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RESEARCH ARTICLE

Personalized approach to cytoprotective treatment in ischemic heart disease

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

Cardiocytoprotection is a big problem in cardiology today and remain unclear using of these drugs to increase the effectiveness of complex treatment of ischemic heart disease (IHD) resulted in the introduction into clinical practice of metabolic pharmacotherapy.

The research hypothesis

The direction of personalized medicine is developing extensively and the main objective of researchers is the genetic factor, despite the fact that it defines only 50% of the ability to individual reaction to drug and 10-20% the chance of developing a multifactorial disease. The methodology of personalized medicine is reduced to the definition of biomarkers, the conduct of pharmacogenetic and pharmacologic studies.

The novelty added by manuscript to the already published scientific literature

To develop the individualized treatment approaches doctors should be taken into account not miss 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.

Summary

Objectives. To assess the efficacy and harmlessness of the cytoprotective treatment with meldonium of ischemic heart disease by developing personalized approaches.

Materials and methods. Our study included 160 patients with IHD (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. The average age of patients was 59.26±0.74 years. All patients were divided into 2 groups: 1 group (n=80) only with background treatment and 2 group included (n=80) with background treatment and meldonium. The observation period was 12 months (one year).

Results. Significant differences were found in the pathogenesis of the underlying pathology and in the effectiveness of meldonium treatment in men and women. In this way, for men on the background of exertion angina is characteristic of more frequent occurrence of myocardial infarction, and for women – heart failure and diabetes mellitus, but meldonium remain the same effectiveness for both groups. Men smoke 16 times more, and women suffer from abdominal obesity 2 times more, which could be the cause of the more atherogenic lipid profile in them. According to the survey, the hereditary predisposition to cardiovascular diseases is higher in women, although most likely women are simply better informed about the pathologies of relatives and they were more disciplined in treatment with meldonium.

Discussions. The effectiveness of treatment in women is significantly better according to the indicators of subjective and objective improvement compared to men, which is confirmed by many existing studies. Sex factor determines the presence of a number of pathogenetic peculiarities of the course of ischemic heart disease, and therefore can be considered as one of the criteria for personalizing pharmacotherapy, however, for the individual choice of metabolic corrector, this factor is not significant. The age factor determines some pathogenetic peculiarities of the course of ischemic heart disease and the effectiveness of pharmacotherapy, however, it is not decisive for the choice of metabolic corrector.

Conclusions. The standard criteria for the personalization of pharmacotherapy in cardiology - sex, age, environmental risk factors, the presence of an underlying disease and concomitant pathology, pharmacogenetic and psychological profile - affect the pathogenesis of the development of coronary artery disease, to some extent determining the sensitivity of patients to meldonium, but they are not decisive for a personalized choice of metabolic corrector.

Keywords: cardiocytoprotector, cardiac metabolism, ischemic heart disease.

Introduction

An attempt to substantially increase the effectiveness of complex treatment of ischemic heart disease (IHD) resulted in the introduction into clinical practice of metabolic pharmacotherapy in order to ensure cardiocytoprotection [1, 2].

Despite the pathogenetic argumentation of the use of metabolic preparations in the complex treatment of ischemic heart disease [2-4], the interest in cardiocytoprotectors is more characteristic for drugs that have demonstrated their effect on the duration of life, with a proven mechanism of action, as demonstrated by the high frequency of prescribing metabolic drugs for the treatment of patients with angina pectoris [2, 3-6]. Lately, cardiologists have also begun to notice the effectiveness of this group of drugs; publications have appeared, indicating the effectiveness of medications of the metabolic group [4]. The solution to the mentioned problem, in our view, lies in the need to personalize the indication of metabolic correctors.

The direction of personalized medicine is developing extensively and the main objective of researchers is the genetic factor, despite the fact that it defines only 50% of the ability to individual reaction to drug and 10-20% the chance of developing a multifactorial disease [1, 5-8]. The methodology of personalized medicine is reduced to the definition of biomarkers, the conduct of pharmacogenetic and pharmacologic studies [3, 5-9]. In our opinion, for the development of individualized treatment approaches should be taken into account not miss 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.

The purpose of the study: to assess the efficacy and harmlessness of the cytoprotective treatment with meldonium of ischemic heart disease by developing personalized approaches.

Material and methods

Our study included 160 patients with IHD (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 with 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. All patients were divided into 2 groups: 1 group (n=80) only with background treatment and 2 group included (n=80) with background treatment and meldonium. The observation period was one year (12 month). 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 April 2012).

The diagnosis of angina pectoris of stable effort was confirmed after conducting the clinical, instrumental and laboratory evaluation, according to the recommendations of the National Clinical Protocol, prepared by the working group of experts of the Institute of Cardiology; diagnosis of unstable angina pectoris – after carrying out the complex assessment.

Results

Initially, the batches were comparable according to the indices of physical capacity: the strength of the last step (SLS), determined in the dosed physical effort test (Table 1). Starting with the 3rd month, but also subsequently, the SLS index marked a continuous and eloquent improvement in both groups of patients, but with a difference with very high statistical significance (p<0.001) starting with the 6th month of medication: 689.00±43.64 m/min (35.54%) in group I vs. 871.21±53.54 (42.82%) in group II. At 9 months of treatment this parameter demonstrated an augmentation with 57.32% in group I vs 62.84% in group II (p<0.001), and at 12 months of medication the SLS index reached the peak of positive dynamics, constituting 845.02±53.05 m/min (66.23%) in group I and 1051.38±57.33 (72.29%) in group II (p<0.001) (Table 1).

Table 1. Evolution of the SLS index depending on the medication

	SLS, m/min				
	Initial	3 months	6 months	9 months	12 months
Group I (n=80)	508.33±35.66	599.33±34.56* 17.9%	689.00±43.64** 35.54%	799.71±48.59** 57.32%	845.02±53.05** 66.23%
Group II (n=80)	610.00±43.83	789.67±51.75** 29.45%	871.21±53.54** 42.82%	993.34±55.29** 62.84%	1051.38±57.33** 72.29%
	P-value between groups				
	p>0.05	p<0.05	p<0.001	p<0.001	p<0.001

***Note:** *- p<0.05 from initial; ** - p<0.001 from initial; SLS - strength of the last step. SLS - strength of the last step.*

Thus, the data obtained revealed a continuous positive evolution of the physical capacity to administer both treatments, the effect being directly proportional to the duration of the medication, but with a superior benefit to the meldonium combination equipment, being recorded statistical authenticity between the batches even from the 3rd month of treatment. In this context, the evolution of tolerance to physical exertion was similar to that of the de-

terminants of physical capacity. If initially the groups did not show statistically significant differences according to the share of patients with low tolerance (64.29% in group I and 62.22% group II) and average (35.71% vs. 37,78%, respectively, p<0.05), with the initiation of treatment, the number of patients with low tolerance was progressively reduced in favor of those with medium and high tolerance, highlighting a superior performance in the group treated with meldonium association. Therefore, after 3 months of medication, the number of patients with low tolerance in group II was statistically significantly reduced compared to group I (35.56% vs. 57.14%, p<0.001) and 3 patients (6.67%) with high tolerance were registered in the group under medication with meldonium association compared to 1 patient (1.79%) in the group treated with basic treatment, p<0,001. Continued treatment led to a decline in the number of patients with low tolerance in both groups (42.86% in group I vs. 17.78% in group II, p<0.001), the increase in the number of patients with medium and high tolerance, maintaining the authentic statistical gap between the groups in favor of treatment with meldonium association (10 patients with high tolerance in group II compared to 2 patients in group I, p<0.001). By the 9th month of treatment, the number of patients with both low and medium tolerances decreased, in favor of the category of patients classified at high tolerance. The same trend was maintained towards the end of the treatment period, with an authentic statistical advantage for meldonium combination medication: low tolerance showed 3 patients (6.67%) in group II vs. 10 patients (17.86%) in group I, p<0.001; average tolerance - 10 patients (22.22%) vs 19 patients (33.93%), p<0,001 and high – 32 patients (71.11%) vs 27 (48.21%), p<0.001, respectively.

Based on the values of Fisher's criterion F (F), we arranged the analyzed factors as the statistical value of their influence increases in the following order: sex (F=2.89, p=0.10), the patient's age (F=2.89, p=0.09), the concomitant presence of diabetes mellitus (F=4.84, p=0.06), the presence of the underlying disease (F=4.84, p<0.05), smoking (F=4.84, p<0.05), the number of affected coronary arteries (F=10.98, p<0.0001), metabolic pharmacotherapy (F=19.51, p<0,0001). The rest of the factors studied (genetic and psychological factor) did not have a significant effect on the integral indicator - the coefficient of effectiveness of treatment, however, when conducting comparative analysis on subgroups of patients, many factors had an essential role in achieving certain effects of complex pharmacotherapy and / or in determining the effectiveness of the use of certain metabolic preparations.

The following describes in detail the value of each factor as a criterion for personalizing the pharmacotherapy of patients with ischemic heart disease.

Sex. We conducted a comparative analysis of the studied parameters in men and women with ischemic heart disease. We received a number of significant differences (Table 2).

Significant differences were found in the pathogenesis of the underlying pathology and in the effectiveness of its treatment in men and women. In this way, for men on the background of exertion angina is characteristic of more frequent occurrence of myocardial infarction, and for women – heart failure and diabetes mellitus. Men smoke 16 times more, and women suffer from abdominal obesity 2 times more, which could be the cause of the more atherogenic lipid profile in them. According to the survey, the hereditary predisposition to cardiovascular diseases is higher in women, although most likely women are simply better informed about the pathologies of relatives. Men show signs of more severe organic changes in the target organs compared to women: subclinical signs of damage to the glomerular apparatus of the kidneys, enlargement of the heart cavities, lower values of the ejection fraction of the left ventricle, more severe disorders of local contractility with corresponding changes in the repolarization phase on the electrocardiogram, tendency to myocardial dystrophy, high degree of stenosis of some coronary arteries. In women there are corresponding changes in the blood as a result of the concomitant and frequent presence of type 2 diabetes mellitus (increase in the level of glycated hemoglobin), fewer organic changes in the heart and vessels, and lower concentrations of endothelial and inducible nitric oxide synthase, a higher level of anxiety of the person.

Table 2. Comparative analysis of the indicators of pathogenic peculiarities and effectiveness of the treatment of ischemic heart disease in men and women

Indicator	Men, n = 117	Women, n = 43	p
Height, m	1.73±0.01	1.60±0.01	0.001
The number of infarcts (MI) in the anamnesis	0.73±0.07	0.41±0.09	0.021
MI: duration in years	2.98±0.49	1.61±0.55	0.070
DM: duration in years	0.99±0.31	2.57±0.79	0.074
Smoking, the number of cigarettes per day	8.56±1.04	0.41±0.41	0.001
Glycated hemoglobin, %	5.66±0.13	7.10±0.63	0.058
LDL mmol / l	3.18±0.12	3.92±0.25	0.005
VLDL, mmol / l	0.58± 0.05	0.77±0.09	0.070
EchoCG: DTD LV, mm	28.01±0.38	26.31±0.65	0.024
EchoCG: VTD LV, ml	140.27±4.68	114.81±6.54	0.004
EchoCG: VTS LV, ml	66.84±3.94	50.33±5.95	0.031
EchoCG: FELV, %	54.53±1.26	60.48±2.19	0.018
eNOS in the erythrocytic lysis, ng / ml	1116.75±358.32	466.03±101.85	0.092
iNOS in the erythrocytic lysis, ng / ml	25.03±3.29	13.74±5.25	0.074

Note. *The statistical significance of the differences was evaluated by the t-Student criterion. MI – myocardial infarct, DM - diabetes mellitus, LDL – low density cholesterol, VLDL – very low density cholesterol, EchoCG – echocardiography, DTD LV– telediastolic diameter of the left ventricle, VTD LV – telediastolic volume of the left ventricle, VTS LV– telesistolic volume of the left ventricle, FELV - ejection fraction of the left ventricle, eNOS - Endothelial nitric oxide synthase, iNOS - Inducible nitric oxide synthase.*

Age. In order to elucidate the importance of the age factor in personalizing the pharmacotherapy of patients with

ischemic heart disease, we performed a comparative analysis between two groups of patients: middle age (up to 60 years) and old age (60 years and older). I received a number of significant differences (Table 3).

Comparison of patients of different age groups showed the presence of pathogenetic peculiarities of ischemic heart disease in people of old age. Thus, elderly patients experience a number of involutional changes: reduction of height and body weight, a longer anamnesis of diabetes mellitus concomitantly with a higher degree of severity, they smoke less. In elderly patients atherosclerosis of the coronary vessels and aorta is significantly more pronounced, according to the data of coronary angiography the average degree of stenosis of almost all vascular basins of the heart is twice as high in the elderly, as well as the number of affected coronary arteries is higher constituting on average 4 vessels. In elderly patients, lower ATP values are observed in the blood both before and after treatment, which indicates the presence of involutional hypoergia.

Table 3. Comparative analysis of the indicators of pathogenic peculiarities and effectiveness of the treatment of ischemic heart disease in patients of middle and old age

Indicator	Middle-aged patients, n = 82	Patients of old age, n = 78	p
Average age, years	51.56±0.61	66.76±0.57	0.001
Height, m	1.71±0.01	1.68±0.01	0.032
Weight, kg	93.46±2.39	84.33±1.60	0.002
DM: duration in years	0,72±0.29	2.11±0.55	0.029
Smoking: the number of cigarettes per day	10.35±1.46	2.84±0.65	0.001
Index Quetelet, kg / m^2	31.87±0.76	29.81±0.51	0.026
EchoCG: AoV pressure gradient, mmHg	6.39±0.41	8.91±0.69	0.002
EchoCG: Regurgitation AoV	0.51±0.07	0.81±0.10	0.015
Coefficient of effectiveness of treatment, %	30.64±3.07	37.96±3.02	0.091
Serum ATP before treatment, mmol / l	227.39±4.34	207.20±3.52	0.001
Serum ATP after treatment, mmol / l	240.38±4.49	224.97±4.16	0.015
Erythrocytic ATP, mmol / l	681.62±2.44	693.64±3.72	0.008

Note. *The statistical significance of the differences was evaluated by the t-Student criterion. DM – diabetes mellitus, EchoCG – echocardiography, AoV – aortic valve, ATP – adenozin triphosphate*

Smoking. In order to elucidate the importance of smoking in the personalized pharmacotherapy of ischemic heart disease, a comparative analysis of the two groups of patients – smokers and non-smokers – was performed. We detected a number of significant differences (Table 4). Smoke to a greater extent the younger ones, probably due to the priority effect of the age factor in this group of patients is less pronounced the severity of the underlying pathology, comorbidities (diabetes mellitus) and the lipid profile is more favorable.

Table 4. Comparative analysis of the indicators of pathogenetic peculiarities and effectiveness of the treatment of ischemic heart disease in smokers and non-smokers

Indicator	Smoking patients, n=60	Non-smoking patients, n=100	p
Average age, years	55.77±1.15	61.27±0.87	0.001
Height, m	1.73±0.01	1.67±0.01	0.001
DM: duration in years	0.60±0.31	1.95±0.48	0.019
BPs: mm Hg	133.09±2.84	141.11±2.31	0.032
BPd: mm Hg	96.67±4.01	83.07±2.41	0.007
Total cholesterol, mmol / l	5.01±0.17	5.70±0.16	0.007
LDL, mmol / l	3.05±0.16	3.56±0.15	0.030
EchoCG: DTD LV, mm	55.51±1.27	51.94±0.96	0.025
EchoCG: VTD LV, ml	151.20±6.77	122.43±4.45	0.001
EchoCG: VTS LV, ml	72.94±5.82	55.91±3.89	0.012
EcoCG: FELV, %	53.41±1.85	57.78±1.36	0.054

Note. *The statistical significance of the differences was evaluated by the t-Student criterion. BPs – blood pressure systolic, BPd – blood pressure diastolic, DM – diabetes mellitus, EchoCG – echocardiography, DTD LV– telediastolic diameter of the left ventricle, VTD LV– telediastolic volume of the left ventricle, VTS LV– telesistolic volume of the left ventricle, FELV - ejection fraction of the left ventricle.*

Smoking patients have a higher level of hemoglobin and chromatic index, which may indicate smoking as an additional factor of hypoxemia. The objective status of smoking patients is significantly more precarious according to echocardiography and electrocardiography: the cavities of the heart are more dilated, the ejection fraction is lower, the disorders of local contractility are more expressed, and the voltage on the ECG is reduced to the level of myocardial dystrophy. The effectiveness of the treatment of the smoking patients was significantly lower according to the indicators of subjective and objective improvement, the integral coefficient of treatment effectiveness.

Discussions

The individual reaction of the body to the administration of the drug depends on several factors: genotype, sex, age, severity of the underlying disease, the presence of comorbidities, especially liver and kidney pathologies, harmful habits (smoking, alcohol consumption), eating style, concomitant administration of other medicinal preparations, etc. [4, 10]. In this chapter it is described whether it is possible to take into account these factors as criteria for personalizing metabolic pharmacotherapy in the treatment of patients with exertion angina pectoris, and their value in choosing the drug.

The effectiveness of treatment in women is significantly better according to the indicators of subjective and objective improvement compared to men, which is confirmed by many existing studies [2, 7]. A tendency to a different reaction of the mitochondria to meldonium administration was determined: in men in the form of inhibition, in women - in the form of activation ($p<0.05$).

Sex factor determines the presence of a number of pathogenetic peculiarities of the course of ischemic heart disease, and therefore can be considered as one of the cri-

teria for personalizing pharmacotherapy, however, for the individual choice of metabolic corrector, this factor is not significant [4, 7, 8].

The age factor determines some pathogenic peculiarities of the course of ischemic heart disease and the effectiveness of pharmacotherapy, however, it is not decisive for the choice of metabolic corrector [1-3, 9].

Thus, our study of patients with stable effort angina pectoris, a significant 4-fold increase in the effectiveness of complex pharmacotherapy in ischemic heart disease was detected when adding mildronate compared to the basic treatment because of the more pronounced antianginal effect, improved physical performance, potentiation of the positive, and hypotensive inotropic effects of basic pharmacotherapy [6, 9, 10]. According to experimental data in patients with myocardial ischemia, mildronate 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 supply of the myocardium [1-3]. Meldonium 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.

The data obtained revealed a continuous positive evolution of the physical capacity to administer both treatments, the effect being directly proportional to the duration of the medication, but with a superior benefit to the meldonium association, being recorded statistical authenticity between groups even from the 3rd month of treatment. In this context, the evolution of tolerance to physical effort was similar to that of the determinants of physical capacity, confirmed by the data of the specialized literature [2, 4]. If initially the groups did not show statistically significant differences after the share of patients with low tolerance (64.29% in group I and 62.22% group II) and average (35.71% vs. 37.78%, respectively, $p<0.05$), with the initiation of treatment, the number of patients with low tolerance in favor of those with medium and high tolerance was progressively reduced, highlighting a superior performance in the group treated with meldonium association. Thus, after 3 months of medication, the number of patients with low tolerance in group II was statistically significantly reduced compared to group I (35.56% vs. 57.14%, $p<0.001$) and 3 patients (6.67%) with high tolerance were registered in the group under medication with meldonium association compared to 1 patient (1.79%) in the group treated with basic treatment, $p<0.001$. Continued treatment led to a decline in the number of patients with low tolerance in both groups (42.86% in group I vs. 17.78% in group II, $p<0.001$), the increase in the number of patients with medium and high tolerance, maintaining the authentic statistical gap between the groups in favor of treatment with meldonium association (10 patients with high tolerance in group II compared to 2 patients in group I, $p<0.001$). By the 9th month of treatment, the number of patients with both low and medium tolerances decreased, in favor of the category of patients classified at high tolerance. The same trend was maintained towards the end of the treatment period, with an authentic statistical advantage for the meldonium combination medication: low tolerance presented 3 patients (6.67%) in the II group vs. 10 patients (17.86%) in the first group, $p<0.001$; average tolerance - 10 patients (22.22%) vs 19 patients (33.93%), $p<0.001$ and high – 32 patients (71.11%) vs 27 (48.21%), $p<0.001$, respectively.

Thus, the long-term treatment with basic treatment and meldonium combination beneficially influenced all the parameters determined in the dosed physical effort test, but the use of meldonium combination improved more effectively compared to the basic treatment the indicators of physical capacity and exercise tolerance.

Conclusions

1. 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.
2. The standard criteria for the personalization of pharmacotherapy in cardiology - sex, age, environmental risk factors, the presence of an underlying disease and concomitant pathology, pharmacogenetic and psychological profile - affect the pathogenesis of the development of coronary artery disease, to some extent determining the sensitivity of patients to meldonium, but they are not decisive for a personalized choice of metabolic corrector.
3. A general concept of personalization of metabolic pharmacotherapy of meldonium has been developed, according to which it is able to present a cytoprotective effect depending on the initial state of the functional adaptation system and the phase of the general adaptation syndrome of a patient with coronary artery disease.

Abbreviations: IHD - ischemic heart disease; HTA - hypertension; CSPI - postinfarct cardiosclerosis; CHF - chronic heart failure; SLS - the strength of the last step; DM - diabetes mellitus; ATP/ADP - adenosine triphosphate and diphosphate; NO - nitric oxide; EchoCG – echocardiography; DTD LV– telediastolic diameter of the left ventricle; VTD LV– the telediastolic volume of the left ventricol; VTS LV– telesistolic volume of the left ventricle; FELV - ejection fraction of the left ventricle; AoV – aortic valve.

Declaration of conflict of interest

Nothing to declare

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