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THE EFFECTIVENESS OF BISOPROLOL AND METFORMIN IN ARTERIAL HYPERTENSION AND METABOLIC SYNDROME

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Abstract
Goal. Evaluation of the effectiveness of treatment of arterial hypertension (AH) with manifestations of metabolic syndrome (MS) with beta-blocker bisoprolol and its combination with metformin.

Material and methods
The study included 20 patients with hypertension and MS, who were divided into 2 groups of 10 people. For 24
weeks, group 1 received bisoprolol 2.5-10 mg/day, group 2 received bisoprolol 2.5-10 mg / day in combination with metformin 850-1700 mg / day.
Before, during and after treatment, blood pressure (BP), body mass index (BMI), carbohydrate metabolism, lipid spectrum, and microalbuminuria (MAU) levels were measured.

Results
There was a significant antihypertensive effect of therapy and a decrease in BMI, most pronounced in patients receiving
combination therapy. By the end of the follow-up, the concentration of insulin decreased in patients of both groups, but a significant decrease occurred in patients receiving combination therapy. Bisoprolol and metformin improved the blood lipid spectrum and reduced MAU levels.

Conclusion
Bisoprolol therapy has an effective effect on pathogenetic processes in hypertension and MS. The appointment of metformin additionally improves the indicators of carbohydrate and lipid metabolism.

Keywords: bisoprolol, metformin, arterial hypertension, metabolic syndrome.

Introduction

Cardiovascular diseases (CVD) continue to be the leading cause of death worldwide. Their prevalence in our country is not decreasing. Abdominal visceral obesity (BMI> 30 kg/m^2 or the ratio of waist circumference to hip circumference of more than 0.9 in men and more than 0.85 in women) with dyslipidemia (an increase in TG of more than 1.7mmol/l and a drop in HDL below 0.9 mmol/l) and hypertension significantly increases the risk of developing CVD. Combination

These risk factors in the presence of insulin resistance are called metabolic syndrome (MS). The most significant consequences of MS are type 2 diabetes mellitus (DM2) and coronary heart disease (CHD). According to the data of the 11-year prospective study of the Kuopio Ischaemic Heart Disease Risk Factor Study, the risk of CVD increases 3 times in MS. The increase in the relative risk of CVD increases from 1.79 with one sign of MS to 3.65 with 4 or more signs. AH is one of the main components of MS. Visceral adipose tissue is considered one of the sources of angiotensinogen, which may be important in the mechanisms of hypertension development in obese patients. Among patients with DM2, hypertension is 2 times more common than in people without diabetes. Insulin resistance and hyperinsulinemia contribute to an increase in the activity of the sympathetic nervous system, which leads to an increase in cardiac output, vasospasm and increased peripheral resistance. Insulin has a direct vasodilatory effect, but at the same time indirectly, through adrenergic stimulation causes vasoconstriction. The vasodilating effect of insulin is determined by its effect on vascular smooth muscle cells or increased synthesis of endothelial relaxation factor – nitric oxide. In conditions of chronic hyperinsulinemia and insulin resistance, endothelium-dependent vasodilation processes are disrupted and a paradoxical vascular reaction occurs due to the predominance of the sympathostimulating component. By MS increases the secretion of plasminogen-1 activator inhibitor by adipose tissue and endothelium, which ensures the procoagulation state of the vascular wall and it leads to an acceleration of the atherogenesis process. The main goal of treating patients with MS is to minimize the overall risk of CVD and mortality. An aggressive approach to MS therapy consists in achieving the target blood pressure (< 130/80mmHg), BMI, lipid profile, as well as reducing lipid-independent risk factors for CVD (C-reactive protein, insulin resistance, fibrinolysis and endothelial function disorders). One of the main classes of antihypertensive drugs drugs include beta-blockers, but in MS they are often abandoned due to fears of a worsening metabolic background. However, a number of studies have proven the benefits of prescribing selective beta-blockers for diabetes. According to the Bezafibrate Infarction Prevention Study (BIP), among patients with diabetes who received beta blockers, overall mortality decreased by 36%. In the UKPDS (UK Prospective Diabetes Study) It has been shown that careful blood pressure monitoring using the selective beta-blocker atenolol or the ACE inhibitor captopril in patients with hypertension and DM2 equally effectively reduces the risk of death and complications associated with diabetes, and is just as important as glucose control. Thus, with an increase in blood pressure by 10 mmHg, the number of macrovascular complications increased by 15%, and with an increase in the level of glycosylated hemoglobin by 1% – by 11%. In recent years, it has been shown that selective β1-blockers are metabolically neutral, so as they do not cause disorders of carbohydrate and lipid metabolism. In the BIP study, patients who received beta-blockers had lower fasting glucose concentrations with the same hypoglycemic therapy and lower mortality than patients who did not take beta-blockers. The UKPDS study found no difference in the level of glycosylated hemoglobin and the severity of glycemic episodes among patients taking captopril and atenolol. Thus, the opinion that DM is a contraindication to the appointment of beta-blockers is not It has been confirmed. The use of selective beta-blockers can reduce the frequency of CVD in patients with hypertension and diabetes; at the same time, there are practically no undesirable effects of these drugs on carbohydrate metabolism.

MATERIALS AND METHODS OF RESEARCH

The criteria for inclusion in our study were the presence of hypertension in individuals with increased BMI or abdominal visceral obesity and their combination with one of the following factors: fasting plasma glucose 6.2 - 6.9 mmol/l, HDL < 40 mg% in men and < 50mg% in women, TG > 150 mg%. The exclusion criteria were: heart rate less than 60 beats/min, significant ECG changes requiring additional therapy, PQ > 0.18 ms, prolonged QT interval. Patients with hypertension should not have severe cerebrovascular diseases, acute coronary syndrome, congestive heart failure. Patients with leukocytosis were also excluded >10x109/l, deforming osteoarthritis, chronic renal failure, cirrhosis of the liver or

active hepatitis, DM 1 and 2, secondary hypertension, oncological diseases and abusers alcohol. The study involved 20 people (12 women and 8 men) aged 47 to 69 years (average age 55.3 ± 2.2 years). Blood pressure indicators corresponded to grade 2 hypertension. The average systolic blood pressure (SAD) was 151.5±5.3 mmHg, diastolic (DBP) -93.75±3.6 mmHg. All patients had an increased BMI (on average 32.11±2.7 kg/m^2). The average venous blood glucose level was in the range of 6.6±0.8 mmol/l. The initial level of total cholesterol was 5.87±1.7 mmol/l. In 70 % of patients (n=14) there was a burdened family history of early CVD development. 55% (n=11) of patients had a high risk of developing CVD, 35%

(n=7) had a moderate risk and 10% (n=2) had a low risk. Before being included in the study, all patients received recommendations on blood pressure self-monitoring, diet, and physical activity. After completing all the studies provided for in the protocol (office blood pressure measurement, calculation BMI, waist and hip circumference, general blood and urine analysis, fasting glucose, postprandial glycemia, fasting insulin concentration, C-reactive protein, lipid profile, MAU, ECG) all patients were prescribed hypotensive therapy. Group 1 patients (10 people) took the selective beta-adrenoblocker bisoprolol (concor) as monotherapy in the starting dose was 2.5 mg per day, which was titrated to 10 mg / day if necessary. Group 2 patients (10 people) also received bisoprolol at a dose of 2.5 – 10mg/day, depending on blood pressure, but in combination with metformin (glucophage), the initial dose of which was 850 mg / day, and after 2 weeks. increased to 850 mg 2 times a day (daily dose of 1700 mg). A feature of metformin is its lack of effect on the beta cells of the pancreas, which It allows the use of this drug in patients with normal glycemia, i.e., use it as the drug of choice for initial disorders of carbohydrate metabolism, including MS. The duration of follow-up was 24 weeks. At control visits (after 2, 8, 12 and 24 weeks), a comprehensive

clinical examination of patients was performed, recording any side effects. The antihypertensive effect of therapy was evaluated based on the data of the diary kept by patients and the values of the office blood pressure measurement during control

visits. Indicators such as insulin and blood glucose fasting, postprandial glycemia, C-reactive protein, lipid spectrum, MAU, were recorded through 24 weeks. treatment. The obtained results were processed using the STATISTICA 6 program. The results are presented in the form of M±m. The distribution pattern was assessed using the Kolmogorov–Smirnov criterion. Since the sample is represented by a small number of patients, nonparametric methods of statistical analysis (Wilcoxon or Mann–Whitney criterion) were used. The differences were considered significant at $p<0.05$.

THE RESULTS AND THEIR DISCUSSION

There were no significant differences between patients in all indicators before the start of treatment. Titration of bisoprolol doses was performed individually for each patient, and there were no differences between the groups in the doses of the drug; the average daily dose was 5 mg. After 24 weeks. hypotensive therapy showed a significant decrease in blood pressure to target levels in both groups. SAD in patients treated with bisoprolol alone was 124.1±9.8 mmHg, DAD – 80.05±7.3 mmHg. SAD in patients with combination therapy reached 125.1±8.8 mmHg, and DAD – 79.0±7.4 mmHg. By the end of the study, all patients had decreased body weight, which may be associated with diet therapy and a regimen of metered-dose physical activity in patients of group 1. This is confirmed by the study DPP (Diabetes Prevention Program), in which, during a 4-year follow -up, the greatest effectiveness of lifestyle changes for weight loss was demonstrated. The rate of weight loss in group 2 patients was higher. Data analysis UKPDS shows that with metformin monotherapy, patients' weight decreases by 1.2 – 4 kg.

Before treatment, the insulin content was 12.34±2.5 IU/l and 15.09±1.8 IU/l in groups 1 and 2, respectively ($p>0.05$). By the end of the follow-up, the insulin concentration decreased in all patients, reaching 9.86±1.7 IU/l and 9.91±1.5 IU/L in groups 1 and 2, respectively. At the same time, a significant decrease ($p<0.05$) occurred only in patients who additionally took metformin, which reduces the resistance of tissues to insulin and leads to a decrease in hyperinsulinemia, which plays an important role in the development of CVD. In addition, metformin It reduces the production and stimulates the utilization of glucose without affecting insulin secretion, which eliminates the risk of hypoglycemia. It is believed that β-blockers worsen the lipid spectrum. Indeed, non-selective beta blockers increase LDL levels and reduce HDL concentrations. However, these changes are expressed slightly or completely absent when using selective β-blockers. Initially, in patients of both groups, an increased TG content was found to 1.99±0.7 mmol/l and 2.15±0.9 in groups 1 and 2, respectively. After 24 weeks. treatment without the use of additional lipid-lowering therapy showed a significant ($p<0.05$) decrease in TG content in both groups (up to 1.44±0.6 and 1.48±0.6mmol/l in groups 1 and 2, respectively). At the beginning of the study, the LDL level exceeded the permissible values, amounting to 3.57±0.93 and 3.4±0.68mmol/l in groups 1 and 2, respectively. By the end of the study, there was a slight decrease in this indicator to 2.75±0.96 in the 1st and 2.67±0.89mmol/l in the 2nd group. A significant increase in the antiatherogenic class of lipoproteins (HDL) was observed only in group 2 (from 1.22±0.4 to 1.47±0.5mmol/l). Perhaps this is due to the effect of metformin on lipid metabolism (a decrease in total cholesterol, TG and an increase in HDL). Thus, in some studies, while taking metformin, a significant decrease in TG levels was demonstrated – by more than 30%. It is believed that the prognostic significance of MAU in assessing the risk of CVD is due to its relationship with the state of endothelial function. The progression of MAU is a significant risk factor for morbidity and mortality from CVD, and especially in patients with DM 2. There was no prognostically significant increase in MAU before the start of therapy. By the time of the control study, the albumin content in urine decreased in patients of both groups.

CONCLUSIONS

1. Hypotensive therapy with bisoprolol during 24 weeks. and its combination with metformin leads to a significant antihypertensive effect and a decrease in BMI, most pronounced in patients receiving combination therapy.

2. A significant decrease in serum insulin concentration is observed only in patients receiving bisoprolol in combination with metformin.
3. Bisoprolol and metformin have a beneficial effect on lipid metabolism, reducing the content of TG and LDL in the blood serum. The additional inclusion of metformin in the treatment regimen significantly increases the level of HDL.

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