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THE EFFECTIVENESS OF CYTOPROTECTION IN THE TREATMENT OF STABLE ANGINA IN PATIENTS WITH ARTERIAL HYPERTENSION AND HYPERURICEMIA, TAKING INTO ACCOUNT THE PECULIARITIES OF THE COURSE OF CORONARY ARTERY DISEASE IN WARTIME

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The aim *of the study is to establish the effectiveness of treatment of severe angina pectoris in patients with hyperuricemia, taking into consideration the peculiarities of the course of coronary artery disease (CAD) in wartime, using ranolazine – a selective inhibitor of the late sodium flow in combined pharmacotherapy.*

Materials and methods. *We studied the anti-anginal effect of ranolazine in 14 patients with CAD, stable angina pectoris III-IV functional class (FC), hyperuricemia and arterial hypertension (AH) during 6 months of the 2022 year. The effectiveness of the study drug on the clinical course of angina pectoris was assessed by questionnaire and clinical examination after three months of treatment.*

The results. *At the end of the second week of ranolazine use, angina attacks at rest, which were registered before the start of the observation, stopped in all patients with angina pectoris III FC and 50 % with angina pectoris IV FC. In 78.6 %, the number of angina attacks and the use of nitrates decreased by more than 2 times; 21.4 % no longer had angina attacks.*

At the end of the first month, anginal attacks were not observed in all patients with angina pectoris III FC and 50 % with angina pectoris FC IV. In 2 patients with angina pectoris IV FC (50 %), anginal attacks continued to be registered during physical exertion and emotional stress, but no more than once a week. At the same time, there were no angina attacks at rest. The same results were obtained during the survey of patients at the end of three months of observation.

Conclusions. *Ranolazine is an effective component of anti-anginal therapy, significantly affecting the patient's quality of life. Therefore, we can recommend ranolazine for patients with hyperuricemia in angina attacks that persist with insufficient effectiveness of zasic therapy with first-line drugs, especially during military conflicts*

Keywords: *cytoprotection, stable angina pectoris, hyperuricemia, coronary artery disease, wartime, arterial hypertension*

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1. Introduction

In wartime, significantly less weight is given to medical care to patients with chronic diseases than injuries, acute conditions, and infectious diseases. Meanwhile, prolonged stress, limited access of patients to timely outpatient medical care, lack of access to inpatient treatment, and restrictions on the purchase of medications lead to the decompensation of many chronic diseases, in particular, negatively affecting the course of coronary artery disease (CAD). According to meta-analyses of studies, anxiety in long-term follow-up is associated with an increased risk of CAD by 26–41 % and cardiovascular diseases by 52 % [1, 2].

In addition, anxiety can increase the risk of myocardial infarction and other acute cardiovascular complications in patients with stable CAD by 74–109 % [3, 4].

During military conflicts, patients with CAD need therapy aimed at reducing the risk of complications and reducing the frequency and intensity of angina attacks, increasing tolerance to physical activity, and psycho-emotional stress factors. This goal cannot always be achieved, despite the use of pharmacological and interventional methods of treatment of angina pectoris.

It is known that the frequency of exposure to stressful stimuli causes a prolonged increase in the activity of the sympathetic nervous system and can cause hyperinsulinemia with its known negative consequences (increased heart rate (HR), delayed renal excretion of sodium and water, impaired cellular transport of electrolytes, metabolic syndrome, etc.)

Recently, much evidence has been published that the level of uric acid in the elderly is a biomarker of poor CAD prognosis. With an increase in serum uric acid

level by each 1 mg/dL (approximately 60 μmol/L), the risk of coronary artery calcification increases by 31 % and cardiovascular mortality by 9 % [5].

One of the possible ways to reduce the frequency of symptoms and improve cardiovascular prognosis in such patients is the administration of metabolic therapy, in particular ranolazine.

Ranolazine, by selectively inhibiting the late sodium current, prevents cardiomyocyte overload with sodium ions, thereby blocking the accumulation of calcium ions in the cells [6–9]; this is one of the main mechanisms of its anti-ischemic action. In addition, ranolazine reduces the severity of ischemic and post-ischemic left ventricular diastolic dysfunction by reducing intracellular calcium overload, which is a secondary effect of inhibition of late sodium flow [10, 11].

Taking into account these data, the use of ranolazine as a second-line drug for the treatment of stable angina pectoris opens up new possibilities for anti-anginal therapy, especially in patients with hyperuricemia.

The aim of the study. To establish the effectiveness of treatment of severe angina pectoris in patients with arterial hypertension (AH) and hyperuricemia, taking into consideration the peculiarities of the course of CAD in wartime, using ranolazine – a selective inhibitor of the late sodium flow in combined pharmacotherapy.

2. Materials and methods

We conducted the open, prospective study of 14 patients with CAD, stable angina pectoris III–IV functional class (FC) at the Center of Reconstructive and Restorative Medicine (University Clinic) of the Odesa National Medical University for 6 months in 2022.

Ethics clearance was given by the Ethics Committee of the Center of Reconstructive and Restorative Medicine (University Clinic) of the Odesa National Medical University, protocol number 224, from Feb 25 2022. Informed consent was taken from all the participants of the study.

The study included patients with stable angina pectoris III–IV FC [12]. All patients received basic, prognosis-modifying therapy (statins, antiplatelet drugs, renin-angiotensin system inhibitors, β-blockers). In order to enhance the anti-anginal effect, ranolazine (Ranexa) was prescribed at a dose of 500 mg 2 times a day in the morning and the evening, regardless of meals. The dose of the drug in 2 patients was increased after 2 weeks from the start of treatment to 1000 mg 2 times a day due to insufficient clinical effect, but with good tolerability. When choosing a drug that eliminates ischemia at the cardiomyocyte level, the presence of hyperuricemia in all patients included in the study was considered. All patients in the study suffered from AH, but at the time of inclusion, they reached the target parameters of blood pressure and heart rate.

Along with CAD and AH, 10 (71.4 %) patients were diagnosed with type 2 diabetes mellitus (T2DM). All patients gave informed consent to participate in the study and had high compliance with basic therapy. Patients with acute coronary syndrome, acute cerebrovascular accident, decompensated heart failure, severe decompensation of T2DM, active cancer, with intolerance to any of the drugs of basic therapy, ranolazine, were not included. The effectiveness of the study drug on the clinical course of angina pectoris was assessed by questionnaire and clinical examination after three months of treatment. Also, in order to rule out adverse events, correct dosages, and make an interim assessment, additional visits were made at the end of the second week, as well as the first month of observation. Therefore, the comparison group was not formed.

The received data was processed using the Microsoft Office Excel 2016 application package. To compare data, non-parametric criteria were used: the significance of differences was assessed using the Mann-Whitney test (U-test). In addition, the Pearson test (χ^2) was used to compare the qualitative characteristics. Differences were considered significant at $p<0.05$.

3. Results

Among the examined patients, 8 (57.1 %) were men, and 6 (42.9 %) were women. Distribution of the total population of patients by age: 60-69 years – 5 (35.7 %), 70–79 years – 6 (42.9 %), 80-89 years – 3 (21.4 %).

Table 1 shows the characteristics of angina attacks in the studied patients at the onset and after 3 months of observation.

Table 1

Characteristics of angina attacks in the studied patients

Indicator	Day 0			Month 3		
	FCIII	FCIV	All	FCIII	FCIV	All
Total number of angina attacks per week	13.5±8.6	21.4±9.2	15.6±9.1	0 *	7.9±4.8 *	2.3±1.0 *
Angina attacks at rest, number per week	6.5±4.2	10.7±6.3	7.7±5.7	0 *	0 *	0 *
Duration of attacks, min	5.7±3.3	11.3±5.6	7.3±3.6	0 *	4.2±2.5 *	1.2±0.6 *
Nitrate intake, number of doses per week	21.7±11.9	36.3±15.7	25.2±12.4	0 *	11.4±7.2 *	3.0±1.2 *

Note: p<0,05 when compared with the corresponding indicator on day 0

Most patients (10 – 71.4 %) observed in the study suffered from angina pectoris III FC; angina pectoris IV FC was present in 4 (28.6 %) patients. At the same time, 11 (78.6 %) of patients experienced angina attacks daily, 8 (57.1 %) had angina at rest.

At the end of the second week of ranolazine use in all patients, both with angina pectoris III FC and IV FC, there were positive dynamics in the form of clinical improvement in the course of angina pectoris, a decrease in the duration and intensity of anginal attacks.

In addition, by the end of the second week of observation, angina attacks at rest, which were registered before the start of the observation, stopped in all patients with angina pectoris III FC (χ^2=20.0, p<0,001) and in 2 (50 %) of patients with angina pectoris IV FC (χ^2=2.67, p=0.103). In 11 (78.6 %) of patients, the number of angina attacks and the use of nitrates decreased by more than 2 times. At the end of the second week of observation, 3 (21.4 %) patients no longer had angina attacks (χ^2=3.36, p=0.67).

At the end of the first month, anginal attacks were not observed in all patients with angina pectoris III FC (χ^2=20.0, p<0,001) and in 2 (50 %) of patients with angina pectoris FC IV (χ^2=2.67, p=0.103). In 2 patients with angina pectoris IV FC (50 %), anginal attacks continued to be registered during physical exertion and emotional stress, but no more than once a week. At the same time, there were no angina attacks at rest. The same results were obtained during the survey of patients at the end of three months of observation (χ^2=21.0, p<0,001).

4. Discussion

Metabolic Processes in the Normal and Failing Heart these processes are the subject of many modern studies. Offers various options for therapy aimed at improving the metabolism of the myocardium and other components of the cardiovascular system. In particular, it is proposed to use some drugs such as trimetazidine, perhexiline, meldonium, ranolazine etc. [13, 14].

Ranolazine demonstrated that people with stable angina who received ranolazine as add-on therapy had fewer angina episodes but an increased risk of presenting non-serious adverse events compared to those given a placebo [15].

Results similar to our study were demonstrated in a big observational study in Austria – the ARETHA AT study of 292 patients with stable angina pectoris. Symptoms were improved, as illustrated by the reduced number of angina attacks, reduced rate of nitrate use, reduced CCS scores and improved quality of life [16]. Moreover, some articles report the antiarrhythmic activity of ranolazine [6, 17].

The limitations of our study are the relatively short follow-up period, given that chronic diseases are the subject of the study, as well as the small number of observations. Subsequently, increasing the number of patients and evaluating them over a longer period will be necessary.

The results of our study can be used in treating patients with CAD, AH and hyperuricemia who are exposed to chronic psychological stress, particularly during military operations or due to other stress factors.

Prospects for further research. We plan to conduct an expanded study with a larger number of patients and additional analysis of different age groups.

5. Conclusions

1. In wartime, long-term stress, depression, and anxiety increase the risk of an adverse course of CAD, which requires mandatory adherence to the tactics of the patient's optimal combined therapy using cytoprotection. An effective component of anti-anginal therapy, which pathogenetically reduces the manifestations of ischemia at the cardiomyocyte level in the treatment of stable angina in patients with hyperuricemia, is the administration of a selective late sodium flow inhibitor – ranolazine, which significantly decreases the total number of angina attacks per week (from 15.6±9.1 to 2.3±1.0, p<0.05), the total number of angina attacks at rest per week (from 6.5±4.2 to 0, p<0.05), mean duration of attacks (from 5.7±3.3 min to 0 min, p<0.05) and a number of nitrate doses intake per week (from 21.7±11.9 min to 0 min, p<0.05).

2. The presented observation demonstrates the positive contribution of ranolazine in the treatment of CAD with a significant decrease in the number of angina attacks in patients of III-IV FC of angina pectoris 3–4 functional class (χ^2=21.0, p<0,001), which allows recommending its use in patients with hyperuricemia in angina attacks that persist with insufficient effectiveness of basic therapy with first-line drugs, especially during military conflicts.

Conflict of interest

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this article.

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