



ANTIARRHYTHMIC EFFECTS OF TRIMETAZIDINE

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ABSTRACT

Coronary heart disease (CHD) is the main cause of mortality among diseases of the cardiovascular system. In recent years, some progress has been made in the treatment of this disease due to the wider use of modern drug therapy and invasive treatment methods, which has led to a significant improvement in the prognosis and quality of life of patients with cardiovascular pathology. One of the manifestations of coronary heart disease is angina pectoris. It is caused by transient myocardial ischemia resulting from a mismatch between the myocardial oxygen demand and its delivery. Standard drug therapy for angina is aimed either at reducing the myocardial oxygen demand or at increasing its delivery. The myocardial oxygen demand depends on the heart rate, blood pressure (BP), and myocardial contractility. To reduce the myocardial oxygen demand, drugs are prescribed that reduce the heart rate, reduce blood pressure, have a negative inotropic effect, and vasodilators are used to increase oxygen delivery to the myocardium. Thus, in the treatment of angina pectoris, drugs with hemodynamic effects are prescribed: beta-blockers, prolonged calcium antagonists, nitrates, inhibitors of if channels of sinus node cells. Optimal drug therapy for angina includes, in addition to antianginal drugs, antiplatelet agents and aggressive lipid-lowering therapy.

Keywords: coronary artery disease, coronary heart disease, angina pectoris, trimetazidine, ventricular tachycardia, Holter ECG monitoring, extrasystole, parasympathetic

INTRODUCTION

Cardiovascular disease remains one of the leading causes of death in the world. Leading among them is ischemic heart disease (CHD). Ischemic heart disease more





often than other diseases becomes an etiological factor in the occurrence of arrhythmias. Ventricular Extrasystoles (VE) Are the most common and at the same time the most prognostic type of ventricular arrhythmia (VA). In this regard, all issues related to heart rhythm disturbances are of great importance. According to the data of daily ECG monitoring, 85% of patients with ischemic heart disease have various rhythm and conduction disorders, the most common of which are those that occur in 90-95% of these patients. Frequent Ves is often a precursor of fatal arrhythmias-ventricular tachycardia (VT), ventricular fibrillation (VF) and sudden death (VS). The presence of ischemia in patients with frequent, paired and polyfocal RE can accelerate the development of malignant and potentially dangerous arrhythmias. A frequent violation of the rhythm in patients with ischemic heart disease is also ventricular parasystole (LC), the question of the prognostic value of which in patients with organic heart disease remains questionable. VA does not have a direct transformation into VA and VF, however, it is capable of stimulating the formation of VA with the possible development of life-threatening zh. The relationship of LC tachycardia with recurrent FH has been observed. At a heart rate of 180-200 in 1 minute. with paroxysmal parasystolic tachycardia, clinical manifestations characteristic of this arrhythmia develop. the search for the most effective and at the same time safe way to treat cardiac arrhythmias is always at the center of attention of cardiologists. It is known that class I (AP) antiarrhythmic drugs (quinidine, novocainamide, ritmilen), Class I (flecainide, etacizine, propafenone) and Class III, which are currently used to treat arrhythmias in patients with ischemic heart disease, are not always effective for reducing the amount of RE and especially VA. In patients with malignant Zha, with the use of AP of all classes, real success was achieved in 58.5% of cases. With VT after a heart attack, this indicator is only 20%. In the process of selecting AP and / or long-term treatment with them, various adverse reactions of cardiac and non-cardiac nature occur in 5-30% of cases. The greatest danger to the patient is the possibility of developing the arrhythmogenic effect of AP with an increase in their dosage. It is known that classes AP ia, C and III extend the interval Q-T, which can lead to the development of polymorphic VT, FJ. Even a low dose of the drug does not protect the patient from the development of side effects, although their severity in this case is less. The result of the CAST study, which examined the effectiveness of AP classes I and III and their complications, including the frequency of VS, was an increase in overall mortality and frequency of VS (2.5 and 3.6 times) in patients with frequent FE who had acute myocardial infarction, against the background of a pronounced antiarrhythmic effect. Despite the good effectiveness of amiordarone, the drug causes a number of side effects, among which the most common are damage to the



respiratory system, nervous system, eyes, skin, arrhythmogenic effects and thyroid dysfunction. Attempts have been made to use the side antiarrhythmic effects of various drugs (nitrates, ACE inhibitors, etc.) based on the etiopathogenetic approach to the treatment of extrasystoles. The antiarrhythmic effect of ACE inhibitors in patients with chronic heart failure, according to many authors, is realized primarily by normalizing the humoral factor. Tranquillizers, neuroleptics and antidepressants can have an indirect antiarrhythmic effect. Recently, work has been carried out demonstrating the possibility of using a number of physical factors to treat patients with Ms. Positive results have been achieved in the treatment of MS in patients with ischemic heart disease with the help of such non-medical methods as hyperbaric oxygenation, the use of baths with carbon dioxide, electromagnetic waves in the decimeter range, as well as laser therapy. However, in the literature available to us, we did not find works devoted to the study of patients with ischemic heart disease with extrasystole and parasytose in their treatment with drugs with a cytoprotective mechanism of action, in particular trimetazidine. It is known that the substrate for electrogenesis of extrasystoles (re-entry with restriction of unilateral conduction) and parasytoses (with restriction of entry into the paracenter) are areas of the myocardium with delayed ventricular depolarization, possibly due to ischemic zones or focal ischemic myocardial damage. Experimentally, it was found that if the heart consumes only free fatty acids, then it needs 17% more oxygen to produce the same amount of ATP as when oxidizing glucose. As a result, the use of compounds that inhibit fatty acid oxidation in ischemia can optimize energy production (ATP) in mitochondria due to the transition from fatty acid oxidation to aerobic glucose oxidation. This will allow the heart to better use residual oxygen and reduce ischemic damage to cardiomyocytes. Trimetazidine has this anti-ischemic mechanism of action. Based on the studies conducted, it was shown that treatment with trimetazidine in patients with angina reduces the frequency of pain attacks, the need for Nitroglycerin by 50-66% and increases load tolerance. At the same time, unlike other antianginal drugs, trimetazidine does not affect blood pressure and heart rate, which makes it possible to use it as an additional antianginal drug in patients with hyper- and hypotension and bradycardia. The anti-ischemic effect of trimetazidine allows cells to maintain their functions in conditions of reduced oxygen supply. The purpose of our study was to study the effect of trimetazidine on reducing the frequency and severity of ventricular extrasystole and parasytose, the frequency of supraventricular extrasystole and parasytose in patients with stable and unstable forms of coronary artery disease.



MATERIALS AND METHODS

We studied 63 patients with coronary heart disease, unstable, stable angina pectoris and small-focal myocardial infarction. All of them had cardiac arrhythmias in the form of frequent, paired or other prognostically unfavorable RE or supraventricular extrasystole, as well as frequent AF or supraventricular parasystole, and were observed for 1-1.5 months.

All patients underwent electrocardiography of rest in dynamics, laboratory blood tests with determination of serum lipids, electrolytes (potassium, sodium), glucose, cardiospecific enzymes; SEE ECG in dynamics (at least 3 times). All patients with coronary heart disease with indications of their arrhythmias, upon admission, an ECG screening was performed to diagnose cardiac arrhythmias and selection according to the relevant study criteria for further observation. If necessary, the correction of conventional antianginal therapy was carried out, including nitrates, b-blockers, ACE inhibitors, calcium antagonists, and disaggregants. Based on the data of a repeated ECG performed after 7-10 days (evaluation of ST dynamics and comparison of rhythm disturbances), patients with persistent frequent RE, NE, ZHP, NLP, paired and group RE, group NE or episodes of NLT were additionally prescribed trimetazidine at a dose of 20 mg x 3 r/day to receive antianginal therapy. The control ECG SM was performed after a month of co-administration of conventional antianginal therapy and trimetazidine.

RESULTS

A decrease in the number of single ventricular extrasystoles by 11-99% (on average by 57.8%), by the end of treatment, was observed in 24 (82.8%) of 29 patients. At the same time, a decrease in VE by 75% (which is considered a good antiarrhythmic effect) or more was observed in 8 (27.6%) of 29 patients. By the end of treatment, the paired VE disappeared in 15 (68%) of 22 patients. In another 5 (22.7%) patients, the number of paired RE decreased by 24-83%. Thus, a decrease or disappearance of paired VE was observed in 20 (91%) patients. Group VE - (3-5 consecutive RE) was observed in 8 patients before treatment with trimetazidine. In 6 of them (75%), it disappeared by the end of treatment with trimetazidine (100% effect), in one it decreased by 97.9%, and in one it remained unchanged. The positive effect was observed in total in 7 out of 8 patients, i.e. in 87.5% of patients who had group VE before the appointment of trimetazidine.

In 51 out of 53 patients registered before the start of combination therapy with trimetazidine, VA almost all had frequent and high gradations (58.5%) of VA. After treatment, grades 1 and 2 were observed in 34 out of 53 (64.2%) patients, i.e. more





than half. At the same time, the percentage of occurrence of high-grade FE decreased from 58.5% (31 out of 53 patients) to 35.8% (in 19 out of 53), i.e. 1.6 times. Thus, there was a tendency to a decrease in the number of high-grade VE during treatment with trimetazidine. Frequent single atrial extrasystole was not registered in 3 out of 22 (13.6%) patients, and a decrease in the number of atrial extrasystoles by an average of 45.6% was observed in 17 patients after a month of combination therapy with trimetazidine. Group atrial extrasystole was noted during the initial examination in 29 out of 63 patients. In 14 of them (48.3%), after a month of combined treatment with trimetazidine, it completely disappeared, and in 9 people it decreased. Thus, a positive antiarrhythmic effect was observed in 23 out of 29 patients (79%). During the control examination, no episodes of LVT were registered in 6 out of 7 patients (85.7%) who had them before the start of combination therapy with trimetazidine. One patient had rare episodes of LVT at the end of treatment, and their decrease compared to the study conducted before the appointment of trimetazidine was 93%. Single LC was studied in 22 patients in whom it was registered before the addition of trimetazidine to standard antianginal therapy. At the end of the month of treatment, a change in the average daily heart rate of the main rhythm was noted in 7 of these patients. In six of them, the heart rate increased by an average of 10-13 beats / min, and in one case it decreased by an average of 15 beats/min. In 14 patients, the average daily heart rate changed slightly - from 0 to 8, on average by 4.4 beats/min. As a result of treatment with trimetazidine, 18 patients showed a decrease in the number of BP by an average of 43%, while 14 of them did not change the average daily heart rate of the main rhythm or even decreased, and only 4 patients showed an increase in the average daily heart rate by more than 10 beats / min at the end of treatment. A decrease in the number of atrial parasytoles (AP) by an average of 17.8% was observed in 5 out of 7 patients. The change in the average daily heart rate ranged from 1 to 4 beats/min (on average by 2.14 beats/min), which could not affect the change in the number of atrial parasytoles. A significant decrease in the number of various cardiac arrhythmias a month after the addition of trimetazidine to conventional antianginal therapy was observed in patients with all types of arrhythmias, except for single atrial extrasystole and atrial parasytole.

DISCUSSION

Of all 63 patients included in the study, 19 people (30.2%) had episodes of significant ST-segment ischemic depression during the monitoring ECG on the eve of trimetazidine administration. After a month of treatment with trimetazidine, episodes of significant ST segment depression disappeared in more than half (in 10





people) of these patients. In general, the positive dynamics of ST with monitoring ECG by the end of treatment (a decrease in the number of episodes of depression per day, a decrease in their depth and duration) was observed in 15 (78.9%) of 19 patients. The difference in the average number of episodes of ST-segment depression a day before the appointment of trimetazidine (3.39 ± 1.21) and at the end of treatment with trimetazidine (1.43 ± 0.39) was statistically significant ($p=0.0391$). There was also a significant difference in the total duration of episodes of depression in minutes per day in these patients (24.56 ± 7.67 minutes before treatment, 11.83 ± 4.32 minutes after treatment; $p=0.0174$) and the maximum recorded depth of depression per day (1.46 ± 0.2 mm before treatment, 0.85 ± 0.17 mm before the end of combination therapy; $p=0.027$).

Thus, we can note a tendency to a greater decrease in the number of rhythm disturbances if this occurs against the background of a decrease in the total duration and maximum depth of ST segment depression, as well as a decrease in the number of episodes of depression, i.e. with a decrease in ischemia. When studying the correlations between the dynamics of arrhythmias and the dynamics of indicators of ischemic displacement of the ST segment (according to the results of monitoring ECG), no reliable correlation values were obtained. This is obviously due to a small number of patients in whom ST segment changes were combined with a certain type of cardiac arrhythmias. For the same reason, it was impossible to calculate the correlation for patients with group FE and atrial parasympole. The analysis of patients' complaints about the sensations of interruptions in the work of the heart ("palpitations", "interruptions", "fading") and pain of an angina character was carried out. The number of interruptions and episodes of pain was taken into account a week before admission, during the first 7-10 days of hospital stay before prescribing trimetazidine and during the last week of follow-up while taking combination therapy with trimetazidine, as well as the average number of episodes of pain and interruptions per day for these periods.

Subjective feelings of heart failure were noted at the admission of 45 patients, the remaining 18 patients did not complain of arrhythmias. The number of episodes of palpitations (according to patients' complaints) averaged 1.74 ± 0.24 per day upon admission; 0.7 ± 0.12 per day on 7-10 days of follow-up; in a control study a month later against the background of trimetazidine treatment, an average of 0.52 ± 0.13 per day. Statistical analysis revealed a significant decrease in episodes of "interruptions" by the end of trimetazidine therapy ($p=0.0151$) compared with their number on day 7-10 of follow-up. It is important to note that by day 7-10, 43 people complained of interruptions, and by the end of treatment with trimetazidine, their number had



decreased to 27 patients. This means that by the end of the observation, 40% of patients stopped worrying about the feeling of heart failure. Similarly, the pain episodes for the above periods were evaluated. At the time of admission, the frequency of anginal episodes averaged 2.61 ± 0.29 per day. By the time trimetazidine was prescribed (7-10 days of hospitalization and receiving standard antianginal therapy), pain bothered patients on average 0.29 ± 0.04 per day. After a month of combination therapy, the number of pain episodes decreased to 0.23 ± 0.04 per day. At the time of admission, among 63 patients, three (4.76%) patients did not complain of pain. By the 7th-10th day of inpatient treatment, the number of these patients increased to 17 people, i.e. in 14 patients (22.2%), the pain that existed before treatment with conventional antianginal agents disappeared during the period of standard antianginal treatment. After a month of therapy in combination with trimetazidine, 32 people (50.8%) did not complain of heart pain. Thus, complete cessation of anginal pain episodes was observed during combined antianginal therapy with trimetazidine in 15 (33%) of 46 patients.

CONCLUSION

1. Administration of trimetazidine at a dose of 20 mg 3 r / day in combination with standard antianginal therapy to patients with coronary artery disease with cardiac arrhythmias for one month leads to a significant decrease in the number of paired and frequent single ventricular extrasystoles (IE), ventricular parasystoles (LP), episodes of group ventricular (3-5 complexes) and supraventricular extrasystole (PrE gr), as well as episodes of paroxysmal supraventricular tachycardia (LVT). The greatest positive effect of antianginal therapy combined with trimetazidine was noted in relation to paired and group ventricular extrasystoles (a decrease in the average per day was 88% and 100%, respectively), episodes of paroxysmal supraventricular tachycardia and intraventricular extrasystole (99% and 86%, respectively). A "complete positive" effect was achieved in patients with paired ventricular extrasystoles - in 68% of patients, group ventricular extrasystoles - in 75% of patients, group atrial extrasystole - in 48% of patients and in patients with episodes of paroxysmal supraventricular tachycardia - in 86% of patients.
2. Complete cessation of anginal pain episodes was observed after the addition of trimetazidine to combined antianginal therapy in 15 (33%) of 46 patients.
3. There was a significant decrease in the number of cases of high-grade extrasystoles before the completion of combination therapy with trimetazidine, which was carried out for a month. At the same time, the number of patients with non-dangerous ventricular extrasystoles (1-2 gradations) increased from 41.5% at the beginning of



treatment to 64% by the end of treatment (1.5 times), and the number of patients with ventricular extrasystoles of high gradations decreased from 58.5% at the beginning of treatment to 35.8% by its end, i.e. 1.6 times.

4. The antiarrhythmic effect of trimetazidine according to monitoring ECG data in patients with positive dynamics of all indicators of ST segment displacement was expressed to a greater extent than in patients without ST segment changes or in patients without its positive dynamics. Thus, there was a connection between the severity of the antiarrhythmic effect of trimetazidine treatment in combination with standard antianginal therapy and the dynamics of ST segment displacement.

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