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EVALUATION OF THE EFFICACY OF ANGIOTENSIN II RECEPTOR ANTAGONISTS (LOSARTAN) ON THE STATE OF CENTRAL HEMODYNAMICS IN PATIENTS WITH THYROTOXICOSIS SYNDROME

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Abstract

Purpose of the study– to study the effectiveness of the drug losartan on the state of central hemodynamics in patients with thyrotoxicosis syndrome.

Material and methods of research. Clinical data collection was carried out at the City Clinical Hospital No. 1 in Andijan

63 people were examined, including 47 women, 16 men, average age49.2±1.62years (for women -47±1.76years, for men -42±2.6years).

Patients with thyrotoxicosis syndrome, depending on the disease, were divided into the following 5 groups: patients with diffuse toxic goiter 50% - DTG- (32 people), multinodular goiter - MUZ-11.6% (7 people), autoimmune thyroiditis - AIT-16.7% (11 people), thyrotoxic adenoma - TA-6.7% (4 people) and mixed toxic goiter - MS-15% (9 people).

Research methods – general clinical, biochemical (bilirubin, direct, indirect, ALT, AST, PTI, coagulogram, CRP), hormonal (TSH, free thyroxine, antibodies to thyroid peroxidase, to thyroglobulin and thyrocyte receptors, prolactin in the blood),anthropometric calculations (height (cm), weight (kg), BMI (kg/m2), waist circumference, waist circumference) and instrumental: ECG, echo-ECG, ultrasound of the thyroid gland, internal organs, chest X-ray

Research results. The study revealed significant changes that suggest that losartan therapy reverses left ventricular hypertrophy (LVH) and improves its structural characteristics in patients with hyperthyroidism syndrome. Left atrial (LA) dilation was found to be a precursor to LVH. Combined use of losartan demonstrated the ability to significantly reduce the size of the left atrium, which was enlarged in most patients examined. Consequently, the observed statistically significant reduction in LA size from 4.42 ± 0.08 to 3.81 ± 0.09 cm ($p < 0.05$) can be interpreted as a positive effect of losartan therapy.

Conclusions.The inclusion of losartan, an angiotensin II receptor blocker, in combination therapy including beta-blockers and antithyroid drugs, against the background of achieved compensation of thyrotoxicosis, led to regression of left ventricular hypertrophy, restoration of sinus rhythm in 43% of patients and a statistically significant improvement in blood pressure.

Keywords: Thyrotoxicosis, treatment of complications.

Introduction

Hyperthyroidism is common among 0.2–1.3% of the population in iodine-sufficient areas, with Graves' disease accounting for over 80% of cases [1,2]. Patients with hyperthyroidism, especially those whose hyperthyroidism is uncontrolled or long-lasting, are at increased risk of cardiovascular morbidity and mortality [3-5]. There are three treatments for Graves' disease: antithyroid drug therapy (ATT), radioiodine therapy (RIT), and thyroidectomy. Currently, guidelines do not recommend any of these three treatments as first-line therapy, as each has its own unique advantages and disadvantages [6-8]. However, ATP is currently used as initial therapy for Graves' disease in North America, Europe, and Asia (9–11).9-11].

The main disadvantage of antithyroid therapy (ATT) is the low remission rate [12]. With the recommended 12–18-month course of ATD therapy, the remission rate can reach approximately 30–40% [13]. This is problematic given the importance of rapid resolution of hyperthyroidism to reduce cardiovascular morbidity and mortality in these patients [5]. It is recommended that patients with persistently high thyrotropin receptor antibody (TRAb) levels after 12–18 months can continue treatment with ATT for another 12–18 months or choose definitive therapy, such as radioimmunotherapy or thyroidectomy. However, treatment guidelines do not clearly indicate the designation of subsequent second-line therapy in this situation [6.7]. Previous studies have reported favorable outcomes of long-term (>24 months) ATT treatment with a low incidence of drug-related adverse events in patients with persistent or recurrent hyperthyroidism after a conventional course of ATT treatment [12, 14-17]. However, the primary efficacy outcome measure of long-term antithyroid drug therapy in these studies was primarily the hyperthyroidism remission rate, and efficacy was not compared with other treatments, such as radioactive iodine or thyroidectomy. Given the increased risk of cardiovascular events in patients with hyperthyroidism and the improved survival associated with effective hyperthyroidism control, it would be worthwhile to evaluate the risk of cardiovascular events in patients with long-standing hyperthyroidism depending on different treatment modalities after a standard course of antithyroid drugs. To our knowledge, no previous studies have directly assessed the impact of second-line therapy on cardiovascular risk in clinical practice in patients with long-standing hyperthyroidism.

All of the above formed the basis for this study.

Purpose of the study

To study the effectiveness of the drug losartan on the state of central hemodynamics in patients with thyrotoxicosis syndrome.

Material and methods of research

Clinical data collection was carried out at the City Clinical Hospital No. 1 in Andijan

63 people were examined, including 47 women, 16 men, average age49.2±1.62years (for women -47±1.76years, for men -42±2.6years).

The control group consisted of20 healthy individuals (10 women and 10 men) whose hormonal parameters were used to assess the reliability of the results obtained.

*Inclusion criteria:*diffuse toxic goiter,multinodular goiter, autoimmune thyroiditis, thyrotoxic adenoma and mixed toxic goiter, men, women

*Exclusion criteria:*The study did not include patients with carbohydrate metabolism disorders, ischemic heart disease, heart defects, idiopathic cardiomyopathy, or patients who had suffered a cerebrovascular accident.

Research methods – general clinical, biochemical (bilirubin, direct, indirect, ALT, AST, PTI, coagulogram, CRP), hormonal (TSH, free thyroxine, antibodies to thyroid peroxidase, to thyroglobulin and thyrocyte receptors, prolactin in the blood),anthropometric calculations (height (cm), weight (kg), BMI (kg/m2), waist circumference, waist circumference) and instrumental: ECG, echo-ECG, ultrasound of the thyroid gland, internal organs, chest X-ray

Patients with thyrotoxicosis syndrome, depending on the disease, were divided into the following 5 groups: patients with diffuse toxic goiter 50% - DTG- (32 people), multinodular goiter - MUZ-11.6% (7 people), autoimmune thyroiditis - AIT-16.7% (11 people), thyrotoxic adenoma - TA-6.7% (4 people) and mixed toxic goiter - MS-15% (9 people) (Table 1).

The basic examination of patients included collecting anamnesis (patient complaints, time of their first appearance, connection of the occurrence of complaints with certain reasons assumed in the patient's opinion, time of first visit to the doctor, time of diagnosis, type of therapy received and its effectiveness), physical (determination of heart rate, blood pressure) and general clinical examinations, study of hormonal levels - free triiodothyronine (free T3), free thyroxine (free T4), thyroid stimulating hormone (TSH), to clarify the autoimmune genesis of the disease, it was determinedthyroid peroxidase antibody titer (TPO)). Hormones were determined in blood serum using reagents from HUMAN (Germany).

The data obtained in the study were statistically processed on a Pentium-IV personal computer using the Microsoft Office Excel-2003 software package, including the use of built-in statistical processing functions. Methods of variational parametric and nonparametric statistics were used, with the calculation of the arithmetic mean of the studied indicator (M), standard deviation (s), standard error of the mean (m), relative values (frequency, %). The statistical significance of the obtained measurements when comparing mean values was determined by the Student's criterion (t) with the calculation of the probability of error (P) when checking the normality of distribution (by the kurtosis criterion) and the equality of general variances (F - Fisher's criterion). A confidence level of $P < 0.05$ was considered statistically significant.

Research results

According to the results of our studies, 60.7% of women and 39.3% of men out of all patients with DTG suffered from diffuse toxic goiter; MUZ occurred in 100% of cases in women;AIT was found in 20% of cases in men and 80% in women; TA was found in 50% of cases in men and 50% in women; SZ was found in 33.3% of cases in men and 66.7% in women (Table 1).

Table 1 Distribution of patients depending on gender and thyroid pathology encountered

	DTZ (n=32)	AIT (n=11)	TA (n=4)	MUSIC (n=7)	SZ (n=9)
Men%	39.3	20	50	-	66.7
Women%	60.7	80	50	100	33.3

Note: n – number of examined patients;

The next step in our work involved selecting a group of patients with thyrotoxicosis syndrome and dividing them into two groups. The first group received bisoprolol at a dose of 2.5 mg/day along with antithyroid therapy. The second group received losartan (50 mg) and bisoprolol (2.5 mg) along with antithyroid therapy. We assessed echocardiography results before and after one month of treatment (Table 2).

Table 2 Changes in left heart remodeling indices inpatients with thyrotoxicosis syndrome of the first group.

Indicators	Bisoprolol + losartan (n=44)		Bisoprolol (n=19)	
	Before treatment	After treatment	Before treatment	After treatment
LV TRT, mm	1.34 ± 0.04	1.05 ± 0.02*	1.29 ± 0.02	1.25 ± 0.03
LV EDR, cm	5.54 ± 1.44	5.21 ± 0.05*	5.43 ± 1.14	5.38 ± 0.08
OTS LZH	0.42 ± 0.08	0.38 ± 0.06	0.42 ± 0.06	0.41 ± 0.03
RLP, cm	4.42 ± 0.08	3.81 ± 0.09*	4.14 ± 0.07	3.9 ± 0.06
LVMI, g/m2	126 (119.5; 138.5)	121 (118.4; 126.5)	123 (116.6; 135.7)	121 (113.4; 119.5)
TMZHP,	1.3 ± 0.05	1.21 ± 0.09*	1.29 ± 0.08	1.26 ± 0.1
KDO	105.2±4.85	115.1±2.57	104.2±4.45	110.3±2.55
KSO	34.2±2.45	50.1±1.33	33.3±10.9	46.2±1.33
PIC E	0.58±0.05	0.89±0.6	0.58±0.05	0.86±0.03
PIK A	0.84±0.07	0.50±0.05	0.85±0.6	0.55±0.05
E/A	0.60±0.03	2.1±0.04	0.64±0.05	1.88±0.16

Note: LV posterior wall thickness, mm — left ventricular thickness; LV EDD, mm — left ventricular end-diastolic dimension; LVRT — relative left ventricular wall thickness; LARV, mm — left atrial volume; LVMI — LV mass index; IVST — interventricular septum thickness; *p< 0.05.

As can be seen from Table 2, in the group of patients receiving atenolol slosartan, the indicators of LV TZS, LV EDD, and RLP significantly improved during treatment, compared with the second group. These significant changes suggest that losartan therapy promotes regression of LVH and improvement of LV geometry in patients with hyperthyroidism syndrome. LVH is preceded by LA dilation. Combined use of losartan significantly reduces the size of the left atrium, which was initially enlarged in most patients examined. Therefore, a significant reduction in LA size from 4.42 ± 0.08 to 3.81 ± 0.09 cm ($p < 0.05$) can be regarded as a positive effect of losartan therapy.

The next stage of the study was to examine the effect of losartan on the blood pressure/diastolic blood pressure and heart rate (Table 3).

Table 3. Dynamics of blood pressure and heart rate during treatment of thyrotoxic heart disease

indicators	2nd group n=44		Group 1 n=19	
	Before treatment	After treatment	Before treatment	After treatment
SBP mmHg	153.4±10.9	137.7±8.8*	152.9±12.6	143.7±8.9*
DBP mmHg	96.4±8.5	84.5±7.2*	96.5±8.9	88.1±8.2*
HR bpm	105.95±1.69	79±2.4*	107.23±0.58	82±1.7*

The combination of losartan + bisoprolol and bisoprolol reduced systolic blood pressure by 10.3% and 6.1%, respectively ($p < 0.05$) and diastolic blood pressure by 12.4% and 8.8%, respectively ($p < 0.05$). Administration of the drugs in both groups was accompanied by a significant change in heart rate. Target blood pressure levels were achieved in 70% of patients taking both bisoprolol and the combination with losartan.

The study revealed significant changes that suggest that losartan therapy reverses left ventricular hypertrophy (LVH) and improves its structural characteristics in patients with hyperthyroidism syndrome. Left atrial (LA) dilation was found to be a precursor to LVH. Combined use of losartan demonstrated the ability to significantly reduce the size of the left atrium, which was enlarged in most patients examined. Consequently, the observed statistically significant reduction in LA size from 4.42 ± 0.08 to 3.81 ± 0.09 cm ($p < 0.05$) can be interpreted as a positive effect of losartan therapy.

In terms of blood pressure effects, the combination of losartan with atenolol and atenolol alone resulted in a 10.3% and 6.1% reduction in systolic blood pressure, respectively ($p<0.05$), and a 12.4% and 8.8% reduction in diastolic blood pressure, respectively ($p<0.05$). Both treatment regimens were associated with statistically significant changes in heart rate. Target blood pressure levels were achieved in 70% of patients, regardless of whether they received atenolol alone or in combination with losartan.

These significant changes suggest that losartan therapy promotes regression of LVH and improvement of LV geometry in patients with hyperthyroidism syndrome. LVH is preceded by LA dilation. Combined use of losartan significantly reduces the size of the left atrium, which was initially enlarged in most patients examined. Therefore, a significant reduction in LA size from 4.42 ± 0.08 to 3.81 ± 0.09 cm ($p < 0.05$) can be regarded as a positive effect of losartan therapy.

The combination of losartan and atenolol and atenolol reduced systolic blood pressure by 10.3% and 6.1%, respectively ($p<0.05$) and diastolic blood pressure by 12.4% and 8.8%, respectively ($p<0.05$). Administration of the drugs in both groups was accompanied by a significant change in heart rate. Target blood pressure levels were achieved in 70% of patients taking both atenolol and the combination with losartan.

Significant changes suggest that losartan therapy promotes regression of LVH and improvement of LV geometry in patients with thyrotoxicosis syndrome. LVH is preceded by LA dilation. Combined use of losartan significantly reduces the size of the left atrium, the initial size of which was enlarged in most patients examined. Therefore, a significant reduction in LA size from 4.42 ± 0.08 to 3.81 ± 0.09 cm ($p < 0.05$) can be regarded as a positive effect of losartan therapy [1, 2].

Conclusions

The inclusion of losartan, an angiotensin II receptor blocker, in combination therapy including beta-blockers and antithyroid drugs, against the background of achieved compensation of thyrotoxicosis, led to regression of left ventricular hypertrophy, restoration of sinus rhythm in 43% of patients and a statistically significant improvement in blood pressure.

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