CLINICAL AND PHARMACOLOGICAL PERSPECTIVES ON THE USE OF ANTIOXIDANT DRUGS

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Abstract. This article explores the clinical and pharmacological aspects of antioxidant drug use, emphasizing their role in preventing and treating oxidative stress-related diseases. Antioxidants play a crucial role in neutralizing reactive oxygen species (ROS) and reducing cellular damage, making them valuable in managing conditions such as cardiovascular diseases, neurodegenerative disorders, and metabolic syndromes. The pharmacokinetics, mechanisms of action, and therapeutic efficacy of various antioxidant agents, including natural and synthetic compounds, are discussed. Additionally, potential risks, drug interactions, and the latest advancements in antioxidant therapy are reviewed to provide a comprehensive understanding of their clinical applications.

Keywords: Antioxidants, oxidative stress, reactive oxygen species, pharmacokinetics, therapeutic efficacy, neurodegenerative diseases, cardiovascular protection.

INTRODUCTION

Currently, antioxidants and pathologies associated with hypoxic conditions continue to receive much attention. It is still difficult to say what comes first, pathology or oxidative stress, but these are two inextricably linked concepts. Oxidation processes constantly occur in the cell and perform various vital functions in the existence of the organism: they participate in the regulation of cellular processes, vascular tone, phagocytosis, activate the immune reactions of leukocytes, participate in chemotaxis, the activity of intracellular enzymes (the system of oxidase enzymes, cytochrome P450, etc.), etc. [1]. Regulation of these reactions is carried out by the body's antioxidant defense system, which includes

enzymatic (superoxide dismutase, catalase, glutathione system) and non-enzymatic (ceruloplasmin, uric acid, ascorbic acid, vitamin E, ubiquinone, etc.) components.

MATERIALS AND METHODS

Oxidative stress is an imbalance of the body's internal antioxidant defense system, when the amount of endogenous and exogenous oxidants greatly prevails over antioxidants, and the latter cannot cope with the load. Oxidative stress is an important pathogenetic factor in many diseases, especially bronchopulmonary and cardiovascular diseases [2, 3]. The participation of free radicals in the pathogenesis of many diseases has been proven (shock of various origins; atherosclerosis; cerebral, coronary and peripheral circulatory disorders; diabetes mellitus and diabetic angiopathy; rheumatoid, inflammatory and degenerative diseases of the musculoskeletal system; eye damage; pulmonary diseases; oncological pathology; Alzheimer's and Parkinson's disease, thermal injuries; various intoxications, etc.) [3, 4]. Some chronic pathologies may be a consequence of the autotoxic action of reactive oxygen species (ROS): for example, inflammation of the pancreas can lead to diabetes. A possible reason for this is the induction of No synthase in beta cells, which, together with NADPH oxidase of phagocytes, causes the destruction of insulin-producing cells [1].

RESULTS AND DISCUSSION

The contribution of various links of free radical oxidation in the development of certain pathologies may differ: for example, in atherosclerosis, the most important are lipid peroxidation reactions, in neurodegenerative diseases - oxidative damage to proteins, in oncological diseases - modification of nucleic acids [1, 3]. Accordingly, the most effective will be drugs with different targets of antioxidant action. At the moment, antioxidants are universal substances that, when present in low concentrations compared to the oxidized substrate, significantly inhibit its oxidation, and also regulate the composition, structure and activity of cell membranes [2, 3]. According to other authors, antioxidants are substances that,

in low concentrations, inhibit the processes of oxidation of organic substances with oxygen by various mechanisms in model systems [4].

Since the mechanism of initiation and course of oxidative stress are different, antioxidant drugs also differ in their chemical structure and have different mechanisms of action. The following groups of antioxidants are distinguished: Group 1 - inhibitors of the main pathways of ROS formation: xanthine oxidase inhibitors (allopurinol, folic acid); No-synthase inhibitors (NG-nitro-l-arginine); Group 2 - ROS scavengers or direct antioxidants that inactivate ROS: inactivation of superoxide anion radical (urea, ceruloplasmin, nicotinic acid); hydroxyl radical (mannitol, dimethyl sulfoxide, hypoxene, tryptophan, l-methionine); peroxynitrite (melatonin), singlet oxygen (histidine); No (glutathione, unithiol, methionine); Group 3 – scavengers of free radicals of fatty acids and lipid hydroperoxides (direct antioxidants-inactivators): derivatives of 6-oxychromanes (tocopherols), derivatives of oxypyridines (mexidol, emoxipine, ethoxidol); derivatives of phenols (ionol, phenosan), flavonoids, aliphatic and aromatic sulfur-containing compounds (glutathione, acetylcysteine, methionine); derivatives of oxyacids (succinic, gallic, chlorogenic, benzoic, ascorbic), ubiquinones, selenites, retinols and carotenoids; Group 4 – recombinant preparations of antioxidant enzymes (superoxide dismutase, catalase); Group 5 – recombinant preparations of factors regulating the expression of endogenous antioxidants (preparations hSP70, hIF (hypoxia-inducible factor – factor inducing hypoxia)-1α, glutoredoxin) [6, 7, 8]. Of the listed groups, the most widely used are direct-acting antioxidants – tocopherols, quinones, phenolic compounds, derivatives of 3-oxypyridine. Currently, three drugs derived from 3-hydroxypyridine have found application in clinical practice: emoxypine, mexidol and ethoxydol (methylethylpyridinol hydrochloride (MEP hydrochloride), ethylmethylhydroxypyridine succinate (EMHP succinate) and ethylmethylhydroxypyridine malate (EMHP malate), as

well as polyquinone derivatives trimetazidine and hypoxene as inhibitors of free radical processes.

The antioxidant activity of oxypyridines depends on the polarity of the hydroxy group and the introduction of electron-donor substituents into the molecule.

Emoxipine began to be successfully used for the treatment of intraocular hemorrhages, diabetic retinopathy, and later also for myocardial infarction and glaucoma.

Since ischemic manifestations sharply increase the formation of ROS in mitochondria during uncoupling of the respiratory chain and oxidative phosphorylation, then derivatives of oxypyridines have been successfully used in such diseases [1]. In patients with chronic coronary heart disease, MEP hydrochloride, unlike trimetazidane, increases the effectiveness of antiarrhythmic therapy for supraventricular extrasystole and ventricular rhythm disturbances in patients with coronary heart disease. When combining antiarrhythmic drugs with MEP hydrochloride and trimetazidine, the ejection fraction increases compared to the initial value. In this case, trimetazidine reliably, unlike MEP hydrochloride, increases the minimum heart rate in combination with atenolol and cordarone. The potentiating effect of MEP hydrochloride and trimetazidine on the antiarrhythmic activity of cordarone and allapinin in supraventricular extrasystoles was revealed according to the criterion of reducing the absolute number of ventricular heart rhythm disturbances [2].

Medicines with antioxidant action

Pharmacotherapeutic group	Active ingredient INN	Trade name
Antioxidants and antihypoxants	ethyl methylhydroxy pyridine succinate	Medomexi, astrox, mexidant, mexidol, mexicor, mexipridol, mexiprim, mexifin, neurox, cerekard
	methyl ethyl pyridinol	Cardioxipin, methylethylpyridinol-escom, emoksi-optik, emoxipin, emoxibel

	ethyl methylhydroxy pyridine malate	ethoxidol
	Sodium polydihydroxyphenylene thiosulfonate	Gipoxen, Olifen
	Trimetazidine	Preductal®, antisten, deprenorm, medarum 20, metagard, predizin®, precard, rimekor, trimetard, trimetazide
	Pentahydroxyethyl naphthoquinone	Histochrome, echinochrome
	Dihydroquercetin	Dihydroquercetin, dikvertin
	Superoxide dismutase (AO)	Rexod-OF, Rexod
Cardiotonic agent of non-glycoside structure	Ubidecarenone	Kudesan, kudevita, valeocor-Q10
Detoxifying agent	Glutathione	Glation
Metabolic agent	Carnitine	Levocarnitine, elkar, Carnitene
	Arginine glutamate	Glutargin
	Cytoflavin	Inosine + Nicotinamide + Riboflavin + Succinic acid
	Cytochrome C	Cyto-mak
	Sodium fumarate	Confumin
Vitamins	Alpha-tocopherol acetate	Vitamin E
	Ascorbic acid	Ascorbic acid, vitamin C
Anti-acidemic agent	Dimethyl oxobutylphosphonyl dimethylate	Dimephosphone
Adaptogenic agent	Hydroxyethylammonium methylphenoxyacetate	Trecrezan
Antigoutagric agent	Allopurinol	Allopurinol-eGIS

The fundamental difference between EMGP succinate and trimetazidine is its ability to activate the succinate dehydrogenase pathway of glucose oxidation, which switches cellular metabolism under hypoxic conditions to a more oxygen-saving direction of energy exchange than trimetazidine. The mechanism of action of EMGP succinate is determined by the presence of succinic acid in its composition, due to which energy metabolism in the cell improves by optimizing the functioning of the mitochondrial respiratory chain, which contributes to the stabilization of the cell membrane, a decrease in post-hypoxic metabolic acidosis, and the activation of macrophages by anaerobic products against the background of

oxygen deficiency [3]. The clinical efficacy of emgp succinate against the background of thrombolytic therapy in an experiment in 120 patients with acute cerebrovascular accidents (ACVA) compared to the control group was manifested by regression of general cerebral disorders and significantly faster restoration of motor functions, and a decrease in the number of somatic complications [4]. In patients with stage I–II cerebrovascular insufficiency who received treatment with emgp succinate, there is a statistically significant relationship between the degree of regression of neurological symptoms in points and the initial level of lipid hydroperoxides, compared to the control group [2]. In the recovery period of ischemic stroke, the use of EMGP succinate improves well-being (reduces headaches, dizziness, improves sleep), memory and mnemonic functions (according to the results of the test, memorizing 10 words), reduces the level of depression (according to the results of the Hamilton Gerontological Depression Scale). Analysis of lipid metabolism and blood coagulation system parameters in patients who have suffered an ischemic stroke before and after taking EMGP succinate showed only a statistically significant decrease in fibrinogen and prothrombin index, while the content of total cholesterol and LDL and VLDL had only a slight tendency to decrease [3].

EMGP malate on the myocardial ischemia model also promotes stabilization of cardiomyocyte membranes, decrease in the degree of tissue hypoxia and accumulation of ATP in the heart homogenate with an increase in the activity of antioxidant enzymes SOD and catalase and a decrease in lipid peroxidation products (LPO) [4]. In endogenous intoxication, the central pathogenetic link in phospholipid destabilization of biomembranes of the studied cellular structures (myocardium, liver, erythrocytes, platelets) is the intensification of LPO processes and phospholipase activity, which determines an important component of the membrane labilization mechanism, causing the depth of destructive processes at the local and systemic levels. The use of EMGP malate in endogenous intoxication

helps to reduce the severity of lipid metabolism disorders in myocardial cellular structures and is determined by its ability to reduce (by 21.68%) the intensity of free radical reactions of lipid peroxidation in the tissue structures of the organ, reduce (by 21.22%) the activity of phospholipase-A2, restore the functional parameters of erythrocytes and platelets, increase the detoxification and lipid-regulating functions of the liver, correct the coagulation-lytic potential of myocardial tissue structures, which is the most important component in the restoration of electrophysiological and metabolic characteristics of the heart muscle [5].

The antihypoxic drugs trimetazidine and hypoxen are not direct antioxidants. Trimetazidine optimizes energy metabolism in the heart, which is the result of inhibiting fatty acid oxidation by suppressing long-chain 3-ketoacyl CoA thiolase, which leads to increased glucose oxidation, restoring the coupling between glycolysis and oxidative decarboxylation, which causes myocardial protection from ischemia, and also has an antioxidant effect on NADPh-dependent lipid oxidation in Smirnov brain homogenates. The anti-ischemic effect of trimetazidine, equivalent to beta-blockers and calcium antagonists, has been proven, but the drug is better tolerated. It has been established that trimetazidine is effective both as monotherapy and in combination with traditional antianginal drugs [7]. The use of hypoxen is clinically justified as part of complex therapy in patients with CHF I–II FC, as a means of improving the clinical course of the disease [6]. The presence of a thiosulfate group in the drug gives it noticeable antioxidant properties that ensure the neutralization of lipid peroxidation products. In addition, hypoxen, due to the peculiarities of its structure, has a high electron-volume capacity due to the polymerization of phenolic nuclei in the ortho-position, which allows it to have a pronounced antihypoxic effect. This lies in its ability to shunt the 1st and 2nd complexes of the mitochondrial respiratory chain, inhibited due to hypoxia, which helps to increase the efficiency of oxygen use. The result of these reactions is the

restoration of aerobic processes of cellular respiration, the generation of macroergs, an increase in the energy-synthesizing function of mitochondria, and also the activation of the mitochondrial respiratory chain, ultimately leading to the rapid resynthesis of ATP.

Many bronchopulmonary pathologies (pneumonia, COPD, asthma, emphysema) are also associated with the development of oxidative stress, which correlates with atmospheric pollution by strong oxidants (No, No2, Co, O3), dust particles, allergens, etc. In inflammatory processes in the lungs, LPO products affect the lipid composition and structural properties of cells, as well as their energetics through a direct effect on the processes of oxidative phosphorylation in mitochondria [3] According to GolD (Global Initiative for Chronic Obstructive Lung Disease), antioxidants are among the promising pharmacological drugs recommended for the treatment of COPD. As a result of treatment with hypoxen in patients with COPD with moderate hypoxemia, a reliable improvement in arterial blood oxygenation, a decrease in shortness of breath during daily activity, an increase in tolerance to physical activity, a statistically significant increase in the distance traveled and optimization of the cardiorespiratory response were recorded [4].

Direct-acting antioxidants also include phenolic compounds and ubiquinone. Their antioxidant effect depends on the presence of hydroxyl groups in the ortho- and para-position of the ring, which have a labile electron structure and the ability to reversibly oxidize to quinone. Dihydroquercetin reduces the intensity of lipid peroxidation in patients with acute pneumonia after just 10 days, normalizes the content of alpha-tocopherol in blood plasma, protects vascular walls from damage, and relieves swelling during inflammation. In patients with unstable angina, it reduces signs of myocardial ischemia (as part of complex therapy) [6]. The use of phenolic antioxidants (dihydroquercetin, tanakan, probucol) in type 2 diabetes mellitus leads to normalization of the blood lipid spectrum and reliably reduces the

manifestations of oxidative stress both at the plasma level and at the level of formed elements of the blood, leading to the normalization of the functional activity of erythrocytes (by the Na+/ h+o6Meha rate) and platelets (by the degree of aggregation). Probucol and diquertin reliably reduce the insulin resistance index (IR-hoMA) and increase the insulin sensitivity index (ISI), which directly correlates with a decrease in oxy-LDL and MDA in LDL in blood plasma [2]. Coenzyme Q10 (ubiquinone) is an endogenous antioxidant and a component of the succinate oxidase part of the electron transport chain in mitochondria. Its protective role in coronary heart disease is due to its participation in the processes of cardiomyocyte energy metabolism, as well as its high donor properties and ability to restore lipid radicals. In the reduced state, ubiquinone inhibits superoxide anion radical and other organic radicals [3]. Clinical studies of recent decades have shown the therapeutic effectiveness of coenzyme Q10 in the complex treatment of coronary heart disease, arterial hypertension, and atherosclerosis. In the treatment of patients with coronary heart disease, its use can be combined with beta-blockers and angiotensin-converting enzyme inhibitors (ACEIs). However, the drug is ineffective in patients with low tolerance to physical activity and in the presence of a high degree of stenosis of the coronary arteries [4]. A large number of experimental studies allow us to classify atherosclerosis as a classic free-radical pathology, since atherosclerosis is characterized by an increase in lipid peroxidation and accumulation of oxidized products with a decrease in the function of the antioxidant system. The studies conducted have shown that atherogenic lipoproteins are simultaneously MDA-modified [5].

In diabetic patients, the formation of radical intermediates of glucose autooxidation during its co-oxidation with polyene phospholipids of the outer layer of LDL particles causes the accumulation of intermediates of glucose oxidative metabolism - glyoxal and methylglyoxal, which provokes the occurrence of carbonyl stress. Moreover, these dicarbonyls, as well as MDA, cause atherogenic

modification of LDL. Therefore, during therapy with metformin, which is capable of utilizing methylglyoxal, oxidation in diabetic patients is inhibited to a greater extent than when taking other hypoglycemic drugs. That is, along with the latter, it is also necessary to use antioxidant drugs [5]. It is known that during the treatment of atherosclerosis against the background of taking statins, the concentration of coenzyme Q10 in the blood plasma decreases [6], therefore it would be advisable to prescribe antioxidant drugs together with statins. An experimental study on rats with cholesterol dyslipidemia showed that the use of emgP malate in combination with lovastatin helps to maintain the level of high-density lipoprotein cholesterol and reduce the atherogenicity index after statin withdrawal and also prolongs its positive effect on heart rate variability, increasing the activity of the parasympathetic component and maintaining the balance of autonomic regulation. EMGP malate, by inducing the cytochrome P450 isoenzyme 3A4, which reduces its activity during the accumulation of hydroperoxides in the body, promotes the regulation of cholesterol metabolism and synthesis by activating the corresponding hydroxylases, while maintaining electron transfer in the mitochondrial respiratory chain [7]. Recently, interest in the thiol-containing amino acid N-acetylcysteine (N-AC) has increased. Direct antioxidant activity is due to the ability of free thiol groups of N-AC to interact with active oxygen species, and indirect antioxidant activity is associated with the fact that it plays the role of a precursor of glutathione.

A derivative of naphthoquinones, pentahydroxyethylnaphthoquinone (histochrome), is a chelator of variable valence ions and is capable of neutralizing the main initiators of non-enzymatic peroxidation of membrane lipids, iron cations, which accumulate in the area of ischemic tissue damage. Histochrome also eliminates damage to the calcium-transforming system of muscle at the level of intracellular structures of the sarcoplasmic reticulum, reduces the release of creatine kinase from damaged structures and the accumulation of toxic peroxides

in them. The use of histochrome in the treatment of central atherosclerotic macular degeneration significantly improves visual functions (visual acuity, expansion of the visual field, improvement of electrophysical parameters, rheographic coefficient) [3]. However, the experiment showed a dose-dependent antioxidant effect of histochrome on an inflammation model: 10 mg/kg of the drug stimulates the prooxidant system, and when the dose is reduced tenfold, its antioxidant effect predominates [4].

CONCLUSION

Overall, it can be noted that there is no area where the use of antioxidants can be recommended without further research. In some areas, there are promising results (in the treatment of complex patients in surgical departments, or in the fight against diabetic neuropathy, as well as the treatment of age-related retinal degeneration). In addition, antioxidants may find application in other specialties, from dermatology to pulmonology, but these agents can still be considered experimental. They need to be studied and used only in specific groups of patients. On the other hand, given the fact that they are relatively cheap, if their effectiveness in these populations is confirmed, the cost-effectiveness of antioxidant drugs may be relatively high, which confirms the need for further research in this area.

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