

EFFECTIVENESS OF COMBINED TREATMENT OF ARTERIAL HYPERTENSION WITH DRUGS FROM THE GROUP "ANGIOTENSIN II RECEPTOR ANTAGONISTS" AND "CALCIUM CHANNEL BLOCKERS"

Nuraliyeva Rano

Samarkand State Medical University

Assistant of the Department of Clinical Pharmacology

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Abstract. *According to epidemiological studies, the prevalence of arterial hypertension (AH) among adults in developed countries ranges from 20 to 40% and increases with age [1]. High blood pressure occurs in more than 50% of men and women over the age of 60 [2]. The urgency of the problem is supported by the increasing urbanization processes of society, which create preconditions for the emergence of risk factors (RF) such as stress, physical inactivity, obesity, bad habits and disturbed ecology. High blood pressure is one of the main risk factors for the development of cerebral strokes, cardiovascular diseases (CVD) and other cardiovascular diseases of atherosclerotic origin, which are associated with more than 50% of all deaths. [3].*

Keywords: *combination antihypertensive therapy multiple benefits, dihydropyridine BMCC + diuretic + beta-blocker.*

Clinical practice and the results of many multicenter studies [4-6] have shown that the use of monotherapy in the treatment of hypertension rarely leads to the target levels of blood pressure, increases the risk of adverse events, and reduces the patient's adherence to treatment. The use of drugs in a rational combination regimen requires compliance with a number of mandatory conditions: safety and effectiveness of the components; the contribution of each component to the expected result; different but complementary mechanisms of action of the components; the best result compared to each of the components; balance of components in terms of bioavailability and duration of action; strengthening of organoprotective properties; effect on the universal (most common) mechanisms of blood pressure increase; decreased adverse events and improved tolerability [7-9]. According to the modern national recommendations [10], the recommendations of the European Society of Arterial Hypertension (EOH) and the European Society of Cardiology (ESC) [11], the tactics of treating essential hypertension depend on the level of blood pressure and the level of blood pressure. risk of cardiovascular complications. The main goal of treatment is to reduce the risk of cardiovascular complications (CVD) and death from them. The main goals are to prevent complications, to prevent adverse reactions (ADRs) in the absence or to a minimum, to correct all modifiable risk factors (smoking, dyslipidemia, hyperglycemia, obesity), prevent, slow down to normalize the level of blood pressure. reducing the rate of progression and/or damage to organs - goals, as well as treatment of joint and concomitant diseases - coronary artery disease, diabetes mellitus (DM), etc. [10, 11]. When treating patients with hypertension, blood pressure should be below 140/90 mm Hg. Art., this is its goal level. If the prescribed therapy is well tolerated, lowering the blood pressure to lower values is recommended. Blood pressure should be reduced to 140/90 mm Hg in patients with high and very high risk of cardiovascular diseases. Art. or less in 4 weeks. In the future, with good tolerance, it is recommended to reduce blood pressure

to 130/80 mmHg. Art. and less. Blood pressure should be reduced to a target value of 130/85 mm Hg in patients with coronary artery disease. Art. In patients with diabetes and/or kidney disease, the target blood pressure level should be below 130/85 mmHg. Art. [10]. Of course, the treatment of hypertension should begin with lifestyle changes: reduce excess body weight, limit salt and alcohol consumption, increase physical activity, etc. Limiting the consumption of table salt is a fairly effective way to lower blood pressure. Limiting table salt intake has been shown to enhance the antihypertensive effects of many antihypertensive drugs, including AT1-angiotensin receptor blockers and β -blockers.

One of the most important conditions for ensuring adequate control of blood pressure and increasing the patient's adherence to treatment is the optimal selection of an antihypertensive drug as part of mono- or combined pharmacotherapy. Five main classes of antihypertensive drugs are currently recommended for the treatment of hypertension [10]:

1. angiotensin-converting enzyme inhibitors (ACE inhibitors) (captopril, enalapril, perindopril, lisinopril, fosinopril, quinapril, trandolapril, etc.);
2. AT1 receptor blockers (ARB) (valsartan, losartan, telmisartan, candesartan, irbesartan, etc.);
3. slow calcium channel blockers (SCBC) (nifedipine, amlodipine, etc.);
4. beta-blockers (BAB) (carvedilol, bisoprolol, nebivolol, metoprolol tartrate, metoprolol succinate, atenolol, etc.);
5. thiazide and thiazide-like diuretics (hydrochlorothiazide (HCTZ), indapamide).

As additional classes of antihypertensive drugs for combined therapy, α -blockers (prazosin, doxazosin), imidazoline receptor agonists (moxonidine) and direct renin inhibitor (aliskiren) can be used. According to these national recommendations [10], the choice of an antihypertensive drug should be based on its effect properties belonging to a certain class, because currently the results of clinical studies are conducted according to the rules of evidence-based medicine. made it possible to establish cases of selection of a preferential class of drugs. When choosing an antihypertensive drug, first of all, it is necessary to evaluate the effectiveness, side effects and benefits of the drug in a specific clinical situation (Table 1).

The choice of drug is influenced by many factors, the most important of which are:

- the patient has a risk factor;
- damage to target organs;
- concomitant clinical conditions, kidney damage, MS, diabetes;
- concomitant diseases that require prescribing or limiting the use of various antihypertensive drugs;
- previous individual reactions of the patient to different classes of drugs;
- the possibility of interaction with drugs prescribed to the patient for other reasons;
- socio-economic factors, including the cost of treatment.

Treatment should be started with the use of one drug in the minimum daily dose (this recommendation does not apply to patients with severe hypertension or in whom previous therapy was ineffective). The use of new drugs should be started with the use of low doses, the goal of each subsequent stage of treatment should be to reduce the level of blood pressure by 10-15% [10]. If the blood pressure does not fall to the required level, further treatment is carried out gradually - gradually - by increasing the doses or adding new drugs. Ineffective drugs (do not reduce blood pressure by 10-15 mm Hg) and drugs that because ADR should be replaced [12]. There are no

single recommendations about which drugs should be used to start the treatment of the patient. The choice of drugs depends on age, gender and the presence of concomitant diseases. Currently, drugs that alter RAAS activity are used in the treatment of most patients with hypertension. These are ACE inhibitors, beta-blockers and angiotensin II receptor blockers (ARBs). ARBs are one of the modern and most dynamically developing classes of antihypertensive drugs. ARBs block the effects of angiotensin II through the AT1 receptor. It was found that hypersecretion of angiotensin II leads not only to the development of hypertension, but also to the damage of target organs, which is one of the main factors in the development of hypertension and its complications, which is remodeling of the heart and blood vessels. It is no coincidence that AT1-angiotensin receptor blockers are classified as the main antihypertensive drugs. Many controlled studies such as LIFE, VALUE, MARVAL, PRIME, IDNT, DETAIL [13] have shown that AT1 blockers are effective and safe antihypertensive drugs. AT1-angiotensin receptor blockers have been shown to be particularly effective in preventing the development of stroke. To prevent stroke in patients with hypertension, AT1 blockers can be used instead of diuretics or calcium antagonists, or in combination with them. ARBs such as ACEIs also prevent the development of type 2 diabetes and reduce its risk by 20-25% [14]. Therefore, it can be assumed that AT1-angiotensin receptor blockers should be used primarily for the treatment of hypertension in patients at high risk of developing stroke or diabetes. The undoubted advantage of AT1 blockers during long-term antihypertensive therapy is excellent tolerance. The use of AT1-angiotensin receptor blockers can improve patient compliance with long-term therapy, since ARBs are less likely to be discontinued due to the development of side effects than other antihypertensive drugs. Unlike thiazide diuretics, beta-blockers and ACE inhibitors, the antihypertensive efficacy of AT1-angiotensin receptor blockers does not depend on the age, gender or race of patients [15].

The renin-angiotensin-aldosterone system (RAAS) plays a central role both in the development of hypertension and in the implementation of pathophysiological processes that lead to serious complications of the cardiovascular system, for example, brain strokes, myocardial infarction, remodeling of blood vessels, nephropathy, congestive heart failure. and the development of atherosclerotic processes. ACE inhibitors are the first group of drugs that directly affect the RAAS, and they are widely introduced into clinical practice. The long period of their use, many clinical studies and the great experience of practicing doctors in their use have led to the fact that these drugs are currently used more often in Russia than other antihypertensive drugs. At moderate doses, ACE inhibitors lower SBP to a slightly lesser extent than diuretics and calcium antagonists. Choosing a specific ACEI for long-term therapy in patients with hypertension is of important clinical importance, since these drugs are mainly prescribed for life. Perindopril and ramipril seem to be the most promising of the ACE inhibitors with proven efficacy [16, 17].

Clinical practice and the results of many multicenter studies have shown that the use of monotherapy in the treatment of hypertension rarely leads to the target level of blood pressure, increases the risk of adverse events, and reduces the patient's adherence to treatment. The most important conditions for increasing the adherence of patients to treatment are their goals, tasks, understanding of modern methods and principles of treatment, as well as the correct selection of antihypertensive treatment by the doctor. At the beginning of treatment, the strategy of using combination therapy with the selection of drugs with different mechanisms of action gives more chances to successfully control blood pressure. Low-dose combined rational antihypertensive therapy can be the first-choice measure, especially in patients with a high risk of developing

cardiovascular complications, its advantages include: a simple and convenient dosing regimen for the patient; facilitate titration; ease of prescribing the drug; increase patient adherence; reduction of negative effects by reducing the doses of the components used; reduce the risk of using irrational combinations; confidence in the optimal and safe dosing regimen; decrease in price [17–21].

It should be noted that the latest American and European recommendations, if possible, emphasize the need to avoid the tactics of frequently changing drugs and their doses in patients. Now it is clear that the effectiveness of monotherapy with drugs of all main groups is low and comparable: after one year of treatment, even with almost perfect adherence to treatment, the effect of monotherapy does not exceed 50% compared to almost 30% with placebo. . In fact, the "sequential monotherapy" tactic may require 4-5 changes in therapy, each of which may be complicated by the development of side effects. This tactic takes a lot of time, deprives the doctor and the patient of confidence in success, which ultimately has a negative psychological effect on the patient and leads to low adherence to hypertension treatment. One of the common reasons for unsatisfactory blood pressure control is the underestimation of the role of combination therapy [17-21].

Combined antihypertensive therapy has many advantages:

due to the multidirectional effect of drugs on the pathogenetic mechanisms of the development of hypertension, strengthening the antihypertensive effect, which increases the number of patients with a stable decrease in blood pressure;

reduction of side effects both due to low doses of combined antihypertensive drugs and due to mutual neutralization of these effects;

provide the most effective protection of organs and reduce the risk and number of cardiovascular complications.

Many randomized clinical trials and actual clinical experience have shown all the advantages of combined therapy, which can be summarized as follows [22, 23]:

simultaneous use of drugs from two different pharmacological groups reduces blood pressure more actively due to the effect on different pathogenetic mechanisms of hypertension;

the combined use of low doses of two drugs acting on different regulatory systems allows better control of blood pressure, taking into account the heterogeneity of the response of hypertensive patients to antihypertensive drugs;

the appointment of a second drug may weaken or balance the activation of mechanisms to counteract the decrease in blood pressure that occurs when the appointment of one drug;

a stable decrease in blood pressure can be achieved with small doses of two drugs (compared to monotherapy);

smaller doses make it possible to avoid dose-dependent side effects, the probability of which is higher with a large dose of a certain drug (during monotherapy);

the use of two drugs prevents damage to target organs (heart, kidneys) due to hypertension;

prescribing the second drug can reduce (and even completely eliminate) the unwanted effects caused by the first (even if it is very effective);

Prescribing a second drug (in particular, a diuretic) allows you to get a quick antihypertensive effect of the combination of drugs, since most antihypertensive drugs (ACE inhibitors, CCBs, ARBs, and partially beta-blockers) have their full effect only after 2 show in the stage. - 3rd week. acceptance (and beyond). The combination of two antihypertensive drugs is

divided into rational (effective), possible and irrational. All the advantages of combined therapy are characteristic only of a rational combination of antihypertensive drugs [24].

ACE inhibitor + diuretic;
ARB + diuretic;
ACEi + dihydropyridine BMCC;
ARB + dihydropyridine BMCA;
dihydropyridine BMCC + BAB;
dihydropyridine BMCC + diuretic;
beta-blocker + diuretic;
BAB + α -adrenergic blocker.

The question of combining three or more drugs has not yet been sufficiently studied, since there are no results of randomized controlled clinical studies studying the triple combination of antihypertensive drugs. Thus, antihypertensive drugs in these compounds are combined on a theoretical basis. However, in many patients, including those with refractory hypertension, target blood pressure can be achieved with only three or more components of antihypertensive therapy [25]. Recommended combinations of three antihypertensive drugs include:

ACE inhibitor + dihydropyridine BMCC + beta blocker;
ARB + dihydropyridine BMCA + BAB;
ACE inhibitor + BMCC + diuretic;
ARB + BMCC + diuretic;
ACE inhibitor + diuretic + beta blocker;
ARB + diuretic + beta blocker;
dihydropyridine BMCC + diuretic + beta-blocker.

Since combination therapy has become one of the main areas of treatment for patients with hypertension, the inpatient combination of antihypertensive drugs with two drugs in one pill has become widespread, which improves the patient's psychological response to treatment and reduces the risk of the disease. complications and side effects. The optimal combination of components means that there is no unwanted hypotension, which leads to increased cardiovascular risk, especially in elderly patients. Reasonable selection of components according to their pharmacokinetic profile creates the necessary conditions for single use of drugs that are required twice or three times in monotherapy.

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