USEFULNESS OF ANTIOXIDANT DRUGS IN BRONCHIAL ASTHMA

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Background: Bronchial asthma is a clinical syndrome with possible correlation to oxidative stress, therefore the effectiveness of some antioxidant drugs has been studied in management of chronic bronchial asthma. **Methods:** This study was carried out in the Al-Kadhimia Teaching Hospital between December 2008 to May 2009 on 56 patients of both sexes who were randomly allocated to 7 groups, plus 10 healthy volunteers as control group. Each group was given one of the following drugs: vitamin E, vitamin C, combination of vitamin E and C, selenium, zinc, allopurinol and garlic oil, in addition to their classical treatment of asthma and their pulmonary function tests were conducted as well as measuring the levels of serum zinc, calcium, and malondialdehyde (MDA) before and after treatment. **Results:** All asthmatic patients were suffering from oxidative stress and this was detected by measuring the level of serum MDA which was 2–3 folds more than the control group, and all antioxidants except allopurinol showed a beneficial effect of different degrees in the pulmonary function tests accompanied with clinical improvement of patients' condition and marked decrease in the number of daily attacks. **Conclusion:** Antioxidants can compensate the oxidative stress that correlates with asthma, can reduce the symptoms of asthma, and improve pulmonary functions.

Keywords: asthma, oxidative stress, antioxidants, pulmonary function tests, malondialdehyde

INTRODUCTION

Asthma is a clinical syndrome of unknown aetiology characterised by three distinct components: Recurrent episodes of airway obstruction, an exaggerated bronchoconstrictor response to stimuli and inflammation of airways with mucosal oedema. Asthma has about 60% heritability, indicating that both genetic and environmental factors are important in its etiology.[1]

Allergens like air pollutants such as ozone and cigarette smoking,[2] infections, exercise, nonsteroidal anti-inflammatory drugs,[3] gastroesophageal reflux, psychosocial factors, and the data indicate that a relationship between obesity and asthma exists.[4]

The pathogenesis of chronic obstructive lung disorders like asthma and chronic obstructive pulmonary disease (COPD) is a complex. It involves both airway inflammation[5] with an oxidant/ antioxidant imbalance.[6]

Reactive oxygen species (ROS) can lead to lung injury as a result of direct oxidative damage to epithelial cells and cell shedding.[7] ROS have been shown to be associated with the pathogenesis of asthma by evoking bronchial hyperreactivity[8] as well as directly stimulating histamine release from mast cells and mucus secretion from airway epithelial cells.[9]

The current study was carried out to evaluate the effectiveness of different antioxidants in improving symptoms of chronic bronchial asthma.

MATERIAL AND METHODS

This study was performed in AL-Kadhimia Teaching Hospital between December 2008 to May 2009. Fifty-six adult patients and 10 healthy subjects of both sexes were included in this study. Their age range was 17–60 years. Patients suffering from any disease other than chronic asthma were excluded and diagnosis based on symptomatology and clinical examination. This study was approved by ethic committee of the collage of medicine.

The patients were divided randomly into 7 groups (8 patients in each group) taking the drugs orally for 2 weeks. Group 1 was given a single dose of Allopurinol (Zyloric®) 300 mg tablet/day. Group 2 was given selenium (Fluka-Garantie) 400 µg capsule/day in two divided doses. Group 3 was given zinc sulphate (Al-Havi) 440 mg capsule/day, (440 mg zinc sulphate equivalent to 100 mg zinc) in two divided doses. Group 4 was given garlic (garlic oil in pearl) (Ranbaxy) 2.5 mg/day in two divided doses. Group 5 was given vitamin E (Jamieson Lab) 400 IU/day soft gelatin capsule (α-tocopheryl acetate from purified Soya oil) in a single dose. Group 6 was given vitamin C (Al-Shahba Laboratories) 1,000 mg/day tablet (in two divided doses). Group 7 was given vitamin C 1,000 mg /day tablets orally in two divided doses and a single dose of vitamin E 400 IU/day soft gelatin capsule (after food).

Pulmonary functions test was performed using a total computerized spirometer (Discom-14 Autospiror, Chest Corporation Tokyo, Japan) that measure Forced Volume Capacity (FVC), Forced Expiratory Volume in First Second (FEV_1), Peek Expiratory Flow Rate (PEFR), and Maximal Mid-expiratory Flow Rate (MMEFR). It also provides predicted values.

Zinc and Calcium levels in serum were determinate by colorimetric method using LTA company kit, and bioMerieux company kit respectively.

In measurement of serum malondialdehyde (MDA) level according to the standard method,[10] MDA is a by-product of lipid peroxidation and its measurement is based on the reaction of thiobarbituric acid (TBA) with MDA.

All data were coded and analysed using SPSS version 14.

RESULTS

The serum MDA levels in patient treated with Allopurinol, Selenium, Zinc sulphate, Garlic oil, Vitamin E, Vitamin C, and combination of vitamin E and C were significantly reduced. The results have been summarized in table-1 and Figures1-4.

Results of serum zinc and calcium levels were not significantly changed except that of zinc sulphate, which significantly increased.

There was no significant increase in FVC%, FEV_1, MMEFR%, and PEFR by using allopurinol, but an increase in FVC%, FEV_1%, and MMEFR% with selenium, zinc sulphate, garlic oil, vitamin C, E, and in combination was observed.

Table-1: The effects of antioxidants on pulmonary functions test

Drug	FVC%		FEV_1%		MMEFR%		PEFR	
	Before	After	Before	After	Before	After	Before	After
Allopurinol	61.38 ± 13.60	63.13±13.66	53.28±14.32	55.50±14.59	50.33± 15.36	52.25 ±13.15	3.33 ±1.60	3.70 ±1.91
Selenium	66.63±11.94	*71.88 ±9.70	62.33 ±15.22	*68.13±12.30	39.29± 21.56	*43.2 6±21.21	2.39±1.29	2.75±0.94
Zinc sulphate	69.38±8.00	*75.50±5.21	66.51±10.04	*72.86±12.61	62.10±18.57	*74.14±16.56	3.17±1.32	*4.29 ±1.23
Garlic oil	70.88 ±9.91	*77.13±8.87	56.70±17.55	*67.53±12.45	48.86±21.50	*61.48±16.95	3.06± 0.91	*4.16 ±1.31
Vitamin E	61.63±12.05	*70.50±10.01	61.14±16.00	*71.50±10.18	57.31±17.65	*65.51±17.36	3.54±1.59	*4.50±1.63
Vitamin C	69.88 ±9.17	*79.00±7.07	64.66±12.88	*74.38±12.63	55.48±25.66	*60.88±22.88	3.15±1.74	*3.92±1.79
Vitamin E and C	66.13±10.16	*76.75±6.30	64.65±16.31	*75.13±11.06	53.69±19.16	*63.00±20.76	3.53±1.87	*4.57± 2.50

*results were significant at (p<0.05)

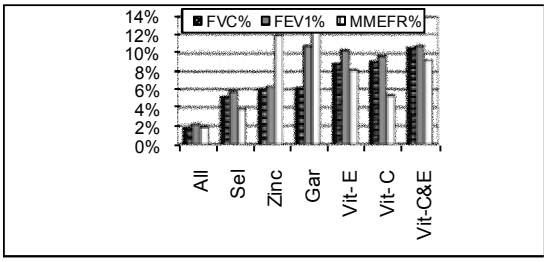

Figure-1: Percentage increment in FVC, FEV_1 and MMEFR after treatment with antioxidants

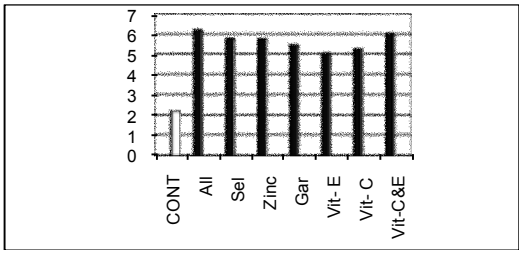

Figure-3: Serum level of MDA ηmol/L in patients with asthma (before treatment with antioxidants) compared with control group

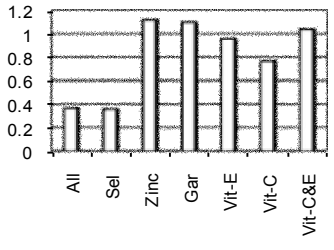

Figure-2: The increment in PEFR after treatment with antioxidants

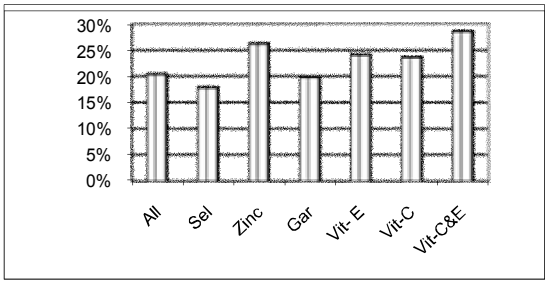

Figure-4: Percentage reduction in MDA after treatment with antioxidants

DISCUSSION

Oxidative stress may have many detrimental effects on airway function, including airway smooth muscle contraction,[11] induction of airway hyperresponsiveness[12] mucus hypersecretion[13], epithelial shedding[14] and vascular exudation.

MDA is a lipid peroxidation product, commonly used as a biomarker of oxidative stress/ damage.[15] In the current study patients with asthma had an increment of 2–3 fold in serum MDA when compared with control group (Figure-3).

Serum MDA levels significantly reduced by the antioxidant drugs. Although the percentage reduction was different from one drug to another yet it ranged from 17% to 29% (Figure-4).

Insignificant effect of Allopurinol may be related to: insufficient dose of the drug used in this study, the pharmacokinetics of the drug which do not allow sufficient concentration to reach the airway epithelium as it is the site of action of the drug, or may be due to its reduction of already existing non-enzymatic antioxidant in the epithelium, the uric acid.[16]

In group 2 selenium was used, a significant improvement in Pulmonary Function Tests associated with improvement in patients' clinical conditions was observed. Rotruck *et al*[17] established the biological function of Selenium as an integral component of glutathione peroxidase, an important antioxidative enzyme that catalyzes the destruction of hydrogen peroxide generated during oxidative metabolism in human. This enzyme required selenium to confer catalytic activity. A number of studies have shown that blood glutathione peroxidase levels are lower in asthmatic than in non-asthmatic subjects and that selenium supplementation ameliorates asthma symptomatology.[18]

The improvement in group 3 is related to different pharmacological properties of zinc in addition to its antioxidant activity that modulate the function not only of airway epithelium, but also of the cells that interact with this tissue, like inflammatory cells such as eosinophils, neutrophils, and mast cells.[19] Zinc is also a component of a major anti-oxidant enzyme Cu/Zn super-oxide dismutase in airway epithelium. Larsen *et al* demonstrated the importance of elevated level of this enzyme in mice lungs and relation to allergen-induced hyper-responsiveness.[20]

In group 4 garlic exerted antioxidant effects by scavenging free radicals, enhancing superoxide dismutase, catalase and glutathione peroxidase, and increasing cellular glutathione[21] with clear effect on pulmonary function tests.

Fogarty *et al*[22] reported that higher concentrations of vitamin E intake were associated with lower serum IgE concentrations and a lower frequency of allergen sensitisation. These findings may explain the beneficial effect of dietary vitamin E in reducing the incidence of asthma.

Vitamin E can protect cellular components from many types of oxidative stress by both free radical scavenging mechanism and stabilizing the cell membranes[23] and this may explain the improvement that occurred in both dynamic performance of the lung in moving air and the elastic recoil force of the lung.

The results of vitamin C group were much similar to the results obtained by vitamin E. Our results showed a clear reduction in the frequency of asthmatic attacks and this was compatible with findings of Anah *et al*[24] who also demonstrated a reduction of asthmatic attacks in patients after taking the patients 1 gram of vitamin C daily over 14 weeks. Vitamin C is well known antioxidant agent that may have a modest corticosteroid sparing effect as shown by Fogarty *et al*.[25]

In combination of two vitamins, vitamin E is a lipophilic chain-breaking antioxidant that acts by stopping the chain reaction involved in lipid peroxidation, while vitamin C is more hydrophilic and acts to quench radicals within the cell. Ascorbate also acts to regenerate vitamin E in cell membranes.[26] The results obtained from this combination were higher than the results obtained from each one alone.

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