

*O.M. Prytuliak***Thiotriazolin Influence on Blood Pressure Changes in Patients with Myocardial Infarction and Concomitant Arterial Hypertension Who Underwent Remedial Treatment and Physical Rehabilitation**

Department of Internal Medicine № 2 and Nursing

Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine

Abstract.

The objective of the research was to study and investigate the efficiency of Thiotriazolin combined with antihypertensive drugs in connection with background therapy (BT) on the daily dynamics of blood pressure (BP) in comparison with the use of antihypertensive drugs only in connection with BT.

Results of the research: Positive dynamics in the reduction of the frequency of the disease subjective clinical signs manifestations in two research groups was observed ($p < 0.05$). Significant decrease in pain syndrome and dyspnea was detected in patients with myocardial infarction (MI) and concomitant arterial hypertension (AH). The use of BT with ramipril and thiotriazolin ensured a gradual increase in the number of patients with the most favorable profile “dipper”. The inclusion of ramipril to BT or its combination with thiotriazolin resulted in a significant decrease in diastolic blood pressure (DBP) variability. Dynamics of systolic blood pressure (SBP) morning rise rate was analyzed. Morning rise rate (MRR) of systolic blood pressure significantly decreased in 3 months of investigation in patients treated with BT and ramipril or its combination with thiotriazolin.

Conclusions: due to combined treatment with ramipril and thiotriazolin in connection with BT a greater number of patients achieved BP target level and decreased BP morning rise indicators.

Keywords: *myocardial infarction; ramipril; thiotriazolin; hypertensive disease.*

Problem statement and analyses of resent research

Cardiovascular disease (CVD) ranks first among causes of death, disability and population incapacity. Hypertensive disease (HD) is the most common chronic disease. According to statistical data, one fifth of the adult population all over the world suffers from HD [3, 4]. Numerous investigations confirm the role of antihypertensive drugs in reducing the risk of HD complications and related mortality. According to the recommendations of the European Society of Cardiology, European Society of Hypertension in 2008 and 2009 (amendments), and to guideline of Ukrainian working group on hypertension of Ukrainian Association of Cardiology (2012), nowadays first-line drugs include diuretics, β -adrenoreceptors blocking agents, calcium channel blockers, angiotensin receptor blockers and angiotensin-converting enzyme (ACE) inhibitors. The advantages of combination therapy in HD treatment were proved by the results of HOT, LIFE, COOPE та ASCOT multicenter double-blind randomized study [1, 2]. There are few studies on the effectiveness of metabolic drugs with their use combined with antihypertensive drugs for HD treatment [2, 4, 8]. In particular, the trimetazidine prescription was accompanied by improvement of systolic and diastolic myocardial function in patients with HD complicated by chronic heart failure (CHF) [2]. In recent years, cardioprotective properties of quercetin and thiotriazolin were detected. They have diverse pharmacological activity and are widely used in clinical practice for cardiovascular and other diseases treatment [4]. However, up to the present moment insufficient number of researches was conducted on the effects of metabolic therapy combined with antihypertensive drugs on BP.

The objective of the research was to study and investigate the efficiency of Thiotriazolin combined with antihypertensive drugs in connection with background therapy (BT) on the daily dynamics of blood pressure (BP) in comparison with the use of antihypertensive drugs only in connection with BT.

Materials and methods of the research

The research was conducted in accordance with the recommendations of the Declaration of Helsinki (1964), including the review of EC-GCP and State Expert Center of Ministry of Health of Ukraine. All patients were informed about conditions before the research. The study was conducted in the Department of Myocardial Infarction Treatment № 2 with rehabilitation in Regional Clinical Cardiology Center on the clinical basis of the Department of Internal Medicine and Nursing №2. Patients' diagnosis and treatment were performed according to existing standards of management of patients with acute ischemic heart syndrome with ST segment elevation (myocardial infarction (MI) with Q wave). The standards are based on clinical protocols of medical care delivered to the patients with acute ischemic heart syndrome with ST segment elevation approved by the order of the Ministry of Health of Ukraine from 03.07.2006 №436, recommendations of Ukrainian and European Society of Cardiology (2012). Normal BP rate, procedure, technique, frequency of its measurement corresponded to unified clinical protocols of providing medical care to the patients with AH approved by the Ministry of Health of Ukraine from 24.05.2012 № 384 and were carried out according to recommendations of the European Society for the Study of Hypertension, recommendations of Ukrainian Society of Cardiology concerning AH prevention and treatment (2012), the European Society of Hypertension and the European Society of Cardiology. The criteria for inclusion were: patients at the age of 45-65 with previous MI with ST segment elevation (within 10-14 days after an acute coronary experience) with concomitant II-III degree AH and had an inadequate response to physical exercise. The criteria for exclusion from the research were: acute left ventricular failure, ventricular fibrillation (VF), ventricular tachycardia in past medical history of MI complication at the time of graduated exercise (early postinfarction angina, not stabilized by medication, I and II degree atrioventricular (AV) block, II-V class ventricular extrasystole by Lown, Dressler's syndrome, III-IV functional class congestive heart failure (CHF), hemodynamically relevant heart abnormality, acute intracardiac and peripheral thrombosis and thrombembolia; recurrent MI, disorder of cerebral circulation with 6 months duration, retinal haemorrhage, acute infectious diseases, aortic dissection; chronic renal failure; thyrotoxicosis; decompensated and severe diabetes mellitus; musculoskeletal system dysfunction that prevents from graduated exercise test. Electrocardiographic signs of graduated exercise included: ST segment elevation more than 1 mm compared to the primary value; ST segment depression by myocardium overload type; arrhythmia (frequent extrasystoles, paroxysmal tachycardia, atrial fibrillation and other arrhythmias); QRS complex changes (a sharp decrease in R wave voltage, deepening of earlier formed Q waves or transition of Q wave into QS complex); inversion or reversion of T wave in one or more chest leads. The subjective clinical signs of graduated exercise inadequacy included the following: angina attack: typical and atypical; patient's refusal from further testing due to unpleasant sensations, discomfort, fatigue. The objective signs of graduated exercise inadequacy comprised asthma attack, cyanosis or pallor, cold sweat, inadequate rapid increase in blood pressure to 200/100 mm of mercury and more, no changes or a decrease in SBP by 25-30% in comparison with the initial level, achievement of heart rate threshold.

According to the objective of the research all the patients were divided into two groups by method of random selection. The first group included 23 patients who took metabolic drug thiotriazolin in a dose of 100 mg 3 times a day, antihypertensive therapy drug ramipril and anti-ischemic BT drugs including clopidogrel in a dose of 75 mg per day, aspirin cardio in a daily dose of 100 mg, bisoprolol in a dose of 2.5-5 mg per day, atorvastatin in a daily dose of 10-40 mg. Nitrates were administered if necessary. The second group consisted of 22 patients who took BT and ramipril in a starting dose of 2.5 mg two times a day. The dose was increased to 10 mg one time a day when required. After the discharge from the hospital, patients continued to receive outpatient treatment according to the previous scheme during 6 months.

Treatment groups were uniform by age, sex, disease severity, intensity of clinical manifestations. Clinical examination was conducted to patients at the beginning of investigation, in 1 and 6 months of treatment. According to methodological recommendations on diagnosis and treatment of patients after suffering from MI with concomitant AH, patients' complaints were collected and detalized; past medical history and case history were taken; common physical examination was conducted; heart rate, SBP, DBP and fractional blood pressure were measured. BP was measured according to recommendations of Ukrainian Association of Cardiology concerning arterial hypertension prevention and treatment (2012) [56, 72, 73]. Daily BP monitoring was conducted with the device ABPM-04 ("Meditech", Hungary). Daily average measurements of SBP, DBP (mm of mercury) and heart rate (beats per minute) were analyzed. BP and heart rate were measured automatically every 15 minutes during a day (from 6 a.m. to 10 p.m.) and every 30 minutes at night time (from 10 p.m. to 6 a.m.). Mathematical processing of the results of BP daily monitoring was conducted with a computer program for results graphical output and interpretation ABPMBASE. According to the ratio of daytime and nighttime blood pressure levels daily index was calculated (DI, %) and BP profile was determined, which was interpreted

as “dipper”, “non-dipper”, “over-dipper”, “night-peaker”. Mathematical processing of the results of BP daily monitoring was conducted with a computer program for results graphical output and interpretation ABPMBASE.

Statistical analysis of the results was performed on the personal computer by means of the application software package STATISTIKA-6 and statistical function package of the program “Microsoft Excel” using variational and statistical method of analysis. Arithmetical mean M , mean-square deviation δ , average error of arithmetical mean m , variant number (n), probability of two arithmetic means difference “ p ”, the value of $p < 0.05$ were considered reliable.

The results of the research and their discussion

Positive dynamics concerning the frequency of subjective clinical signs of the disease in two groups was observed ($p < 0.05$). A significant decrease in pain syndrome and dyspnea was noticed in patients with previous MI and concomitant AH. Patients of the first group did not observe palpitation and heart intermissions as late as in three months of treatment. 6 months after the treatment dizziness was not detected in patients, but dyspnea symptoms remained in the two groups during the treatment period. However, significant difference in the dynamics of the disease subjective symptoms depending on the method of treatment of patients with previous MI and concomitant AH in two groups was not observed. Distribution of patients with daily BP profiles varied in the course of the treatment (Table 1.1.). Thus, the use of BT with ramipril and thiotriazolin provided gradual increase in the number of patients with the most favorable profile “dipper”. For instance, the number of the latter in the group of patients treated with ramipril on the background of BT increased from 27.3% to 81.8% after treatment. Generally, such redistribution of patients was caused by a decrease in percentage of people with a daily profile “non-dipper” from 22.7% to 4.5%.

Table 1.1

Dynamics of Daily Blood Pressure Profile Types under the Influence of the Proposed Treatment Regimen

Profile Type	Before the Treatment	After the Treatment
The first group: BT with ramipril (n=22)		
Dipper	6 (27.3 %)	18 (81.8 %) $p < 0.001$
Non dipper	5 (22.7 %)	1 (4.5 %) $p < 0.01$
Over dipper	6 (27.3 %)	2 (9.2 %) $p > 0.05$
Night peaker	5 (22.7 %)	1 (4.5 %) $p < 0.01$
The second group: BT with ramipril + thiotriazolin (n=23)		
Dipper	6 (26.1 %)	19 (82.5 %) $p < 0.001$
Non dipper	6 (26.1 %)	1 (4.4 %) $p < 0.05$
Over dipper	6 (26.1 %)	2 (8.7 %) $p > 0.05$
Night peaker	5 (21.7 %)	1 (4.4 %) $p < 0.001$

Note: 1. The percentage to the total number of people in group is shown in parentheses. 2. p – the reliability of mean values difference before and after treatment.

In the group of patients where BT was applied with ramipril and thiotriazolin, probable increase in the number of patients with the BP profile “dipper” was provided, indices data constituted 26.1% before the treatment and 82.5 % after the treatment ($p < 0.001$). The number of patients with profile “Over dipper” ($p > 0.05$) and “Night peaker” ($p < 0.001$) decreased.

Daily average levels of SBP in patients with the use of BT with ramipril and BT with ramipril and thiotriazolin before treatment constituted 158.73 ± 5.78 mm of mercury and 160.02 ± 6.70 mm of mercury. After the course of treatment in 6 months this index amounted to 160.02 ± 6.70 mm of mercury, 126.96 ± 2.84 mm of mercury, and 126.32 ± 2.76 mm of mercury ($p < 0.001$). The dynamics of DBP reduction under the influence of proposed antihypertensive treatment was less intense in comparison with the decrease in SBP. Significant reduction in the daily average level of DBP was not observed in most of the studied groups after 3 months of treatment. However, continued therapy up to 6 months resulted in significant decrease in DBP in the study groups.

Comparison of DMBP established that ramipril was more effective in reducing SBP in patients with previous MI and concomitant AH. After 6 months of therapy SBP constituted 126.32 ± 2.76 mm of mercury in patients who had taken ramipril. SBP reduction in patients who took ramipril was 31.77 ± 2.94 mm of mercury, adding of thiotriazolin to the treatment regimen resulted in SBP reduction to 33.7 ± 3.94 mm of mercury. The influence of antihypertensive therapy on DBP was analyzed. The use of BT with ramipril was accompanied by decrease in DAT to 14.98 ± 2.01 mm of mercury.

Combined treatment with ramipril and thiotriazolin in connection with background therapy resulted in reduction of this indicator to 18.97 ± 2.48 mm of mercury. Analysis of the pulse pressure (PP) indicators determined that the suggested antihypertensive therapy regimen was effective in case of decrease in PP average value after six months of treatment.

Pulse pressure constituted 56.42 ± 2.01 mm of mercury after the treatment in patients who took ramipril in connection with BT. The same results were obtained in patients who took BT with ramipril and thiotriazolin, where pulse pressure was 67.97 ± 1.19 mm of mercury.

Statistically significant reduction of SBP and DBP variability was observed in all groups under the influence the proposed treatment regimens. It should be noted that the inclusion of ramipril to BT or its combination with thiotriazolin led to a significant decrease in DBP variability. The analysis of the dynamics of systolic blood pressure (SBP) morning rise rate detected that SBP morning rise rate decreased after 3 months of the research in patients treated with BT and ramipril or its combination with thiotriazolin. A similar tendency could be observed concerning DBP morning rise rate indicators in the patients' groups.

Cardiovascular complications of hypertension most often occur in the morning. BP morning rise is an independent factor that influences on the targeted organs complications development. Thus, the frequency of cerebral and vascular "catastrophes" is higher in patients with morning rise of blood pressure. It was established that SBP morning rise by 10 mm of mercury increases the risk of stroke by 25% [7].

Conclusions:

1. Antihypertensive therapy did not significantly BP daily profile while adding od thiotriazolin to the complex treatment increased the number of patients with physiological type of BP profile "dipper" by 20%.
2. The effectiveness of antihypertensive therapy concerning the decrease of morning rise of blood pressure was increased. Due to the use of this drug BP and morning rise rate decreased: SBP – by 18.0 ± 3.7 mm of mercury, DBP – by 13.0 ± 2.8 mm of mercury, and SBP – by 12.6 ± 1.8 mm of mercury per hour, DBP – by 6.6 ± 1.4 mm of mercury which was in 2.2; 1.9; 1.8 ta 2.0 times higher than in the second group.

The prospects for further research

The obtained data indicate the necessity to develop remedial treatment complexes involving metabolic therapy to improve the rehabilitation of patients with previous MI and to prevent recurrent MI and fatal arrhythmias development.

References

1. Amosova EN. Arterial hypertension treatment – 2010: comments on the fundamental principles of the latter (2009) recommendations of the European Society of Cardiology and the European Society of Hypertension. Part II. Focus on combined antihypertensive therapy. *Sertse i sudyny*. 2010; 3: 17–28.
2. Dzyak GV, Vasilieva LI, Sapozhnicenko LV. [et al.] Evaluation of the thiotriazolin effectiveness according to the treadmill test in the complex treatment of patients with stable coronary heart disease. *Novosti meditsiny i farmatsii*. 2011; 13–14: 6–9.
3. Kovalenko VM, Kornatskyi VM. Implementation of the State program to combat hypertension in Ukraine. *Ukr. kardiolog. zhurnal*. 2010; 6: 7-12.
4. Kovalenko VM, Kornatskyi VM. Regional medical and social problems of cardiovascular diseases. Dynamics and analysis. Kyiv. 2008; 238.
5. Mancia G, Grassi G. What changes we may expect in 2010 hypertension diagnosis and management: Insights from European update document. *Curr. Vasc. Pharmacol*. 2010; 8 (6): 788–791.
6. Parkhomenko OM, Kozhukhov SM, Irkin OI [et al.] New possibilities of pharmacological effect on prognosis in patients who suffer from myocardial infarction with ST segment elevation and acute heart failure. *Ukr. med. chasopys*. 2010; 4 (78): 34-37.
7. Sirenko YuM, Radchenko HD, Martsovenko IM. Experience in treatment of patients with hypertension using domestic drugs. *Ukr. kardiolog. zhurnal*. 2010; 1: 27-37.
8. Sirenko YuM, Radchenko HD, Mikheyeva KV, Rekovets OL. Comparative efficacy of thiotriazoline and meldonium in patients with stable angina of II-III functional class: results of a prospective open comparative randomized parallel studies. *Novosti meditsiny i farmatsii*. 2011; 17: 6–9.
9. Yena LM, Hrushovska VM. Hypertension and diastolic dysfunction in senile age: the impact of long-term combined antihypertensive and metabolic therapy. *Sertse i sudyny*. 2010; 2: 90–96.