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CLINICAL EVALUATION OF THE USE OF AZILSARTAN MEDOXOMIL AND INDAPAMIDE IN PATIENTS WITH ARTERIAL HYPERTENSION

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Abstract: This article conducted a scientific study of the clinical assessment of the use of azilsartanmedoxomil and indapamide in patients with arterial hypertension.

Keywords: diagnosis, azilsartan, medoxomil, clinical, receptor, hepatic transaminases, hemodynamic.

Introduction. It is known that the problem of early diagnosis, prevention and treatment of arterial hypertension (AH) is becoming threatening, reducing life expectancy, leading to disability of patients, disrupting quality of life. According to the research, in Uzbekistan AH diagnosis among male population is worse than that among women [3]. The high percentage of undiagnosed cases of AH and ineffectiveness of ineffectiveness of antihypertensive therapy is one of the main problems health care in Uzbekistan. Thus, the problem of increasing of improving the effectiveness of AH treatment by improving the control of arterial (BP) is still urgent.

In the treatment of arterial hypertension, the key issue is the the right choice of combination therapy is a key issue, especially since there are a large number of BP-lowering drugs available today. There are a large number of blood pressure lowering drugs available nowadays. One of the class of drugs that block the activity of the renin-angiotensin. Angiotensin II receptor antagonists are a class of drugs that block the activity of the renin-angiotensin-aldosterone system (RAAS), are an increasingly commonly prescribed medication for AH. A large number of controlled studies have shown a large number of controlled studies have demonstrated not only their ability to slow the progression of target organ damage (reduction of left ventricular hypertrophy, decrease in the severity of microalbuminuria and proteinuria, slowing the rate of decline in renal function, cerebral-protection), but also to prevent organ damage. Azilsartanmedoxomil is a new representative of the class of angiotensin II receptor antagonists [6, 8], in our country it was registered in 2016. Being a prodrug, azilsartanmedoxomil is rapidly converted into the active molecule azilsartan, which selectively prevents the effects of angiotensin II by blocking its binding to AT1 receptors in various tissues. Angiotensin II is the the primary vasoactive hormone of the RAAS, and its effects include vasoconstriction, cardiac stimulation, stimulation of synthesis and aldosterone release and, consequently, renal sodium reabsorption. Blockade of AT1 receptors inhibits the negative regulatory response of angiotensin II to renin secretion, but the resulting increase in plasma renin activity and circulating angiotensin II levels does not suppress the antihypertensive effect of the drug.

The antihypertensive effect may be enhanced when the drug is combined with other hypotensive agents, including diuretics and dihydropyridine calcium channel blockers [9]. In the treatment of arterial hypertension, thiazide-like diuretics are recommended either as the drugs of first choice or as one of the five groups of first-line drugs in the treatment of AH [1]. In our country indapamide (Indap) is the most widespread, which together with drugs blocking the RAAS is often used as part of combined antihypertensive therapy.

The purpose of the study was to investigate the clinical efficacy of azilsartanmedoxomil and indapamide in patients with grade 1-2 essential hypertension on cardiac and vascular remodeling as well as on intrarenal hemodynamic parameters and renal functional status.

Material and methods

The open prospective clinical trial enrolled 62 patients (32 men and 30 women) aged 40 to 65 years with AH and chronic kidney disease (CKD). Depending on the value of the The study group was divided into 3 groups depending on glomerular filtration rate (GFR): Group 1. (25 patients) - a GFR of 90 ml/min/1.73 m^2 or more (I stage of CKD), the 2nd group (22 patients) - a GFR of 89-60 ml/min/1.73 m^2 (II stage of CKD), Group 3. (15 patients) - a GFR of 59=45 ml/min/1.73 m^2 (III a stage of CKD). Azilsartanmedoxomil (Edarbi) was given as 40mg or 80mg tablets once a day based on target BP levels. Indapamide (Indap) 2.5 mg was prescribed once daily. Exclusion criteria were GFR less than 45 ml/min/1.73 m^2; diabetes mellitus; hyperuricemia; myocardial infarction and cerebral myocardial infarction and cerebral circulation disorder within the last 3 months; chronic liver and kidney diseases; oncological diseases.

In all patients, antihypertensive medications used before the study were discontinued 7 days before the study. In addition to standard laboratory tests (total blood count, serum creatinine, urea, hepatic transaminases, bilirubin, uric acid, glucose, potassium, sodium) we determined albumin content by immunoassay in the first morning portion of urine. Albumin excretion was expressed in milligrams per 1 liter of urine (30-300 mg/L is normal).

Doppler echocardiography was used to calculate end-diastolic systolic and end-diastolic size of left ventricle (LV), cardiac index (CI), LV ejection fraction and peripheral vascular resistance, left ventricular posterior wall thickness (LV PWT) and interventricularseptal thickness (IVT). Left ventricular hypertrophy (LVH) was diagnosed with myocardial mass index

value. Diastolic function of LV was studied by transmitral blood flow and maximum velocity of fast and slow blood flow (Ve, Va) and isovolumic relaxation time (IVRT) were calculated.

Quantitative processing of the results was carried out using of variation statistics using Statistica 6.0 and Excel for Windows. Data are presented as mean values (M) ± standard deviation (SD). Mean values of two independent samples with normal distribution of variables were compared using Student's t-test. Differences and correlations were considered significant at $p < 0.05$.

Results and discussion

Against the background of treatment, the most pronounced dynamics of LV structural and functional indices were observed in group 3, which is explained by significant LV shape abnormalities in the initial state (Table 1). Thus, in the 3rd group the cardiac index increased on average by 9.7% ($p < 0.05$), the ejection fraction increased by 12.7% ($p < 0.05$). In the 1st and 2nd groups, only transmitral diastolic blood flow significantly changed, indicating the improvement of active LV myocardial relaxation. Besides, the myocardial mass index reliably decreased in the 2ndand 3rd groups: by 14.7% ($p <0.05$) and 17.9% ($p <0.01$) on average, respectively. While in the 2nd group the LV wall thickness indices (LV WTI, IVST) decreased in general, in the 3rd group both the wall thickness and LV end-diastolic volume decreased in the 3rd group.

Table 1 Changes in structural and functional cardiac parameters with combined therapy of azilsartanmedoxomil and indapamide

(M ± SD)

Parameters	Group 1 (n = 25)		Group 2 (n = 22)		Group 3 (n = 15)	
BP, mm.Hg.	before treatment	after treatment	before treatment	after treatment	before treatment	after treatment
Systolic BP	163,7± 11,5	128,4±7,2***	166,7±10, 4	127,5±6,7	165,9±11, 6	132,6±7,1
Diastolic BP	103,2 ± 6,5	86,4±5,9***	104,6± 6,8	88,5± 5,4	104,2± 7,1	89,2 ± 6,0
Cardiac index, l/min/m^2	2,95 ± 0,21	3,01 ± 0,19	2,88± 0,17	2,95±0,18	2,67± 0,15	2,93± 0,17*
End-diastolic dimension LV, mm:	51,2 ± 0,6	49,8 ± 0,4	53,5±0,6	50,2 ± 0,5	58,3 ± 0,5	50,6 ± 0,4*
End-systolic dimension LV, mm:	30,8 ± 0,4	29,1 ± 0,4	35,6 ± 0,3	31,3± 0,4	35,6 ± 0,4	32,0 ± 0,4
LV WTI, mm	9,6 ± 0,4	9,6 ± 0,5	10,9 ± 0,7	9,6± 0,4*	11,8 ± 0,7	10,4± 0,6*
Fraction ejection fraction %	64,5 ± 4,6	62,1 ± 4,8	62,6 ± 5,1	62,2±5,5	56,1 ± 4,9	63,2± 5,0*
LVMI, g/m^2	112,6 ± 9,1	106,3 ± 7,9	120,8± 8,3	103,1±7,2 *	140,4±9,4	115,3±7,5 *

Note: the reliability of the difference between the indices before and after treatment in the groups: * - $p < 0.05$, ** - $p< 0.01$, *** - $p < 0.001$.

One of the early manifestations of hypertensive LV remodeling is its diastolic dysfunction, which often precedes the development of systolic heart failure. At baseline, transmitral flow spectrum in all groups corresponded to diastolic dysfunction caused by impaired active LV myocardial relaxation. Under the influence of treatment and as a result of decreased post-load and HLV regression, transmitral flow indices improved in all studied groups, especially in groups 2 and 3. Expressed structural changes of vascular wall and significant decrease of endothelial function were revealed in group 3 patients.

Microalbuminuria (MAU) is one of the early signs of renal dysfunction and is a factor in the progression of renal failure and cardiovascular mortality [12]. Our results confirmed that remodeling of intrarenal vascular system, endothelial dysfunction and increased resistance in interstitial arteries play the leading role in the genesis of MAU and decreased FFR [7, 12]. Thus, urinary albumin excretion significantly decreased in patients with MAU against the background of treatment in all groups. As a result, in the 1st group MAU disappeared in 4 (62.5%) patients, in the 2nd group - in 6 (57.1%), in the 3rd group - in 5 (44.4%). Decrease of MAU along with increase of GFR and improvement of endothelial function indicates a pronounced nephroprotective effect of azilsartanmedoxomil (Edarbi) and indapamide (Indapa) combination. In group 3 patients there were also revealed correlation relations of the parameters, characterizing the functional state of the kidneys, and the parameters intrarenal hemodynamics.

The investigation demonstrated an important role of intrarenal hemodynamic changes in assessing the severity of renal damage and cardiovascular remodeling in patients with AH. It has been shown that a decrease in GFR of less than 60 ml/min/1.73 m2 is associated with HLF and MAU. This once again emphasizes the commonality of risk factors and interdependence of subclinical cardiac and renal lesions in patients with AH, which mutually aggravate the long-term

prognosis [2, 4, 10]. The study showed that therapy with a combination of azilsartanmedoxomil (Edarbi) and indapamide (Indap) in patients with AH and reduced GFR significantly reduces the resistive characteristics of the interstitial renal arteries and improves vascular endothelial function and systolic heart function. In addition, urinary albumin excretion and the frequency of episodes of MAU. It should be noted that the pronounced organ-protective effects of azilsartanmedoxomil and indapamide are due to complementary pharmacological mechanisms of action that contribute to potentiation of the therapeutic effect and expansion indications for use [5,11].

In conclusion, azilsartanmedoxomil (Edarbi) is a new drug with high affinity for AT1 receptors that is registered in Uzbekistan for treatment of patients with AH. Indapamide (Indap) is a long-acting thiazide-like diuretic with proven favorable effect on cardiovascular prognosis in patients with AH in clinical trials. The combination of azilsartanmedoxomil and indapamide, combining good tolerability and ease of use, acts on cardiac and vascular remodeling and intrarenalhemodynamics and may be recommended for combination therapy in patients with AH,including those combined with CKD.

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