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RESEARCH ARTICLE

Cardiocytoprotection with metabolic drugs - study of the effectiveness of meldonium in ischemic heart disease

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What is not yet known on the issue addressed in the submitted manuscript

From the point of view of evidence-based medicine, in the treatment of effort angina, priority is given to drugs, which have a level of proof of efficacy in class I and IIa, and an attempt to increase the effectiveness of complex treatment by introducing metabolic pharmacotherapy into clinical practice in order to ensure cardiocytoprotection.

The research hypothesis

After the administration of meldonium, a significant reduction in the level of malonic dialdehyde in erythrocytes was observed, which is a sign of a significant decrease in the degree of tissue hypoxia. A significant decrease in serum concentrations of organ-specific myocardial enzymes was also detected.

The novelty added by manuscript to the already published scientific literature

This randomized controlled clinical trial of patients with angina pectoris of stable effort has found a 4-fold increase in the effectiveness of complex pharmacotherapy in ischemic heart disease when adding meldonium compared to the basic treatment because of antianginal effect, improvement of physical performance, potentiation of the positive inotropic and hypotensive effects of basic pharmacotherapy.

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Summary

Introduction. Ischemic heart disease is one of the most widespread cardiovascular diseases. In Republic of Moldova the total number of patients with ischemic heart disease is 30-40 thousand per 1 million population and is observed more of working age with important social value.

Materials and method. An open randomized clinical trial involving 139 patients with chronic heart failure (107 men and 32 women) aged 37 to 81 years: 111 patients had angina pectoris of stable effort from different functional classes, and 28 – unstable angina pectoris, which include: basic treatment n = 43; basic treatment + meldonium (non-infarct) n = 52; basic treatment + meldonium (post-infarct) n = 35; basic treatment + meldonium, (aggravated) n = 9. Study groups were compared according to the frequency of using background (basic) drugs and meldonium. Statistical processing of the results was carried out in Statistics Software Package 9.0.

Results. During the treatment, the increase of the nitric oxide level was registered even from the discharge stage, and in the second group being approximately at the same level as the initial stage. At the 3-month, nitric oxide level reached the normal level. There is an improvement of the endothelial dysfunction by the significant increase of the nitric oxide under the treatment at 6 months (in group I – 87.26±4.3 μM/L (p = 0.01), in group II – 95.33±10.85 μM/L).

Conclusions. The inclusion of meldonium in the complex treatment of patients with stable angina increases the clinical efficacy of basic pharmacotherapy when prescribing meldonium, mainly due to increased antianginal actions.

Keywords: cardiocytoprotector, cardiac metabolism, ischemic heart disease.

Introduction

Diseases of the cardiovascular system in most countries of the world are on the first place among the causes of deaths [1-3]. The epidemiological situation in the Republic of Moldova is characterized by the term „supermortality" due to cardiovascular diseases, compared to economically developed countries [2-4]. Ischemic heart disease (IHD) is one of the most widespread cardiovascular diseases [5]. In our country, the total number of patients with ischemic heart disease is 30-40 thousand per 1 million population [2, 4, 6]. Nowadays, a process of "rejuvenation" of the CHF is observed, the hospital beds being occupied more often by patients of working age, occupying important positions in society, which is why this disease needs to be considered as one with important social value.

In the current time, based on the results offered by multicenter studies on the efficacy of contemporary drugs, international and national guidelines have been developed for the treatment of stable exertional angina pectoris [5, 7]. From the point of view of evidence-based medicine, in the treatment of exertional angina, priority is given to drugs, which have a level of proof of efficacy in class I and IIa, from the groups of antiplatelets and anticoagulants, beta-blockers, 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 [6, 8, 9].

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 cardiocytoprotection [7-10].

The purpose of the study was to study the effectiveness and safety of the metabolic drug meldonium in ischemic heart disease.

Material and methods

Our study included 160 patients with CHF (107 men and 32 women) aged 37 to 81 years. Of them, 139 patients had angina pectoris of stable effort from different functional classes, and 20 – 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 was 59.26±0.74 years. All patients were divided into 2 groups – with and without using meldonium and consist of: n = 43 only with background treatment; non-infarct IHD (n = 52) with background treatment and meldonium, post-infarct IHD (n = 35) with background treatment and meldonium and n = 9 with aggravated IHD who were treated with background treatment and meldonium. The observation period was 6 weeks. Each participant was introduced to the research program and signed an informed agreement (a favorable decision of Ethics Committee of the Nicolae Testemitanu State University of Medicine and Pharmacy nr. 17 from 10th of April 2012).

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 the hospital setting, after which patient continued the treatment with capsules as an outpatient. Study groups were comparable according to the frequency of indication of background drugs.

Table 1. *Frequency of indication of background remedies in study groups of patients with stable exertion angina pectoris*

Group of medicinal remedies	Study groups			
	Background treatment, n = 43	Background treatment + meldonium, (non-In) n = 52	Background treatment + meldonium, (post-In) n = 35	Background treatment + meldonium, (Aggravated) n = 9
Disaggregating drugs	43 (100%)	52 (100%)	35 (100%)	9 (100%)
Statins	27 (62%)	32 (61%)	23 (65%)	6 (65%)
Beta-blockers	34 (80%)	41 (79%)	30 (86%)	8 (84%)
ACE inhibitors	34 (80%)	40 (77%)	27 (78%)	7 (78%)
Calcium antagonists	18 (42%)	21(40%)	15 (43%)	4 (41%)
Prolonged nitrates	27 (63%)	30 (58%)	21 (59%)	5 (57%)

Note: ACE – angiotensin-converting enzyme; non-In – non-infarction; post-In – postinfarct

Results

The clinico-experimental research of meldonium in myocardial ischemia was investigated in patients with a diagnosis of ischemic heart disease: angina pectoris of stable effort functional class (CF) 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, CF 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.

At the addition of meldonium, there was an improvement on the ECG in the repolarization phase in the form of reducing the depth of the negative wave „T" from 1.5 mm to 0.2 mm ($p < 0.05$) and the decrease in the number of negative wave derivatives „T" from 2.6 to 0.4 ($p = 0.07$), compared to the basic therapy those indices did not undergo significant changes. At the end of the observation period, patients treated with meldonium were able to walk in 6 minutes 166 meters more than before treatment, increasing their result from 310.66±24.74 meters to 476.50±43.5 meters ($p < 0.05$), while patients who received only basic treatment, were able to walk 352.45±18.28 meters to treatment, and at the end of the observation period practically as much as 365.00±5.00 meters ($p > 0.05$). The addition of meldonium offered an additional hemodynamic effect in the form of a significant decrease in blood pressure – systolic from 161.76±4.39 mmHg to 143.45±5.13 mmHg ($p < 0.05$) and diastolic from 95.09±2.88 mmHg to 87.54±2.52 mmHg ($p = 0.06$). The summary coefficient of effectiveness of the basic therapy made up 15.55±4.21%, and of complex pharmacotherapy with meldonium 59.16±3.31% ($p < 0.001$), which in fact is 4 times higher. In order to elucidate the mechanism of action of meldonium on energy exchange in cardiomyocytes, an extensive study was carried out. Meldonium administration induced a significant increase in the concentration of adenosine triphosphate (ATP) in blood serum and erythrocytes practically to the optimal level, suggesting the elimination of energy deficiency caused by ischemia (table 2).

Table 2. *Indicators of myocardial metabolism in the norm, in non-infarct and post-infarct ischemic heart disease (M±m)*

	Indicators	Norm	Background treatment	Background treatment + Meldonium
Erythrocytes	ATP, μmol/l	664.54±14.49$^{\Delta\Delta}$	594.44±5.75**$^{\$}$	638.88±14.96$^{\Delta}$
	ADP, μmol/l/l	315.11±8.78	330.53±16.05	319.27±7.51
	2,3-DAM, μmol/l/l	4.82±0.29$^{\Delta\Delta\$}$	7.21±0.32**$^{\$\$}$	5.70±0.8*$^{\Delta\Delta}$
Blood serum	ATP, μmol/l/l	200.08±3.47$^{\Delta\Delta}$	162.81±4.57**$^{\$\$}$	192.32±5.36$^{\Delta\Delta}$
	ADP, μmol/l/l	75.92±1.58	79.31±1.13	77.33±2.29
	Pyruvate, μmol/l/l	58.59±2.26	59.95±1.02$^{\$}$	53.44±1.99$^{\Delta}$
	Lactate, μmol/l/l	0.50±0.03	0.62±0.14$^{\$\$}$	0.59±0.03
	CFK-MB, μmol/l	0±0$^{\Delta\Delta}$	0.25±0.04**$^{\$\$}$	0±0$^{\Delta\Delta}$
	LDH_1, μmol/l	0.02±0.00$^{\Delta\Delta\$\$}$	0.09±0.01**$^{\$\$}$	0.05±0.01**$^{\Delta\Delta}$
Mitochondria	SOD, nmol/min	17.82±1.10$^{\Delta\Delta\$}$	11.83±0.47**	13.68±0.65*
	CAT, nmol/min	3.94±0.23$^{\Delta\Delta\$}$	2.38±0.21**$^{\$}$	3.12±0.10*$^{\Delta}$
	PDH, μmol/l	31.04±0.89$^{\Delta\Delta\$\$}$	21.68±0.90**$^{\$\$}$	27.30±0.45**$^{\Delta\Delta}$

Note. The statistical significance of the differences was evaluated by the modified t-Student criterion with the Bonferroni correction: * – $p < 0.05$; ** – $p < 0.01$ compared to the optimum value; $^{\Delta}$ – $p < 0.05$; $^{\Delta\Delta}$ – $p < 0.01$ compared to the group with ischemic heart disease; $^{\$}$ – $p < 0.05$; $^{\$\$}$ – $p < 0.01$ compared to the group with ischemic heart disease + meldonium.

DAM – malonic dialdehyde; ATP/ADP – Adenosine triphosphate and diphosphate; CFK – creatine phosphokinase; LDH – lactate dehydrogenase; SOD – superoxide dismutase; CAT – catalase; PDH – pyruvate dehydrogenase.

Compared with the background treatment, the addition of meldonium was associated with a significant reduction in the level of malonic dialdehyde (DAM) in erythrocytes, a sign of a significant decrease in the degree of tissue hypoxia. A significant decrease in serum concentrations of organ specific myocardial enzymes – creatinine phosphokinase (CFK) and lactate-dehydrogenase (LDH1) has been detected, which speaks of reducing the „leakage" of enzymes from the cytoplasm of cells following the stabilization of cardiomyocytic membranes. A significant decrease in the plasma concentration of pyruvate was detected, and in the mitochondria – activation of pyruvate-dehydrogenase (PDH), indicating the stimulation of the oxidative decarboxylation process of pyruvate. In addition, in the mitochondria, a significant activation of catalase (CAT) and insignificant activation of superoxide-dismutase (SOD) was revealed. These data suggest the slight stimulation of the processes of oxidative phosphorylation, which, on the one hand, provides the cell with energy, and on the other hand, uses only the oxygen that is available, without increasing the need in conditions of tissue hypoxia. We can say that meldonium acts quite harmoniously, activating the aerobic processes of energy intake to cardiomyocytes according to the degree of reduction of tissue hypoxia. In addition, signs of activation of anaerobic mechanisms for extracting energy from carbohydrates by stimulating the glycolysis process, as evidenced by the increase in CFK activity and the increase in lactate capture by the myocardium have been detected. Thus, in patients with myocardial ischemia meldonium activates glycolysis, oxidative phosphorylation and oxidative decarboxylation, stabilizes the cardiomyocyte membrane, significantly reduces the degree of hypoxia, which leads to the restoration of the initial level of ATP and adequate energy intake to the myocardium.

Until the initiation of the treatment, a compromised antioxidant system is attested in patients from all groups statistically significant ($p<0.001$) (table 2). 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 groups. At the period of 1, 3, 6 months, increased SOD values were recorded. Thus, at 6 months, the SOD level reached 11.83±0.47 μmol/l in group I and 13.68±0.65 μmol/l in group II. At 12 months the SOD level decreased, statistically significant ($p<0.01$) in group II. 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 the hospitalization stage (50.62±2.84 μmol/l vs 50.03±2.25 μmol/l). At 3 months, the practical NO level reached the reference level of group I (78.51±7.0 μmol/l vs. 78.66±2.72 μmol/l), in group II there was an insignificant increase compared to the initial stage (64.70±9.13 μmol/l vs. 50.62±2.84 μmol/l). There is an improvement of the endothelial dysfunction attested by the significant increase of nitric oxide at 6 months: in the I group – 87.26±4.3 μmol/l ($p = 0.01$), in the II group – 95.33±10.85 μmol/l. All levels are higher than the initial ones.

Discussion

The analysis of the peculiarities of the influence of meldonium on the metabolism of cardiomyocytes in myocardial ischemia in young and old patients leads to the idea of a striking harmony. The explanation of the obtained results may be due to the mechanism of action of meldonium. This drug blocks carnitine biosynthesis from the butyrobetain range, causing a double positive effect [3-6]. First, it reduces the concentration of carnitine, a transporter of fatty acids through the mitochondrial membrane, which causes energy-saving effects [2, 4, 10]. Secondly, it increases the concentration of gamma-butyrobetaine, which excites acetylcholine receptors and stimulates nitric oxide biosynthesis – the mediator of the

STRESS-limiting NO-ergical system, universal regulator of the adaptation process [2, 5, 9]. In clinical trials, the ability of meldonium to provide an adaptogenic effect by regulating the biosynthesis of NO has been demonstrated [1-8]. Probably this mechanism has a certain contribution to the realization of such a harmonious influence of the preparation on the metabolism of cardiomyocytes in the conditions of myocardial ischemia in both young and old patients.

Limiting the adaptive capacities of cells to restore their own energy and plastic resources in old age reduces the possibilities of meldonium to corrode metabolism in myocardial ischemia in elderly patients. The mechanisms of action of meldonium revealed in the experiment explain in many aspects the positive effects of this drug that we observed in the clinic.

In 10 (10.4%) of the patients examined by us, the monovascular damage of the coronary circuit was detected, in 9 (9.4%) – bivascular and in 72 (75.0%) – polyvascular. The trunk of the left coronary artery was affected in 37 (28.5%) of patients with the average stenosis degree of 17.92±2.67%, the anterior interventricular artery – in 82 (85.4%) patients with the average degree of stenosis of 57.32±3.33%. The same were described the circumflex artery at 67 (69.8%) with the average degree of stenosis of 44.01±3.71%, the intermediate artery at 23 (24.0%) patients with the average degree of stenosis of 14.89±3.01%. Besides that, we may mention the fact that the right coronary artery – in 67 (69.8%) patients with the average degree of stenosis of 46.41±3.95% and the posterior interventricular artery – in 19 (19.8%) patients with the average degree of stenosis of 12.11±2.81% were affected.

Thus, in our 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 and potentiation of the positive and hypotensive inotropic effects of basic pharmacotherapy were observed in groups with meldonium. 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 drug 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.

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 DAM, catalase and SOD, which become more pronounced in the first 24 hours after starting the treatment and although by month 6 a decrease in the activity of the prooxidant status is detected, it intensifies at 12 months. Patients with more pronounced deviations of oxidative stress markers have a higher risk of developing IHD. 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

The inclusion of metabolic drugs in the complex treatment of patients with stable angina increases the clinical effectiveness of basic pharmacotherapy by 4 times when prescribing meldonium (59.16% compared to basic therapy 15.95%, $p < 0.001$), mainly due to increased antianginal actions.

Using 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. In elderly patients, meldonium retains its activity in the best possible way.

Abbreviations

ATP/ADP – adenosine triphosphate and diphosphate; CAT – catalase; CF – functional class; CFK – creatine phosphokinase; CHF – chronic heart failure; CSPI – postinfarct cardiosclerosis; DAM – malonic dialdehyde; DM – diabetes mellitus; ECG – electrocardiogram; HTA – hypertension; IHD – ischemic heart disease; LDH – lactate dehydrogenase; NO – nitric oxide; PDH – pyruvate dehydrogenase; SOD – superoxide dismutase.

Declaration of conflict of interest

Nothing to declare

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