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Efficacy of Oxidative Stress Correction During Asthma Treatment

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Abstract

Background: The improvement of asthma treatment is still one of the urgent issues of modern medicine. The objective of this study was to evaluate the dynamics of lipid peroxidation parameters in patients with asthma receiving complex therapy with ceruloplasmin (Cp).

Methods and Results: The study included 92 patients with severe uncontrolled asthma. Patients were divided into 2 groups. The case group consisted of 45 patients, whose treatment was conventional therapy combined with Cp produced by "MICROGEN" (Russia). Cp 100 mg was administered intravenously once daily for 7 days. The control group consisted of 47 patients who received conventional treatment: inhaled and systemic corticosteroids, bronchodilators, and, if necessary, antibiotics and oxygen therapy. All participants underwent a comprehensive examination, including clinical investigation, chest radiography, assessment of spirometry parameters (VC, FVC, FEV1, FEV1/FVC ratio, PEFR, FEF 25-75), and determination of MDA, metHB, HbCO, total sulfhydryl groups, and SOD activity in blood plasma. Patients of the case group showed a statistically significant decrease in elevated rates of MDA and HbCO, an increase in SOD activity and the content of sulfhydryl groups.

Conclusion: Cp in complex treatment of patients with asthma allows eliminating the imbalance in the prooxidant-antioxidant system and providing an obviously positive clinical effect. **(International Journal of Biomedicine. 2017;7(2):104-107.)**

Key Words: asthma • lipid peroxidation • oxidative stress • ceruloplasmin

Abbreviations

FEV1, forced expiratory volume in one second; **FVC**, forced vital capacity; **FEF**, forced expiratory flow; **HbCO**, carboxyhemoglobin; **LPO**, lipid peroxidation; **MDA**, malondialdehyde; **metHB**, methemoglobin; **OS**, oxidative stress; **PEFR**, peak expiratory flow rate; **RNS**, reactive nitrogen species; **ROS**, reactive oxygen species; **SAD**, superoxide dismutase.

Introduction

Asthma is a global health problem affecting 1%–18% of the population in different countries.[1] An estimated 300 million people worldwide suffer from asthma, with 250,000 annual deaths attributed to the disease.[2] The improvement of asthma treatment is still one of the urgent issues of modern medicine.[3-5] The long-term goals of asthma management are to achieve good symptom control, and to minimize future risk of exacerbations, fixed airflow limitation and side-effects of treatment.[1]

There is strong evidence that asthma is associated with a strong oxidant stress (OS), which is a result of both increased oxidant forces and decreased antioxidant capacity.[6,7] Endogenous and exogenous ROS and RNS play a major role in airway inflammation and are determinants of asthma severity.[6] One key component of the oxidant-antioxidant hypothesis centers on the huge burden of oxidants derived from inflammatory cell infiltration into the lung.[8] Lung tissue contains large amounts of unsaturated fatty acids, substrates of lipid peroxidation (LPO). Alveolar macrophages and other phagocytic cells are activated in inflammation and produce ROS, triggering peroxidation.[9] In addition, ROS and RNS

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contribute to an imbalance in the proteolysis-antiproteolysis system. Oxidative damage to proteins and glycoproteins results in enzyme inactivation and modification of receptor activity. It has been established that the damages caused by ROS are localized mainly in areas with transition metal ions, primarily iron and copper ions.[10] Karmen et al.[11] described the structural and functional changes in erythrocyte membranes associated with peroxidation hyperactivation in asthma. Disturbances caused by an imbalance in the oxidant-antioxidant system—which are manifested by bronchial hyperresponsiveness, lowered lung volume, and vaso- and broncho- constriction—are revealed in all structures of the respiratory tract.[12]

Anti-inflammatory therapy using corticosteroids remains to be the mainstay of treatment and is emphasized in all guidelines.[13,14] The efficacy of current asthma therapy in preventing the effects of oxidative stress is not yet clear and sometimes controversial.[15-17] Sartorelli et al.[18] suggested that imbalance in the oxidant-antioxidant system is associated with the resistance to corticosteroid therapy. The use of antioxidants or other pharmacological agents to boost the endogenous antioxidant system could be used to redress the imbalance in the oxidant-antioxidant system. There is enough evidence to support the conclusion that antioxidants can play a positive role in complex therapy of diseases associated with LPO, including asthma.[19]

The main extracellular antioxidant in the body is ceruloplasmin (Cp), which inhibits LPO by 50% due to the superoxide radical inactivation. The known functions of Cp include copper transport, iron metabolism, antioxidant defense, and involvement in angiogenesis and coagulation.[20,21] The antioxidant activity of Cp has been reported in several studies, and there are reasons to believe that this is one of the most important functions of Cp during inflammatory and acute-phase reactions.[20]

The objective of this study was to evaluate the dynamics of lipid peroxidation parameters in patients with asthma receiving complex therapy with Cp.

Materials and Methods

The study included 92 patients with severe uncontrolled asthma: 42(45.7%) men and 50(54.3%) women aged from 18 to 65 years. The diagnosis was made according to the criteria of Global Initiative for Asthma.[1] The inclusion criteria were the variability of PEFR>30% and FEV1<60% of predicted. Exclusion criteria were malignant tumors, pneumonia, anaphylactic reactions in medical history, and associated chronic diseases in exacerbation state.

The study was approved by local ethics committee. Written informed consent was obtained from each patient. Patients were divided into 2 groups. The case group consisted of 45 patients, whose treatment was conventional therapy combined with Cp produced by "MICROGEN" (Russia). Cp 100 mg was administered intravenously once daily for 7 days. The control group consisted of 47 patients who received conventional treatment: inhaled and systemic corticosteroids, bronchodilators, and, if necessary, antibiotics and oxygen therapy.

All participants underwent a comprehensive examination, including clinical investigation, chest radiography, assessment of spirometry parameters (VC, FVC, FEV1, FEV1/FVC ratio, PEFR, FEF 25-75), and determination of MDA, metHB, HbCO, total sulfhydryl groups, and SOD activity in blood plasma.

Statistical processing of the data was performed with STATGRAPHICS Plus 5.1. The mean (M) and standard error of the mean (SEM) were calculated. Student's unpaired and paired t-tests were used to compare average values for data with normal distribution. A probability value of $P<0.05$ was considered statistically significant.

Results

Patients of the case group demonstrated faster improvement in basic clinical and laboratory parameters compared to patients of the control group. After complex treatment with Cp, 40(88.9%) patients showed controlled asthma signs: nighttime awakenings disappeared, day symptoms reduced to less than 2 times a week, the drug use for the symptoms' management reduced to less than 2 times a week, and no activity limitations for 4 weeks. Dyspnea and cough significantly decreased. In 5(11.1%) patients of this group, nocturnal symptoms/awakening (partially controlled asthma) persisted. Patients of the case group also showed a statistically significant improvement in the spirometry parameters. With only conventional therapy, the dynamics of these indicators was less pronounced; 45(95.7%) patients of the control group continued showing nocturnal symptoms/awakening or daily episodes more than 2 times a week(partly controlled asthma), 2 patients (4.3 %) had uncontrolled asthma (Table 1).

Table 1.

Spirometry parameters in patients with asthma during therapy

Variable	Case group		Control group	
	Before	After	Before	After
VC	62.39±1.7	82.4±1.73*	60.62±1.76	66.84±1.55*#
FVC	56.98±1.59	82.1±1.79*	54.39±1.63	58.97±1.81#
FEV1	41.27±0.91	74.86±1.1*	40.82±0.95	50.88±1.15*#
FEV1/FVC, %	74.64±2.3	90.2±1.33*	76.64±1.89	86.3±1.6*
PEFR	42.01±1.57	72.53±1.58*	41.18±1.42	50.08±1.37#
FEF25	41.48±0.78	73.97±1.05*	40.4±0.83	44.64±0.89#
FEF50	39.58±0.8	71.61±0.98*	38.18±1.82	41.59±0.86#
FEF75	37.96±0.76	64.49±1.01*	35.18±1.85	39.04±1.79#

** - P<0.05 – intragroup differences before and after treatment;*
 # - P<0.05 – differences between groups after treatment
VC, FVC, FEV1, PEFR, FEF25-75 - in % of predicted

Patients of the case group showed a statistically significant decrease in elevated rates of MDA from 20.67±0.63 nmol/ml to 12.25±0.48 nmol/ml and HbCO from 11.96±0.24% to 9.43±0.22%, an increase in SOD activity from 0.75±0.02 AU/ml to 1.07±0.04 AU/ml and the content of sulfhydryl

groups from 98.27±2.2mg% to 110.56±1.67mg%. There was no statistically significant reduction in metHb level. However, in the control group, lipid peroxidation indicators remained high, while antioxidant protection indicators were low (Table 2).

Table 2.

Parameters of the oxidant-antioxidant system in patients with asthma during therapy

Variable	Case group		Control group	
	Before	After	Before	After
MDA, nmol/ml	20.67±0.63	12.25±0.48*	20.18±0.65	16.76±1.66#
metHB, %	1.64±0.12	1.14±0.07	1.57±0.09	1.49±0.08#
HbCO, %	11.96±0.24	9.43±0.22*	11.63±0.28	10.6±0.6
SOD, AU/ml	0.75±0.02	1.07±0.04*	0.76±0.01	0.82±0.03#
SG, mg %	98.27±2.2	110.56±1.67*	97.62±2.26	99.26±2.47#

** - P<0.05 – intragroup differences before and after treatment*
\# – P<0.05 – differences between groups after treatment
SG- sulfhydryl groups

Discussion

Asthma is an inflammatory lung disease that is characterized by systemic and chronic localized inflammation and OS.[7,8] Sources of oxidative stress arise from the increased burden of inhaled oxidants, as well as elevated amounts of reactive oxygen species (ROS) released from inflammatory cells.[8,22] Environmental antigens stimulate ROS overproduction and abnormal function of DNA, proteins and lipids, which lead to hyperreactivity and inflammation in airways.[23] Oxidants decrease the activity of the surfactant and damage fibroblasts. They also cause an increase of epithelial permeability and stimulate the production of thromboxane, which provoke inflammatory changes in the lungs.[24] It is established that OS leads to dysfunction, cytolysis and apoptosis of bronchial epithelial cells.[25] A number of studies have shown that OS is involved in the development of asthma exacerbation and persistence of inflammation in the bronchi that plays an important role in repeated episodes of airway obstruction.[26,27] It is noted that treatment aimed at the recovery of redox processes is a potential strategy to reduce airway inflammation induced by OS. The use of antioxidants in the treatment of asthma contributes to the elimination of imbalance in the oxidant-antioxidant system and improves the clinical course of the disease.[23] Cp is a major protein that circulates in the plasma. Cp has either antioxidant or prooxidant effects, depending on the particular environment.[20,28] Purified human Cp inhibits the oxidation of tissue lipid extracts, lisosomal membranes, polyunsaturated fatty acids, and phospholipids.[29] Several mechanism have been hypothesized for the antioxidant activity of Cp, including a mechanism which acts through sequestration of free copper ions and $O_2^{-\bullet}$ scavengers.[29] Most of the experimental proofs seem to indicate the ferroxidase activity of Cp as the mechanism underlying its antioxidant effects. The conversion of Fe^{2+} into Fe^{3+} can decrease oxidation by blocking the Fenton reaction through a decrease in the quantity of oxidant Fe^{2+} or sequestration of iron by apotransferrin.[30] In our study, Cp reduced the imbalance in the oxidant-antioxidant system and increased the efficiency of the treatment.

Conclusion

Thus, the data obtained have proved OS presence in asthma, which is consistent with the findings of other studies.[6-8,11,18,31] Cp in complex treatment of patients with asthma allows eliminating the imbalance in the prooxidant-antioxidant system and providing an obviously positive clinical effect. In this regard, it is useful and justified to use antioxidants, including Cp, in the complex treatment of patients with asthma.

Competing Interests

The authors declare that they have no competing interests.

References

1. Global Initiative for Asthma. The Global Strategy for Asthma Management and Prevention, 2017. Available from: http://www.ginasthma.org/.
2. Global surveillance, prevention and control of chronic respiratory diseases: A comprehensive approach. WHO 2007. Available from: http://www.who.int/respiratory/publications/global_surveillance/en/
3. Provotorov VM, Budnevsky AV, Filatova YI. [Clinical manifestations of asthma during combination therapy using ceruloplasmin]. Ter Arkh. 2016;88(3):36-9. [Article in Russian].
4. Provotorov VM, Budnevsky AV, Filatova YI, Perfil'eva MV. [Antioxidant therapy of bronchial asthma]. Klin Med (Mosk). 2015;93(8):19-22. [Article in Russian].
5. Ermolova AV, Budnevsky AV, Yu ME, Ovsyannikov ES, Drobysheva ES. [Bronchial asthma and metabolic syndrome]. Klin Med (Mosk). 2015;93(6):44-9. [Article in Russian].
6. Sahiner UM, Birben E, Erzurum S, Sackesen C, Kalayci O. Oxidative stress in asthma. World Allergy Organ J. 2011;4(10):151-8. doi: 10.1097/WOX.0b013e318232389e.
7. Latysheva AN, Smirnova SV, Kolpakova AF. Bronchial asthma and chronic obstructive pulmonary disease: characteristics of oxidant-antioxidant state. Krasnojarsk: KraGMU; 2011.
8. Kirkham P, Rahman I. Oxidative stress in asthma and COPD: antioxidants as a therapeutic strategy. Pharmacol Ther. 2006;111(2):476-94.
9. Soodaeva SK. [Free radical mechanisms of injury in respiratory disease. Russian Pulmonology]. 2012;(1):5-10. [Article in Russian].
10. Lushchak VI. Oxidative stress and mechanisms of protection against it in bacteria. Biochemistry (Mosc). 2001;66(5):476-89.
11. Karmen NB, Abdullaeva MA, Tokareva LV. [Electropulse therapy in the treatment of severe bronchial asthma]. MEDLINE.RU (Pul'monologiia) 2011;12:679-689. [Article in Russian].
12. Soodaeva SK, Klimanov IA. [Disorders of oxidative metabolism in diseases of the respiratory tract and modern approaches to antioxidant therapy]. Atmosfere. Pul'monologiia i Allergologiia (Mosk). 2009;(1):34-8. [Article in Russian].

13. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. J Allergy Clin Immunol. 2007;120(5 Suppl):S94–138.
14. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, et al. Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J. 2008;31(1):143–78. doi: 10.1183/09031936.00138707.
15. Majori M, Vachier I, Godard P, Farce M, Bousquet J, Chanez P. Superoxide anion production by monocytes of corticosteroid-treated asthmatic patients. Eur Respir J. 1998;11(1):133–8.
16. De Raeve HR, Thunnissen FB, Kaneko FT, Guo FH, Lewis M, Kavuru MS, et al. Decreased Cu, Zn-SOD activity in asthmatic airway epithelium: correction by inhaled corticosteroid in vivo. Am J Physiol. 1997;272(1 Pt 1): L148–54.
17. Fenech AG, Ellul-Micallef R. Selenium glutathione peroxidase and superoxide dismutase in maltese asthmatic patients: effect of glucocorticoid administration. Pulm Pharmacol Ther. 1998;11(4):301–8.
18. Sartorelli CF, Rehder J, Neto AC, Vilela MM. Assessment of inflammation based on the release of oxygen radicals by granulocytes in chronic uncontrolled asthma. J Pediatr. (Rio J) 2009;85(2):143-8. doi:10.2223/JPED.1881.
19. Farhutdinov UR, Farhutdinov ShU. [Efficacy of ceruloplasmin in patients with asthma]. Ter Arh. 2012;84(12):45-8. [Article in Russian].
20. Giurgea N, Constantinescu MI, Stanciu R, Suciu S, Muresan A. Ceruloplasmin - acute-phase reactant or endogenous antioxidant? The case of cardiovascular disease. Med Sci Monit. 2005;11(2):RA48-51.
21. Moshkov KA, Zaitsev VN, Romanovskaya EV, Stefanov VE. Ceruloplasmin: intramolecular transfer and ferroxidase activity. Fundamental Research (Mosk). 2014;3(Part 1):104–8.
22. Al-Khalaf MI, Kholoud S Ramadan KS. Oxidants and Antioxidants Status in Bronchial Asthma. Asian Journal of Applied Sciences. 2013;1(4):123-33.
23. Jiang L, Diaz PT, Best TM, Stimpfl JN, He F, Zuo L. Molecular characterization of redox mechanisms in allergic asthma. Ann Allergy Asthma Immunol. 2014;113(2):137-42. doi: 10.1016/j.anai.2014.05.030.
24. Birben E, Sahiner UM, Sackesen C, Erzurum S, Kalayci O. Oxidative stress and antioxidant defense. World Allergy Organ J. 2012;5(1):9-19. doi: 10.1097/WOX.0b013e3182439613.
25. Demko IV, Sobko EA, Chubarova SV, Soloveva IA, Kraposhina AYu, Medvedeva NN, et al. [Features of the systemic inflammation, external respiration functions and morphological structure of the bronchial mucous membrane in severe bronchial asthma.]Siberian Medical Review (Krasnoyarsk). 2014;(5):47-52. [Article in Russian]
26. Raju KR, Kumar MN, Gupta S, Naga ST, Shankar JK, Murthy V, et al. 5-Aminosalicylic acid attenuates allergen-induced airway inflammation and oxidative stress in asthma. Pulm Pharmacol Ther. 2014;29(2):209-16. doi: 10.1016/j.pupt.2014.07.007.
27. Al-Harbi NO, Nadeem A, Al-Harbi MM, Imam F, Al-Shabanah OA, Ahmad SF, et al. Oxidative airway inflammation leads to systemic and vascular oxidative stress in a murine model of allergic asthma. Int Immunopharmacol. 2015;26(1):237-45. doi: 10.1016/j.intimp.2015.03.032.
28. Kang JH1, Kim KS, Choi SY, Kwon HY, Won MH. Oxidative modification of human ceruloplasmin by peroxyl radicals. Biochem Biophys Acta. 2001; 1568(1):30–6.
29. Goldstein IM, Kaplan HB, Edelson HS, Weissmann G. Ceruloplasmin. A scavenger of superoxide anion radicals. J Biol Chem. 1979; 254(10): 4040–5
30. Gutteridge JM. Inhibition of the Fenton reaction by the protein ceruloplasmin and other copper complexes. Assessment of feroxidase and radical scavenging activities. Chem Biol Interact. 1985;56(1):113–20.
31. Lazutkina EL, Muzychenko LM, Landyshev JuS, Tsyrendorzhiev DD, Lazarenko LL. Peculiarities of pro- and antioxidant status of blood serum in bronchial asthma patients with varied sensitization. Bulletin Physiology and Pathology of Respiration (Blagoveshchensk). 2014;51:15-19. [Article in Russian].