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CYTOPROTECTIVE EFFECT OF MELDONIUM ON CARDIOMYOCYTE

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Summary

Background. The use of myocardial cytoprotectors (meldonium) in patients with exertional angina is a scientific-practical dilemma.

Material and methods. An open randomized clinical trial was conducted involving 160 patients with chronic heart failure (117 men and 43 women) aged 37 to 81 years. Of them, 142 patients had angina pectoris of stable effort from different functional classes, and 21 – unstable angina pectoris. Study groups were comparable according to the frequency of indication of background drugs and meldonium.

Results. The results of our study indicate the activation of oxidative stress in patients with stable angina pectoris, relevant in this regard being the changes of malonic dialdehyde, catalase and superoxide-dismutase, which become more pronounced in the first 24 hours after the start of the treatment and, although, by the 6th month an attenuation of the activity of the prooxidant status is detected, it intensifies by 12 months it intensifies.

Discussions. All results completes the vision based on the link between the antioxidant defense and the aggravated cardiovascular evolution. Another consolidated aspect is to demonstrate the superior effectiveness of meldonium administration. There was demonstrated the effectiveness feasibility of meldonium *vis-à-vis* the markers of oxidative stress, endothelial dysfunction and comparable systemic inflammation.

Conclusions. The inclusion of metabolic drugs in the complex treatment of patients with stable angina increases the clinical effectiveness of basic pharmacotherapy 4 times when prescribing meldonium (p <0,001), mainly due to increased antianginal actions.

Keywords: cardiocitoprotector, cardiac metabolism, ischemic heart disease

Introduction

In the current time, based on the results offered by multicenter studies on the efficacy of medicinal preparations, international and national standards have been developed for the treatment of stable exertional angina pectoris [1, 2]. From the point of view of evidence-based medicine, in the treatment of effort angina, priority is given to preparations, which have a level of proof of effectiveness of class I and IIA, from the groups of antiplatelet agents and anticoagulants, beta-adrenoblockers, statins, angiotensin-converting enzyme inhibitors; drug forms from other groups (nitrates, calcium antagonists) can also be used, but have less influence on the indices of survival and life span of patients.

An attempt to substantially increase the effectiveness of complex treatment of ischemic heart disease is the introduction into clinical practice of metabolic pharmacotherapy with the aim of providing cardiocitoprotection [2-4]. Although the range of metabolic correctors is vast, many preparations have not been studied multicentric and do not possess a sufficient evidence base, and therefore have not been included in the standards of treatment of angina pectoris.

The direction of personalized medicine is developing extensively abroad [1, 3] and in our country [1, 4]. The main objective of the researchers is the genetic factor, despite the fact that it defines only 50% of the individual reaction capacity to drug preparations and 10-20% the chance of developing a multifactorial disease [5-6]. The methodology of personalized medicine is reduced to the definition of biomarkers, the conduct of pharmacogenetic and pharmacotranscryptomic studies [1, 3, 5]. In our opinion, for the development of individualized treatment approaches should be taken into account not only the genetic factor, but also a number of other phenotypic characteristics of each individual patient. In this paper, an attempt was made to expand the understanding about personalized medicine by developing a separate direction – personalized metabolic pharmacotherapy.

Purpose of the study was to increase the effectiveness and safety of the pharmacotherapy of ischemic heart disease by developing personalized approaches for indicating metabolic preparations – meldonium.

Material and methods

An open randomized clinical trial was conducted that included 160 patients with chronic heart failure (CHF) (117 men and 43 women) aged 37 to 81 years. Of them, 142 patients had angina pectoris of stable effort from different functional classes, and 21 – unstable angina pectoris. In most patients angina pectoris was associated with hypertension (HTA) (143 [89.4%]), rhythm disturbances (39 [24.4%]), postinfarct cardiosclerosis (CSPI) (78 [48.8%]), chronic heart failure (CHF) (151 [94.4 %]), some with diabetes mellitus (DM) type II (37 [23.1 %]). The average age of patients was 59.26±0.74 years. The control group involved 30 healthy people. The patients underwent inpatient treatment in the cardiology department in the years 2011 – 2015, and they continued to outpatient treatment. The observation period

was 6 weeks. Each participant was introduced to the research program and signed an informed agreement.

Meldonium was administered at a dose of 0.5 g/24 hours for a period of 6 weeks: in the first 10 days the preparation was administered intravenously in hospital, after which the outpatient drug was continued in capsules. Study groups were comparable according to the frequency of indication of background drugs.

Results

Modified ischemic albumin (MIA) is a marker that denotes both myocardial ischemia and a very important predictor of oxidative stress activation, which originates from compromised coronary reactivity dependent on endothelium. At the initial stage, patients present with a high level of MIA (Table 1) compared to the reference level, being statistically significant in both groups (p<0.001): 398.62±15.48 uM/L – group I, 430.48±23.22 uM/L – group II.

Table 1

The level of modified ischemic albumin and its evolution at different stages

Stages	Group I			Group II			P
	N	M	m	N	M	m	
Initial	43	398.6	15.5	17	430.48	23.2	>0.05
Outpatient	49	440.8	14.6	22	430.06	18.5	>0.05
1 month	47	430.9	14.7	20	436.44	18.9	>0.05
3 months	14	366.1	24.5	3	412.01	57.8	>0.05
6 months	18	310.5	12.4	5	320.62	13.8	<0.05
12 months	19	405.3	14.5	2	467.84	3.7	<0.05

An increase of MIA was observed in both study groups, being statistically significant (p<0.05) in the first group with basic treatment (440.79±14.63 uM/L). In the second group with meldonium association, the aim level was maintained practically the same (430.06±18.46 uM/L). Regarding the dynamics of aim evolution there was a decrease under the treatment with meldonium of the oxidative marker at 1, 3, 6 months, being statistically significant at 3 and 6 months compared to the initial stage and below even the reference level (group I – 310.46±12.44 uM/L vs 340.0±4.0 uM/L with p<0.01; group II – 320.62±13.82uM/L vs 340.0±4.0uM/L, p<0.05). At 12 months we find the data being close to the initial ones (405.26±14.46 uM/L; 467.84±3.69 uM/L *vs* initially 398.62±15.48uM/L; 430.48±23.22 uM/L corresponding to the groups).

Malonic dialdehyde (MDA) being one of the final products of lipid peroxidation, denotes about the activation of oxidative stress. From the statistical point of view, the MDA data (Table 2) at the initial stage in the 2 groups were not distinguished (p>0.05): group I – 11.8±0.99 uM/L, group II – 10.87±2.29 uM/L, data that reveals its elevation compared to the statistically significant reference level.

In all groups at the discharge stage, MDA increased, noting the activation of oxidative stress related to maintaining the acute state. Thus, in group I, the MDA level – 16.3±3.49 uM/L, in group II – 20.19±5.07 uM/L. Subsequently MDA decreased up to 3 months to 8.47±0.86 uM/L in group I, in group II – 8.83 ±0.81 uM/L.

Table 2

Malonic dialdehyde indices and their dynamics at all stages of study

Stages	Group I			Group II			P
	N	M	m	N	M	m	
Initial	43	11.80	0.99	17	10.87	2.29	>0.05
Outpatients	49	16.30	3.49	22	20.19	5.07	>0.05
1 month	46	12.47	1.66	20	14.70	3.04	>0.05
3 months	14	8.47	0.86	3	8.83	0.81	>0.05
6 months	19	7.63	0.87	5	5.47	0.82	>0.05
12 months	19	12.70	2.49	2	11.52	0.66	>0.05

A statistically significant decrease of the oxidizing marker was recorded at the 6-month stage compared to the initial in group I (7.63±0.87 uM/L *vs* 11.8±0.99 uM/L with p<0.05) and in group II (5.47 ±0.3uM/L *vs* 15.43±3.21 uM/L). Data from 12 months shows the rising of MDA in both batches (12.7±2.49 uM/L; 11.52±3.58 uM/L with p>0.05).

Catalase is an intracellular enzyme that faithfully signifies about the antioxidant system. Catalase in patients with atherosclerotic coronary pathology enrolled in the study demonstrates the compromise of the antioxidant system by its statistically significant low level (p<0.001) at the initial stage compared to the second group of patients (19.51±1.35 uM/L in group I, 13.56±1.02 uM/L in group II). At the initial stage, the level of catalase was higher in the first group (p<0.05) compared to the II group, although patients were randomly assigned to the groups without certain principles (Table 3). Under treatment with standard preparations, as well as in combination with meldonium, the level of catalase began to rise even at the discharge stage, although statistically insignificant (19.53±1.56 uM/L for group I, 16.46±1.37 uM/L for group II). This growth continued at the next stages, the highest figures being recorded at the 6-month stage for both lots (22.15±1.9 uM/L, 18.7±0.52 uM/L respectively), being higher in lot I (p <0.05). However, at the 12-month stage, the results were better compared to the initial results that were in the second lot (17.35±0.08 umol/L).

Table 3

Catalase indices and its dynamics at all stages of study

Stages	Group I			Group II			P
	N	M	m	N	M	m	
Initial	43	19.5	1.35	24	13.6	1.02	<0.001
Outpatient	49	19.5	1.56	26	16.5	1.37	>0.05
1 month	47	19.5	1.53	22	13.7	1.07	<0.01
3 months	14	21.5	1.86	5	13.1	2.18	<0.05
6 months	19	22.2	1.9	2	18.7	0.52	<0.05
12 months	19	15.7	0.86	2	17.4	0.08	>0.05

Superoxide-dismutase (SOD) is the enzyme that ensures the transformation of superoxide anion into hydrogen peroxide and is thus recognized as an important component of the antioxidant system. The quantitative decrease of SOD compared to the reference level means about a compromised antioxidant system and indicates about the activation of oxidative stress. Therefore, the reduction of SOD is associated with the elevation of the malonic diadehyde.

Table 4

Superoxide-dismutase indices and its dynamics at all stages of study

Stages	Group I			Group II			P
	N	M	m	N	M	m	
Initial	43	874.0	41.7	24	878.3	56.4	p>0.05
Outpatient	49	886.8	40.2	26	911.3	57.7	p<0.05
1 month	47	948.4	35.9	22	980.5	80.0	p>0.05
3 months	14	1069.3	80.0	5	1146	63.4	p<0.05
6 months	19	1014.3	61.9	2	1088.9	151.7	p<0.05
12 months	19	805.1	55.8	2	741.2	2.7	p<0.05

Until the initiation of the treatment, a compromised antioxidant system is attested in patients from all groups, statistically significant (p<0.001): 874.04±41.74 u/c; 878.29±56.44 u/c (Table 4). The antioxidant system was activated from the first hours after the initiation of the treatment. At the initial stage the SOD level showed no significant differences between the batches. At stages of 1, 3, 6 months, increased SOD values were recorded. Thus, at the 6-month stage, the SOD level reached 1014.3±61.85 u/c in group I and 1038.91±151.75 u/c in group II. At the 12-month stage, the SOD level decreased, statistically significant (p<0.01) in group II.

Nitric oxide – the most powerful vasodilator at the endothelial level, at the initial stage showed a decrease in the level, statistically significant (61.72±3.25 uM/L; 50.62±2.84 uM/L) (Table 5). Comparing the study groups with each other we can note the lowest level in group II compared to group I (50.62±2.84 uM/L *vs* 61.72±3.25 uM/L) with p<0.05. During the treatment, the increase of the NO level was registered even from the discharge stage, and in the second group being approximately at the same level as in the hospitalization stage (50.62±2.84 uM/L *vs* 50.03±2.25 uM/L). At the 3-month stage, the practical NO level reached the reference level of group I (78.51±7.0 uM/L *vs* 78.66±2.72 uM/L), in group II there was an insignificant increase compared to the initial stage (64.70±9.13 uM/L *vs* 50.62±2.84 uM/L).

There is an improvement of the endothelial dysfunction by the significant increase of nitric oxide under the treatment at 6 months, namely: in the I group – 87.26±4.3 uM/L (p=0.01), in the II group – 95.33±10.85 uM/L. All levels are higher than the initial ones.

Table 5

Nitric oxide indices and its dynamics at all stages of the study

Stages	Group I			Group II			P
	N	M	m	N	M	m	
Initial	43	61.7	3.3	25	50.6	2.8	<0.05
Outpatient	49	64.3	4.6	26	50.0	2.3	<0.05
1 month	47	61.3	3.0	22	51.6	2.6	<0.05
3 months	14	78.5	7.0	5	64.7	9.1	>0.05
6 months	19	87.3	4.3	2	95.3	11	>0.05
12 months	19	57.2	3.8	2	48.7	0.4	<0.05

Oxidative stress, conceptually exposed by the imbalance between the rate of formation of reactive oxygen species (ROS) and the potential of endogenous systems with antioxidant action, represents a universal mechanism of cell lesion that is the basis of the evolution of various organic diseases, including cardiovascular [7, 8].

Discussions

Alteration of cell membranes and decoupling of oxidative phosphorylation, activation of extracellular matrix metalloproteinases, expression of proinflammatory cytokines, cell adhesion molecules, as well as cell migration and proliferation, are the key phenomena that associate oxidative stress and ensure its pathological sustainability. Enough evidence has been accumulated on the role of oxidative stress in the pathogenesis of coronary diseases, primarily in the normalization of the facilitation of the transendothelial passage of cholesterol due to the oxidation of low density lipoprotians (LDL), the activation of collagenases and gelatinases resulting in the destabilization of the atherogenic plaque and the risk of acute coronary syndrome (ACS), as well as manifestation of trombotic effect. In this context, it is worth mentioning the pathophysiological significance of oxidative stress in coronary remodeling, the quality of evolution of which influences notably the feasibility and efficiency of pharmacological and interventional anti-ischemic cardiac treatment [1-3, 6, 9].

Cytoprotective tactics have considerably optimized the treatment of coronary heart conditions, especially severe ones such as ACS and coronary stenosis >70%. At the same time, the application of long-term cardiocitoprotective treatment has been shown to be associated with the decrease in the risk of immediate or distant evolution of various major cardiovascular events (ECVM): acute myocardial infarction (IMA), thrombosis and the appearance of unstable angina pectoris.

In turn, ROS increases the NO deficiency, through the excessive formation of peroxinitrite (ONOO-) from its reaction with the peroxide anion, and amplifies the cellular and molecular mechanisms involved in the negative coronary remodeling. The infiltration of neutrophils and macrophages in the neointime area, proven as an important component, represents a source of formation of oxygen free radicals, which respectively will associate and support at a distance the coronary remodeling process. Therefore, the modulation and correction of the mechanisms of negative coronary remodeling that are influenced by oxidative stress, endothelial dysfunction, exaggerated inflammatory response can be an important therapeutic support. At this connotation, the priority of cytoprotectors is announced, which, although they initially emitted at the ramp through their generalized action, remained in the socket of cardiovascular treatment due to their pleiotropic effects of antioxidant, anti-inflammatory, antiproliferative, antithrombotic, antimigrant nature, etc [5-8, 10].

The results of the clinical-experimental research of meldonium in myocardial ischemia have been studied in patients with a diagnosis of ischemic heart disease: angina pectoris of stable effort functional class (FC) I-IV, postinfarct cardiosclerosis (in 17 [48%] patients) in combination with hypertension stage II-III, grade 2-3, complicated with chronic heart failure (CHF) stages I-II A, FC I-III NYHA, in 8 (23%) patients with concomitant type II diabetes mellitus. The control group consisted of 43 patients who received only basic treatment (antiplatelet agents, beta-adrenoblockers, statins, angiotensin-converting enzyme inhibitors, if necessary – diuretic, antiarrhythmic and hypoglycemic preparations).

Thus, in a randomized controlled clinical trial of patients with angina pectoris of stable effort, a significant 4-fold increase in the effectiveness of complex pharmacotherapy in ischemic heart disease was found when adding meldonium compared to the basic treatment on account of the more pronounced antianginal effect, the improvement of physical performance, the potentiation of the positive and hypotensive inotropic effects of basic pharmacotherapy. According to experimental data in patients with myocardial ischemia meldonium activates glycolysis, oxidative phosphorylation and oxidative decarboxylation, stabilizes the cardiomyocyte membrane, significantly reduces the degree of hypoxia, thereby restoring the initial level of ATP and achieving adequate energy intake of the myocardium. This preparation quite harmoniously manages the metabolism of cardiomyocytes in conditions of experimental myocardial ischemia given the initial energy status, the degree of tissue hypoxia and the age of the patients [1-3, 6]. Until initiation of treatment, a compromised antioxidant system is attested in patients from all groups, statistically significant ($p<0.001$).

The antioxidant system was activated from the first hours after the initiation of the treatment.

Therefore, the results of our study indicate the activation of oxidative stress in patients with stable angina pectoris, relevant in this regard being the changes of MDA, catalase and SOD, which become more pronounced in the first 24 hours after the start of the treatment and, although by the 6th month an attenuation of the activity of the prooxidant status is detected, it intensifies by 12 months. This completes the vision based on the link between the antioxidant defense and the aggravated cardiovascular evolution. Another consolidated aspect is to demonstrate the superior effectiveness of meldonium administration. For the first time in the Republic of Moldova it was demonstrated the feasibility of the effectiveness of meldonium vis-à-vis the markers of oxidative stress, endothelial dysfunction and comparable systemic inflammation. The worldwide experience of using meldonium is very limited, therefore the results obtained have a conclusive impact on the accumulation of evidence in this regard.

Conclusions

1. The molecular structure of the pharmacologically studied drug of the metabolic series - meldonium, has a duality of action; under certain conditions, the metabolic corrector is able to exhibit complex pharmacodynamic effects.

2. The inclusion of metabolic drugs in the complex treatment of patients with stable angina increases the clinical effectiveness of basic pharmacotherapy 4 times when prescribing meldonium ($p < 0,001$), mainly due to increased antianginal actions.

3. The administration of meldonium in patients with myocardial ischemia leads to the accumulation of ATP inside cardiomyocytes due to the activation of various bonds of energy metabolism: meldonium activates anaerobic glycolysis, oxidative phosphorylation and oxidative decarboxylation of pyruvate, leading to a complete restoration of the amount of ATP in the myocardium. The introduction of meldonium metabolic corrector in patients with coronary heart disease is accompanied by stabilization of the membranes of cardiomyocytes and a decrease in the degree of tissue hypoxia.

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