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The Influence of Combined Pharmacotherapy with the Use of Trimetazidine and Potassium and Magnesium Salts of Gluconic Acid in Patients with Chronic Heart Failure of Ischemic Origin

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Keywords: myocardial infarction; heart failure; daily duration of ischemia; trimetazidine

Abstract.

The objective of the research was to improve the efficiency of treatment of patients with chronic heart failure (CHF) of ischemic genesis by adding potassium and magnesium salts of gluconic acid and trimetazidine to the background therapy (BT).

Materials and methods. Registration of electrocardiogram (ECG) and ECG Holter Monitoring (ECG HM) was performed in order to achieve the aim. The study involved 84 patients with postinfarction cardiosclerosis with CHF. Patients were randomized into four groups depending on treatment characteristics. The first group included patients with heart failure of ischemic genesis treated with BT; the second group consisted of patients with CHF, who were treated with BT and potassium and magnesium salts of gluconic acid; the third group included patients with CHF who were prescribed trimetazidine on the background of BT; the fourth group consisted of patients treated with BT in combination with potassium and magnesium salts of gluconic acid and trimetazidine.

Results of the research. The proposed treatment regimens were proved to be effective in reducing ischemic parameters after 6 and 12 months of treatment. Anti-ischemic treatment using a combination of potassium and magnesium salts of gluconic acid and trimetazidine on the background of BT led to the most significant change in the average number of myocardial ischemia episodes in examined patients. Indicator of the average daily number of ischemic episodes before the research in the first group decreased after treatment by 29.21 %. The average number of myocardial ischemia episodes during the day in the second group decreased by 38.50 % and constituted (2.78±0.10) after treatment. The addition of trimetazidine to BT in patients of III group was accompanied by significant anti-ischemic effect reducing the average daily number of ischemic episodes by 43.8 % ($p<0.001$). It should be noted that the anti-ischemic treatment of group IV patients using a combination of BT, potassium and magnesium salts of gluconic acid and trimetazidine resulted in the most statistically significant change in this indicator in examined patients, namely by 48.90 % ($p<0.001$).

Conclusions. Thus, a more significant anti-ischemic effect was observed when using combined treatment with potassium and magnesium salts of gluconic acid and trimetazidine compared with BT in a separate combination with each of these drugs.

Problem statement and analysis of the recent research

Cardiovascular diseases (CVD) constitute one third of deaths in the world, and thus, are the most important problem of modern health care system [9]. According to American Heart Association (AHA), coronary artery disease (CAD) is the most common cause of death and constitutes 52% in the structure of mortality from cardiovascular diseases (CVD) [7]. The main causes of mortality in case of CAD are primarily acute myocardial infarction and sudden cardiac death [2]. According to multicentre studies (CONSENSUS, SOLVD, ATLAS, CIBIS, NETWORK, ELITE, Val-HeFT, DIG), CAD has become the leading cause of heart failure, it was detected in 64% of patients with CHF [9].

Recently, metabolic therapy has become one of the directions in the treatment of coronarogenic CHF [1]. This is caused by the fact that myocardium dysfunction in case of CHF of ischemic genesis is based on intrinsic cellular metabolism disorder occurring in cardiomyocytes as a result of decrease in coronary blood flow [9]. Myocardial reperfusion develops after each episode of transient ischemia. It is accompanied by a significant activation of lipid peroxidation and lipid peroxide release into the blood. Pathogenetic results of oxidative stress include increased activity of pro-coagulation blood system, acceleration of nitric oxide (NO) degradation with the formation of peroxynitrite that is an extremely cytotoxic compound. Under the conditions of chronic coronary insufficiency, above mentioned processes are the additional pathological causes along with hyperactivation of sympathetic-adrenal, renin-angiotensin-aldosterone systems, activation of cardial natriuretic peptides secretion, etc. in CHF development and progression [10].

Therefore, the use of drugs optimizing energy exchange in the myocardium, eliminating the effects of oxidative stress and other metabolic disorders underlying myocardium structural changes in patients with CHF are pathogenically caused. Thus, the use of gluconic acid potassium and magnesium salts in patients with MI and CHF may be one of pathogenetically reasoned approaches of impact on metabolic processes, energy supply and ionic homeostasis in atypical myocardial cells.

According to modern recommendations, trimetazidine is one of the few cytoprotectors that can be prescribed in addition to the main treatment of patients with CHF. Randomized study METRO has proved that long-term intake of trimetazidine can positively influence the prognosis of patients after myocardial infarction who are at major risk of CHF development [5].

Long-term trimetazidine intake improves not only clinical state of patients with CHF after myocardial infarction and quality of life, but also an increase in ejection fraction (approximately by 7%) and decrease in left ventricular remodeling [11].

The largest cohort study (669 patients) on the use of trimetazidine in the treatment of patients with CHF of ischemic genesis detected a decrease within 50% in the risk of hospitalization because of the disease exacerbation [4]. Treatment with trimetazidine was likely to reduce the risk of mortality and the disease exacerbation by 11.4% and continued life without complications for 7.8 months [6].

All the above mentioned information indicates that there are prerequisites for the use of such myocardial cytoprotectors as trimetazidine and rhythmocor drug in the treatment of patients with CHF and further study of these drugs effect on the incidence and progression of the disease in patients with past MI.

The objective of the research was to improve the efficiency of treatment of patients with chronic heart failure (CHF) of ischemic genesis by adding potassium and magnesium salts of gluconic acid and trimetazidine to the background therapy.

Materials and methods of the research

The research was conducted at Ivano-Frankivsk Regional Clinical Cardiology Dispensary. 84 patients with CHF and postinfarction cardiosclerosis were examined. Patients were randomized into four groups depending on treatment characteristics. The first group included patients with CHF after myocardial infarction with stenting who recieved BT (metoprolol succinate in a dose of 25 mg/day, Clopidogrel in a dose of 75 mg/day, cardioaspirin in a dose of 75 mg/day, atorvastatin in a dose of 20 mg/day and enalapril in a dose of 5 mg/day) (n=20). The second group consisted of patients with CHF after myocardial infarction, who were treated with BT and 1 capsule of potassium and magnesium salts of gluconic acid three times a day (n=21). The third group included patients with CHF who were prescribed trimetazidine in a dose of 70 mg two times a day on the background of BT (n=23). The fourth group consisted of patients who received BT and 1 capsule of potassium and magnesium salts of gluconic acid three times a day and trimetazidine in a dose of 70 mg two times a day (n=20).

The diagnosis of past myocardial infarction was determined according to the criteria ESC/ACCF/AHA/WHF (2012) [8]. CHF diagnosis was made in accordance with the recommendations of Ukrainian Association of Cardiologists of diagnosis and treatment of CHF (2012) [3].

Registration of electrocardiogram on the electrocardiograph Cardiofax (Electrokardiograph, ECG 8820G, Germany) and ECG Holter Monitoring in automatic mode using the system "Cardiosens" XAI-MEDICA (Kharkiv) according to 24-hour record of cardiorhythmogram was performed in order to achieve the aim.

Statistical processing of the results was performed using a computer program STATISTIKA-7 and a package of statistical functions of "Microsoft Excel" program. Fisher's exact test was used to compare the reliability among research groups.

Results of the research and their discussion

The results of ECG study of the examined patients are presented in Table 1.

Table 1

Dynamics of ECG parameters in patients with CHF after treatment

Parameters	Before the treatment	1 month of therapy	6 months of therapy	12 months of therapy
Background therapy (n=20)				
ST-segment depression (absolute value %, p)	4 (20.0%)	3 (15.0%) p>0.05	2 (10.0%) p>0.05	1 (5.0%) p>0.05
T-wave inversion (absolute value %, p)	5 (25.0%)	3 (15.0%) p>0.05	1 (5.0%) p>0.05	1 (5.0%) p>0.05
Supraventricular extrasystole (absolute	3 (15.0%)	2 (10.0%) p>0.05	-	-
Ventricular premature beats (absolute value %, p)	2 (10.0%)	1 (5.0%) p>0.05	-	-
Background therapy + Rhythmocor drug (n=21)				
ST-segment depression (absolute value %, p)	5 (23.8%)	4 (19.0%) p>0.05	1 (4.8%) p<0.01	-
T-wave inversion (absolute value %, p)	4 (19.0%)	3 (14.3%) p>0.05	1 (4.8%) p>0.05	-
Supraventricular extrasystole (absolute	2 (9.5 %)	1 (4.8%) p>0.05	-	-

Ventricular premature beats (absolute value %, p)	1 (4.8%)	1 (4.8%) p>0.05	-	-
Background therapy + trimetazidine (n=23)				
ST-segment depression (absolute value %, p)	5 (21.7%)	4 (19.0%) p>0.05	1 (4.3%) p>0.05	1 (4.3%) p>0.05
T-wave inversion (absolute value %, p)	6 (26.1%)	5 (21.7%) p>0.05	1 (4.3%) p<0.05	1 (4.3%) p>0.05
Supraventricular extrasystole (absolute	4 (19.0%)	3 (13.0%) p>0.05	-	-
Ventricular premature beats (absolute value %, p)	3 (13.0%)	2 (8.7%) p<0.05	-	-
Background therapy + Rhythmocor drug + trimetazidine (n=20)				
ST-segment depression (absolute value %, p)	6 (30.0%)	3 (15.0%) p>0.05	-	-
T-wave inversion (absolute value %, p)	5 (25.0%)	2 (10.0%) p>0.05	-	-
Supraventricular extrasystole (absolute	3 (15.0%) p>0.05	1 (5.0%) p<0.05	-	-
Ventricular premature beats (absolute value %, p)	2 (10.0%)	1 (5.0%) p<0.05	-	-

Note. 1. The percentage of the total number of persons in the group is indicated in parentheses.

2. p – probability of difference in mean values before, during and after the treatment.

According to the data in Table 1, the use of potassium and magnesium salts of gluconic acid and trimetazidine proved to be effective in reducing ischemic manifestations of postinfarction cardiosclerosis.

The dynamics of ischemia indices according to ECG Holter Monitoring in patients with CHF and postinfarction cardiosclerosis is presented in Table 2.

Table 2

Dynamics of ischemia indices according to ECG Holter Monitoring in patients with CHF

Groups of patients / Index	I group (background therapy), n=20		II group (background therapy + Rhythmocor drug), n=21		III group (BT+ trimetazidine), n=23		IV group (Rhythmocor drug + trimetazidine +BT) n=20	
	Before the treatment	After the treatment	Before the treatment	After the treatment	Before the treatment	After the treatment	Before the treatment	After the treatment
Average number of myocardial ischemia episodes during the day	4.45±0.31	3.15±0.14 Δ-29.21 p<0.01	4.52±0.31	2.78±0.10 Δ-38.50 p<0.001, p_{1-2}<0.05	4.34±0.21	2.44±0.12 Δ-43.8 p<0.001, p_{1-3}<0.001, p_{2-3}<0.05	4.13±0.16	2.11±0.08 Δ-48.9 p<0.001, p_{2-4}<0.001, p_{3-4}<0.05
Total duration of ST segment depression, min/day	51.56±1.9	38.2±2.05 Δ-25.9 p<0.001	48.93±1.87	32.86±1.32 Δ-32.8 p<0.001, p_{1-2}<0.05	50.3±2.34	28.7±1.54 Δ-42.9 p<0.001, p_{1-3}<0.001, p_{2-3}<0.05	50.49±2.12	22.7±1.65 Δ-55.0 p<0.001, p_{2-4}<0.001, p_{3-4}<0.05

Average value of ST segment depression depth, mm	1.33±0.05	0.91±0.06 Δ-31.6 p<0.001	1.17±0.08	0.79±0.07 Δ-32.5 p<0.01 p_{1-2}>0.05	1.35±0.09	0.61±0.03 Δ-54.8 p<0.001, p_{1-3}<0.001, p_{2-3}<0.05	1.29±0.07	0.45±0.04 Δ-65.1 p<0.001, p_{2-4}<0.001, p_{3-4}<0.01
Average value of maximum ST-segment displacement, mm	2.35±0.11	1.73±0.14 Δ-26.4% p<0.001	2.06±0.13	1.54±0.09 Δ-25.2% p<0.001 p_{12}>0.05	2.43±0.12	1.41±0.08 Δ-42.0% p<0.001, p_{1-3}>0.05, p_{2-3}>0.05	2.25±0.12	1.23±0.11 Δ-45.3 p<0.001, p_{2-4}<0.05, p_{3-4}>0.05
Average heart rate during ST segment depression, per minute	74.1±2.91	64.9±2.51 Δ-12.42% p<0.05	71.5±2.62	62.23±2.51 Δ-12.97% p<0.05	73.25±2.65	63.24±2.69 Δ-13.67% p<0.05	72.31±2.78	61.46±2.45 Δ-15.0% p<0.01

Note. p – the probability of changes regarding the treatment.

According to the data presented in Table 2, the rate of the average daily number of ischemic episodes before the examination in group I constituted 4.45 ± 0.31 and decreased by 29.21% after the treatment amounting 3.15 ± 0.14 (p<0.01). The average number of myocardial ischemia episodes during the day in the second group decreased by 38.50% and equaled 2.78 ± 0.10 (p<0.001; p_{1-2}<0.05) after the treatment. The addition of trimetazidine to BT in patients of group III was accompanied by more significant anti-ischemic effect reducing the average daily number of ischemic episodes by 43.8% (p<0.001). It should be noted that anti-ischemic treatment of group IV patients resulted in statistically the greatest change in this index in the examined patients (p<0.001) with the use of a combination of BT and potassium and magnesium salts of gluconic acid and trimetazidine. Thus, the average number of ischemic episodes in patients before the examination constituted 4.13 ± 0.16 and reduced by 48.9% after twelve months of therapy to 2.11 ± 0.08 (p<0.001) being significantly different from similar index in groups I, II and III.

The average and maximum values of ST segment depression depth were analyzed. According to the data presented in Table 2, positive dynamics of these indices reduction was observed in all groups of patients with CHF after myocardial infarction with performed reperfusion. Twelve months treatment of group I with BT drugs was accompanied by a decrease in the average value of ST segment depression by 31.6% to (0.91 ± 0.06) mm (p<0.001). At the same time the maximum value of ST segment depression decreased by 26.4% (p<0.001). Improved dynamics of ST segment depression depth by 32.5 % and 54.8% was observed in patients of groups II and III. Maximum ST segment depression decreased by 25.2 and 42.0% in these groups.

Total duration of ischemia a day after the treatment constituted (38.2 ± 2.05) min / day in group I patients who received atorvastatin, metoprolol succinate, clopidogrel, aspirin and enalapril. It was significantly lower in comparison with the same index in patients who were treated with BT and potassium and magnesium salts of gluconic acid. It constituted (32.86±1.32) min/day (p_{1-2}<0.05).

According to Fig. 1, the analysis of ischemia average daily duration in patients of groups II, III and IV indicated that the index was significantly lower in comparison with BT group. At the same time the most significant anti-ischemic effect was observed in the group of adequate combination anti-ischemic therapy with the use of potassium and magnesium salts of gluconic acid and trimetazidine (IV group). The use of anti-ischemic treatment group IV patients led to a decrease in the total duration of ischemia per day by 55.0%, which was significantly higher than the same index in patients of I, II, and III groups (p<0.001; p_{1-4}<0.001; p_{2-4}<0.001; p_{3-4}<0.05). The high

efficiency of the studied drugs and their combinations in reduction of the duration and frequency of myocardial ischemia was established.

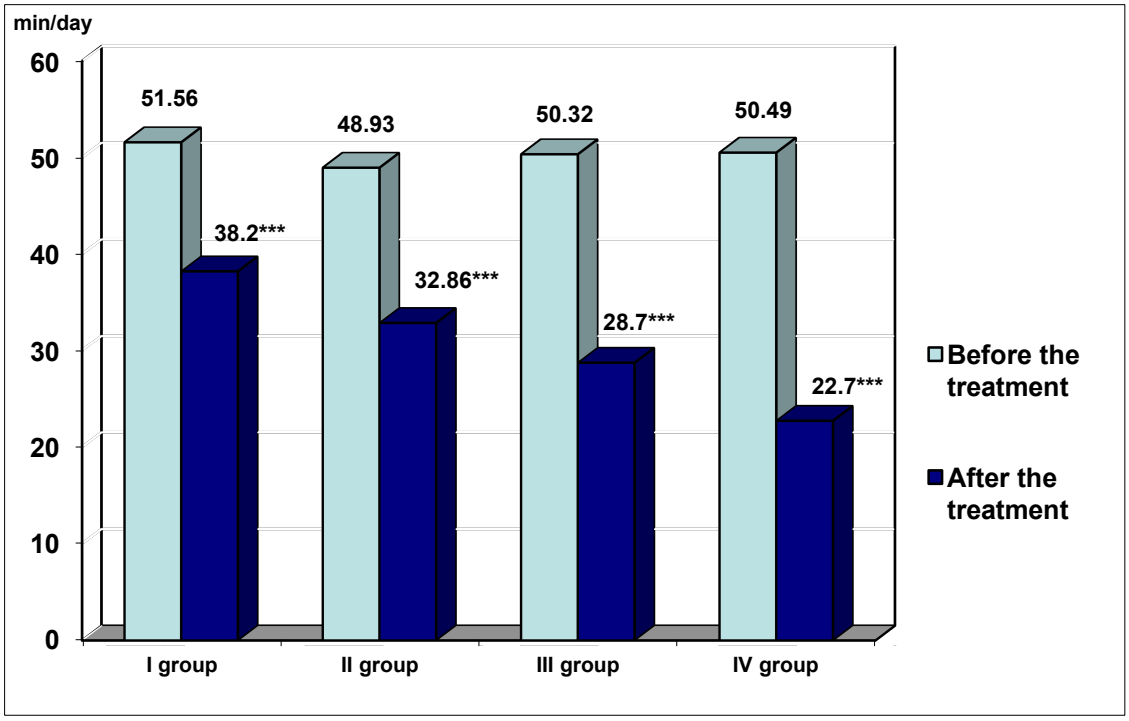

Fig. 1. Indices of daily duration of myocardial ischemia after the course of anti-ischemic therapy in patients of different examined groups.

Note. Probability of compared to almost healthy individuals – *p<0.05; ***p<0.001.

Conclusions

1. The results of ECG and ECG HM indicated that the investigated treatment regimens were effective in ischemia indices reduction.
2. Comparing the basic data and the data from 6 and 12 months of patients' observation, the following consistent patterns were obtained: total duration of ischemia, the frequency of the daily number of episodes, average and maximum ST segment depression depth decreased in all four groups.
3. More significant anti-ischemic effect of combined treatment with potassium and magnesium salts of gluconic acid and trimetazidine was noted in comparison with BT in a separate combination with each of these drugs.
4. The use of potassium and magnesium salts of gluconic acid and trimetazidine in patients with CHF of ischemic genesis was determined to be appropriate, pathogenetically reasonable and safe.

Prospects for further research involve monitoring of the treatment efficiency. Determination of biological marker galectin-3 may be also considered promising.

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