FEATURES OF MEDICAL CORRECTION OF ARTERIAL HYPERTENSION IN METABOLIC SYNDROME

I.A. Muminov

Assistant of the Inner diseases Department of Andijan State Medical Institute, Andijan city, Uzbekistan.
Ispandiyor Abduraximovich Mo'minov

Abstract. In article the literature review of an arterial hypertension in metabolic syndrome is presented. Antihypertensive and metabolic effects, positive influence on organs-targets (heart, vessels, kidneys) of inhibitors angiotensin-converting enzyme and antagonists of calcium are surveyed in metabolic syndrome.

Keywords: arterial hypertension, metabolic syndrome, inhibitors ACE, metabolic effects, organoprotection.

Currently, cardiovascular diseases (CVDs) are actual problem of world and national medicine. Leading place among this pathology belongs to arterial hypertension (AH) [1, 2], the prevalence of which in the world among the adult population is from 450 to 900 million (30-40%), and in Russia - more than 40 million people (39% of men and 41% of women) [2]. Every year, more than 3 million people worldwide die from its associated diseases and complications [2].

The prognosis becomes even more unfavorable with the combination of hypertension with metabolic disorders, which are based on insulin resistance (IR) [3]. Over the past decades, metabolic syndrome (MS) has been called the "epidemic of highly developed countries" due to the large prevalence. In the world, among the population over 30 years old, its frequency reaches 15–25% [4]; in Russia, about 20 million adults suffer from MS [5], and its prognostic significance is reflected in the name "deadly quartet" [6]. According to epidemiological studies, more than 50-70% patients with AH is combined with metabolic syndrome [7, 8].

In the classical sense, according to the International Diabetes Federation, MS implies a combination of abdominal obesity (AO), IR, hyperglycemia, dyslipidemia, hypertension, impaired hemostatic system and chronic subclinical inflammation, which are based on complex neurohumoral and hormonal disorders. De Fronzo [9] compared this condition with an iceberg, on the surface of which lie clinical manifestations - IHD, hypertension, obesity, diabetes mellitus (DM), etc.

Target organ damage and complications on their part dictate the need for early diagnosis and tighter control of arterial blood pressure in patients with metabolic syndrome. However, despite the urgency of the problem, adequate control of blood pressure can be achieved only in a small number of patients with hypertension [2]. Issues related to the diagnosis and treatment of patients with MS, including

antihypertensive therapy, are even more are complex and require changes in standard treatment regimens. Therefore, in the latest European guidelines for the control of hypertension, an important clinical significance of metabolic disorders and their correction during antihypertensive therapy [12].

The main objectives of the treatment of hypertension is not only to achieve the target level of blood pressure, but also to prevent damage. target organs, reducing the risk of associated clinical conditions and mortality [1]. Despite a wide range of drugs, effective control of blood pressure remains an urgent problem. In Russia, the real the effectiveness of treatment of arterial hypertension does not exceed 12% [2]. The multicomponent manifestations of MS complicates the choice of tactics for the medical correction of arterial hypertension. Antihypertensive drugs should have a prolonged effect during the day, normalize the daily blood pressure profile, promote the regression of target organ damage and have a metabolically positive and / or neutral effect. These requirements are fully met by angiotensin-converting enzyme inhibitors (ACE inhibitors) and calcium antagonists (CA) [3].

These classes of drugs effectively reduce blood pressure [13-15] and the risk of cardiovascular complications (CVS) [13, 16-20], positively affect carbohydrate and lipid metabolism [17, 20], as well as target organs [15, 21, 22].

Treatment of hypertension refers to the pathogenetic therapy of metabolic syndrome, because, as mentioned earlier, it can make a certain contribution to the formation and progression of this syndrome, being one of its main symptoms along with hyperinsulinemia and insulin resistance [23].

The goal of antihypertensive therapy is to achieve target blood pressure levels - less than 140/90 mm Hg. (and in patients with MS and diabetes mellitus - less than 130/80 mm Hg), especially DBP, since under this condition the smallest number of CCOs is observed [19, 23]. It has been established that the DBP level, at which CVD mortality is minimal, is 77–82 mm Hg. As DBP decreases further, CAD mortality increases again due to impaired myocardial perfusion [24]. The choice of the most effective drug depends on the leading pathogenetic mechanism of hypertension. The pathogenesis of arterial hypertension is complex, and various pressor systems are involved in maintaining a high level of blood pressure [25]. With metabolic syndrome along with activation of the sympathetic-adrenal system (SAS), the leading mechanisms of AH formation are activation of the renin-angiotensin-aldosterone system (RAAS) [26] and an increase in intracellular calcium concentration as a result of membrane pathology [26] and insulin resistance [3]. In addition, drugs should have a positive effect on target organs (heart, blood vessels, kidneys).

In the metabolic syndrome, it is necessary to take into account the effect of the antihypertensive drug on insulin sensitivity, carbohydrate and lipid metabolism.

Medications that are neutral to metabolic processes are preferred, even better if they will reduce IR and improve indicators of carbohydrate and lipid metabolism [23].

Thus, antihypertensive therapy in MS should be multipurpose and not only "break" the pathogenetic chain of hypertension, but also compensate for metabolic disorders, prevent early damage or contribute to the regression of target organ damage and reduce the overall CVD risk and mortality [12], as demonstrated in studies CAPPR and HOPE [17, 20]. From this point of view, ACE inhibitors and AKs can be considered drugs of choice for the treatment of arterial hypertension in MS. due to pronounced antihypertensive and organoprotective properties, metabolic neutrality, which has been proven in studies ALLHAT, CAPPR, HOPE, UKPDS, ABCD, FACET, ELSA and PREVENT, AASK, ELVERA [15–22, 27–29].

ACE inhibitors in the treatment of patients with metabolic syndrome

The effectiveness of ACE inhibitors in the treatment of arterial hypertension in the framework of MS is undeniable. There are two possible mechanisms of influence ACE inhibitors for metabolic disorders:

1) blockade of the formation of angiotensin II (AT II), leading to the elimination of the vasoconstrictor action, a decrease in the production of aldosterone and antidiuretic hormone and sodium and water retention in the body and vascular wall, suppression of the direct mitogenic effect of AT II, prevention and reduction of the degree of already existing hypertrophy and hyperplasia smooth muscle layer in the vessels and myocardium;
2) an increase in the level of bradykinin, a powerful endogenous vasodilator factor, leading to the formation of nitric oxide in the vascular wall, an endothelial relaxing factor, which enhances the vasodilating effect of ACE inhibitors and improves tissue sensitivity to insulin [30].
3) With monotherapy with ACE inhibitors, normalization or decrease in blood pressure were observed in 60–80% of patients with hypertension, including those associated with MS [3, 31]. In the metabolic syndrome, the antihypertensive effect of ACE inhibitors is reinforced by an improvement in glucose metabolism. Regarding the effect of ACE inhibitors on the sensitivity of tissues to insulin, the literature data are contradictory. Most studies show a positive their influence on IR. T. Pollare et al. against the background of 16 weeks of treatment with captopril, an improvement in stimulated glucose uptake was noted in patients with hypertension [32]. An increase in tissue sensitivity to insulin was also found during therapy with enalapril [31], fosinopril [33], cisalapril [34]. Other studies have proven their neutral effect on IR [35, 36]. In any case, none of the literature sources studied indications of the negative effect of ACE inhibitors on carbohydrate metabolism, which is important in the treatment of MS patients.

The hemodynamic basis of the action of ACE inhibitors is a decrease in total peripheral vascular resistance (OPVR) through the blockade RAAS, and the positive effect on carbohydrate metabolism can be explained by vasodilation leading to improved blood supply to skeletal muscles and, as a result, improved insulin-stimulated glucose transport in the muscles. Moreover, by indirectly reducing the production of norepinephrine and entry into the cell of calcium (the main intracellular "transmitter" constrictor signals), the mechanism of action of ACE inhibitors to some extent repeats the mechanism of action of AK [25]. Possibly decreased concentration calcium ions in the blood and an increase in magnesium ions during ACE inhibitor therapy is the reason for the decrease in IR, which is consistent with the theory of L. Resnik [37].

Along with such risk factors for CVD as arterial hypertension and violation of carbohydrate metabolism, in patients with MS, as a rule, dyslipidemia leading to rapid progression of atherosclerosis. Therefore, it is important that the drugs have no negative effects on lipid metabolism [3, 33, 36].

Initially, it was thought that ACE inhibitors reduce the level of AT II only in blood plasma. Later, the existence of so-called tissue RAAS was proved in the vascular endothelium, in the heart, kidneys, and adrenal glands [25]. It is the effect of ACE inhibitors on tissue RAAS that is associated with their organoprotective effects, which manifest themselves during their long-term use (starting from the 3rd–4th week of treatment) [25], cardio-, vaso- and nephroprotective, as well as metabolic.

The choice in favor of an ACE inhibitor should be made in the presence of hypertrophy left ventricular (LVH), since these drugs are the most effective in terms of LVH regression [34] due to the suppression of local RAAS activity. From literary sources it is known that in patients with AH the degree of reduction in the mass of the left ventricular myocardium (LVML) is determined by three main factors - the degree of reduction in SBP, the duration therapy and initial values of LVMM (Schmieder R., 1998). The VACS study (Gottdiener J., 1997) found that a decrease in LVMM was observed during treatment with captopril in subgroups of patients with severe LVH (with MMLV more than 350 g). In less severe LVH, antihypertensive drugs had no significant effect on LVMM. The literature provides different data on the degree of regression of LVH on during treatment with ACE inhibitors - from 12 to 38.6% [38, 39].

A number of works demonstrate the contribution of remodeling and increased arterial stiffness in the progression of CVD and their significance as independent predictors of cardiovascular mortality [40]. Arterial hypertension and especially MS increase the stiffness of large arteries, which is obviously due to the direct and indirect effect of GI on the vascular system. wall [3, 41].

The ability of ACE inhibitors to cause regression of vascular remodeling is discussed in a number of publications [33, 41, 42]. In some works, it is noted that the improvement in arterial compliance may be due not only to a decrease in systemic blood pressure, but also an improvement in the structural properties of blood vessels [41]. There is evidence of a positive effect of ACE inhibitors on the vascular wall (through normalization of endothelial function) [33, 42]. The largest number information has been accumulated regarding the positive effects on stiffness arteries [43]. The COMPLIOR study [41] deserves special attention. the results of which showed that a three-month intake of perindopril led to the normalization of the compliance of large muscle-type arteries (the stiffness of the arteries decreased and the rate of propagation of pulse wave (PWV). at the Research Institute of Cardiology. A. L. Myasnikov in the background 6-month treatment with enalapril revealed a trend towards a decrease in stiffness and an increase in vascular compliance [44].

ACE inhibitors reduce proteinuria without changing systemic AD, blocking the formation of AT II and expanding predominantly efferent arterioles. Thus, they reduce intraglomerular pressure and glomerular permeability to protein. The positive effect of ACE inhibitors on microalbuminuria (MAU) has been shown in the Micro-HOPE, ABCD, CAPPP, FACET [16, 17, 18, 45] and in other studies [46].

Most of the research is devoted to the study of enalapril and captopril. They are often compared to each other and to others. groups of antihypertensive drugs, in particular with amlodipine. However the most promising for the treatment of hypertension in metabolic syndrome are prolonged forms of ACE inhibitors, which include spirapril (Quadropril®, Pliva, Croatia). Spirapril is a prodrug of an ACE inhibitor. without a sulfhydryl group, a carboxyl-containing drug. Biotransformation takes place in the liver to the active metabolite - spiraprilat with the help of specific esterases, which allows for the gradual development of the hypotensive effect without a sharp decrease in blood pressure. The maximum concentration of spirapril in the blood occurs within an hour. Plasma protein binding is 86-91%, the half-life is about 40 hours, what causes a 24-hour action with a single dose; excreted from the body by the kidneys and liver (50/50). Spiraprilat binds strongly to ACE, which determines the long half-life. Main pharmacological effects are a decrease in OPSS, suppression RAAS and SAS.

The high antihypertensive efficacy of spirapril has been documented in many clinical studies [13, 47, 48]. According to I. Schmidt et al., the effectiveness was 89.4% for SAD and 85.4% for DBP [49]. Some studies have shown a smooth (biphasic) decrease in SBP and DBP [47, 49, 51], others have shown a more significant decrease in DBP. [49]. In a comparative study of spirapril and amlodipine in patients with hypertension a comparable antihypertensive effect on

SBP and DBP was obtained, with a stable effect of spirapril and a weakening of the effect of amlodipine by the eighth week of treatment [50]. In addition, spirapril is positive [48] or neutrally [51] influenced carbohydrate and lipid metabolism, had proven cardioprotective, nephroprotective [48, 51] and vasoprotective [104] effects, reduced the risk of CVD by 50% (PROLOG study) [13].

Thus, all of the above allows you to successfully apply ACE inhibitors for the treatment of hypertension with metabolic disorders.

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