

CORRECTION LIPID PEROXIDATION WHEN EXPOSED TO INDUSTRIAL AEROSOLS COPPER PRODUCTION

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Abstract

The article presents the results of experimental studies of bronchoalveolar lavage and oxidative metabolism of lipids in the impacts of industrial copper smelting production factors. Considered features changes of LPA products and antioxidant enzyme activity under the influence of aerosols and condensation disintegration. Correction of imbalances in the system of lipid peroxidation and antioxidant defense held antioxidant drugs orientation.

Key words: Copper smelting production, industrial aerosols, rats, bronchoalveolar lavage, lipid peroxidation, antioxidant enzymes, correction, probucol, revenol, tagansorbent

INTRODUCTION

In the hygienic assessment of working conditions in the production of non-ferrous metals is essential formation and release of dust into the work area, the components of which have toxic, fibrogenic, carcinogenic and other adverse biological actions (tall OF, Likhachev EI Tartakovskaya L. J. et al. 2004).

One of the key problems of occupational diseases is remain bronchopulmonary disease caused by exposure to industrial aerosols.

Their physico-chemical properties of industrial dust metallurgical industry are highly dispersed aerosols disintegration (handling, crushing, sorting and drying of raw materials) or condensation (melting and casting metal) (tall OF, Likhachev EI Tartakovskaya LY, 2000).

If occupational diseases multiplicity of mechanisms of formation of reactive oxygen species in the body, the ambiguity and interdependence of antioxidant systems creates certain difficulties in diagnosis of oxidative stress and therapy (VS Belyaev, Shmelev LT, 1987; Dubinin EE 2001). Regulation LPO activity carried out not only with antioxidants, but also by changing the composition of fatty acids within the lipid bilayer of the cell membrane (Velichkovski BT, 1995, Tedtoeva AI Dzugkoeva IV et al, 2010) .

The aim of this work - to study the mechanism of action on lipid metabolism of harmful factors of production - aerosols smelting industry and evaluate the results of the correction drugs with antioxidant properties.

Material and methods. Explored hygienic characteristics of aerosols copper smelting production, conducted cytomorphological and cytochemical study macrophage content of the bronchi (BAL). Identified by biochemical methods the activity of antioxidant enzymes in the blood and the content of lipid peroxidation products in lung tissue, the liver of experimental animals.

In experimental modeling the effects of industrial aerosols copper smelting production animals were divided into two series depending on the method of dust : in the first series - intratracheal and the second - the inhalation method. In the first series 1 - Group - control animals (intact), the corresponding periods of the experiment - 1,2,3,4 and 6 months. Rats 2 group - injected intratracheally aerosol concentrator (spray disintegration) in terms of 1,2,3,4 and 6 months. 3 animal groups after 3 months of dust, intraperitoneally for 1 month was administered daily mixture of native enzymes - SOD at a dose of 400 units. And catalase - 750. , manufactured by "Serva" (Fein biochemica, GmbH & Co, Germany). 4 animal groups with the term dust correction was performed 6 months using therapeutic dose (50 mg / kg) probucol (production " quinacrine ") within 30 days daily. To improve the absorption of the drug was administered with vegetable oil. 5 - group of animals on the background of intratracheal administration of BP were corrected tagansorbentom that intragastrically administered by gavage once a day 1 at a dose of 40 mg / kg body weight for 10 days at the end of the 6- month period dust. Sorbent is based on bentonite clays in the Institute of Geological Sciences of the Republic of Kazakhstan and registered Head Office of Supervision and quality and standardization of medicines and medical equipment for the MoH number 481 Sorbent is montmorillonite (smectite) . Tagansorbent recommended for withdrawal from the body of heavy metals, metabolic disorders, allergic diseases.

For II series intratracheal dust animals has been used condensation aerosol, in terms of experience as the previous series. Animals 1 - probucol group administered at a dose of 12.5 mg / kg for 10 days for preventive purposes and then subjected to a 4-month dusting. 2 - Group animals exposed to dust for 6 months revenol received 90 mg / kg for 1 month before the end of the experiment.

Revenol - drug antioxidant nature containing special form of vitamin C, beta -carotene, maritime pine bark extracts , grape seed , turmeric fitozamin , ginkgo biloba, natural vitamin E. . Made in the USA, the company Newys, VMP Hematinsky branch company „Manos „certificate issued on the basis of expert opinion nutrition Institute.

Revenol has a powerful antioxidant effect due to its composition: pycnogenol , vitamin E, vitamin C, beta carotene, ginkgo biloba extract. Pycnogenol is extracted from grape seed and pine bark under strict pharmaceutical standards, without pesticides and cleaners tannins. Of all the currently known antioxidants - pycnogenol most effective. By its efficiency it exceeds 50 vitamin E and vitamin C once in 20 times. If vitamin C is excreted within the first 3 hours, and output per day is almost completely, pycnogenol is present in the body for about three days. Vitamin E, beta carotene and antioxidant effects reinforce each other and pycnogenol . Used special form of vitamin C, which increases its effectiveness. If within 24 hours of normal vitamin C excreted within 73 %, the shape special form of vitamin is within 5%. Undoubted effectiveness Revenol ingredients provided, inter alia, sound delivery system using a special microsphere shell - phytosomes . Due to the electric charge, phytosomes securely on the mucosa of the small intestine and releases its contents are not just in the intestinal lumen and in the area of membrane digestion , absorption of ingredients that provides almost no losses.

In the III series experience, the group of animals exposed to dust, inhalation chamber AK 4 months, they were corrected with a mixture of native enzymes - SOD at a dose of 400 units. And catalase - 750 manufactured by "Serva" (Fein biochemica, GmbH & Co, Germany intraperitoneally within 1 month before the end of the experience.

RESULTS OF STUDY

Research of sanitary conditions basic labor:

shops Balkhash Mining and Metallurgical Combine has revealed that one of the major harmful

factors is a manufacturing base metal aerosol. In the air of the working area of the basic trades motes smaller than 5 microns ranged from 75.9% to 81.3%, the proportion of dust particles 5-10 microns increased from 10.3% to 14% and more than 10 microns in size from 7.1 to 10% 5%.

Aerosol disintegration (AP) of concentrating factory is a multicomponent comprising: Copper - 0.6% free silicon dioxide - 14.2% - 15% lead and - 0.01%, 0.02% zinc, barium-0 15% arsenic - 0.03%, and other metals.

Manufacturing spray metallurgical plant relates to condensation aerosols (AA) multicomponent containing: Copper - 10% and free silicon dioxide - 2.5%, lead - 1%, 1% zinc, barium - 1%, titanium oxide - 1 2% of arsenic - 0.3% chromium - 0.1% cobalt - 0.03%, Ni - 0.03%, and other metals.

The results of cytomorphological and cytochemical studies macrophage contents of bronchi (BAL) have shown that disintegration of the dust has a pronounced cytotoxic effect. After 1 month intratracheal injection of aerosols disintegration of experimental animals in the bronchoalveolar lavage fluid of rats is reduced the number of alveolar macrophages (AM) and an increasing number of destructive AM to a greater extent than the effects of aerosol condensation. Such dynamics is observed at the level of phospholipids (PL) in phagocytes: in the first month of the experiment under the influence of aerosols disintegration PL content exceeds 2 times compared to the impact of polymetallic condensation aerosol, but with increasing duration of the experiment, the difference decreases. Predominance of neutrophils in the BAL fluid by the action of condensation aerosols indicates inflammatory impact on her lungs.

Under the influence of aerosol condensation after 1 month in the morphological picture of bronchoalveolar lavage changes were less pronounced compared with aerosol disintegration: NL content increased 2-fold reduction of the number of AM at 56%, although the number of destroyed alveolar macrophages was similar to that in the previous series ($54 \pm 7,04\%$), but only the content of the PL increased by 40%. After 4 months of the experiment, after condensation aerosol administration the level of AM decreased on average by 78%. As against the increase in the amount of destructive macrophages observed increase in PL (2.5 times). After 6 months the animals intratracheal dust level condensation aerosol alveolar macrophages remained reduced by 70% and the

AM was destroyed by $64 \pm 7,2\%$, the number of lymphocytes decreased by 80% compared with the control. Contents of PL 3 times higher than the benchmarks.

Thus, the results of studies BAL - aerosols for disintegration characteristic more cytotoxic effect, and for the condensation aerosol - inflammatory. Polymetallic spray disintegration, causing activation of phagocytosis and oxidative "explosion" in phagocytes and the generation of reactive oxygen species, leads to increased lipid peroxidation (Okada Mitsushi, Inoue Yoko, Karube Hitomi, et.al., 2001), which was manifested in increasing conjugated diene and ketodienes plasma in erythrocytes almost all periods of the experiment. Activation of lipid peroxidation (LPO) accompanied by an increase of TBA- reactive products in the early stage of the experiment and at the stage of severe pathology in the bronchopulmonary system (6 months) , while in the stage of pathological changes (3 and 4 months), the level of TBA- reactive products were not significantly different from the control. According V.A.Guseva (1987), chemiluminescent study showed decreased ROS generation alveolar macrophages and leukocytes in the peripheral blood in comparison with those at the early stage of interstitial lung diseases.

Apparently, changes may reflect the identified characteristics of the alveolar macrophage function in late sclerotic stage of phagocytic cells when it is transformed into the cell mainly secreting and inducing proliferation and sclerosis. However at the same time, in the late stage in the blood was found an increase the content of lipid peroxidation products, probably as a consequence of severe hypoxia in the progression of the air-blood barrier block, but not due to increased generation of reactive oxygen species (ROS) by leukocytes. Final products of lipid peroxidation - Schiff bases (SHO) in serum were increased after 2 and 4 months of the experiment. Changes were moderate ($P < 0.01$) and lower ($P < 0.05$) degree of reliability, while noting the parallel increase in the content of TBA-reactive products in erythrocytes.

Under the influence of aerosols and condensation occurs activation of lipid peroxidation processes, evaluated to improve primary and secondary products - diene conjugates (DC) and ketodienes in blood plasma. However, the degree of activation of lipid peroxidation smaller, as evidenced by the lack of dynamics of DC and ketodienes 2 and 6 months. Similar situation A.V.Paranich et al. (2000) is considered as an indirect confirmation of a new level of dynamic equilibrium, providing the body's adaptation. TBA-RP level in plasma confirms lesser degree LPO activity at the organism level in this case. Significant increase in the level of TBA-RP noted in 1 month experience ($P < 0.05$) and stage of development of perivascular and peribronchial fibrosis ($P < 0.05$). Schiff bases were significantly elevated in the early ($P < 0.01$) and at the end of the experiment ($P < 0.01$). In erythrocyte the level of TBAreactive products significantly increased at a later date experience. Thus, at the organismal level, the activation of lipid peroxidation caused by exposure to both types of pollutants. However, this activation is caused largely aerosol condensation.

Assessment of the antioxidant defense system of the organism under the influence of aerosols disintegration revealed that plasma catalase activity increased at 3 and 4 months after intratracheal administration. The degree of reliability being respectively $P < 0,05$ and $P < 0,01$. In erythrocyte catalase activity has increased after 2 and 6 months ($P < 0,01$ and $P < 0,01$). These results suggest that activation of lipid peroxidation processes accompanied by increasing activity of catalase through 2, 3, 4 and 6 months, which indicates the relative safety of protective mechanisms against the background of the generalization of LPO processes.

At the beginning of the experiment the main role in the suppression of lipid peroxidation processes, apparently belongs to ceruloplasmin (CP) blood and superoxide dismutase (SOD) in erythrocytes. Under the influence of CPU activity reduces blood pressure in the blood is 3.4 times ($P < 0.001$), with oxidative stress is consumed primarily extracellular enzyme, which confirms the view (Menshikov EB, Zenkov NK, 1993; Klebanov GI Teselkin JO, Babenkova IV et al, 1999) that the enzyme in oxidative stress protection is less effective than protective effect of low molecular weight antioxidants. SOD activity increased 1.6-fold ($P < 0.05$). Subsequently, the activity of SOD in erythrocytes increased in almost all periods of the experiment except for 4 months, whereas ceruloplasmin activated in 3 months ($P < 0.01$) and GAP erythrocytes - in 2 months.

Results suggest that the action of polymetallic disintegration aerosols in reducing the activity of lipid peroxidation enzyme protection is inadequate. Reason for this is - rapid inactivation of constitutive enzymes pool free radicals and necessity of considerable time to induce their synthesis. Under these conditions, increases the value of low molecular weight compounds, whose redundancy and relative freedom of migration comes to the fore in the cell and tissue environment. Major role in antioxidant protection in the later stages of experience, apparently, is given in erythrocyte SOD, to a lesser extent catalase revealed part of the plasma and red blood cells, the smallest role is GAP erythrocytes with the conservation of ceruloplasmin.

In turn, under the influence of aerosols on the animal organism condensation ceruloplasmin activity decreased significantly by 53% ($P < 0.001$) (picture 1).

Significant contribution to the state of the LPO contributed SOD activity in red blood cells, which was significantly reduced in all terms of experience, ranging from 2 months. Catalase activity was significantly decreased in the blood 2, 3, 4 and 6 months, erythrocyte catalase - during 2, 3 and 6 months.

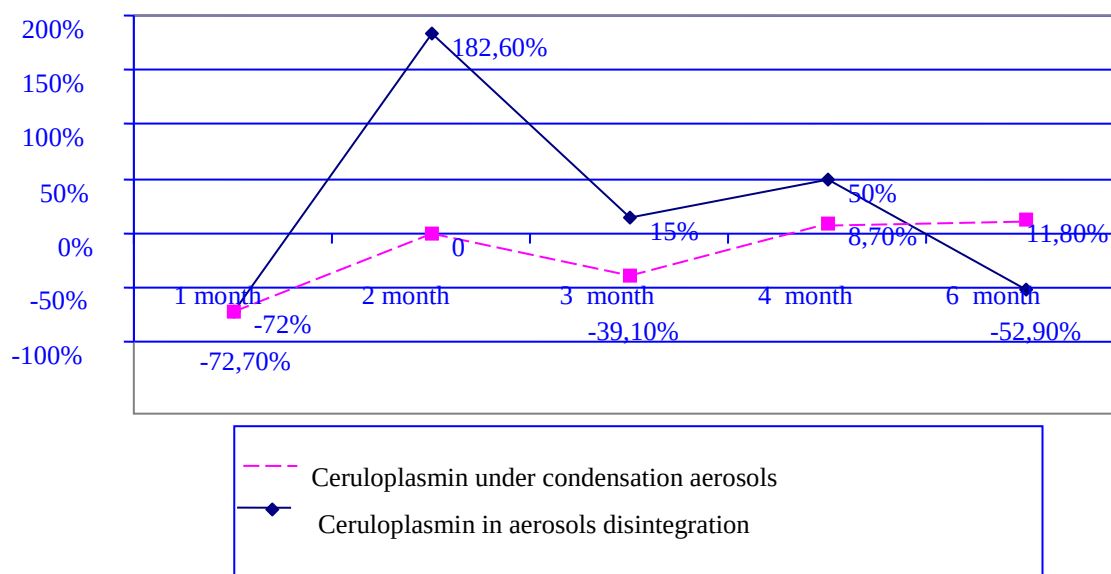


Figure 1 - Dynamics of ceruloplasmin activity of blood under the influence of aerosols and condensation disintegration

The main enzyme that allows to maintain a balance POL-AOP under the action of polymetallic condensation aerosol is glutathione peroxidase (MPO) activity, which does not change in 1 , 2, 3 and 4 months , but significantly increased after 6 months .According to Wetlands AA et al . (2003) , the catalase activity of the copper ions under the influence of changes slightly , indicating that the enzyme stability to copper ions . The results indicate that the effects of condensation aerosols reduce lipid peroxidation processes promoted increased use of enzymes AOD - SOD, catalase , GPO , ceruloplasmin , which enabled interrupt reaction PAUL stage of ROS .Research processes POL-AOP under the action of the rats disintegration aerosols and condensation allowed to establish features of the interaction of these systems and their conservation relative equilibrium : the products of lipid peroxidation in the blood largely accumulated by the action of aerosols disintegration due lack of effective use of the enzyme AOP system. Under the action of polymetallic condensation aerosol is much less accumulate in the blood products of lipid peroxidation, probably by making full use of the enzyme activity of the HPA system and save GPO activity.

Study of intermediate LP - TBA-RP in lung tissue under the action of aerosols disintegration established his significant increase only in the early experience and 6 months later. Under the action of condensation aerosols in the lungs tendency to increase the level of TBA-RP noted in one month experience. In the liver, a significant increase in its concentration was observed after 6 months of exposure to aerosols condensation. Aerosol disintegration caused tendency to increase in liver tissue at 2 and 3 months experiment.

Thus, the identified imbalance in the LPO-AOD is accompanied by increased levels of TBA-reactive substances by the action of disintegration aerosols in the lung tissue at the stage of fibrosis, and the action of condensation aerosols in the early stages at the height of "oxidative" stress (1 and 2 months of the experiment) .

Detected imbalance between the rate of lipid peroxidation and functional activity of the antioxidant system under the influence of factors of production - industrial aerosols involves the use of drugs with antioxidant properties.

Correction exposure aerosols disintegration SOD enzyme mixture (400 units.) And catalase (750 units.) In experimental animals, despite the activation of the erythrocyte catalase ($P < 0.01$) and in plasma ceruloplasmin (2 times) content indicators products LPO in the blood did not have a significant impact. At the same time, the use of SOD and catalase led to a significant reduction in the TAC-RP 21% of lung and in the liver by 22% ($P < 0.05$) as compared to the experimental group.

Tagansorbent at 6-month experiment helped to reduce the DC content in erythrocytes by 17% and the CD in plasma by 13%. From the TBA-RP in erythrocytes and plasma was a downward trend. At the same time tagansorbent suppresses the activity of SOD by 25% and the activity of extracellular enzyme CPU increased by 1.7 times. The preparation helped reduce the concentration of TBA-RP in lung by 39% in liver tissue by 29%.

Application of probucol in a dose of 50 mg / kg for correcting exposure aerosols disintegration for animals with advanced pathology (6 months) improved the oxidative metabolism in the blood.

Prophylactic administration of probucol in a dose of 12.5 mg / kg animals exposed to aerosol condensation within 4 months promoted the activation in erythrocyte SOD (2.2-fold) and catalase in plasma (4.8 times) and significantly reduces the levels of DC and NiO in the blood plasma ($p < 0.05$) compared with the experimental group, but the level of TBA-RP in the lungs and liver had no positive effect. Increasing the enzymatic function of SOD and catalase, presumably, is due to competitive binding of the active site of enzymes probucol rather than components of aerosols, which led to a decrease in the DC level and tendency to reduce the final products of lipid peroxidation.

The use of revenol on experimental animals exposed to aerosol condensation polymetallic revealed significant activation in plasma ceruloplasmin (2 times). Enzyme CPU chelated compound tying variable-valence metal ions, thereby preventing their involvement in the decomposition reaction of peroxides.

It is believed that this mechanism is one of the most important in the protection against oxidation of serum proteins and cell receptors, because in the intercellular fluids is weakened an enzymatic decomposition of peroxides that is well penetrating the cell membrane. By influence of revenol SOD activity in erythrocytes and GP suppressed as compared to the group without correction (respectively 56% and 57%).

There is a decline in the primary, secondary and final products of lipid peroxidation in the blood. Thus, the content of the DC plasma decreased in numbers by 78% in erythrocytes - 62% ketodienes - by 64% and the level of SHO - 86%. In lung homogenates and inhibition of hepatic lipid peroxidation processes by revenol not happens. Apparently, this may be due to different lipid content and antioxidant security tissues. But the revenol reduces the level of cholesterol in the liver by 54%, which may not exclude the effects of the drug on its synthesis.

Still remains an open question about the doses of antioxidant vitamins, having therapeutic value. It is obvious that the dose should be significantly higher than the recommended daily intake. Balanced composition of antioxidant vitamins in the drug - revenol significantly reduces the relative content of hydroxyproline in the lungs at the stage formed pathology.

Injection to rats exposed by inhalation exposure, a mixture of native enzymes - SOD and catalase, stabilized the LPO, acting as a replacement therapy enzyme activity. Couple "of vitamins E and C" are real examples of coordinated interaction of hydrophobic and hydrophilic antioxidants (AA Boldyrev, 2003).

Findings: Polymetallic aerosol concentrating factory Balkhash minning combine with copper content - 0.6% free silica - 15%, according to cytomorphology, cytochemistry bronchial alveolar macrophage content, is characterized as a cytotoxic spray disintegration and moderately fibrogenic action. Dust metallurgical shop - spray condensation with a copper content - 10% free silicon dioxide - 2.5% is characterized as weak fibrogenic with "inflammatory" action.

Disintegration of the impact of aerosols and condensation in the blood causes the activation of lipid peroxidation, more pronounced in the first case. In the step of forming under the influence of aerosols pneumofibrosis disintegration significant accumulation occurs RP - TAC (143 %) in the lungs, and by the action of condensation aerosol - in the liver (70 %). In the early stages of exposure to aerosols of both main antioxidant enzyme performs the role of ceruloplasmin, and in later stages - when exposed to an aerosol of disintegration - SOD enzyme by condensation - glutathione peroxidase.

Using native enzymes SOD and catalase, as well as drug tagansorbenta for correction of oxidative lipid metabolism under the influence of aerosols on the body disintegration stabilize lipid peroxidation in lung and liver. Prophylactic administration of probucol significantly reduces the levels of DC and the SHO in the blood plasma. Correction drug condensation aerosol exposure revenol helped to reduce the level of primary, secondary and final products of lipid peroxidation in the blood. In lung homogenates and inhibition of hepatic lipid peroxidation processes revenolom not is probably due to the different lipid content and antioxidant security tissues.

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