL increased GSH to 8.3 +/- 1.6 x 10⁻⁶ mol per 10⁶ cells. NAC and NAL administration also induced extracellular GSH secretion; about two-fold (NAC), and 1.5-fold (NAL), respectively. The GSH precursor potency of cystine was about two-fold higher than that of NAL and NAC, indicating that the deacetylation process of NAL and NAC slows the ability of both drugs to induce cellular glut production and secretion. Buthionine-sulphoximine, which is an inhibitor of GSH synthetase, blocked the cellular GSH precursor effect of all substances. In addition, these data demonstrate that NAC and NAL reduce H₂O₂ released by freshly-isolated cultured blood PMN from smokers with chronic obstructive pulmonary disease (COPD) (n = 10) in a similar manner (about 45% reduction of H₂O₂ activity by NAC or NAL at 4 x 10⁻⁶ mol l⁻¹). In accordance with the results obtained from cell-free, in vitro assays, O₂⁻ released by PMN was not affected. Ambroxol (concentrations: 10⁻⁹-10⁻³ mol l⁻¹) did not reduce activity levels of H₂O₂ and O₂⁻ in vitro. Due to the basic effect of dissolved lysine, which separates easily in solution from NAL, the acidic function of the remaining NAC molecule is almost completely neutralized [at concentration 2 x 10⁻⁴ M: pH 3.6 (NAC), pH 6.4 (NAL)]. Due to their function as H₂O₂ scavengers, and due to their ability to enhance cellular glutathione levels, NAL and NAC both have potent antioxidant capabilities in vitro. The advantage of NAL over NAC is two-fold; it enhances intracellular GSH levels twice as effectively, and it forms neutral pH solutions whereas NAC is acidic. Concluding from these in vitro results, NAL could be an interesting alternative to enhance the antioxidant capacity at the epithelial surface of the lung by aerosol administration.

Retinoic acid treatment abrogates elastase-induced pulmonary emphysema in rats

Nat Med (UNITED STATES) Jun 1997, 3 (6) p675-7

Pulmonary emphysema is a common disease in which destruction of the lung's gas-exchange structures (alveoli) leads to inadequate oxygenation, disability and frequently death; lung transplantation provides its only remediation. Because

treatment of normal rats with all-trans-retinoic acid increases the number of alveoli, we tested whether a similar effect would occur in rats with emphysema. Elastase was instilled into rat lungs, producing changes characteristic of human and experimental emphysema: increased lung volume reflecting a loss of lung elastic recoil, larger but fewer alveoli and diminished volume-corrected alveolar surface area due to destruction of alveolar walls. Treatment with all-trans-retinoic acid reversed these changes providing nonsurgical remediation of emphysema and suggesting the possibility of a similar effect in humans.

The level of antioxidant enzymes in red blood cells of patients with chronic obstructive pulmonary disease

Tuberculosis and Respiratory Diseases (South Korea), 1997, 44/1

Background: Toxic oxygen free radicals have been implicated as important pathological mediators in many clinical disorders. Enhancing the intracellular content of antioxidant enzymes (superoxide dismutase, glutathione peroxidase, and catalase) can provide means of limiting biological damage caused by oxygen free radicals. The oxygen free radicals and changes of antioxidant enzymes are thought to play a role in pathogenesis of chronic obstructive pulmonary disease. **Method:** To investigate the pulmonary oxygen radical injury and the protective role of antioxidant enzymes in Chronic obstructive pulmonary disease (COPD), author measured the amount of thiobarbituric acid reactants, the activities of antioxidant enzymes and the sulfhydryl groups of glutathione in serum and red blood cells from the patients with COPD (COPD patients) and the normal controls. **Results:** The thiobarbituric acid reactant in serum and red blood cells of COPD patients was increased than those of the normal controls, and the superoxide dismutase activity in red blood cells was no statistical difference in both groups. But the glutathione peroxidase and catalase activities in red blood cells of COPD patients were significantly lowered than those of the normal controls. The sulfhydryl groups in serum and in red blood cells were no statistically difference in both groups. **Conclusion:** These results suggest that the increased thiobarbituric acid reactants in serum and RBCs of chronic obstructive pulmonary disease mean oxygen radical toxicity, and the decreased glutathione peroxidase and catalase activities in RBC could take part in pathogenesis of chronic obstructive pulmonary disease.

Systemic oxidative stress in asthma, COPD, and smokers

American Journal of Respiratory and Critical Care Medicine (USA), 1996, 154/4 I (1055-1060)

An imbalance between oxidants and antioxidants is proposed in smokers and in patients with airways diseases. We tested this hypothesis by measuring the Trolox equivalent antioxidant capacity (TEAC) of plasma and the levels of products of lipid peroxidation as indices of overall oxidative stress. The plasma TEAC was markedly reduced (0.66 plus or minus 0.07 mmol/L; mean plus or minus SEM; n = 11), with increased levels of lipid peroxidation products, in healthy chronic smokers as compared with healthy nonsmokers (1.31 plus or minus 0.10 mmol/L, n = 14, p < 0.001), an effect that was exaggerated in those who had smoked 1 h before the study. Plasma TEAC was also low in patients presenting with acute exacerbations of chronic obstructive pulmonary disease (COPD) (0.46 plus or minus 0.10 mmol/L, n = 20, p < 0.001) or asthma (0.61 plus or minus 0.05 mmol/L, n = 9, p < 0.01) with increases in plasma lipid peroxidation products. There was a negative correlation between superoxide anion release by stimulated neutrophils and plasma antioxidant capacity (r = -0.73, p < 0.001) in patients with acute exacerbations of COPD. The profound decrease in TEAC was associated with a decreased plasma protein sulfhydryl concentrations in acute exacerbations of COPD but not in smokers or in asthmatic subjects. Therefore smoking, acute exacerbations of COPD, and asthma are associated with a marked oxidant/antioxidant imbalance in the blood, associated with evidence of increased oxidative stress. The decreased antioxidant capacity in plasma may result from different mechanisms in these conditions.

Role of oxidants/antioxidants in smoking-induced lung diseases

Free Radical Biology and Medicine (USA), 1996, 21/5 (669-681)

An imbalance between oxidants and antioxidants has been considered in the pathogenesis of smoking-induced lung diseases, such as chronic obstructive pulmonary disease (COPD), particularly emphysema. Recent evidence indicates that increased neutrophil sequestration and activation occurs in the pulmonary microvasculature in smokers and in patients with COPD, with the potential to release reactive oxygen species (ROS). ROS generated by airspace phagocytes or inhaled directly from the environment also increase the oxidant burden and may contribute to the epithelial damage. Although much research has focused on the protease/antiprotease theory of the pathogenesis of

emphysema, less attention has been paid to the role of ROS in this condition. The injurious effects of the increased oxidant burden in smokers and in patients with COPD are opposed by the lung antioxidant defences. Hence, determining the mechanisms regulating the antioxidant responses is critical to our understanding of the role of oxidants in the pathogenesis of smoking-induced lung diseases and to devising future strategies for antioxidant therapy. In this article we have reviewed the evidence for the presence of an oxidant/antioxidant imbalance in smoking-induced lung disease and its relevance to therapy in these conditions.

Effect of beta2-adrenoceptor agonists on plasma potassium and cardiopulmonary responses on exercise in patients with chronic obstructive pulmonary disease

European Journal of Clinical Pharmacology (Germany), 1996, 49/5 (341-345)

Objective: The effect of beta2-adrenoceptor agonist-induced hypokalaemia on cardiac arrhythmias might be exacerbated during exercise, especially in patients with more compromised airway function. **Methods:** To evaluate the effect of beta2-adrenoceptor agonists on plasma potassium and cardiopulmonary function during exercise, two identical submaximal treadmill exercise tests were performed, at least 48 h apart, by 13 patients with moderate to severe COPD (11 men and 2 women, mean age 66 y, mean FEV1/FVC ratio 48.9 (2.8)%) 30 min after they had received nebulised fenoterol or salbutamol (2 mg). The experiment was done as a randomised, double-blind, crossover trial after an initial baseline study with vehicle (0.45% saline). Plasma potassium concentration, spirometry and the degree of breathlessness (Borg scale) were measured before treatment and immediately after exercise; oxygen saturation, QTc interval and cardiac rhythm were monitored continuously before, during and for 30 min after exercise. **Results:** After the saline control, exercise caused an increase in Borg rating (of 4.9), a premature ventricular contractions (VPC) (2.8 beats/min), and a fall in oxygen saturation (-6.7%), but no significant change in plasma potassium (+0.04 mEq . dl-1), FEV1 or QTc interval. Inhalation of fenoterol and salbutamol did not affect QTc interval, Borg scale or VPC frequency at rest, but significantly increased the duration of exercise undertaken to reach the submaximal levels (786 s, versus 783 s) compared to the vehicle control. Following exercise, plasma potassium fell after fenoterol by 0.2 mEq . dl-1 and it increased after salbutamol by 0.1 mEq . dl-1 compared to baseline levels. Plasma potassium after exercise was significantly lower after fenoterol (3.2 mEq . dl-1) compared to the saline control (3.7 mEq . dl-1) and salbutamol (3.6 mEq . dl-1). Neither fenoterol nor salbutamol had any significant effect on the change in FEV1, oxygen saturation, Borg scale, frequency of VPCs or QTc interval during or after exercise compared to the saline control. **Conclusion:** When compared to salbutamol 2 mg, fenoterol 2 mg caused more marked hypokalaemia but no significant difference in cardiopulmonary response in patients with COPD during exercise.

Muscle and serum magnesium in pulmonary intensive care unit patients.

Crit Care Med (UNITED STATES) Aug 1988, 16 (8) p751-60

Muscle specimens by means of quadriceps femoris needle biopsy and blood samples were obtained in 32 patients consecutively admitted to a pulmonary ICU for chronic obstructive pulmonary disease and acute respiratory failure, and in 30 age and sex-matched healthy control subjects. Muscle magnesium (Mg) and potassium (K) content was assessed by atomic absorption spectrophotometry; serum electrolytes were also measured. The presence of clinical and biochemical correlates of low serum and muscle Mg was investigated. Three (9.4%) out of 32 patients had hypomagnesemia (Mgs less than or equal to 0.7 mmol/L) with normal muscle Mg values, whereas low muscle Mg values were found in 15 (47%) of 32 patients, with no alterations of serum Mg levels. Muscle Mg was decreased significantly in pulmonary ICU patients as compared to control subjects. No significant correlation was present between serum and muscle Mg, or between serum and muscle K. Significant relationships between muscle Mg and both muscle and intracellular K concentrations were also found. Lower values for muscle and intracellular K and a higher incidence of both more prolonged ICU stays and ventricular extrasystolic beats characterized the ICU patients with altered muscle Mg levels. We conclude that, given the serious complications of Mg metabolism derangements, the presence of altered cell Mg content should be taken into account in pulmonary ICU patients. Moreover, in these patients, serum Mg levels are of little value in the diagnosis of intracellular Mg deficits.

Fluid and electrolyte considerations in diuretic therapy for hypertensive patients with chronic obstructive pulmonary disease.

Arch Intern Med (UNITED STATES) Jan 1986, 146 (1) p129-33

When a patient with chronic obstructive pulmonary disease (COPD) requires medical therapy for systemic hypertension, a number of special considerations may affect the choice of antihypertensive drug and subsequent management. Thiazide diuretics have no adverse effect on airway function and are the agents of choice for initial therapy. beta-Antagonists are usually considered first-line agents in antihypertensive therapy, but even relatively cardioselective ones may increase airway resistance in patients with obstructive lung diseases, and they should be used with caution, if at all, in such patients. Although potassium-wasting diuretics are the preferred agents for treating hypertension in patients with COPD, they may worsen carbon dioxide retention in hypoventilating patients and potentiate hypokalemia in those receiving corticosteroids. In addition, beta-agonists may substantially lower serum potassium levels in patients already rendered hypokalemic by diuretics. Patients with COPD receiving potassium-wasting diuretics who have chronic respiratory acidosis or are receiving corticosteroids or beta-agonists should undergo close monitoring of electrolyte levels and be considered for therapy with potassium supplements or, preferably, potassium-sparing agents.

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Safety and effectiveness of ticarcillin plus clavulanate potassium in treatment of lower respiratory tract infections.

Am J Med (UNITED STATES) Nov 29 1985, 79 (5B) p78-80

The safety and effectiveness of ticarcillin plus clavulanate potassium was evaluated in an open study of 43 patients with community-acquired lower respiratory tract infections. The mean age of the 28 patients in whom bacteriologic evaluations were possible was 55 years; at least two thirds of the patients had a history of alcoholism or chronic obstructive pulmonary disease. A pathogen was isolated from sputum samples in 23 patients; five of these 23 also had documented bacteremia. There were five additional cases of bacteremia associated with clinical signs and symptoms of pneumonia but with no organisms isolated from sputum cultures. Thirty-five pathogens were isolated from the 33 evaluable infection sites, primarily *Streptococcus pneumoniae* and *Hemophilus influenzae*. *S. pneumoniae* was the causative organism in all 10 cases of bacteremia. Ticarcillin plus clavulanate potassium (3 g of ticarcillin and 100 mg of clavulanic acid) was administered intravenously for a mean of six days. All 35 organisms isolated before treatment were eradicated. In one patient a superinfection with *Pseudomonas aeruginosa* developed after treatment with ticarcillin plus clavulanate potassium. A clinical evaluation was possible for 32 of the 33 infection sites; clinical cure was achieved at 31 sites and improvement was seen at the other site. All 43 patients were monitored for adverse reactions by both clinical observation and laboratory tests. In one patient, reversible thrombocytopenia developed that required discontinuation of ticarcillin plus clavulanate potassium. In another patient, there was a slight decrease in the potassium level during therapy. No systemic adverse reactions occurred, nor was there any instance of local effects associated with the intravenous infusion of the drug.

Frequently nebulized beta-agonists for asthma: effects on serum electrolytes.

Ann Emerg Med (UNITED STATES) Nov 1992, 21 (11) p1337-42

STUDY OBJECTIVE: To determine the magnitude of the changes in serum potassium, magnesium, and phosphate during the treatment of acute bronchospasm with repeated doses of beta-adrenergic agonists. **DESIGN:** Prospective study of a convenience sample of asthmatic patients. **SETTING:** University teaching hospital emergency department. **TYPE OF PARTICIPANTS:** Twenty-three patients met the inclusion criteria of age of more than 16 years; a history of asthma or chronic obstructive pulmonary disease; and an acute exacerbation. **INTERVENTIONS:** Baseline peak expiratory flow rate and serum potassium, magnesium, and phosphate levels were measured. Nebulized albuterol (2.5 mg) was administered every 30 minutes until the patient was discharged from the ED. Before each albuterol treatment, repeat serum levels of potassium, magnesium, and phosphate were determined. **MEASUREMENTS AND MAIN RESULTS:** Baseline peak expiratory flow rate averaged 188 +/- 119 L/min. Serum potassium levels decreased significantly ($P = .0001$ by repeated-measures analysis of variance) from 4.10 +/- 0.468 (baseline) to 3.55 +/- 0.580 mmol/L (90 minutes) and 3.45 +/- 0.683 mmol/L (180 minutes). Potassium decreased to less than 3.0 mmol/L in 22% of patients at some point during the study. Magnesium decreased from 1.64 +/- 0.133 mmol/L (baseline) to 1.48 +/- 0.184 mmol/L (90 minutes) and 1.40 +/- 0.219 mmol/L (180 minutes) ($P = .0001$). Phosphate levels also decreased, from 3.74 +/- 1.029 (baseline) to 2.84 +/- 0.957 mmol/L (90 minutes) and 2.55 +/- 0.715 mmol/L (180 minutes) ($P = .0001$). **CONCLUSION:** Aggressive administration of nebulized albuterol during the emergency treatment of acute bronchospasm is associated with statistically significant decreases in serum potassium, magnesium, and phosphate. The mechanism and clinical significance of these findings are unknown and warrant further study.

Effect of nebulized albuterol on serum potassium and cardiac rhythm in patients with asthma or chronic obstructive pulmonary disease.

STUDY OBJECTIVE. To evaluate the metabolic and cardiopulmonary effects of nebulized albuterol in patients suffering moderate to severe exacerbations of asthma or chronic obstructive pulmonary disease. **DESIGN.** Open-label, prospective study. **SETTING.** The emergency department of a university medical center. **PATIENTS.** Ten patients with moderate to severe exacerbation of asthma. **INTERVENTIONS.** Each patient received nebulized albuterol 2.5 mg for approximately 10 minutes. **MEASUREMENTS AND MAIN RESULTS.** Serum potassium, heart rate and rhythm, blood pressure, and pulmonary function were measured before treatment and every 15 minutes for 2 hours after treatment. Serum potassium concentrations decreased significantly ($p < 0.05$) within 75 minutes after initiation of treatment, from a baseline value of 4.5 ± 0.6 mEq/L (range 3.5-5.5 mEq/L) to 3.7 ± 0.5 mEq/L (range 2.8-4.4 mEq/L) at the end of the collection period (120 minutes). Forced expiratory volume in 1 second significantly increased over time in patients with asthma ($p < 0.05$). No statistically significant changes in blood pressure, heart rate, or corrected QT intervals occurred. Pre-emergency department use of a beta 2-agonist by metered-dose inhaler was not associated with a decreased serum potassium on admission. **CONCLUSIONS.** Nebulized beta 2-agonists are generally efficacious and safe in patients with acute bronchospasms. However, close monitoring of serum electrolytes, heart rate, and rhythm in patients at risk (elderly, those with pre-existing cardiac disease) is advised before these individuals receive repeat doses by continuous aerosol administration.

The intrabronchial microbial flora in chronic bronchitis patients: a target for N-acetylcysteine therapy?

Eur Respir J (DENMARK) Jan 1994, 7 (1) p94-101

Chronic bronchitis is common among smokers, often together with recurrent infectious exacerbations. *Streptococcus pneumoniae* and *Haemophilus influenzae* are the pathogens traditionally considered most important. N-acetylcysteine (NAC) treatment has been shown to reduce the number of infectious exacerbations in patients with chronic bronchitis. The mechanism behind this is unknown. We attempted to characterize the intrabronchial bacterial flora in patients with chronic bronchitis in an infection-free interval, and to determine whether pharmacological and immunological factors effected the bacterial occurrence. Twenty two smokers with non-obstructive chronic bronchitis, 19 smokers with chronic bronchitis and chronic obstructive pulmonary disease (COPD) and 14 healthy nonsmokers underwent bronchoscopy. To obtain uncontaminated intrabronchial samples, a protected specimen brush was used. Quantitative bacterial cultures and virus isolations were performed. Significantly positive bacterial cultures ($> 1,000$ colony-forming units (cfu).ml⁻¹) were found only in the patients. *S. pneumoniae* and *H. influenzae* were found in five patients, and only in the patients without NAC treatment. The most common bacterium was alpha-haemolytic streptococcus. Negative cultures were more common in the healthy controls. Of the various factors examined, only NAC medication had an influence on bacterial numbers. Significantly fewer patients with NAC medication had positive cultures (3 out of 16) than in the group of patients without NAC therapy (15 out of 21). Our results confirm that chronic bronchitis in smokers leads to increased intrabronchial bacterial colonization. We could also confirm that 1,000 cfu.ml⁻¹ is an adequate cut-off level for significant bacterial growth when using the protected specimen brush. NAC medication was associated with low bacterial numbers.

[The influence of n-acetylcysteine on chemiluminescence of granulocytes in peripheral blood of patients with chronic bronchitis]

Pneumonol Alergol Pol (POLAND) 1993, 61 (11-12)

The effect of NAC on exacerbation of chronic obstructive pulmonary disease (COPD) may be due to its mucolytic properties due to the thiol group of NAC and to its reducing and antioxidant properties. It has been postulated that NAC may protect lung cells from inhaled oxidants or oxidants produced by inflammatory leukocytes by increasing intra and extra cellular GSH. The FMLP induced granulocyte chemiluminescence (CL) in 6 healthy and 12 patients with COPD was determined. Peripheral blood polymorphonuclear leukocytes were incubated with NAC. The results obtained show a significant decrease of CL after incubation with NAC in both groups. We also found higher CL in healthy subjects than patients with COPD. This study showed a significant increase of FVC, FEV1 and a significant decrease of granulocyte CL after treatment with oral NAC 200 mg three times daily.

Effects of coenzyme Q10 administration on pulmonary function and exercise performance in patients with chronic lung diseases.

Clin Investig (GERMANY) 1993, 71 (8 Suppl) pS162-6

Serum coenzyme Q10 (CoQ10) levels were measured at rest and during incremental exercise in 21 patients with chronic obstructive pulmonary disease (COPD) and 9 patients with idiopathic pulmonary fibrosis (IPF). The mean serum CoQ10 levels at rest in patients with COPD and IPF were 0.56 +/- 0.20 and 0.45 +/- 0.16 microgram/ml, respectively. In both groups these levels were decreased compared with those of healthy subjects. In the patients with COPD, CoQ10 levels were significantly correlated with body weight, however, there was no correlation between CoQ10 levels and ventilatory function, PaO₂, VO₂/kg at rest, or maximal VO₂. In eight of nine patients whose PaO₂ at rest was lower than 75 torr, serum CoQ10 levels were lower than 0.5 microgram/ml. We studied the effects of the oral administration of CoQ10 at 90 mg/day for 8 weeks on pulmonary function and exercise performance in eight patients with COPD. Serum CoQ10 levels were significantly elevated in association with an improvement in hypoxemia at rest, whereas pulmonary function was unaltered. Oxygen consumption during exercise was not changed, whereas PaO₂ was significantly improved, and heart rate was significantly decreased compared with the results obtained at an identical workload at baseline. Furthermore, lactate production was suppressed during the anaerobic exercise stage after CoQ10 administration, and exercise performance tended to increase. These data suggested that CoQ10 has favorable effects on muscular energy metabolism in patients with chronic lung diseases who have hypoxemia at rest and/or during exercise

Protection by N-acetylcysteine of the histopathological and cytogenetical damage produced by exposure of rats to cigarette smoke.

Cancer Lett (NETHERLANDS) Jun 15 1992, 64 (2) p123-31

Adult male Sprague-Dawley rats were exposed whole-body to mainstream cigarette smoke (CS) once daily for 40 consecutive days. Such a treatment resulted in a significant decrease of body weight growth and in intense histopathological changes of terminal airways, including a severe inflammation of bronchial and bronchiolar mucosae, with multiple hyperplastic and metaplastic lesions and foci of micropapillomatous growth as well as emphysema, with extensive disruption of alveolar walls. All histopathological changes were efficiently prevented by the daily administration of the thiol N-acetyl-L-cysteine (NAC) by gavage. Cytological and cytogenetical changes were monitored in bronchoalveolar lavage (BAL) fluid and bone marrow cells of groups of rats killed after 1, 3, 8, 28, or 40 days of treatment. From the first day of exposure, CS significantly enhanced the proportion of polymorphonucleates among BAL cells and the frequency of micronucleated (MN) bone marrow polychromatic erythrocytes. After 8 days, a reduction was observed in the polychromatic/normochromatic erythrocytes ratio and an increase in the frequency of MN pulmonary alveolar macrophages (PAM) was also recorded, followed, after 28 days, by an increase of binucleated PAM. All these alterations immediately reached a plateau and persisted unchanged until the end of the experiment. NAC administration exhibited a significant and considerable protective effect towards the CS-induced alterations of BAL cellularity, the increase of MN PAM and bone marrow cytotoxicity.

Investigation of the protective effects of the antioxidants ascorbate, cysteine, and dapsone on the phagocyte-mediated oxidative inactivation of human alpha-1-protease inhibitor in vitro.

Am Rev Respir Dis (UNITED STATES) Nov 1985, 132 (5) p1049-54

Oxidants derived from the atmosphere or from activated pulmonary phagocytes mediate functional inactivation of alpha-1-protease inhibitor (alpha-1-PI). Chronic exposure to these oxidants may cause emphysema. In this study we have investigated the effects of the antioxidants ascorbate, cysteine (10⁻⁴ M to 10⁻¹ M), and dapsone (10⁻⁶ M to 10⁻³ M) on the oxidative inactivation of human alpha-1-PI by leukoattractant-activated polymorphonuclear leukocytes (PMNL) in vitro. During exposure of alpha-1-PI to stimulated PMNL in the presence of ascorbate and cysteine at concentrations of greater than 10⁻⁴ M and dapsone at greater than 10⁻⁶ M, the elastase inhibitory activity of alpha-1-PI was preserved. However, exposure of the alpha-1-PI to the antioxidants subsequent to PMNL-mediated oxidative inactivation was not associated with reactivation of elastase inhibitory capacity. Ascorbate, cysteine, and dapsone at concentrations that caused 50% protection of alpha-1-PI did not affect degranulation or the binding of radiolabeled leukoattractant to PMNL. It is suggested that the protective effects of the antioxidants are related to their ability to scavenge superoxide and oxidants generated by the PMNL-myeloperoxidase/H₂O₂/halide system. Because the effects of ascorbate and especially those of dapsone were observed at concentrations of these agents that are attainable in vivo, our results may have clinical significance

The role of dornase alfa (PULMOZYME) in the treatment of cystic fibrosis

Annals of Pharmacotherapy (USA), 1996, 30/6 (656-661)

Objective: To review the current utility and proper role of dornase alfa (recombinant human DNase or rhDNase), which has been approved for use in cystic fibrosis. Several aspects related to these issues are addressed including the drug's mechanism of action, administration and dosing, and clinical safety and efficacy. We also critically examine the agent's role in the treatment of cystic fibrosis and consider the controversies involved with its use. Data Source: A MEDLINE search was conducted to identify pertinent literature, including review articles and clinical trials. Study Selection: Studies examining the efficacy and safety of dornase alfa in patients with cystic fibrosis. Data Extraction: Results from published, prospective, randomized trials are presented and critique. Data Synthesis: Production of viscous respiratory secretions is a hallmark phenomenon of cystic fibrosis, leading to a variety of symptoms. Dornase alfa targets this symptom and decreases the viscosity of these secretions. Clinical trials have indicated a small but statistically significant improvement in forced expiratory volume in 1 second and forced vital capacity. Enhancement in a patient's dyspnea and quality of life has varied between the trials, with few of the studies noting no statistically significant improvement. Adverse reactions are minimal and did not result in any patients withdrawals from the trials. A positive impact on infection rates, length of hospitalization, and need for intravenous antibiotic therapy was noted in one trial. However, reports of similar results have not yet been published, and thus the clinical significance or impact of this phenomenon is not fully understood. Moreover, results of more long-term use and in patients whose conditions are less stable have yet to undergo the scrutiny of peer/editorial review. Administration of the drug, which must be maintained continuously, is relatively expensive. Conclusions: dornase alfa appears to produce small but sustained improvement in lung function in patients with cystic fibrosis. It may also slow the progression of pulmonary disease. Infection rate appear to be reduced, which may well have important long-term consequences. However, evidence to date has not clarified the most appropriate use of dornase alfa in the treatment of cystic fibrosis. Whether quality of life is affected in a meaningful and measurable way is yet to be clarified. A trial of the drug in patients with cystic fibrosis who have obvious lung disease is reasonable, but continued treatment should be based on clear clinical response. Therefore, questions about the drug's exact role in the overall management of cystic fibrosis remain to be answered. Although benefits received may not prove to be cost-effective, long-term effects on disease progression may well justify use of this agent.

Inhalation therapy with recombinant human deoxyribonuclease I Gonda I (PULMOZYME).

Advanced Drug Delivery Reviews (Netherlands), 1996, 19/1 (37-46)

Infections of the respiratory tract are often associated with production of purulent sputum. One of the most important components contributing to the abnormal rheological properties of this sputum is neutrophil-derived extracellular DNA. Recombinant human deoxyribonuclease I (rhDNase, dornase alfa) was developed as a therapeutic protein that is administered by inhalation of a nebulized aqueous solution to break up this DNA into small fragments, and thus to correct the viscoelastic properties of the sputum. The stability of rhDNase during storage and aerosol generation was investigated. The methodology used in these studies and in the quantitation of the therapeutic aerosol available to the patient is reviewed. The results of the key findings in the clinical trials in cystic fibrosis and other chronic obstructive pulmonary diseases are presented.

Aerosolized dornase alpha (rhDNase-PULMOZYME) in cystic fibrosis

Journal of Clinical Pharmacy and Therapeutics (United Kingdom), 1995, 20/6

Advances in the treatment and management of respiratory and pancreatic disorders has increased the life expectancy of patients with cystic fibrosis to 28 years (1). Despite the use of potent antibiotics and chest physiotherapy, persistent bacterial infection of the lung is the major cause of morbidity and mortality in these patients (2). This occurs, in part, because of the production of copious amounts of pulmonary secretions. It has been found that these secretions contain high amounts of human DNA (3-8). This high DNA concentration causes two problems. First, it increases the viscosity of sputum. This, in conjunction with reduced mucociliary clearance, decreases the removal of sputum. Second, the DNA binds to aminoglycosides, which decreases their antimicrobial efficacy (9, 10). Until recently there was no effective drug to decrease the viscosity of sputum in patients with cystic fibrosis. Dornase alpha (Pulmozyme (R)) is the first drug to offer a safe and effective method to treat excessive DNA in sputum. In vitro studies demonstrated that rhDNase greatly decreased the viscosity of sputum by decreasing the concentration of DNA in a concentration-dependent manner.

New pharmacologic approaches: rhDNase

Revue de Pneumologie Clinique (France), 1995, 51/3 (193-200)

rhDNase (Pulmozyme (R)) is a new agent in the therapeutic strategy for patients with cystic fibrosis. It is one of the first

specific treatments aimed at the respiratory tract. It affects the extracellular DNA which is present in abundant quantities in the bronchial secretions of these patients. rhDNase significantly reduces the incidence of infections and improves respiratory function. It should be used as a major treatment in combination with all other treatments in patients over 5 years of age with a vital capacity of at least 40% the theoretical value. It is important to schedule the respiratory exercises as a function of rhDNase intake. The long-term therapeutic benefit remains to be evaluated.

Taurine and serine supplementation modulates the metabolic response to tumor necrosis factor alpha in rats fed a low protein diet

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Plasma taurine and serine decrease following trauma and in severe inflammatory disease. These changes may signify an increase in requirements for sulfur amino acids. We previously demonstrated that cysteine supplementation can restore the impaired ability of rats fed an 8% casein diet to increase hepatic zinc, glutathione (GSH) and protein concentrations in response to tumor necrosis factor alpha (TNFalpha). Here we examined whether serine or taurine produces a similar effect, because serine provides the carbon skeleton of cysteine and taurine is its major metabolite. After 7 d of receiving either a 20% casein diet supplemented with cysteine or an 8% casein diet supplemented with alanine, serine or taurine, rats received an intraperitoneal injection of human TNFalpha. Tumor necrosis factor caused no change in hepatic GSH but resulted in a lower GSH concentration in lung in rats fed the alanine-supplemented diet. Neither taurine nor serine increased liver GSH relative to that in rats fed alanine, but the depression in lung due to TNF injection was lessened. The absolute increase in ceruloplasmin in response to TNF was enhanced in rats fed the alanine-supplemented diet relative to those fed the 20% casein diet. Serine normalized this response. This observation-the effects of taurine and serine on lung GSH and a significant negative correlation between ceruloplasmin and liver and lung GSH concentration in rats fed TNF-suggests that supplemental serine and taurine may improve antioxidant defenses when dietary supplies of cysteine are low but do not influence cysteine availability for a normal response to TNF.

L-Carnitine and its role in medicine: A current consideration of its pharmacokinetics, its role in fatty acid metabolism and its use in ischaemic cardiac disease and primary and secondary L-carnitine deficiencies

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L-Carnitine (L-beta-hydroxy-4-N-trimethylaminobutyric acid) is an essential nutrient in animals and humans, which is synthesised endogenously, mainly in liver and kidney, or obtained from diet, with principal sources red meat in adults and human milk in infants. L-Carnitine is a cofactor of several enzymes, including carnitine-acylcarnitine translocase embedded in the inner mitochondria membrane, and two acylcarnitine (palmitoyl) transferases I and II, located respectively in the outer and inner mitochondrial membrane; these biomolecules are required in mammalian tissues to transfer long-chain acyl CoAs across the inner membrane for beta-oxidation in the matrix. Furthermore, intramitochondrial L-carnitine and the matrix enzyme L-carnitine acetyltransferase can react with short- and medium-chain acyl CoAs to produce acylcarnitines, which can be shuttled out of mitochondria. Through this mechanism, L-carnitine is able to modulate the intracellular concentrations of free CoA and acetyl CoA via reversible formation of acetylcarnitine. Therefore, besides shuttling long-chain fatty acids into mitochondria, L-carnitine facilitates the oxidation of pyruvate and branched-chain ketoacids and, by preventing their accumulation, it contributes to the protection of cells from the potentially membrane-destabilising acyl CoAs. In the absence of L-carnitine, the accumulation of free fatty acids in the cytoplasm produces a toxic effect on the cell, and an energy deficit arises from the unavailability of fatty acids within the mitochondria. L-Carnitine is present in tissues and biological fluids in free and esterified forms. In humans, acylcarnitine esters account for about 25% of total L-carnitine in serum and for about 15% of total L-carnitine in liver and skeletal muscle. Total L-carnitine concentration in human tissues is higher in the heart and skeletal muscle (3.5-6.0 and 2.0-4.6 micromol/g, respectively) than in the liver and the brain (1.0-1.9 and 0.5-1.0 micromol/g, respectively): these values reflect the higher rates of fatty acid oxidative metabolism in the former tissues. The pharmacokinetics of exogenously administered L-carnitine have not been completely described. In the case of L-carnitine preparations from Sigma Tau Pharmaceuticals, peak plasma concentrations of free L-carnitine of 25 and 91 micromol/l have been attained 3 and 3.5 hours following single oral 30 and 100 mg/kg doses, respectively. L-Carnitine is actively transported into tissues via a saturable system, although passive diffusion also occurs. The apparent volume of distribution is about 37 l. The compound is likely metabolised in humans by partial conversion to acyl-carnitine esters and therefore is eliminated through the kidneys. The portion of a dose of L-carnitine excreted in the urine within 24 hours depends on the route of administration; thus, after an intravenous dose 86% has been recovered, in contrast to 7% of a dose recovered within 24 hours after an oral dose. Faecal elimination accounts for less than 2% of a dose. In healthy volunteers, the biological half-life of L-carnitine varies from 3 to 12 hours, depending on the dosage schedule. Over the past decade many clinical trials have suggested that L-carnitine may be administered to patients with ischaemic cardiac disease. The rationale for the use of L-carnitine in such patients initially originated from the findings that myocardial L-carnitine concentrations are lower in patients

with fatal myocardial infarction, due to an increased lactate production and decreased energy output of cardiac muscle, than in those dying from non-cardiac causes. L-Carnitine has been shown to improve pyruvate metabolism, to reduce lactate production and acidosis and to act as a scavenger of toxic catabolic products of free fatty acids, which accumulate in the heart during ischaemia. Also, there is evidence for skeletal muscle L-carnitine deficiency in some patients with atherosclerotic vascular disease; therefore, L-carnitine supplementation may have potential to improve skeletal muscle metabolic and mechanical function. This double effect in cardiac and skeletal muscle makes L-carnitine attractive for patients with ischaemic heart disease; L-carnitine seems to play an important role, not only by enhancing carbohydrate utilisation, but also by reducing FFA toxicity and acting as a metabolic modulator in the heart.

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