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THE EFFECT OF TREATMENT WITH TRIMETAZIDINE ON THE COURSE OF ARRHYTHMIA IN PATIENTS WITH ISCHEMIC HEART DESEASE AND DIABETES MELLITUS

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Abstract. *It was studied the effect of trimetazidine in patients with ischemic heart disease and diabetes mellitus with concomitant cardiac arrhythmias: ventricular and supraventricular extrasystoles and cardiac fibrillation. It was investigated 35 patients, among them 12 with registered supraventricular extrasystoles, 12 with ventricular extrasystoles, 11 patients with paroxysmal form of cardiac fibrillation. It has been shown that the treatment with trimetazidine is accompanied by decreasing of the number of supraventricular and ventricular extrasystoles in patients with ischemic heart disease and diabetes mellitus 2 type. The treatment with trimetazidine is accompanied by the reduction of severity of myocardial ischemia.*
Key words: *arrhythmia, trimetazidine, chronic ischemic heart disease, diabetes, lipid, carbohydrate metabolism.*

At last time, much attention is given to drugs that have a positive effect on the metabolism of ischemic myocardium [1, 10]. Some drugs in this group, not having electrophysiological properties have antiarrhythmic effect by influencing on the different mechanisms of arrhythmogenesis [3, 5], including myocardial fibrosis, left ventricular remodeling. Indirect antiarrhythmic properties of drugs of metabolic actions serve as an additional argument in favor of their appointment in patients with ischemic heart disease, including patients with concomitant diabetes mellitus.

Among the drugs of metabolic action the special interest is induced by trimetazidine [7]. Recently, the drug entered in the arsenal of preparations that are used to treat patients with ischemic heart disease and concomitant diabetes mellitus. Trimetazidine selectively inhibits the enzyme 3-ketoacyl-KoAtiolazu and causes a partial decrease of β-oxidation of free fatty acids [7, 8]. It is noted the increasing of

glucose metabolism, increasing of formation of adenosinediphosphate, the improving of myocardial contractility [4, 11]. In patients with diabetes mellitus trimetazidine optimizes the myocardial metabolism by restoring the balance between glycolysis and glucose oxidation [4, 11]. This results in a more economical way of the oxidation of carbohydrates and reduce the manifestations of ischemia. It is important to emphasize that the drug exerts the antihypoxiaand cytoprotective effect onmyocardium, reduces the negative effect on its free-radical oxidation [9]. It is now established that free radicals contribute to the appearance of cardiac arrhythmias and cause electrical instability of the myocardium [6]. Arrhythmias are often observed in patients with coronary artery disease with concomitant diabetes, especially in the presence of myocardial dysfunction [6, 10]. With the development of clinically significant chronic heart failure, the ventricular arrhythmias are regarded as predictor of sudden death [12].

The purpose of the study. The studying of the effects of trimetazidine in patients with coronary artery disease and diabetes mellitus II types with concomitant cardiac arrhythmias: ventricular extrasystoles, supraventricular extrasystoles and cardiac fibrillation.

Materials and methods. It was examined 35 patients, among them 12 with registered supraventricular extrasystoles, 12 with ventricular extrasystoles, 11 with paroxysmal cardiac fibrillation. The age of the patients was from 48 to 63 years. The study was conducted by open way without prescribing a placebo. Trimetazidine was administered at a dose of 30 mg 3 times a day on a background of standard therapy, which included nitrates, angiotensin-converting enzyme inhibitors, disaggregants. Initially and after 3 months of treatment the electrocardiogrammonitoring was performed. Together with arrhythmias it was evaluated the number and duration of ischemic episodes with reduction of S-T segment below the isoelectric line by 1 mm or more.

Results and discussion. The results of investigation of patients are shown in table 1. After treatment with trimetazidine heart beat rate, systolic blood pressure, diastolic blood pressure did not change from baseline values. Number supraventricular

extrasystoles significantly decreased from 314,7 ± 9,4 to 168,8 ± 7,6 per day (p <0,05).

Table 1.

The results of daily electrocardiogram monitoring during the treatment with trimetazidine

Indicators	The period of observation	Group of patients		
		Supraventricular extrasystoles (n = 10)	Ventricular extrasystoles (n = 11)	Cardiac fibrillation (n = 10)
Heart beats rate / min.	Beforetreatment	76,0 ± 3,8	73,2 ± 1,2	74,1 ± 2,2
	After treatment	75,0 ± 2,3 p>0,05	74,4 ± 2,4 p>0,05	72,3 ± 3,3 p>0,05
Systolic blood pressure	Before treatment	138,4 ± 6,4	139,6 ± 5,8	130,7 ± 2,9
	After treatment	137,7 ± 7,2 p>0,05	135,7 ± 6,3 p>0,05	131,8 ± 3,8 p>0,05
Diastolic blood pressure	Before treatment	76,5 ± 2,9	72,4 ± 3,3	71,7 ± 1,9
	After treatment	74,3 ± 2,3 p>0,05	71,5 ± 2,1 p>0,05	72,8 ± 2,2 p>0,05
Number of supraventricular extrasystoles per day	Before treatment	314,7 ± 9,4	-	-
	After treatment	168,8 ± 7,6 p <0.05	-	-
The number of ventricular extrasystoles per day	Before treatment	-	892,7 ± 11,7	-
	After treatment	-	474,8 ± 12,4 p<0,05	-
The number of paroxysmal cardiac fibrillation per day	Before treatment	-	-	1,2 ± 0,4
	After treatment	-	-	1,1 ± 0,5 p>0,05
The number of episodes of S-T per day	Before treatment	4,3 ± 0,7	4,6 ± 0,8	3,1 ± 0,2
	After treatment	2,1 ± 0,6 p<0,05	2,0 ± 0,3 p<0,05	1,6 ± 0,4 p<0,05
The duration of episodes of reducing S-T, min.	Before treatment	3,3 ± 0,2	3,8 ± 0,4	3,0 ± 1,8
	After treatment	2,9 ± 0,3 p>0,05	3,0 ± 0,2 p>0,05	2,8 ± 2,2 p>0,05

A significant change in the frequency of paroxysmal cardiac fibrillation in patients was not detected (p> 0,05). The number of ventricular extrasystoles per day after treatment with trimetazidine decreased from 892,7 ± 11,7 to 474,8 ± 12,4 (p <0,05). Attention is drawn to the fact that the drug therapy was accompanied by statistically reliable significant reduction in the number of episodes of myocardial ischemia in all groups of patients regardless of the type of disturbances of heart rhythm (table. 1).

It is important to determined thecharacter of the influence of trimetazidine on the performance of renin-angiotensin-aldosterone system, lipid metabolism, the level of endotelin-1, catecholamines and cyclic guanosine monophosphate in patients with coronary artery disease and diabetes II with concomitant cardiac arrhythmias.

As it is seen from the table 2 the data of treatmentwith trimetazidine was not associated with significant changes in indicators of renin-angiotensin-aldosterone system. There were no significant changes in plasma renin activity, aldosterone, angiotensin II, electrolytes (p> 0,05) (table 2).

Table 2.

System status of renin-angiotensin-aldosterone system in patients with ischemic heart disease and diabetes mellitus II types with concomitant cardiac arrhythmias

Indicators	The period of observation	Group of patients		
		1st	2nd	3rd
		Supraventricular extrasystoles (n = 10)	Ventricular extrasystoles (n = 11)	Cardiac fibrillation (n = 10)
Activityof plasma renin ng/ml/g^{-1}	Before treatment	4,29 ± 0,42	6,32 ± 0,86	6,12 ± 0,98
	After treatment	4,31 ± 0,31 p<0,05	6,43 ± 0,9 p>0,05	6,21 ± 0,76 p>0,05
Aldosterone pg /ml	Before treatment	326,3 ± 41,2	331,8 ± 38,7	392,7 ± 29,4
	After treatment	327,9 ± 56,3 p>0,05	330,8 ± 42,9 p>0,05	397,4 ± 31,5 p>0,05
Angiotensin II pg/ml	Before treatment	17,3 ± 2,41	24,7 ± 3,2	22,4 ± 2,7
	After treatment	17,4 ± 2,52 p>0,05	23,9 ± 4,1 p>0,05	22,01 ± 2,9 p>0,05
Na^+mmol/l	Before treatment	142,7 ± 3,51	134,3 ± 2,08	137,6 ± 4,1
	After treatment	141,7 ± 4,32 p>0,05	135,6 ± 1,92 p>0,05	136,8 ± 3,9 p>0,05
K^+mmol/l	Before treatment	4,18 ± 0,15	3,76 ± 0,19	3,89 ± 0,11
	After treatment	4,19 ± 0,18 p>0,05	3,74 ± 0,18 p>0,05	3,85 ± 0,14 p>0,05

During evaluation of the influence of trimetazidine on lipid metabolism it was unable to identify any changes in the dynamics of therapy (tab. 3).

During the treatment with trimetazidine it was unable to identify its influence on the level of plasma catecholamines (tab. 4).

Table 3.

Lipid metabolism during the treatment with trimetazidine

Indicators	The period of observation	Group of patients		
		1st	2nd	3rd
		Supraventricular extrasystoles (n = 10)	Ventricular extrasystoles (n = 11)	Cardiac fibrillation (n = 10)
Total cholesterol, mmol/l	Before treatment	7, 14 ± 0,19	7, 21 ± 0,26	7,08 ± 0,17
	After treatment	7, 12 ± 0,18 p>0,05	7,18 ± 0,32 p>0,05	7, 12 ± 0,26 p>0,05
Triglycerides,mmol/l	Before treatment	2, 96 ± 0,15	3, 12 ± 0,20	2,94 ± 0, 17
	After treatment	2.9 8 ± 0,18 p>0,05	3, 16 ± 0,19 p>0,05	2,98 ± 0,21 p>0,05
Low density of lipoproteins, mmol/l	Before treatment	4,61 ± 0,16	4,94 ± 0,19	4,79 ± 0,14
	After treatment	4,62 ± 0,18 p>0,05	4,92 ± 0,18 p>0,05	4,83 ± 0,20 p>0,05
High density of lipoproteins, mmol/l	Before treatment	1,02 ± 0,05	0,70 ± 0,01	0,72 ± 0,03
	After treatment	1,03 ± 0,04 p>0,05	0,76 ± 0,02 p>0,05	0,73 ± 0,05 p>0,05

Table 4.

Catecholamine levels during the treatment with trimetazidine

Indicators	The period of observation	Group of patients		
		1st	2nd	3rd
		Supraventricular extrasystoles (n = 10)	Ventricular extrasystoles (n = 11)	Cardiac fibrillation (n = 10)
Adrenaline, mmol/l	Before treatment	5,26 ± 0,31	5,41 ± 0,25	5,32 ± 0,28
	After treatment	5,24 ± 0,32 p>0,05	5,37 ± 0,29 p>0,05	5,33 ± 0,29 p>0,05
Noradrenaline, mmol/l	Before treatment	39,41 ± 2,02	40,01 ± 1,12	39,82 ± 2,01
	After treatment	38,59 ± 3,01 p>0,05	41,02 ± 1,11 p>0,05	37,86 ± 1,92 p>0,05

The therapy with trimetazidine did not cause the significant changes in the level of plasma endotelin-1 (tab. 5), although the tendency to its decreasing was observed in all groups of patients, but it did not reach the statistically significant importance.

During evaluationof the influence of trimetazidine on cyclic guanosine monophosphateit was determined that the drug does not effect on its level in patients with supraventricular extrasystoles and cardiac fibrillation, but it is observed the

tendency to its increasing in patients with ventricular extrasystoles, although it did not reach the statistical significance (tab. 5).

Table 5.

The changes in the level of endotelin-1 and cyclic guanosine monophosphatein the course of treatment with trimetazidine

Indicators	The period of observation	Group of patients		
		Supraventricular extrasystoles (n = 10)	Ventricular extrasystoles (n = 11)	Cardiac fibrillation (n = 10)
Endotelin-1, ng/ml	Before treatment	14,12 ± 1,07	16,52 ± 0,64	15,12 ± 0,81
	After treatment	14,13 ± 0,84 p>0,05	15,84 ± 1,2 p>0,05	15,10 ± 0,94 p> 0,05
Cyclic guanosine monophosphate,nmol/l	Before treatment	6,97 ± 0,83	6,54 ± 0,67	7,01 ± 0,94
	After treatment	6,99 ± 0,91 p>0,05	7,21 ± 0,56 p>0,05	7,02 ± 0,88 p>0,05

In studying the effects of the drug on carbohydrate metabolism it was not noted its significant effect on the level of immunoreactive insulin and plasma glucose (tab. 6).

Table 6.

The indexes of carbohydrate metabolism

Indicators	The period of observation	Group of patients		
		1st	2nd	3rd
		Supraventricular extrasystoles (n = 10)	Ventricular extrasystoles (n = 11)	Cardiac fibrillation (n = 10)
Immunoreactive insulin,kED/m	Before treatment	13,4 ± 0,38	15,3 ± 0,96	14,9 ± 0,74
	After treatment	12,9 ± 0,78 p>0,05	15,2 ± 0,84 p>0,05	14,0 ± 0,76 p>0,05
Blood glucose, mmol/l	Before treatment	6, 63 ± 0,32	7, 42 ± 0,41	6,96 ± 0,51
	After treatment	6, 61 ± 0,28 p>0,05	7,39 ± 0,52 p>0,05	6,97 ± 0,29 p>0,05

Conclusions:

1. The therapy with trimetazidine is accompanied by decreasing of the number of supraventricular and ventricular extrasystoles in patients with ischemic heart disease and diabetes mellitus.

2. The drug has no effects on the incidence of paroxysmal cardias fibrillation. The treatment with trimetazidine is accompanied by a reduction of severity of myocardial ischemia.

3. The drug has no effects on the indexes of carbohydrate and lipid metabolism, the state of renin-angiotensin-aldosterone system, cyclic guanosine monophosphate, endotelin-1, immunoreactive insulin.

4. The antiarrhythmic and anti-ischemic effects of the drug are due to primarily to its effects on the intracellular metabolism in cardiomyocytes.

5. Trimetazidine inhibits □oxidation by inhibiting the metabolism of fatty acids, and this contributes to a more economical use of oxygen in the oxidation of carbohydrates and thus results in reducing the occurrence of myocardial ischemia and anti-arrhythmic action.

The study of the effect of treatment with trimetazidine on the course of arrhythmias in patients with ischemic heart disease and diabetes mellitus 2 type will be continued and studied in subsequent scientific investigations.

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Резюме. Був вивчений ефект тріметазідіну у хворих на ІХС і СДІІ з супутніми порушеннями серцевого ритму: шлуночкова, суправентрикулярна ектрасистолія і миготлива аритмія. Обстежено 35 хворих, серед яких у 12 реєструвалася суправентрикулярна екстрасистолія, у 12 шлуночкова екстрасистолія, у 11 - пароксизмальна форма миготливої аритмії. Показано, що терапія тріметазідіном супроводжується зменьшенням кількості суправентрикулярних і шлуночкових екстрасистол у хворих на ІХС і СДІІ. Лікування тріметазідіном супроводжувалося зменшенням вираженості ішемії міокарда.
Ключові слова: аритмії, тріметазідін, хронічна ішемічна хвороба серця, цукровий діабет, ліпідний обмін, вуглеводний обмін.

Резюме. Был изучен эффект триметазидина у больных ИБС и СДІІ с сопутсвующими нарушениями сердечного ритма: желудочковая, суправентрикулярная эктрасистолия и мерцательная аритмия. Обследовано 35 больных, среди которых у 12 регистрировалась суправентрикулярная экстрасистолия, у 12 желудочковая экстрасистолия, у 11 – пароксизмальная форма мерцательной аритмии. Показано, что терапия триметазидином

сопровождается урежением числа суправентрикулярных и желудочковых экстрасистол у больных ИБС и СДII. Лечение триметазидином сопровождалось уменьшением выраженности ишемии миокарда.

Ключевые слова: аритмии, триметазидин, хроническая ишемическая болезнь сердца, сахарный диабет, липидный обмен, углеводный обмен.

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