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OXIDATIVE STATUS AND STATE OF ERYTHROCYTE MEMBRANES IN PATIENTS WITH CONTROLLED AND TRUE RESISTANT ARTERIAL HYPERTENSION

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Today, arterial hypertension is a global health problem in the whole world. The purpose of the study is to assess the oxidative status and the structural condition of erythrocyte membranes in patients with controlled and true resistant arterial hypertension. In patients, a deterioration in the oxidative status in the development of oxidative stress is observed as evidenced by a significant ($p < 0.05$) increase in myeloperoxidase activity, accumulation of lipid and protein oxidation products, decreased antioxidant enzyme activity and reduced glutathione content. Structural and dynamic changes in the membranes of erythrocytes in these patients by the method of spin probes using the nitroxyl radical AdTEMPO and the damage to the structural organization of the lipid layer and proteins integrated in it as well as antioxidant system of erythrocytes were demonstrated. The obtained results may indicate an impairment of the structural organization of the lipid layer and its integrated proteins.

Key words: controlled and true resistant arterial hypertension, oxidative status, erythrocyte membranes, electron paramagnetic resonance.

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ОКСИДАТИВНИЙ СТАТУС І СТАН МЕМБРАН ЕРИТРОЦИТІВ У ПАЦІЄНТІВ ІЗ КОНТРОЛЬОВАНОЮ ТА РЕЗИСТЕНТНОЮ АРТЕРІАЛЬНОЮ ГІПЕРТЕНЗІЄЮ

На сьогодні артеріальна гіпертензія є глобальною проблемою охорони здоров'я у всьому світі. Метою роботи є дослідження оксидативного статусу та структурного стану мембран еритроцитів у пацієнтів із контрольованою і резистентною артеріальною гіпертензією. У пацієнтів спостерігається порушення оксидативного статусу в бік розвитку оксидативного стресу, що підтверджується достовірним ($p < 0,05$) зростанням активності мієлопероксидази, накопиченням продуктів окислення ліпідів та білків, зниженням активності антиоксидантних ферментів та вмісту відновленого глутатіону. Вперше досліджено структурно-динамічні зміни мембран еритроцитів у цих пацієнтів методом спінових зондів із застосуванням нітросильного радикалу AdTEMPO та продемонстровано порушення структурної організації ліпідного шару та інтегрованих в ньому білків, а також антиоксидантної системи клітин еритроцитів. Отримані результати можуть свідчити про порушення структурної організації ліпідного бішару та інтегрованих в ньому білкових структур мембран еритроцитів.

Ключові слова: контрольована і резистентна артеріальна гіпертензія, оксидативний статус, мембрани еритроцитів, електронний парамагнітний резонанс.

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Today, arterial hypertension (AH) is a global health problem in the whole world. In Ukraine, more than 40 % of the adult population has elevated arterial pressure [1]. AH is an important risk factor for the development of cardiovascular diseases first of all atherosclerosis, which leads to the dysfunction of many organs, including the heart, blood vessels, and kidneys [1]. The etiology of AH includes the interaction of genetic, environmental and pathophysiological factors that affect the regulatory systems of the body.

With this, the effect of many factors leads to the development of oxidative stress, which is characterized by a disrupted balance between the functioning of prooxidant and antioxidant systems. Excessive production of reactive oxygen species (ROS) against the background of reduced functional

activity of the antioxidant system can lead to the development of endothelial dysfunction, inflammation, increased vessel contractibility, remodeling of the cardiovascular system, renal dysfunction and stimulation of the sympathetic nervous system [10, 13, 14]. In the development of oxidative stress, one of the important targets of the excessive ROS amount effect is biological membranes, where “avalanche” reactions of free radical oxidation of lipids, proteins are activated resulting in structural and functional changes in membranes, leading to disruption of their functions [14].

Electronic paramagnetic resonance (EPR) is a modern method of studying the structural and dynamic properties of biological membranes and macromolecules. The EPR method using spin probes permits to assess the barrier function of biological membranes that are permeable to hydrophilic spin probes, and lipophilic probes can be integrated into the lipid bilayer of membranes [7]. Spin probes can be used to study the state of cell membranes in the early stages of metabolic disorders.

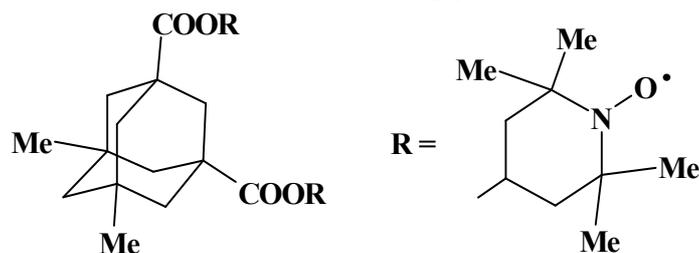
Despite significant advances in the treatment of AH, many patients with hypertension fail to achieve the recommended blood pressure values even in treatment with 3 or more antihypertensive drugs, including diuretics in the maximum or greatest possible doses [8]. Resistance to antihypertensive therapy is associated with an increase in the risk of cardiovascular complications by more than 2 times compared to patients with controlled AH (CAH) [6]. Observational studies show that patients with true resistant hypertension (TRAH) have a higher risk of cardiovascular complications even after reaching the target blood pressure compared to patients who do not have resistance to treatment [6].

The purpose of the study was to explore the oxidative status and structural organization of the lipid layer of erythrocyte membranes in patients with controlled and true resistant arterial hypertension.

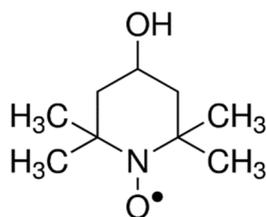
Materials and methods. The study included 60 people, including 40 patients (NSC “Strazhesko Institute of Cardiology”, NAMS of Ukraine, Department of Hypertension) male and female aged 45 to 65 years with CAH (AH stage II) (group 1, 20 patients) and TRAH (group 2, 20 patients). The number of men (52 %) and women (48 %) did not differ significantly. The control group consisted of 20 healthy donors of the appropriate age and gender.

Patients with TRAH received standardized therapy in the form of a triple fixed combination of renin-angiotensin-aldosterone system blocker/calcium antagonist/diuretic in the maximum tolerated doses. Patients were familiar with the terms of the study and gave informed consent to participate in it. The study did not include patients who suffered myocardial infarction less than 6 months before, revascularization, stroke, clinical manifestations of heart failure, valvular heart disease requiring surgery, cancer in the past 5 years, pregnancy, alcohol or drug abuse, decompensated diabetes mellitus. Patients received basic therapy in accordance with the Recommendations of the European Society of Cardiology and the Association of Cardiologists of Ukraine.

Blood sampling was performed from the ulnar vein in the fasted state. Studies were also performed on erythrocytes before and after three washes with 0.9 % sodium chloride solution. The arylesterase activity of paraoxonase-1 (PON-1) (EC 3.1.1.2) was determined spectrophotometrically by the rate of phenylacetate conversion to phenol at 270 nm [15]. Peroxidase activity of myeloperoxidase (MPO) (EC 1.11.1.7) in blood plasma was assessed by oxidation of chromogenic substrate 3,3'-dimethoxybenzidine spectrophotometrically. To exclude the possible effect on the result of other peroxidases, MPO inhibitor - 4-aminobenzoic acid hydrazide was added to the plasma [15]. The activity of superoxide dismutase (EC 1.15.1.1) was determined by the decrease in the intensity of adrenaline autooxidation to adrenochrome [3]. The activity of catalase (EC 1.11.1.6) in the samples was determined spectrophotometrically [3]. The content of products that react with thiobarbituric acid (TBA-PP) and the content of protein oxidation products (POP) in the blood serum were determined spectrophotometrically [15]. The content of reduced glutathione was determined in hemoglobin-free blood filtrates using Elman's reagent [12]. The microviscosity of erythrocyte membranes was assessed by spin probes using a nitroxyl radical based on adamantane [7].



5,7-Dimethyladamantane-1,3-dicarboxylic acid bis(1-oxyl-2,2,6,6-tetramethylpiperidinyl-4) ester (AdTEMPO) (synthesized at SE “V.P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry of the National Academy of Sciences of Ukraine”, Kyiv, Ukraine).



4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (OH-TEMPO).

The final probe concentration in the samples was $5 \cdot 10^{-4}$ M. EPR spectra were recorded using a Varian E-3 X-band spectrometer (9 GHz). The scan of the magnetic field in the center was 3210 Gs (Gauss). The time constant was equal to 1 s. Scan time was 4 minutes.

The studies used quartz capillaries with an outer diameter of 3 mm, inner – 1 mm and the length of 40 mm. To standardize the experimental conditions, a standard signal with known values of the g-factor Mn^{2+}/MgO (lines 3 and 4) was recorded simultaneously with the EPR probe signal. The following parameters were calculated from the obtained spectra: correlation time of rotational diffusion (τ_{eff}), hyperfine interaction constant (HIC) and change of signal intensity with time [11].

Sorption capacity of erythrocytes (SCE) was analyzed by the method [2].

Statistical processing was performed using the software package for biometric studies WinPEPI. Student's t-test was used for the parameters corresponding to the normal distribution (according to the results of the Shapiro-Wilk test). The results are presented as $M \pm m$. Differences were considered significant at $p < 0.05$.

Results of the study and their discussion. Studies have shown that in patients with CAH and TRAH there is an increase in MPO activity by 46 % and 79 % ($p < 0.05$), respectively, compared to the control group (table 1). The content of free radical oxidation products of lipids – TBA-PP in the blood serum of patients with CAH and TRAH increased by 22 % and 23 %, respectively, compared to the control ($p < 0.05$). At the same time, patients have more pronounced activation of free radical oxidation of proteins, as evidenced by the accumulation of protein oxidation products in blood serum by 35 % and 39 %, respectively, for CAH and TRAH compared to the control group ($p < 0.05$).

Table 1

Indices of oxidative status in patients with CAH and TRAH

Indices/groups	Control, (n=20)	Group 1 (patients with CAH), n=20	Group 2 (patients with TRAH), n=20
Myeloperoxidase activity in blood plasma, units/min	0.0024±0.0005	0.0035±0.0005	0.0043±0.0005 $p < 0.05$
TBA-positive products in blood serum, units/l	9.11±0.21	11.15±0.09 $p < 0.05$	11.22±0.07 $p < 0.05$
Products of oxidation of proteins in blood serum, units/ml	4.13±0.16	5.59±0.70 $p < 0.05$	5.74±0.11 $p < 0.05$
Paraoxonase-1 activity in blood serum, kU/l	5.66±0.93	1.99±0.21 $p < 0.05$	2.09±0.23 $p < 0.05$
Catalase activity in blood serum, units/l	12.50±2.50	6.80±0.35 $p < 0.05$	6.14±0.22 $p < 0.05$
Superoxide dismutase activity in blood serum, units/l	1906±117	1642±71	1469±60 $p < 0.05$
Reduced glutathione in hemoglobin-free blood filtrates, mmol/l	6.68±0.74	4.99±0.25 $p < 0.05$	4.44±0.30 $p < 0.05$

Notes: p – significance of the difference between the control and experimental groups.

The demonstrated changes occur against the background of reduced activity of the redox system's antioxidant part. Thus, the activity of SOD in patients with CAH and TRAH decreased by 14 % and 23 % ($p < 0.05$), respectively, compared to the control group, and catalase activity – by 46 % and 51 %, respectively ($p < 0.05$). The arylesterase activity of PON-1 in patients is reduced by 65 % and 63 %, respectively, compared to the control group ($p < 0.05$). At the same time, patients have decreased content of reduced glutathione. Thus, in patients with CAH and TRAH the content of reduced glutathione is decreased by 25 % and 34 %, respectively, compared to the control ($p < 0.05$).

Spin probes can be incorporated into the model lipid bilayer, where the nitroxyl group is localized between the aqueous and lipid phases. To characterize the spin probe environment before the experiments, the HIC constant was measured from the EPR spectra for both radicals in the erythrocyte suspension of all groups. For AdTEMPO, it is 16.625 G in all cases, indicating that this radical is incorporated into the lipid bilayer of the erythrocyte membrane with a nitroxyl fragment, located at the boundary of the aqueous and lipid phases.

For the other radical in all cases, this value is 16.75 G, which indicates that OH-TEMPO is located in the aqueous phase. In addition, because various substances can be adsorbed by cell membranes and block their receptors, increasing their lability and impairing permeability, all experiments were performed with erythrocytes before and after washing with 0.9 % sodium chloride solution.

The mobility of the biradical in the membrane medium was expressed as the correlation time of rotational diffusion (τ_{eff} – inversely proportional to the rotation rate of the radical, the higher the value, the slower the rotation). The process of the lipophilic probe's diffusion can be divided into two successive stages: sorption on the cell membranes' surface and penetration into the layers of the lipid membranes' bilayer. Therefore, in the membrane by the EPR spectra of probes different values of the correlation time of rotational diffusion can be observed for the period of the probe binding to the membrane surface (5 min) and during the probe in the lipid bilayer of the erythrocyte membrane (60 min).

When using the AdTEMPO spin probe, the value of τ_{eff} in patients with CAH before erythrocyte washout increases by 24 % and 41 % compared to the controls after 5 and 60 minutes of exposure, respectively. After washout, the value of this index in this group also increases significantly compared to the control by 24 % and 35 % after 5 and 60 minutes of exposure, respectively. Significant differences between the results obtained before and after erythrocytes washout were not found (table 2).

Table 2

Effective correlation time of AdTEMPO and OH-TEMPO rotational diffusion in the environment of erythrocyte membranes and signal intensity of the EPR spectrum after 60 min in erythrocytes in patients with CAH and TRAH before and after washout

Groups	Erythrocytes before washout			Erythrocytes after washout		
	Effective correlation time		Signal intensity	Effective correlation time		Signal intensity
	$\tau_{\text{eff}} \cdot 10^{-10}$, c		%	$\tau_{\text{eff}} \cdot 10^{-10}$, c		%
	5 min	60 min		5 min	60 min	
	AdTEMPO					
Control, n=20	4.69±0.16	5.09±0.18	47.14±2.35	4.56±0.13	5.01±0.20	48.71±2.68
Group 1 (patients with CAH), n=20	5.81±0.39 p<0.02	7.19±0.41 p<0.001	48.71±7.79	5.64±0.22 p<0.001	6.74±0.45 p<0.001	52.52±7.49
Group 2 (patients with TRAH), n=20	5.79±0.18 p<0.001	6.29±0.41 p<0.02	57.07±4.13 p<0.05	5.91±0.18 p<0.001	6.63±0.21 p<0.001	62.29±4.65
	OH-TEMPO					
Control, n=20	2.52±0.13	2.73±0.14	60.24±1.94	2.36±0.08	2.56±0.04	75.35±1.24
Group 1 (patients with CAH), n=20	2.78±0.13	2.92±0.19 p ₁ <0.001	49.37±5.00 p<0.05	2.54±0.06	2.22±0.07 p<0.001	68.63±9.30
Group 2 (patients with TRAH), n=20	2.92±0.09 p<0.05 p ₁ <0.05	3.11±0.13 p<0.05 p ₁ <0.02	54.85±2.17 p ₁ <0.001	2.62±0.09 p<0.05	2.70±0.04 p<0.05	80.88±3.44

Notes: p – significance of the difference between the control and experimental groups; p₁ – significance of the difference between the values before and after erythrocytes washout in the same group.

In patients with TRAH, the value of this index was also significantly higher compared to the control group. Thus, the value of τ_{eff} before erythrocyte washout increased by 23 % and 24 % compared to the control after 5 and 60 minutes of exposure, respectively. After washout, the value of this index in this group also increased significantly compared to the control by 30 % and 32 % after 5 and 60 minutes of exposure, respectively. No significant differences between the results obtained before and after washout of erythrocytes were found.

The rotation rate of the OH-TEMPO spin probe was slower compared to the control in erythrocyte samples of patients with CAH and TRAH. The value of τ_{eff} in patients with CAH after erythrocyte washout is also not significantly changed after 5 minutes, but after 60 minutes there is greater mobility of OH-TEMPO in erythrocytes of patients with CAH. In addition, there is a significant difference between the results before and after the erythrocytes washout after 60 minutes of exposure, which indicates the acceleration of the rotation of the probe. The value of τ_{eff} in patients with TRAH significantly increased compared to controls by 16 % and 14 % after 5 min and 60 min exposure, respectively. After erythrocyte washout, the value of τ_{eff} significantly increased compared to the control by 11 % and 5 % after 5 min and 60 min exposure, respectively. There is also a significant difference between the results before and after washout, which indicates the acceleration of the probe rotation.

In patients with CAH, the spectrum of the residual AdTEMPO signal before and after erythrocytes washout is close to the control level. In patients with TRAH, this figure index grew significantly compared

to the controls by 21 % and 28 % before and after erythrocyte laundering. There is no significant difference between the signal spectra before and after erythrocytes washout.

In patients with CAH, the residual spectrum of OH-TEMPO signals before and after erythrocyte washout is reduced by 18 % and 9 % compared to the controls. There is no significant difference between the spectra of signals before and after erythrocyte washout in this group of patients. In patients with TRAH, this index before erythrocyte washout was lower than the control level by 9 %. The residual signal spectrum increased after erythrocyte washout in this group of patients compared to the control. In addition, there is a significant difference between the results before and after erythrocyte washout in this group of patients.

One of the most common methods of assessing the state of erythrocyte membranes is the determination of SCE using methylene blue, which provides information about the state of regenerative capacity of erythrocytes, which changes as the barrier properties of the plasma cell membrane change. The SCE of patients with CAH (0.69 ± 0.26 %) and TRAH (0.53 ± 0.17 %) was significantly lower compared to the SCE of control subjects (45.89 ± 3.51 %).

The MPO activity increase demonstrated in patients with AH indicate leukocyte activation and the presence of an inflammatory response. In the circulation, MPO may form a complex with the HDL-associated enzyme PON-1, resulting in inactivation of PON-1 and oxidation of HDL. Local exacerbation of vascular inflammation is possible with binding of MPO to the endothelium and its activation [9, 15]. The activation of the prooxidant link of the redox system, in addition to increasing activity of MPO, also testifies to the accumulation of free radical oxidation products of lipids and proteins in the circulation. It should be noted that the examined patients have more pronounced activation of free radical oxidation of proteins in blood serum compared to the process of lipid oxidation. The demonstrated changes may indicate an increase in atherogenic potential of the blood. The demonstrated changes occur against the background of reduced activity of the redox system's antioxidant part. First of all, a decrease in the arylesterase activity of PON-1 is observed. PON-1 is able to hydrolyze lipid peroxides and promote the elimination of oxidized LDL, inhibit cholesterol biosynthesis and stimulate HDL-mediated cholesterol release from macrophages. In addition, PON-1 protects HDL from excessive peroxidase [9, 15]. At the same time, the activities of two other antioxidant enzymes, SOD and catalase, as well as the content of reduced glutathione, decrease. A decrease in the level of reduced glutathione – a tripeptide, which plays a central role in maintaining redox balance in cells, accelerates the formation of oxidative stress [14].

The demonstrated changes reflect the general response of the patient's body and indicate the formation of oxidative stress with the participation of both lipid and protein components, and the suppression of antioxidant defense mechanisms. At the same time, no significant difference between the changes in patients with CAH compared to TRAH was demonstrated, with the exception of activity of MPO and SOD. In particular, the activity of MPO in patients with TRAH is significantly higher ($p < 0.05$), and the activity of SOD is lower ($p < 0.05$) in comparison with control and CAH. This may indicate a deeper impairments of redox balance in the blood of patients with TRAH, an increase in their atherogenic potential, which may cause the development and progression of atherosclerotic process.

The development of various by pathogenesis pathological processes and conditions is accompanied by molecular changes in the plasma membranes of cells, which are a direct target of the damaging effects of pathogenic factors and are involved in the pathological process due to the initiation of universal mechanisms of cell damage. Erythrocyte membranes are characterized by general principles of molecular organization of plasma membranes. Therefore, the patterns of changes in the structure and function of the erythrocyte membrane with a certain correction, which is due primarily to the species specificity of cells, can be extrapolated to other membrane systems. In addition, the simplicity of erythrocyte organization permits to study the functional properties of plasma membranes without interference caused by intracellular membrane formations and organelles [14].

EPR spectroscopy is an informative method that permits to detect metabolic disorders in cells. In particular, spin probes can be used to study structural changes in cell membranes at the early stages of metabolic disorders. The molecule of the spin probe is paramagnetic and, thus, can be studied in a magnetic field [11]. Nitroxyl radicals are most widely used as spin probes. The synthesis and study of stable nitroxyl radicals were aimed at creating effective spin probes [5]. It is known that adamantane derivatives interact with natural and model membranes. They are capable of membrane integration and interaction with lipid bilayers and integral proteins. In the work, bis (1-oxyl-2,2,6,6-tetramethylpiperidinyl-4) ether 5,7-dimethyladamantane-1,3- dicarboxylic acid ester (AdTEMPO), lipophilic nitroxyl biradical, was used, which can be incorporated into the model lipid bilayer, where the nitroxyl group is localized between the aqueous and lipid phases [5]. Therefore, this substance can be used as a spin probe for the study and evaluation of erythrocyte membrane structures. Also, 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (OH-TEMPO), a

heterocyclic compound, was used as a spin probe to study biological compounds and to evaluate redox reactions in biological systems [4].

The obtained results indicate a slowing of the probe rotation rate in the erythrocyte membranes of patients with CAH and TRAH, which may be associated with an impairment of the structural organization of the lipid bilayer and the spectrum of proteins integrated into it. Comparing the results before and after erythrocyte washout, it should be noted that in erythrocytes of patients with CAH increase the rate of the probe rotation after erythrocyte washout is observed, while in erythrocytes of patients with TRAH, on the contrary, there is a decrease in the value of this index.

The state of the antioxidant system of erythrocytes and the presence of oxidized proteins and membrane lipids were assessed by changing the signal intensity of the spin probe spectrum per hour. In patients with TRAH, the permeability of erythrocyte membranes is significantly decreased, so that antioxidants contained inside the cell or bound to its membrane cannot respond with the probe nitroxyl radical outside. Therefore, the residual signal of the probe will be greater. In the erythrocytes of practically healthy individuals, the cell membrane functions normally and is more accessible to AdTEMPO. Due to the interaction with antioxidants of erythrocytes, the spin probe is restored, and the intensity of the residual signal is decreased. The results obtained are consistent with the data of other studies using spin probe data [7].

The demonstrated significant increase of SCE in patients with CAH and TRAH may indicate an impairment of erythrocyte membranes and lead, in particular, to disorders of energy metabolism in erythrocytes, which plays an important role in the pathogenesis of hypertension, as also shown in [10].

Conclusions

1. In patients with CAH and TRAH there is an impairment of oxidative status towards the development of oxidative stress, as evidenced by a significant ($p < 0.05$) increase in MPO activity, accumulation of lipid and protein oxidation products, decreased antioxidant enzyme activity and reduced glutathione content. At the same time, patients with TRAH by certain indices (activity of MPO, SOD and catalase, the content of reduced glutathione) have deeper changes in redox balance compared to patients with CAH.

2. The obtained results indicate an impairment of the structural organization of the lipid layer and its integrated proteins, which is expressed in an increase of τ_{eff} in patients with CAH and TRAH compared to practically healthy individuals. The difference in the intensity of the residual signal of spin probes for the studied groups indicates an impairment of the erythrocyte antioxidant system, which correlates with the obtained biochemical parameters.

3. Changes in the functional activity of the erythrocyte membrane surface are also evidenced by a decrease in blood SCE in patients with CAH and TRAH. Demonstrated structural and dynamic changes in erythrocyte membranes in patients with CAH and TRAH may be caused by impairment of redox status in the direction of oxidative stress, as the latter is one of the common mediators underlying the pathophysiological processes of hypertension.

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COMPUTER SIMULATION OF THE COMBINED USE OF AZATHIOPRINE WITH METHYLPREDNISOLONE UNDER THE CONDITIONS OF PHARMACOTHERAPY OF MULTIPLE SCLEROSIS

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The combined use of physiologically active compounds is aimed at optimizing their combined pharmacotherapeutic effect, which provides for reducing adverse reactions of ingredients, reducing their doses under conditions of potential synergism of the used components and increasing the convenience of taking ready-made medicinal forms. The purpose of this study was to assess the possibility of combined use, effectiveness and safety of azathioprine and methylprednisolone in the treatment of myasthenia gravis. Possible chemical reactions of the compounds were predicted based on the presence and reactivity of the functional groups included in their structure. The analysis of the acid-base properties of the compounds was carried out using the ACD/pK_aDB and ChemAxon programs. Analysis of physicochemical properties and data on the interaction with enzyme systems for methylprednisolone and azathioprine suggests the absence of possible interactions between these drugs at the chemical and pharmacokinetic levels (with the need to adjust dosage regimens). At the pharmacological level, the combined therapeutic effect of methylprednisolone and azathioprine is expected to contribute to more effective treatment of multiple sclerosis by inhibiting the development and course of inflammatory reactions.

Key words: myasthenia gravis, computer modelling, pharmacotherapy, combined effect, methylprednisolone, azathioprine, treatment.

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КОМП'ЮТЕРНЕ МОДЕЛЮВАННЯ СУМІСНОГО ВИКОРИСТАННЯ АЗАТІОПРИНУ З МЕТИЛПРЕДНІЗОЛОНОМ ЗА УМОВ ФАРМАКОТЕРАПІЇ РОЗСІЯНОГО СКЛЕРОЗУ

Сумісне використання фізіологічно активних сполук направлене на оптимізацію їх сумісного фармакотерапевтичного ефекту, що передбачає ослаблення побічних реакцій інгредієнтів, зменшення їх доз за умов потенційного синергізму використовуваних компонентів і збільшення зручності прийому готових лікарських форм. Метою даної роботи була оцінка можливості комбінованого застосування, ефективності та безпечності азатіоприну та метилпреднізолону при лікуванні міастенії. Можливі хімічні реакції сполук було спрогнозовано на підставі наявності та реакційної здатності функціональних груп, які входять до їх структури. Аналіз кислотно-лужних властивостей сполук здійснювався за допомогою програм ACD/pK_aDB та ChemAxon. Аналіз фізико-хімічних властивостей та даних про взаємодію з ферментними системами для метилпреднізолону та азатіоприну дозволяє припустити відсутність можливих взаємодій між цими препаратами як на хімічному, так у на фармакокінетичному рівні (з необхідністю корекції режимів дозування). На фармакологічному рівні сукупна терапевтична дія метилпреднізолону та азатіоприну очікувано сприятиме більш ефективному лікуванню розсіяного склерозу за рахунок пригнічення процесів розвитку та перебігу запальних реакцій.

Ключові слова: міастенія, комп'ютерне моделювання, фармакотерапія, комбінований вплив, метилпреднізолон, азатіоприн, лікування.

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Myasthenia gravis is the most frequent autoimmune disease of the neuromuscular synapse, leading to pathological fatigue and weakness of the striated muscles [3–6].

Over the past decades, the trend of a gradual increase in the incidence and prevalence of myasthenia has been maintained in most countries. This is due to the improvement of the diagnosis of the disease, the progress of the effectiveness of treatment and the increase in the life expectancy of patients suffering from