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CLINICAL AND PHARMACOLOGICAL APPROACH TO THE RATIONAL USE OF ANTIHYPERTENSIVE DRUGS

Resume: Metabolic syndrome (MS) is a complex of risk factors for cardiovascular diseases and type 2 diabetes mellitus (DM). The main components of MS are arterial hypertension (AH), obesity, disorders of carbohydrate and lipid metabolism. Currently, in most countries of the world there is a trend of increasing the incidence of MS.

The prognostic value of MS is determined by the powerful influence of numerous cardiovascular risk factors, the correction of which is an important direction of therapeutic and preventive measures. There is no doubt that the correction of blood pressure (BP) in MS should be carried out in parallel with careful monitoring of plasma glucose, total cholesterol, body weight and other risk factors.

Keywords: anti-hypertensive drugs, inflammation, metabolic syndrome.

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КЛИНИКО-ФАРМАКОЛОГИЧЕСКИЙ ПОДХОД К РАЦИОНАЛЬНОМУ ПРИМЕНЕНИЮ АНТИГИПЕРТЕНЗИВНЫХ ПРЕПАРАТОВ

Резюме: Метаболический синдром (МС) представляет собой комплекс факторов риска сердечно-сосудистых заболеваний и сахарного диабета (СД) типа 2. Основными компонентами МС являются артериальная гипертензия (АГ), ожирение, нарушения углеводного и

липидного обмена. В настоящее время в большинстве стран мира наблюдается тенденция роста заболеваемости МС.

Прогностическое значение МС определяется мощным влиянием многочисленных факторов кардиоваскулярного риска, коррекция которых представляется важным направлением лечебно-профилактических мероприятий. Не вызывает сомнений тезис о том, что коррекция уровня артериального давления (АД) при МС должна проводиться параллельно с тщательным контролем уровня глюкозы плазмы, общего холестерина, массы тела и других факторов риска.

Ключевые слова: анти-гипертензивные препараты, воспаления, метаболический синдром.

Relevance. Metabolic syndrome is a condition in which pathophysiological changes have been well studied. In the last two decades, the idea of the role and functions of adipose tissue has changed, which is now considered not only as an organ of endocrine regulation of energy balance, but also as an integral link between the formation of metabolic disorders and cardiovascular pathology.

With excess body weight, infiltration of adipocytes by macrophages also occurs, followed by the development of inflammatory reactions, as a result of which the metabolic activity of adipose tissue changes. The severity of this inflammation clearly correlates with the degree of obesity. Since the inflammatory reaction occurs in the tissue, the proportion of which can be up to 50% or more of the total body weight, the assumption of systemic manifestations becomes natural. That is, local inflammatory processes in adipose tissue are accompanied by chronic mild systemic inflammation.

The issues of rational pharmacotherapy, optimal choice of drugs for various diseases are of particular relevance [2,5,7]. This is determined, on the one hand, by the expansion of the pharmaceutical market and the emergence of a large number of new drugs, on the other hand, by an increase in the prevalence of various comorbid conditions, which in many ways complicate drug therapy

and require special attention to monitoring the effectiveness and safety profile of drugs [4,6,7].

In recent decades, there has been a steady increase in the prevalence of MS worldwide, which combines a complex of cardiovascular risk factors: abdominal obesity, arterial hypertension (AH), dyslipidemia, insulin resistance. According to various authors, the prevalence of MS among people over 30 years of age is 10-30%, and MS occurs 2.4 times more often in women than in men [1,3,5].

The purpose of the study. To substantiate the effectiveness of antihypertensive drugs in patients with arterial hypertension with metabolic syndrome based on an assessment of their effect on markers of inflammation and insulin resistance.

Materials and methods of research. The study included 111 patients (men - 53, women -58) with grade 1-2 hypertension and MS. All patients gave written informed consent to participate in the study.

The results of the study. Baseline indicators of markers of inflammation and insulin resistance in patients with hypertension with metabolic syndrome.

In patients with hypertension with MS, the initial level of BsCRB was 3.37 (2.3;6.4) mg/l, which is 36.5% higher than the same indicator in the control group (p=0.001). The level of 1SAM-1 initially amounted to 331.6 (297.3;396.4) ng/ml, which is significantly higher by 29.2% than the same indicator in the control group (p=0.003). The initial indicator of the NOMA index was 3.82 (2.93;4.40), which exceeds the same indicator by 45.3% (p=0.006)

Significant sex differences were revealed: the level of MSRP in women was significantly higher and amounted to 3.43 (2.74;6.31) mg/l, in men - 3.17 (2.12;5.64) mg/l (p=0.02). The activity of NSRP in postmenopausal women was 3.49 (2.59;7.0) mg/l and significantly exceeded the same indicator in the group of women before menopause 3.29 (2.63;6.38) mg/l (p=0.04). The activity of

BCRP in postmenopausal women was significantly higher than in men (p=0.03). Smoking patients had significantly higher IHD activity of 4.08 (2.96;7.04) mg/l compared with non-smokers 2.92 (1.78;4.70) mg/l (p=0.001). There were no significant differences in the activity of ESRP depending on the degree of increase in blood pressure (p= 0.74). In the presence of carbohydrate metabolism disorders, the level of ESRB was significantly higher (p=0.021).

The level of 1SAM-1 did not significantly differ in men and women: 327.83 (276.47;365.9) ng/ml and 332.2 (298.09;396.37) ng/ml, respectively (p=0.78). Women in the postmenopausal period tended to have a higher level of 1C-1 compared to the group of women in the menopausal period (p=0.07). There was a significant increase in the activity of 1SAM-1 in smoking patients 344.23 (301.22;400.3) ng/ml compared with non-smokers 316.68 (268.92;376.2) ng/ml (p=0.005). The degree of hypertension had no significant effect on the activity of 1SAM-1 (p=0.09). The presence of carbohydrate metabolism disorders also did not significantly affect the level of 1SAM-1 (p=0.62).

The NOME index did not significantly differ in men and women: 3.78 (2.85;4.37) and 3.91 (3.10;4.52), respectively (p=0.76). The NOME index in menopausal women was significantly higher: 3.44 (2.63;4.15) before menopause and 4.02 (3.24;4.72) after menopause (p=0.044). At the same time, the NOME index in women before menopause was significantly lower compared to men (p=0.035). There was a tendency to increase insulin resistance in smoking patients compared with non-smokers (p=0.062). In the presence of carbohydrate metabolism disorders, the insulin resistance index was significantly higher (p=0.038).

Correlation analysis of the relationship of biochemical markers with cardiovascular risk factors and other parameters revealed significant direct links of ESRD with smoking (g=0.28, p=0.001), female sex (g=0.30, p=0.023), menopause (g=0.32, p=0.016), 1SAM-1 (g=0.35, p=0.009), age (g=0.38, p=0.002), BMI (g=0.43, p=0.004)

The effect of antihypertensive drugs on markers of inflammation in patients with hypertension with metabolic syndrome.

Univariate analysis of variance (AIUA) showed that initially the level of BCRP in 4 groups did not differ statistically (p=0.73). In an intragroup comparison (Wilcoxon's criterion) under the influence of zofenopril, perindopril and nebivolol for 12 weeks, a significant decrease in the level of ESRP was revealed by 13.4% (from 3.35 (2.25; 6.31) mg/l to 2.9 (1.34; 3.68) mg/l (p= 0.043)), by 17.3% (from 3.23 (2.73; 4.59) mg/l to 2.67 (2.35;

3.89) mg/l (p=0.04)) and by 27% (hsCPB from 3.15 (2.0;4.18) mg/l to 2.3 (1.18; 4.03) mg/l (p=0.001)), respectively. When treated with enalapril, there was a tendency to decrease the activity of hsCPB, which did not reach statistical significance: from 3.21 (2.6; 4.62) mg/l to 2.98 (1.43; 3.9) mg/l (p=0.08).

An intergroup comparison (ANOVA) after 12 weeks of treatment revealed significant differences between the groups in the dynamics of the decrease in hsCPB (p=0.003). In an intergroup comparison (Mann-Whitney criterion), no statistically significant differences were found between the zofenopril and perindopril groups in the dynamics of a decrease in hsCPB levels after 12 weeks of treatment (p=0.7). An intergroup comparison (Mann-Whitney criterion) of the nebivolol group with the zofenopril and perindopril groups revealed a statistically significant advantage of nebivolol in terms of the effect on the decrease in hsCPB activity (p=0.009 and p=0.004, respectively).

An intergroup comparison (Mann-Whitney criterion) of the zofenopril and perindopril groups with the enalapril group revealed a statistically significant advantage of zofenopril and perindopril in terms of the effect on the decrease in hsCPB activity (p=0.04 and p=0.01, respectively). An intergroup comparison (Mann-Whitney criterion) of the nebivolol group with the enalapril group revealed a significant advantage of nebivolol in terms of the effect on the decrease in hsCPB activity (p<0.001).

Similar changes were found in relation to the dynamics of the ICAM-1 level. Initially, the level of ICAM-1 did not differ in the intergroup comparison of 4 groups (ANOVA) ($p=0.58$). Under the influence of zofenopril, perindopril and nebivolol after 12 weeks of treatment, a significant decrease in ICAM-1 activity was revealed ($p=0.045$, $p=0.036$ and $p=0.044$, respectively), against the background of enalapril treatment, a downward trend was revealed that did not reach statistical significance ($p=0.07$) (Wilcoxon criterion).

An intergroup comparison of 4 groups (ANOVA) after 12 weeks of treatment revealed a significant difference from each other in the dynamics of a decrease in the level of ICAM-1 ($p=0.04$). An intergroup comparison of 3 groups (ANOVA) of zofenopril, perindopril and nebivolol after 12 weeks of treatment showed no significant differences from each other in the dynamics of the decrease in ICAM-1 levels ($p=0.09$). An intergroup comparison (Mann-Whitney criterion) of the zofenopril, perindopril and nebivolol groups with the enalapril group revealed a statistically significant advantage of zofenopril, perindopril and nebivolol in terms of the effect on the decrease in ICAM-1 activity ($p=0.04$, $p=0.03$ and $p<0.05$, respectively).

The effect of antihypertensive drugs on insulin resistance, carbohydrate and lipid metabolism in patients with hypertension with metabolic syndrome.

Fasting glucose and insulin indices, which are the basis for calculating the NOME index, decreased against the background of ACE inhibitors zofenopril and perindopril, tended to decrease against the background of enalapril and nebivolol. There was a tendency to decrease the serum glucose level 2 hours after taking 75g of glucose under the influence of taking all three ace inhibitors. In an intergroup comparison of 3 groups (ANOVA) of zofenopril, perindopril and enalapril after 12 weeks of treatment, there were no significant differences from each other in the dynamics of a decrease in fasting glucose, postprandial glucose and insulin ($p=0.06$, $p=0.06$, $p=0.07$, respectively).

Under the influence of zofenopril, perindopril and enalapril, a significant decrease in the NOME index was revealed by 34.2% (from 3.71 (2.8; 4.2) to 2.44 (1.56;3.3) (p=0.0064)), by 15.6% (from 3.34 (2.6;4.0) to 2.82 (1.9;3.84) (p=0.01)) and by 16.9% (from 3.9 (2.9; 4.5) to 3.24 (2.72; 3.96) (p=0.03)), respectively (Wilcoxon criterion). Changes in the NOME index under the influence of nebivolol were not detected: 3.75 (2.7; 4.3) before treatment and 3.4 (2.5; 4.1) after 12 weeks of therapy (p=0.62) (Wilcoxon criterion).

An intergroup comparison of 4 groups (ANOVA) after 12 weeks of treatment revealed a significant difference from each other in the dynamics of the decrease in the NOME index (p=0.035). An intergroup comparison (Mann-Whitney criterion) of the zofenopril group with the perindopril and enalapril groups revealed a statistically significant advantage of zofenopril in its effect on the NOME index (p=0.01 and p=0.02, respectively). In an intergroup comparison (Mann-Whitney criterion), no statistically significant differences were found between the enalapril and nebivolol groups in the dynamics of a decrease in the NOME index after 12 weeks of treatment (p=0.08). An intergroup comparison (Mann-Whitney criterion) of the differences between the perindopril group and the enalapril and nebivolol groups in reducing the NOME index after 12 weeks of treatment revealed the advantage of perindopril (p=0.045 and p<0.05, respectively). An intergroup comparison (Mann-Whitney criterion) of the zofenopril group with the nebivolol group revealed a highly reliable advantage of zofenopril in terms of the effect on the decrease in the activity of the NOME index (p<0.001).

Analysis of the effect of the studied antihypertensive drugs on lipid profile indicators showed the absence of reliable dynamics of most of the estimated parameters in all observation groups, with the exception of a significant decrease in TG levels by 15.6% against zofenopril (p=0.04) and by 19.9% against perindopril (p=0.047).

Nebivolol did not have a negative effect on the indicators of carbohydrate and lipid metabolism, and against its background there was a tendency to increase the level of HDL cholesterol from 1.1 (0.98; 1.43) mmol/l to 1.35 (1.12; 1.82) mmol/l (p=0.055) (Wilcoxon criterion).

Antihypertensive efficacy and impact on quality of life of antihypertensive drugs

The target blood pressure level (<140/90 mmHg) according to "office" measurements after 12 weeks of treatment was achieved in 75.8% (22) patients on zofenopril therapy; in 78.3% (18) patients on perindopril therapy; in 69.2% (18) patients on enalapril therapy and in 74% (20) patients on nebivolol therapy.

According to the office measurement of blood pressure, the maximum degree of decrease in SAD was in the perindopril group and was -20.0 (7.5;26.5) mmHg, the minimum in the enalapril group was -10.0 (0;20.0) mmHg. The degree of decrease in DAD was comparably the same in all groups. Heart rate did not significantly change against the background of ACEI and statistically significantly decreased in patients receiving nebivolol from 74.9±10.6 to and 62.4±6.2 in 1 minute after 12 weeks of treatment (p<0.005).

The results of SMAD confirm the antihypertensive efficacy of all the studied drugs and a significant decrease in mean SAD and DAD in all time intervals, most significant against the background of ACE inhibitors perindopril and zofenopril. A significant decrease in the average daily heart rate was observed in the group of patients taking nebivolol - from 77.1±9.4 beats/min to 71.3±8.3 beats/min (p=0.002). Also according to the results of SMAD

there was an improvement in the daily blood pressure profile: after 12 weeks of treatment, the number of patients with a normal daily profile increased in the zofenopril group by 20.7%, in the perindopril group by 21.8%, in the enalapril group by 15.4% and in the nebivolol group by 18.6%. At the same time, the proportion of patients with daily profile disorders on the background of therapy with zofenopril, perindopril, enalapril and nebivolol decreased: "pop-

dipper" by 17.3%, 13%, 11.6% and 7.5%, respectively, "night-peaker" - by 3.4%, 8.8%, 7.6% and 7.4%, respectively.

The clinical condition of patients with hypertension in combination with obesity was assessed according to the questionnaire "Quality of life in patients with hypertension". Before the appointment of therapy, the total score according to the questionnaire was 29.51 ± 7.46 points. The assessment of general well-being according to VAS was 65.9±14.8 mm, the assessment of well-being associated with the presence of hypertension was 69.75± 17.22 mm. Against the background of antihypertensive therapy, improvement of indicators characterizing the quality of life was noted in all patients. The average score on the questionnaire "Quality of life in patients with hypertension" significantly decreased in all groups, which indicates a decrease in the severity of symptoms associated with hypertension. Against the background of therapy with zofenopril, perindopril and nebivolol, there was a significant decrease in the total score on the questionnaire, an improvement in the assessment of general well-being and well-being associated with hypertension according to your "thermometer". Against the background of enalapril therapy, there was a significant decrease in the total score on the questionnaire and a tendency to improve the assessment of general self-feelings

The level of 1SAM-1 against the background of the use of all antihypertensive drugs tended to decrease, which did not reach statistical significance in both groups of men and groups of women.

In the zofenopril group, a significant decrease in the insulin resistance index was revealed in both men from 3.67 (2.75;4.1) to 2.06 (1.35;2.86) (p=0.001) and women from 3.8 (2.86;4.31) to 2.86 (1.97;3.2) (p=0.02) (p between groups 0.10). The tendency to decrease the NOME index was revealed during treatment with perindopril in the group of men from 3.31 (2.52;3.72) to 2.81 (1.94; 3.09) and in the group of women from 3.36 (2.53; 3.7) to 2.79 (1.94;3.02) (p=0.06 in both groups, p between groups 0.92). Under the influence

of enalalril, the NOME index significantly decreased in the group of men from 3.82 (2.84;4.4) to 3.16 (2.23;3.57) (p=0, (p=0.07) (p between groups 0.57).04), and tended to decrease in the group of women from 4.09 (3.26;4.68) to 3.51 (2.59;3.86). Significant changes in the insulin resistance index under the influence of nebivolol were not detected either in the group of men or in the group of women.

Thus, the assessment of the dynamics of inflammatory parameters and insulin resistance under the influence of treatment with zofenopril, perindopril, enalapril and nebivolol, depending on the tender

the difference revealed a unidirectional change in these parameters without statistically significant differences.

Conclusion. The results of the work showed that in patients with hypertension with MS, the levels of markers of inflammation and insulin resistance were more significantly increased compared to patients with hypertension without MS.

It has been proved that, along with high antihypertensive efficacy, ACE inhibitors zofenopril, perindopril, enalapril and the highly selective beta-adrenoblocker nebivolol have additional pleiotropic properties and can be used for pharmacological correction of violations of the activity of markers of inflammation and insulin resistance.

The effectiveness of the use of antihypertensive drugs in patients with hypertension with MS is substantiated based on the study of their effect on markers of inflammation and insulin resistance.

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