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Efficacy of Moxonidine in Therapy of Arterial Hypertension in Type 2 Diabetes Mellitus

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At a combination moxonidine and enalapril in 107 patients 2 type of diabetes with arterial hypertension the more expressed hypotensive effect in matching with monotherapy of enalapril is obtained. Metabolic parameters of a blood also were improved, and the functional activity of a sympato-adrenal system has decreased.

KEYWORDS: moxonidine, enalapril, arterial hypertension, type 2 diabetes

Every year, the number of patients with type 2 diabetes mellitus (DM) is increasing all over the world. A large number of studies have demonstrated that type 2 diabetes mellitus (DM) is often combined with cardiovascular diseases, including arterial hypertension (AH). The development of diabetes and hypertension are interrelated diseases. Thus, in a study by T.W. Gress et al (2000) showed that over 6 years of follow-up, the incidence of type 2 diabetes in patients with hypertension was more than 2 times higher than in normotensive patients. On the other hand, an increase in the level of glycemia is also associated with an increase in the risk of developing hypertension [1,2,3,5].

Large clinical trials have shown that tight blood pressure control reduces the incidence of cardiovascular disease and mortality in people with type 2 diabetes [7]. Metabolic disorders of all types observed in diabetes, as well as dysregulation of the endocrine system, primarily significant changes in the level of counterinsular hormones, including catecholamines, are the reasons for an increase in blood pressure (BP), which not only aggravates the course of diabetes, but also serves as an additional factor contributing to the deterioration of the function of the cardiovascular and other systems [5,8,10,11].

An effective drug used for the treatment of arterial hypertension is moxonidine, a sympatholytic, an agonist of imidazoline receptors of the central nervous system. A number of clinical studies have shown the effectiveness of moxonidine in the treatment of hypertension, which was comparable to the effectiveness of other modern antihypertensive drugs [4,6,9,11].

The aim of this study is to evaluate the effectiveness of the use of combination therapy of moxonidine with an ACE inhibitor (enalapril) on the functional state of the sympathoadrenal system (SAS), the activity of the key enzyme of oxidative deamination of catecholamines (CA) - monoamine oxidase (MAO) in patients with type 2 diabetes with hypertension.

Material and methods of research: 107 men aged 35 to 65 years (mean age - 55.82 ± 1.3 years) were studied with a diagnosis of type 2 diabetes with hypertension, which was established in accordance with the WHO criteria (1999) and VNOK. The control group consisted of 20 apparently healthy men aged 30-55 years. Patients with type 2 diabetes with hypertension by the method of random sampling after the survey were divided into 2 subgroups, which were comparable in terms of age, duration of arterial hypertension and diabetes mellitus, office systolic and diastolic blood pressure (Table 1). Patients of subgroup - A - 67 people received traditional treatment, consisting of a diet (table No. 9), antihypertensive therapy, antihypertensive therapy (enalapril at a dose of 10 mg per day);



Table 1
Clinical characteristics of patients with type 2 diabetes with hypertension

| Indicators | Subgroup A (n=67) | Subgroup B (n=40) |
|-------------------------------------|-------------------|-------------------|
| Average age, years | 55,73±1,46 | 56,0±2,68 |
| Blood glucose mmol / l | 11,05±0,67 | 11,14±0,74 |
| Duration of hypertension, years | 9,32±0,53 | 9,9±0,95 |
| Duration of type II diabetes, years | 4,96±0,65 | 5,10±1,07 |
| SBP, mm Hg Art. | 163,24±1,86 | 164,5±3,11 |
| DBP, mm Hg Art. | 94,19±0,89 | 94,5±1,74 |

Subgroup - B - 40 patients who also received traditional treatment, consisting of a diet (table No. 9), antihypertensive therapy, in addition to antihypertensive therapy (enalapril at a dose of 10 mg per day) received moxonidine (physiotens) in doses of 0.2-0, 6 mg.

To judge the functional state of the SAS, the daily urinary excretion of adrenaline (A), norepinephrine (HA), dopamine (DA) and DOPA was determined by the fluorometric method modified by E.Sh. Matlina. In the blood serum, the MAO activity was determined by the colorimetric method of A.V. Balakleevsky. Determination of lipid peroxidation products (LPO) by the level of malondialdehyde (MDA) in blood serum was carried out according to the method of V.B. Gavrilova, A.R. Gavrilova and A.M. Mazhul, determined by reaction with 2-thiobarbituric acid.

The diagnosis in the examined patients was established on the basis of clinical examination data, functional and laboratory-instrumental research methods. The study was carried out on the 1st day of admission to the hospital before the start of treatment, and 12 weeks after the start of treatment.

The arithmetic mean values for the compared groups and their mean errors ($M \pm m$) were calculated by the method of variation statistics, the reliability of the difference between the compared values was determined using the Student's t-test.

Results of the study: After the treatment, after 12 weeks in patients of subgroup A, there was a positive dynamics of blood pressure levels, as the levels of SBP and DBP decreased by 15.0% and 9.7%, respectively, and in subgroup B these indicators decreased by 16.8% and by 11%, respectively.

From the data in Table 2, it follows that both drugs are comparable in terms of the hypotensive effect on office SBP and DBP, while Physiotens reduced the magnitude and rate of the morning rise in blood pressure, which makes it a promising drug for the prevention of cerebral and cardiac complications of hypertension.

When analyzing the activity of the sympathoadrenal system after treatment (Table 3) in subgroup A, we observed a statistically significant decrease in the daily excretion of CA and DOPA in relation to the initial values. Thus, the excretion of total A decreased by 12.8% (1.13 times) ($P < 0.05$), HA - by 13.6% (1.14 times) ($P < 0.02$), YES - by 6.4% (1.1 times) ($P < 0.001$), DOPA - by 25.0% (1.25 times) ($P < 0.001$). Also, the indicators of the coefficient ratios of CA, their precursors and metabolites were normalized.

In subgroup B, after treatment with moxonidine, we observed a more pronounced statistically significant decrease in the daily excretion of CA and DOPA, and the values of these parameters approached those of the control group. Thus, the excretion of total A decreased by 20.4% (1.2 times), AN by 25.6% (1.3 times), YES - by 8.9% (1.1 times), DOPA - by 45.4% (1.25 times) ($P < 0.01-0.001$). Also, the indicators of the coefficient ratios of CA, their precursors and metabolites were normalized (Table 2).

Table 2

Daily excretion of catecholamines in healthy and patients with type 2 diabetes in combination with hypertension before and after treatment

| KA, mg/cyt | fraction s | group | | | | |
|------------|------------|--------------------|-------------------|-----------------|-------------------|------------------|
| | | I – control (n=20) | subgroup A (n=67) | | subgroup B (n=40) | |
| | | | Before treatment | After treatment | Before treatment | Before treatment |
| A | free | 4,6±0,17 | 6,74±0,27 | 5,87±0,24 | 6,16±0,34 | 5,36±0,29 |
| | cong. | 3,6±0,10 | 8,43±0,38 | 7,6±0,34 | 7,85±0,4 | 6,28±0,32 |
| | sum. | 8,2±0,21 | 15,17±0,6 | 13,45±0,53* | 14,01±0,66 | 11,64±0,55^ |
| NE | free | 9,9±0,21 | 11,76±0,51 | 10,82±0,47 | 11,39±0,59 | 10,48±0,54 |
| | cong. | 8,7±0,21 | 15,66±0,59 | 13,31±0,5 | 14,74±0,71 | 10,32±0,5 |
| | sum. | 18,6±0,29 | 27,42±0,9 | 24,13±0,8** | 26,12±0,78 | 20,79±0,62^^ |
| DA | free | 152,0±2,69 | 160,95±2,91 | 157,73±2,85 | 153,18±4,14 | 150,11±4,06 |



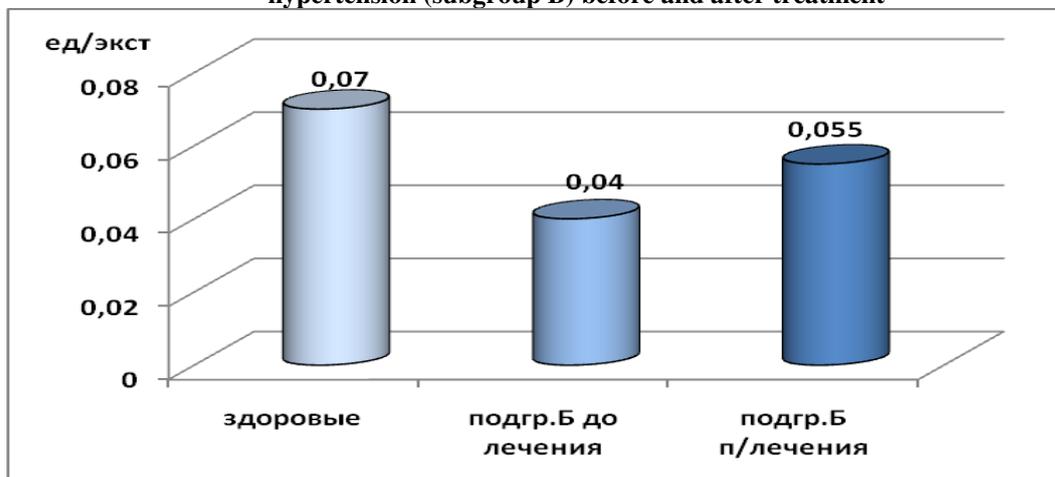
| | | | | | | |
|------|------------|------------|------------|--------------|-------------|--------------|
| | cong. sum. | 135,7±2,51 | 165,48±2,4 | 148,93±2,16 | 161,33±4,62 | 138,74±3,97 |
| DOFA | | 45,4±0,5 | 59,99±1,37 | 47,99±1,10^^ | 60,20±2,25 | 48,16±1,80^^ |

Note: P is the reliability of the differences between the indicator before and after treatment according to Student's t-criterion: * - P < 0.05; ** - P < 0.02; ^ - P < 0.01; ^^ - P < 0.001.

Assessment of monoamine oxidase activity of blood in patients with type 2 diabetes with AH revealed a statistically significant decrease in MAO activity (Table 4). After active therapy with antioxidants, we noted a significant increase in enzyme activity by 20.9% (1.3 times) (P < 0.001), which is higher than the initial level (Fig. 2)

Fig. 1

MAO content in blood serum in the control group and patients with type 2 diabetes in combination with hypertension (subgroup B) before and after treatment

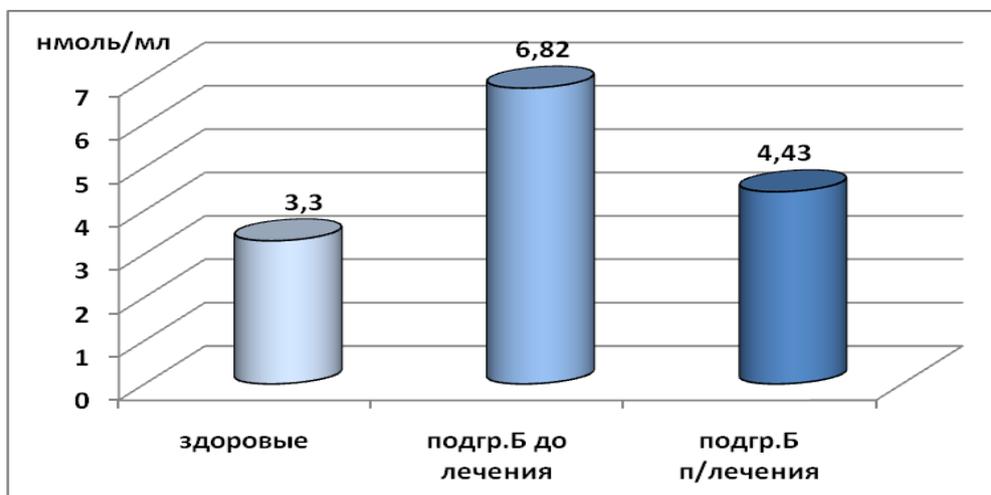


In the group receiving combined antihypertensive therapy with moxonidine, we noted a more significant increase in MAO activity by 27.5% (1.4 times) (P < 0.001) in relation to the initial level and the approach of these indicators to the values of the control group.

The results of the analysis of LPO processes showed that there is a significant decrease in the secondary products of LPO - MDA, the level of which decreased from 6.82 ± 0.44 nmol / ml to 4.43 ± 0.28 nmol / ml, which amounted to 53.8% (in 1.54 times). The MDA values after treatment in this subgroup were significantly close to the value of the control group (Fig. 2).

Fig. 1

Serum MDA content in the control group and patients with type 2 diabetes in combination with hypertension (subgroup B) before and after treatment





Discussion. Currently, diabetes is considered not only as a syndrome of hyperglycemia, but also as a systemic metabolic disorder, which is often combined with chronic activation of the sympathoadrenal system.

Moxonidine, which selectively binds to imidazoline receptors, reduces SAS activity and produces a hypotensive effect due to a decrease in peripheral vascular tone, catecholamine secretion, renin and aldosterone activity [7], which is also confirmed by our data. Our studies have shown that a significant change in the LPO system immediately affects the SAS activity, which was expressed by a decrease in the daily excretion of adrenaline, norepinephrine, dopamine and DOPA, an increase in the level and improvement of the catalytic activity of MAO.

In the HOT study, it was shown that target blood pressure levels are very rarely achieved with the use of a single antihypertensive drug [8]. In people with type 2 diabetes, the drug of choice for lowering blood pressure should be an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, to which a second antihypertensive drug is added as needed.

The results of this study indicate that when moxonidine is added to the first-line antihypertensive drug, along with an increase in the hypotensive effect, it also has a beneficial effect on the normalization of metabolic processes, which reduces the risk of cardiovascular complications in type 2 diabetes with hypertension. Thus, the combined antihypertensive therapy of enalapril with moxonidine in patients with type 2 diabetes with hypertension effectively reduces both systolic and diastolic blood pressure, suppressing the activity of the sympathoadrenal system, and also favorably affects the parameters of carbohydrate metabolism.

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