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Review Article / Преглед литературе

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Fixed combination of bisoprolol and a low-dose hydrochlorothiazide in arterial hypertension

Фиксна комбинација бисопролола и хидрохлортиазида у малој дози у лечењу артеријске хипертензије

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SUMMARY

Beta-blockers showed better results in lowering elevated blood pressure in younger age group of patients with higher renin plasma levels. Actual recommendations from European Society of Cardiology for treatment of arterial hypertension from the year 2013, insist that heart rate should be always measured along with measurement of blood pressure. These recommendations point out the significance of resting heart rate as an independent predictor of cardiovascular morbidity and mortality in patients with arterial hypertension. Beta-blockers have a compelling indication for treatment of arterial hypertension in patients with coexistence of coronary artery disease, especially post myocardial infarction, as well as in patients with systolic heart failure. Bisoprolol, a highly selective beta-blocker with a long half-life and a prolonged antihypertensive effect, has shown a consistent blood pressure control over the period of twenty-four hours.

It has been demonstrated in placebo control studies that administration of thiazide diuretics, besides lowering blood pressure levels, had been also associated with a reduction of cardiovascular morbidity and mortality rates. It is evident that effectiveness of thiazide diuretics is dose-dependent; however, undesirable effects of drug are also dose-dependent. Depending on dose, they aggravate glucose intolerance, increase lipids levels, cause hypokalemia, hyponatremia and hypomagnesemia, and increase levels of uric acid. The administration of very low dose of the thiazide diuretic is absolutely acceptable in combination with other antihypertensive drugs, because it potentiates action of other drugs without causing undesirable metabolic effects. The effectiveness and safety of combination of bisoprolol (in various doses) and a thiazide diuretic in a small dose is proved in clinical trials.

Keywords: hypertension, drug therapy; antihypertensive agents; administration & dosage; beta-blockers; bisoprolol; thiazides;

САЖЕТАК

Бета блокатори имају бољи учинак у смањењу повећаног крвног притиска код млађих болесника са вишим нивоом ренина у плазми. Актуелне препоруке европског удружења кардиолога за лечење артеријске хипертензије из 2013 године предлажу да се увек уз мерење крвног притиска одредјује и срчана фреквенција. Ове препоруке истичу значај срчане фреквенције у миру, као независног предиктора кардиоваскуларног морбидитета и морталитета болесника са артеријском хипертензијом. Посебан разлог за увођење бета блокатора у терапију артеријске хипертензије представља постојање придружене коронорне болести, као и систолне срчане инсуфицијенције. Бисопролол је високо селективни бета блокатор са дугим полуживотом у плазми и продуженим антихипертензивним учинком, који показује конзистентну контролу крвног притиска у току двадесет четри часа.

У плацебо контролисаним студијама показано је да је примена тиазидних диуретика поред редукције висине артеријског притиска повезана са смањењем кардиоваскуларног морбидитета и морталитета. Евидентно је да је ефикасност тиазидних диуретика дозно зависна, међутим дозно зависни су и нежељени ефекти лека. Они дозно зависно погоршавају интолеранцију глукозе, повећавају ниво липида, узрокују хипокалемију, хипонатремију и хипомагнезиемију и повећавају ниво мокраћне киселине. Примена веома ниске дозе тиазидног диуретика, је прихватљива у комбинацији са са другим антихипертензивима зато што она потенцира деловање других лекова без изазивања нежељених метаболичких ефеката. Ефикасност и сигурност комбинације бисопролола (у различитим дозама) и тиазидног диуретика у малој дози је доказана у клиничким студијама.

Keywords: хипертензија, лечење; антихипертензивни лекови, ординирање; бета блокатори; бисопролол; тиазиди;

INTRODUCTION

The main treatment goal in patients with arterial hypertension is normalization of blood pressure levels, prevention, stopping or regression of the target organs damages, with the ultimate goal to decrease cardiovascular morbidity and mortality rate. Under normalization of blood pressure levels, we consider a decrease to less than 140/90 mmHg, and to less than 140/85 mmHg in patients with diabetes mellitus respectively. However, this goal is very difficult to achieve for the most of the

patients. According to results from BP CARE study, in which 7,860 patients from Central and Eastern Europe, treated for arterial hypertension, were included, it was found that satisfactory control of blood pressure was achieved in only 27.1%. According to that study, target blood pressure levels were reached in 23.3 % of the patients in Serbia. [1]. Possible reasons for treatment failure are physicians' inertia on the one hand, and patients' low awareness of the problem severity and significance of adherence to advised treatment, on the other hand. Therapeutic inertia is reflected in satisfaction with achieved reduction without normalization of blood pressure values, and in insisting on monotherapy.

Administration of more than one antihypertensive agent is advised in the international guidelines, for patients with systolic blood pressure that is 20 mm Hg higher, and diastolic one that is 10 mm Hg higher than border levels, as well as in patients with high level risk due to associated risk factors and subclinical damages of target organs, diabetes mellitus, associated cardiovascular or kidney disease. The best evidence in favour of benefits of combined therapy are results of a meta-analysis in which 42 studies (10,968 patients) were included, and which showed that combination of two antihypertensive agents lowered arterial blood pressure five times better than maximal dose of one drug [2]. It is possible to achieve the desired effectiveness by combining medicaments with different mechanism of action due to their synergistic action. Fixed combinations of diuretics and system renin – angiotensin - aldosterone inhibitors or beta-blockers are useful, because they ensure numerous benefits, starting with better blood pressure control, a simplified dosage regime, and improvement of compliance with reduction of dose - dependent undesirable effects.

The objective of this paper is to summarize advantages of fixed combination of bisoprolol and a low dose thiazide diuretic administration.

BETA-BLOCKERS IN THERAPY OF ARTERIAL HYPERTENSION

Ten years follow-up of 3,195 healthy persons with average age of 48.5 years in Framingham Heart Study [3] has shown that overweight younger men, especially if they continue to further gain weight, predominantly develop diastolic arterial hypertension. Isolated systolic hypertension in older patients was found more often in women, and usually occurred in persons with history of normal or high-normal blood pressure. It has been found that heart rate, as well as minute volume, and peripheral vascular resistance as well, were increased in proportion with body mass index and waist circumference [4]. Sympathetic neural activity in skeletal muscles, the index of sympathetic nervous system activation, increases in proportion with waist circumference and abdominal fat tissue mass [5]. Abdominal adipocytes cause sympathetic nervous system activation trough leptin production. An increased sympathetic tone leads to an increase in renin and angiotensin II production, which in return, additionally activate sympathetic nervous system trough feedback. Abdominal adipocytes stimulate an increase in interleukin 6 and tumor necrosis factor alpha trough adipokine, and cause development of increased insulin resistance. An increase in insulin level occurs with additional

feedback activation of sympathetic nervous system. In this manner, central obesity and an increased leptin production increase catecholamines plasma levels with unfavorable effects on heart and blood vessels.

The increased sympathetic nervous system activation leads to an increase in heart rate and an increased strentgh of the myocardial contraction, and causes an increase in ventricular stroke volume and an increase in minute volume (minute volume is equal to the product of heart rate and stroke volume). The elevated adipokines, interleukin 6 and tumor necrosis factor alpha levels, intensify oxidative stress and cause development of endothelial dysfunction and inflammation [6]. The disorder of endothelial function is the underlying cause of inadequate vasodilatation of the arterioles in response to metabolic stimuli and an increased peripheral vascular resistance. In addition to functional component, an anatomical substrate of an increased peripheral vascular resistance develops. Hypertrophy of small arteries' and arterioles' media develops at the expense of lumen reduction; this is an anatomical change, which is the underlying cause of development and progression of diastolic arterial hypertension and is referred to as eutrophic remodeling of small resistant arteries. The activation of sympathetic nervous system causes a development and a progression of arterial hypertension trough a increment of minute volume and peripheral vascular resistance. It has been demonstrated that in treatment of arterial hypertension, beta-blockers showed better results in lowering elevated blood pressure in younger age group of patients with higher renin plasma levels [7]. Older patients with lower renin levels show a better therapeutic response to calcium antagonists [8]. It has been found that highly selective beta-blocker bisoprolol, in a group of male patients, age between 35 and 60 years, and with moderate hypertension, showed a better results after four weeks of treatment, compared to drugs from other groups of antihypertensive agents [9]. In these patients, monotherapy with bisoprolol with daily dose of 5 mg showed a better efficacy in lowering both systolic and diastolic blood pressure compared with treatment with losartan 50 mg, amlodipine 5 mg, or hydrochlorthiazide 25 mg once a day. The strategy for arterial hypertension treatment in earlier guidelines was based on assessed sympathetic nervous system activity degree [10, 11, 12]. In younger patient with arterial hypertension and increased sympathetic tone and higher renin plasma levels, drugs with antiadrenergic effects were recommended for initiation of hypertension treatment: beta-blockers and ACE inhibitors, or angiotensin receptor blockers. Diuretics and calcium antagonists (ABCD treatment strategy for arterial hypertension) were recommended as an initial therapy for elderly patients with lower rennin levels.

While comparing antihypertensive effects of bisoprolol and atenolol in a single daily dose by using method of ambulatory blood pressure monitoring, bisoprolol showed a better blood pressure control in 659 patients with mild to moderate hypertension during the entire period of twenty-four hours follow-up. A greater efficacy of bisporolol was exhibited especially in the last hours of twenty-four hours interval, in the morning of the following day, before the next scheduled dose of the drug

[13]. For consistent blood pressure control during time-period of twenty-four hours, it is necessary to use a medicament with longer elimination half-life and higher minimal to maximal effect ratio as a monotherapy. As opposed to atenolol, which has average elimination half-life of 6-7 hours and minimal to maximal effect ratio of 31%, the highly selective beta-blocker bisoprolol has elimination half-life of 10-12 hours and minimal to maximal effect ratio of 78%. Under current FDA criteria for approval of a single daily dose drug for treatment of arterial hypertension, minimal to maximal effect ratio over the period of twenty-four hours, must be higher than 50%. Blood pressure values in the early morning hours, prior to taking the next dose for the following day, is of particular importance. At that time of the day, a pronounced increase in sympathetic nervous system activity and an increased catecholamines level occur with awakening and beginning of daily activities. At that time, a sudden increase in hart rate and blood pressure is recorded, and an increased frequency of ischemic episodes, both symptomatic as well as asymptomatic ones, is also registered in patients with coronary disease at that time. In the early morning hours, after awakening, a higher frequency of sudden cardiac death, as well as ischemic stroke, is recorded. Bisoprolol, a beta-blocker with a long half-life and a prolonged antihypertensive effect, and a consistent blood pressure control over the period of twenty-four hours, has shown a reduction of ischemic episodes in patients with coronary artery disease in the early morning hours [14].

HEART RATE AND CARDIOVASCULAR MORTALITY

In a study with 2,037 men with untreated arterial hypertension, and thirty-six years follow-up, it has been found that elevated resting heart rate at a baseline increased the risk of mortality [15, 16]. It has been demonstrated that elevated resting heart rate increased the risk of mortality from coronary artery disease, the risk of cardiovascular mortality, but, also the risk of overall mortality. It has been reported that resting heart rate higher than 84 beats per minute at baseline, had been associated with an increased mortality, compared to lower heart rate levels. It has been confirmed in a study with elderly patients with arterial hypertension that elevated resting heart rate at baseline increased the risk of mortality. This has been demonstrated as in men, as well as in women [17]. Patients with arterial hypertension and resting heart rate over 79 beats per minute, have the greater risk of mortality by 89%, in comparison with patient with heart rate lower than 79. It has been found, trough follow-up of 5,713 asymptomatic men over the period of 23 years, that elevated resting heart rate at the baseline increased the risk of sudden cardiac death, and the risk of mortality from myocardial infraction as well [18].

An analysis of risk factors has shown that in addition to classic risk factors for atherosclerosis, resting heart rate values in men had an independent significance as a predictor of mortality risk [19]. Heart rate higher than 80 beats per minute, along with classic risk factors: systolic and diastolic blood pressure, diabetes, smoking and age, indicates an increased risk of mortality. Actual recommendations

from European Society of Cardiology for treatment of arterial hypertension from the year 2013, insist that heart rate should be always measured along with measurement of blood pressure [20]. These recommendations point out the significance of resting heart rate as an independent predictor of cardiovascular morbidity and mortality in patients with arterial hypertension. [21].

An elevated heart rate increases myocardial oxygen demand, and may cause occurrence of myocardial ischemic episodes in patients with coronary disease. It is less known that an elevated heart rate accelerates progression of atherosclerosis, predisposes occurrence of a vulnerable atheroma rupture and development of acute coronary syndrome. An increased activation of sympathetic nervous system has unfavourable effects on heart and stimulates hypertrophy of the left ventricle in patients with arterial hypertension. A sudden increase in catecholamines plasma level may even lead to direct toxic myocardial lesion, with an increase in markers of myocardial necrosis level. An excessive sympathetic stimulation may have initiation of apoptosis of myocardial cells as a result. An elevated sympathetic nervous system tone increases frequency of disorders of heart rhythm and lowers threshold for occurrence of malignant arrhythmias.

Secondary prevention with beta-blockers reduces cardiac mortality rate in patient with history of myocardial infarction. A meta analysis of 12 studies has shown that each 10 beats per minute reduction in heart rate reduce the cardiac mortality rate by 26% on an annual basis [22]. It has been also demonstrated that an excessive neurohumoral stimulation had an unfavourable effect on patients' prognosis in patients with heart failure. An increased sympathetic activation accelerates dilatation of the left ventricle, intensifies remodeling of the ventricle and aggravates heart failure. A meta analysis of a larger number of studies with patients with heart failure has shown an unfavourable effect of elevated resting heart rate on an increased patients mortality rate [23]. Guidelines for treatment of systolic heart failure propose beta blockers bisoprolol, carvedilol and metoprolol succinate as a chronic treatment. It has been demonstrated that these drugs exhibit a prognostic effect and reduce mortality of patients with heart failure. It has been found that the risk from cardiovascular mortality in such patients had been decreased in proportion with reduction in resting heart rate [23].

ACE inhibitors, angiotensin receptor blockers and calcium antagonists in therapy of arterial hypertension have shown a better effect on reduction of cardiovascular risk in a larger number of studies. In studies, the most common comparator from beta blockers group was atenolol, a moderately selective beta-blocker. Atenolol, with its shorter elimination half-life, in a single daily dose, could not maintain a consistent antihypertensive effect during the period of twenty-four hours. As opposed to highly selective beta-blockers and vasodilating beta-blockers, atenolol has shown a weaker effect and has had a lower efficacy in reduction of central arterial pressure in population of patients of an advanced age. Because of that, some more recent guidelines from national and international cardiology associations have diminished the role of beta-blockers in initiation of treatment of uncomplicated arterial hypertension. The new American JNC 8 guidelines for treatment

of arterial hypertension emphasize that in making recommendation only the most recent clinical studies have been included [24]. Nowadays widely used beta blockers, with expired patents' protection, have not been studied in new mega trials of arterial hypertension treatment, and it is required to limit treatment concerns to earlier comparators from beta-blockers group, which were studied in the older trials. This is also the case with the current European Society of Cardiology guidelines for treatment of arterial hypertension from the year 2013. In these recommendation, from beta-blockers group, vasodilating beta – blockers and highly selective beta blockers with a better blood pressure regulation profile, better metabolic effects and more effective reduction of the cardiovascular risk, stand out [25].

THE ADVANTAGES OF A LOW DOSE THIAZIDE DIURETIC ADMINISTRATION

The use of thiazide diuretics started in the late fifties. Since then, they have remained one of the most significant groups of drugs for lowering blood pressure due to their effectiveness and low cost. Their primary mechanism of action is inhibition of Na-Cl cotransporter in the renal distal convoluted tubules and adjacent nephron segments. This inhibition initially leads to a diuretic effect, which causes a reduction of plasma volume and decreased blood pressure. After continuation of therapy, a partial restitution of blood volume occurs, and the vasodilating mechanism based on opening of the ATP - potassium sensitive channels is responsible for continuation of antihypertensive action.

The effectiveness of thiazide diuretics in blood pressure regulation is shown in comparison with placebo and other antihypertensive agents. It has been demonstrated in placebo control studies that administration of thiazide diuretics, besides lowering blood pressure levels, had been also associated with a reduction of cardiovascular morbidity and mortality rates. A meta-analysis of these studies has proved that low dose of a diuretic reduced overall mortality rate by 10%, stroke risk by 29%, decreased heart failure risk by 49% and cardiovascular disease risk by 24% [26]. It has been demonstrated at the same time, that neither group of antihypertensive agents, with which they had been compared (beta blockers, ACE inhibitors, potassium channel blockers, alpha blockers and AT1 receptor blockers), had not been significantly better than thiazide diuretics administered in low doses. Numerous randomized studies have determined that thiazide diuretics, in addition to efficient blood pressure regulation, also reduced risk from coronary events, strokes and heart failure in the elderly [27, 28]. The ALLHAT study has shown that a thiazide diuretic was equally efficient as an ACE inhibitor and a calcium channel blocker in coronary and cerebrovascular events prevention, and that it was more efficient than a calcium channel blocker in heart failure prevention, and more efficient than an ACE inhibitor in stroke prevention [29].

There are disagreements about existence of differences in effectiveness of individual thiazide diuretics. In the MRFIT study, patients were treated with chlorthalidone or hydrochlorothiazide (HCTZ), depending on clinical centers' experiences. After 7 years, Advisory Committee

recommended chlorthalidone for use in all treated patients with a thiazide diuretic, on the basis of an unfavorable mortality trend in patients treated with HCTZ in 9 centers, in comparison with a favorable trend registered in patients treated with chlorthalidone in 6 centers [30]. A meta analysis and a mini-study conducted in one centre, in which effectiveness of administered diuretics was studied during 24-hours ambulatory monitoring, confirmed the advantage of chlorthalidone in comparison with HCTZ [31, 32]. More complete data on effectiveness of individual thiazide diuretics (bendrofluazide, cyclopenthiazide, indapamide, hydrochlorothiazide, chlorthalidone, metazolone) were obtained in the the Cochrane analysis [33]. 60 double-blind placebo controlled studies published until February 2014 were included in the stated analysis. The analysis comprised 11,282 patients with average age of 55, out of which 53% were male. The mean blood pressure in the subjects was 158/99 mm Hg. A similar effectiveness of studied thiazide diuretics was found. In general, systolic blood pressure was reduced by 9 mm Hg, and diastolic by 4 mm Hg in comparison with placebo group. The most information about HCTZ was obtained from 35 randomized studies that included 6,725 patients. HCTZ was administered in daily doses of 6.25 mg, 12.5 mg and 25 mg. The dose of 6.25 mg showed a statistically significant better reduction of blood pressure levels in comparison with placebo; however, in lowering systolic blood pressure, a clear dose-dependent response was registered. HCTZ dose of 12.5 mg lowered systolic pressure by 2.2 mm Hg more than dose of 6.25 mg, and dose of 25 mg lowered systolic pressure by 2.7 mm Hg more than dose of 12.5 mg. Dose of 12.5 mg lowered diastolic pressure by 1.1 mm Hg more than dose of 6.25 mg, and the difference in effectiveness was only 1 mm Hg for doses of 12.5 and 25 mg. The more efficient dose-dependent reduction of systolic, but not diastolic blood pressure as well, was also responsible for dose-dependent reduction in pulse pressure, which was 4 up to 6 mm Hg at maximal doses. Other groups of antihypertensive agents, such as ACE inhibitors and AT1 receptor blockers, lower pulse pressure independently of administered dose by 3 mm Hg, and non-selective beta-blockers by 2 mm Hg. It is obvious that reduction in pulse pressure achieved by HCTZ administration in the lowest dose (6.25 mg) was bigger than one achieved by other antihypertensive agents.

It is evident that effectiveness of thiazide diuretics is dose-dependent; however, undesirable effects of drug are also dose-dependent. Depending on dose, they aggravate glucose intolerance, increase lipids levels, cause hypokalemia, hyponatremia and hypomagnesemia, and increase levels of uric acid.

A meta-analysis of 22 studies has shown that use of thiazide diuretics, in comparison with placebo and other antihypertensive agents, was associated with an increased risk of new-onset diabetes mellitus [34]. The mechanism of development of glucose intolerance and reduction in insulin sensitivity is not completely clear. According to generally accepted assumption, thiazides induced decreased level of potassium is responsible for reduction in insulin secretion and reduction in insulin mediated glucose uptake in skeletal muscles with consequential reduction in insulin sensitivity,

which leads to impaired glucose tolerance and hyperglycemia. This assumption is based on results from smaller studies, and it was reinforced in a post hoc analysis of the SHEP study, in which it was found that risk from of new-onset diabetes mellitus was increased with each 0.5 mEq/L decrease in K level [35, 36]. Zillich and al. have found a significant negative correlation between potassium level and glucose level ($r = -0.28$, 95% confidence interval [CI] -0.47 to -0.07, $p<0.01$) [37].They have concluded that maintaining of potassium levels above 4 mEq/L may reduce the risk of hyperglycemia development caused by treatment with thiazide diuretics. As a contributing factor to development of this unfavorable effect of thiazide diuretics, obesity [38] was reported; as well as treatment duration >9 years that may contribute to development of diabetes mellitus.

In addition to individual risk assessment for each patient (existing disorder of glucose metabolism, obesity), as a preventive measure for diabetes mellitus development, administration of a thiazide diuretic in a low dose is reported.

A dose-dependent increase in total cholesterol, LDL and triglyceride level may occur even after short-term administration of thiazide diuretics [39,40]. These changes are more often in the patients with diabetes mellitus. Mechanism of development of these changes is not clear, but it is associated with decrease in insulin sensitivity and/or reflex activation of sympathetic nervous system and renin – angiotensin – aldosterone system in diuretics induced volume depletion. This increase is a reversible one, lipids levels return to range prior to therapy initiation, a year after cessation of diuretics administration [41]. Considering that a thiazide diuretic in a low dose does not induce a significant change in volume, it is expected that it will not have impact on disorders of lipid status.

Hypokalemia (K level <3,5mEq/l) is often an adverse effect of thiazide diuretics [42]. In the first few days from therapy initiation, thiazide diuretics cause the average of 0.6 mEq/L dose-dependent decrease in potassium level (which is more than decrease in K level of 0.3 mEq/L caused by administration of loop diuretics). An increased sodium intake, decrease in chlorides level in the distal tubules, metabolic alkalosis and secondary hyperaldosteronism contribute to the increase in flow – dependent potassium secretion.

Hypokalemia is, in addition to aforementioned metabolic disorders, responsible for other disorders as well. In the MRFIT study, a significant inverse relationship between potassium concentrations and VES was found [30]. The risk of thiazide induced hypokalemia and rhythm disorders is more significant in the patient with existing hypertrophy of myocardium, heart failure and ischemia; therefore, in such patients, a greater caution should be exercised and dosage of a thiazide diuretic lowered.

Hyponatremia is a rare, but a serious complication of diuretic therapy with the remark that thiazide diuretics are more likely to cause it than loop diuretics. Eventual hyponatremia has very rarely a degree that requires a correction [43]. Metabolic alkalosis is also a very rare complication of

thiazide diuretics administration. Its occurrence is also dose-dependent, as well as are all listed adverse effects.

Thiazide diuretics, as well as loop diuretics, increase excretion of magnesium trough urine, which may lead to decrease in magnesium levels by 5 up to 10%. Hypomagnesemia is found more often in the elderly and those on high doses of diuretic therapy, and often coexist with hypokalemia, hyponatremia and hypocalcemia. Hypomagnesemia is suspected when ECG signs develop (prolonged QT and/or PR interval, a wide QRS complex, ST depression and low amplitude T wave along with supraventricular and ventricular arrhythmias), neurological changes (the change in mental status, and/or neuromuscular irritability such as tetany, tremor, muscle spasms). It is very rarely that parenteral supplementation of magnesium is required because of administration of thiazide diuretics, but oral supplementation should be considered when any of the listed symptoms occur [43].

A high dose of thiazide diuretics causes the increase in urates concentration for more than 35% due to their clearance reduction. This reduction in clearance may be a consequence of an increased tubular reabsorption caused by diuretics induced reduction of volume and/or competitive secretion of urates and thiazides since they have the same anion transporter. The occurrence of gout attacks requires temporary therapy cessation, and, if not acceptable, a drug should be administered in the lowest possible dose along with allopurinol [44].

The deleterious effect of thiazide and thiazide-like diuretics on male sexual function is not negligible. According to various studies, decreased libido, erectile dysfunction and ejaculation problems are seen in 3 up to 32% of the patients [30].

In spite of all listed adverse effects of thiazide diuretics, the statement of N. Kaplan is absolutely acceptable "... Appropriate use of diuretics can still be a safe and effective way to treat hypertension..." [45]. It is necessary to adapt the premise "appropriate use" to our midst, since only HCTZ and indapamide (which we have classified as thiazide-like diuretics) are registered. Having in mind a wide use of HCTZ, it is necessary to define what is that "low" dose that would be effective in blood pressure control, and that the least affects development of adverse effects. It has been shown in the aforementioned Cochrane analysis that HCTZ administered in the dose of 6.25 mg achieves an antihypertensive effect. The administration of this, very low dose of the thiazide diuretic is absolutely acceptable in combination with other antihypertensive drugs, because it potentiates action of other drugs without causing undesirable metabolic effects.

THE IMPORTANCE OF FIXED COMBINATION OF BISOPROLOL AND LOW-DOSE HIDROCHLORTHIAZIDE ADMINISTRATION

The effectiveness and safety of combination of bisoprolol (in various doses) and a thiazide diuretic in a small dose (6.25 mg) is proved in experimental and clinical trials. It has been demonstrated in an animal model that this combination caused a successful reduction in blood

pressure and heart rate, that it caused a lower renin activation compared to a thiazide diuretic alone, and that it caused a reduction of myocardial hypertrophy [46].

It has been demonstrated on the sample of 106 patients that eight-week treatment with a combination of bisoprolol and a low-dose thiazide diuretic caused a successful reduction of systolic blood pressure from 157.4 to 137.3 mmHg, and of diastolic from 98.8 mmHg to 87.4 mmHg [47]. The desired therapeutic response was achieved in 61% of the patients - normalization of blood pressure levels, with adverse effects occurring in 18.9%, out of which headache and fatigue were the most common. Disorders of glucose and lipids metabolism, potassium and uric acid levels were not recorded.

Even better results of blood pressure control in patients with mild to moderate hypertension have been obtained in a multicentric, randomized, double blind, placebo controlled study. Combination of bisoprolol and a thiazide diuretic reduced systolic blood pressure levels by 15.8 mm Hg, and diastolic by 12.6 mm Hg, which was significantly more compared to bisoprolol or a thiazide diuretic as monotherapy [48]. Normalization of blood pressure levels was achieved in 71% of the patients. A similar result has been obtained in another randomized, double blind, placebo controlled study. Using combination of a low dose bisoprolol (2.5 mg) and a thiazide diuretic (6.25 mg), a reduction of diastolic blood pressure was achieved in 61% of the patients with safety profile comparable to placebo [49]. In a randomized, double blind, parallel study, the effectiveness of combination of bisoprolol and a low dose thiazide diuretic was compared to enalapril or amlodipine monotherapy [50,51]. The desired therapeutic response was achieved in 71% of the patients treated with the combination, and in 69% and 45% of the patients treated with amlodipine and enalapril, respectively. Another similar randomized, double blind, parallel study has shown that a low dose combination of bisoprolol and a thiazide diuretic and amlodipine were equipotent, but it was more efficient compared to enalapril [52]. The same authors has shown, using efficacy analysis depending on race, that combination of bisoprolol and a thiazide diuretic in non-black population led to more significant lowering of diastolic pressure compared to amlodipine, enalapril or placebo [53]. The incidence of adverse effects has been similar in all treatment modalities, but treatment cessation was rarer in combination of bisoprolol and a thiazide diuretic use.

Papadopoulos and Papademetriou have concluded in their review paper on effectiveness of a fixed low-dose combination of bisoprolol and a thiazide diuretic that period in which a satisfactory response to therapy is to be expected is about 4 weeks, and after that period, in case of failure, a combination with a higher bisoprolol dose should be administered [54]. Combination of bisoprolol and a low dose of a diuretic showed both effectiveness and safety in treatment of isolated hypertension in elderly persons [55]. This combination has found its place in treatment of arterial hypertension in children [54].

CONCLUSION

Bisoprolol, a highly selective beta-blocker with a long half-life and a prolonged antihypertensive effect, has shown a consistent blood pressure control over the period of twenty-four hours. The administration of very low dose of the thiazide diuretic is acceptable in combination with beta blockers, because it potentiates antihypertensive action without causing undesirable metabolic effects. The effectiveness and safety of combination of bisoprolol (in various doses) and a thiazide diuretic in a small dose is proved in clinical trials.

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