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EFFICIENCY EXAMINATION OF ANTIHYPERTENSIVE FIXED-DOSE COMBINATION IN PATIENTS PREVIOUSLY TREATED WITH ANTIHYPERTENSIVE MONOTHERAPY

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Arterial hypertension is the condition where the blood pressure is higher than 140/90 mm Hg. Along with its complications, it is the leading factor for cardiovascular mortality. Arterial hypertension can be systolic, diastolic and combined. Diagnosis of arterial hypertension cannot be established on the basis of a single measurement, but it is necessary to make measurements in different situations and environments. The study aimed to evaluate efficacy of fixed combination antihypertensives in patients with stage I and II hypertension after antihypertensive monotherapy failed to deliver results in reducing blood pressure. In this study, we analyzed data of 395 hypertension patients aged between 65-80 years, previously treated with monotherapy. During 4 months of examination, 3 doctor visits were scheduled when their TA values were measured, and each of them received fixed-dose combination antihypertensives. The data obtained were processed by appropriate statistical analyzes.

At the third doctor visit, 69.8% patients achieved blood pressure target value, and the blood pressure decreased by 16.6/12.3% (p = 0.000). The noninvasive 24h Holter monitoring showed significantly less oscillation in blood pressure values throughout the day, and also, much smaller percentage of patients forgot to take therapy. During this study, the efficiency of fixed-dose combination antihypertensives was proved considering that in a considerable number of patients blood pressure reached the target values, there were no unwanted side effects, the patients rarely forgot to take the medicine, and there were significantly less oscillation in blood pressure on Holter monitoring.

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Key words: *arterial hypertension, fixed combination antihypertensives, antihypertensive monotherapy*

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Introduction

Arterial hypertension (high blood pressure) is the condition where one or both components of the blood pressure are elevated. The normal value for systolic blood pressure is < 140 mm Hg and for diastolic < 90 mm Hg (3, 5).

Arterial hypertension with its complications (ischemic heart disease, cardiomyopathies, cerebrovascular disease) is the leading factor of cardiovascular mortality (1).

The condition where the systolic blood pressure is ≥ 140 mm Hg and diastolic ≤ 90 mm Hg, is defined as isolated systolic hypertension. The values of systolic blood pressure ≤ 140 mm Hg and ≥ 90 mm Hg for diastolic blood pressure are common for isolated diastolic hypertension.

To diagnose arterial hypertension, several measurements are necessary. It is not recommended to confirm diagnosis based on one measurement, particularly not the one measured in the ambulance. The measurements should be done at

different times and different environment (home, office, ambulance) (1-4).

The treatment has as a goal to lower the blood pressure to < 140/90 mm Hg in all patients. If the treatment is well tolerated, the values should go bellow 130/80 mm Hg in most patients. In patients younger than 65 it is recommended to lower systolic blood pressure to the range 120-129 mm Hg in most cases. In older patients (≥ 65-80 years old), it is recommended to keep the systolic blood pressure between 130 to 139 mm Hg. A target diastolic blood pressure at or below 80 mm Hg should be considered for all hypertensive patients, regardless of the degree of risk or comorbidity (3).

Fixed combination is recommended as an initial treatment of arterial hypertension with the exception of old vulnerable persons and persons with low risk persons and stage one hypertension (3).

The aim

The study aimed to evaluate efficacy and safety of antihypertensive drugs in the fixed combination (ACE inhibitors/Ca-antagonist) in patients with stage I and II hypertension after the monotherapy failed to deliver results in reducing blood pressure.

Materials and methods

Patients

Patients between 65-80 years old with stage I and II hypertension were included in the study after the monotherapy (beta blockers, calcium channel blockers, diuretics, etc.) failed to deliver results. According the newest ESH/ECS guidelines, target blood pressure in hypertensive patients between 60-85 years old is 130-139/80 mm Hg.

The exclusion criteria were: not signed informed consent, non-compliance, hypersensitivity to calcium channel blockers and ACE inhibitors, pregnancy, neoplastic diseases with short life expectancy, severe heart defect, abnormalities in biochemical values that are clinically relevant, especially hyperkalemia.

Blood pressure measurement and biochemical assays

During four months, patients had three visits to a medical doctor (1 day = visit 1, the first month = visit 2, and the fourth month = visit 3). The blood pressure was measured twice at every visit in the range of 3 min. To every patient, one of four combinations of the fixed dose was prescribed (5/5 mg, 5/10 mg, 10/5 mg or 10/10 mg) by the medical doctor, based on the blood pressure values with the possibility of drug dose titration.

Furthermore, the biochemical assays were also performed during each visit: blood count, liver and kidney function tests, electrolytes values, blood glucose, serum cholesterol, uric acid, creatinine kinase.

Statistical analysis

The values are presented as mean ± standard deviation for continuous variables and numbers (percentages) for categorical variables. The data were analysed by descriptive statistics (mean and standard deviation) and by comparative parametric (t-test) and non-parametric (Fischer test) tests using GraphPad Prism 5.03 (San Diego, USA); $p < 0.05$ was considered as statistically significant.

Results

Three hundred and ninety-five patients of average age 72.2 ± 7.0 were involved in the study (Table 1). Of them, 289 (73.16%) were males and 106 (26.84%) were females. The average body mass index (BMI) was 31.6 ± 4.9 kg/m^2. Before the study was started, the average blood pressure was 157.5/91.3 ± 9.6/7.6 mm Hg. Hypertension was present in patients of average age 13.2 ± 7.9 years. One hundred and forty-six patients (36.96%) were diagnosed with stage I hypertension and 249 (63.03%) with stage II hypertension. Cardiovascular risk factors were notices in 308 (77.97%) patients. Dyslipidemia was the most common risk factor for cardiovascular complications in 333 (84.4%) patients. Other risk factors, as obesity (BMI ≥ 30 kg/m^2) was noticed in 181 (45.9%) patients, smoking in 92 (23.4%), family anamnesis (early acute myocardial infarction) in 86 (21.7%) and hyperuricemia in 83 (21.1%) patients. The target organ lesions were detected in 192 (48.7%) patients, left ventricular hypertrophy in 128 (32.5%), elevated values of serum creatinine in 22 (5.6%) and microalbuminuria in 36 (9.2%) patients.

The effects of fixed dose ACE inhibitors/Ca-antagonists combination

The treatment was successful in 276 (69.8%) patients after four months (visit 3). Based on the blood pressure values, the recommended fixed dose of ACE inhibitors/Ca-antagonists was proposed by cardiologists (Table 2).

The blood pressure was significantly reduced (16.6/12.3%) from 157.5/91.3 ± 9.6/7.6 mm Hg at visit 1 to 130.9/79.6 ± 7.4/5.9 mm Hg at visit 3 ($p = 0.000$). During the 2nd and 3rd visit, in 32.3% and 69.8% of patients the blood pressure was reduced, respectively. The level of blood pressure reduction depended on the fixed dose used during the treatment. After four months of treatment, at the 3rd visit, targeted blood pressure values were achieved in 24.1% of patients taking 10/10 mg, 21.8% of patients taking 5/5 mg, 20.5% taking 10/5 mg, and 1.8% of patients who were treated with 5/10 mg (Table 3). The reduced blood pressure was followed with the changes in the heart rate. Heart rate significantly decreased (5.1 ± 7.5/min, $p = 0.000$)

from 78.0 ± 8.5/min at visit 1 to 72.9 ± 6.0/min at visit 3.

The second aim of the study was to evaluate the efficacy and safety and the effects on the metabolism of the fixed dose of ACE inhibitors and Ca-antagonists. Considering lipid profile, total cholesterol was reduced from 5.50 ± 1.13 mmol/L at visit 1 to 5.20 ± 0.95 mmol/L at visit 3 (p = 0.000), LDL cholesterol from 3.20 ± 0.93 mmol/L at visit 1 to 3.00 ± 0.77 mmol/L at visit 3 (p = 0.000), triglycerides were reduced from 2.20 ± 1.14 mmol/L at visit 1 to 2.00 ± 1.97 mmol/L at visit 3 (p = 0.000), while the levels of HDL cholesterol increased from 1.30 ± 0.42 mmol/L at visit 1 to 1.35 ± 0.30 mmol/L at visit 3 (p = 0.001). There were no changes in the other biochemical parameters. The fixed doses of ACE inhibitors/Ca-antagonists were well tolerated and no adverse effects were reported.

Table 1. Patients previously on antihypertensive monotherapy (n = 395)

Drugs	(%)
Beta-blockers	23 (5.9)
Diuretics	41 (10.3)
ACE inhibitors	193 (48.9)
Ca-antagonists	138 (34.9)

Table 2. Subsequent dosing of ACEI/Ca antagonists in a fixed dose within each visit (n = 395), n (%)

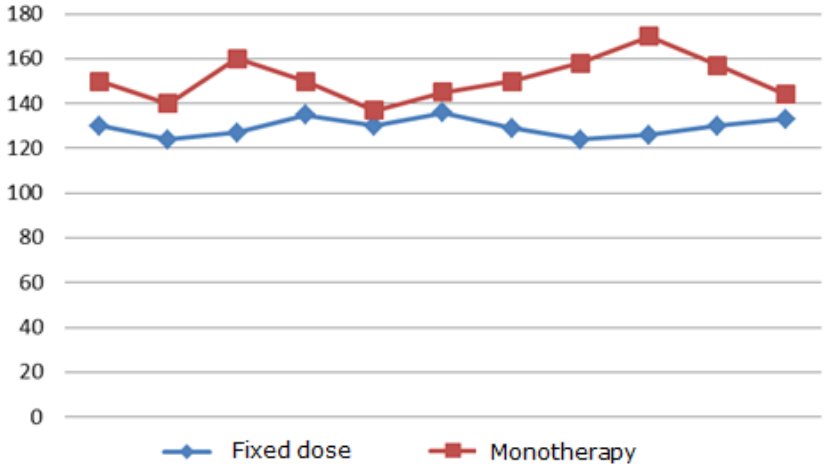
Doses of ACEI/Ca-antagonists fixed combination	Visit 1	Visit 2	Visit 3
5/5 mg	155 (39.3)	115(29.2)	111 (28.1)
5/10 mg	22 (5.6)	21 (5.3)	21 (5.2)
10/5 mg	105 (26.5)	118 (29.9)	116 (29.3)
10/10 mg	113 (28.5)	141 (35.7)	148 (37.5)

Table 3. Doses of fixed combination of ACEI/Ca antagonists in patients reached the target blood pressure values at visits 2 and 3 (n =395), n (%)

Drugs Dose	Visit 2	Visit 3	*p*
	126 (32.3)	276 (69.8)	0.000
5/5 mg	47 (11.8)	86 (21.8)	0.000
5/10 mg	7 (1.8)	13 (3.4)	0.000
10/5 mg	37 (9.4)	81 (20.5)	0.000
10/10 mg	37 (9.3)	95 (24.1)	0.000

The noninvasive Holter monitoring was used for 24h (Schiller BR-102 plus system) in 176 (44%) patients. The system was programed to measure the blood pressure at every 15 min from 07 am to 11 pm, and at every 20 min from 11 pm to 07 am. The patients were practicing a normal daily routine. This monitoring revealed that patients treated with the antihypertensive in fixed dose had statistically significant reduction in the blood pressure oscillation during 24h (Graph 1). The blood pressure was in the range 130.4/78.7 ± 6.5/3.8 mm Hg. However, the blood pressure significantly oscillated during 24h in patients treated with monotherapy, i.e., the values were 143.9/89.7 ± 9.8/7.6 mm Hg.

The patients involved in the study have been checking the blood pressure on their own. It was noticed that patients treated with fixed dose were taking the therapy more regularly (96.5%) than patients treated with monotherapy. The patients on combined monotherapy mostly forgot evening dose of the drug (26.6%).



Graph 1. Blood pressure oscillations during ingestion of fixed dose/monotherapy detected with 24h Holter

Discussion

In this clinical study, it has been shown that the combination of fixed dose of ACE inhibitors/Ca-antagonists significantly reduced blood pressure in patients with high risk factor for cardiovascular diseases. In patients in whom previous mono-antihypertensive therapy had failed to achieve target blood pressure (130-139/80 mm Hg), the treatment was continued with combined fixed dose of ACE inhibitors/Ca-antagonists. This approach led to a moderate decrease in the blood pressure values (26.6/11.7 mm Hg) and the rate of achieving the target level of blood pressure was 69.8%. In these patients, the lower level of blood pressure was noticed already after one month of treatment with the fixed dose of ACE inhibitors/Ca-antagonists (10).

Our data suggest that this approach can have long-lasting benefits in later cardiovascular events. The rate of achieving the target level of blood pressure could be even higher with a higher dose of combined fixed dose therapy (10/10 mg) because until last visit only 37.5% of patients took this dose of the drug. Furthermore, the metabolic effect of this therapy approach was significant in patients with dyslipidemia. The lipid profile was improved after four months of treatment. During the treatment, no adverse effects were noticed.

It has been shown that a fixed combination of antihypertensive drugs significantly lower oscillation in blood pressure during 24h compared to the monotherapy approach. Moreover, this study showed that patients using this treatment approach forget less to take the therapy, what significantly increases the comfort for the patient.

The randomized, prospective, 18 weeks lasting double-blind study was carried out in Brazil with an aim to compare the efficacy and tolerability of the fixed dose of amlodipine/ramipril (8, 11). The patients involved in the study with basic hypertension type I and II. They were taking 2.5/2.5 mg ramipril/amlodipine or 5 mg amlodipine. Thereafter, the doses were titrated based on blood pressure, ramipril/amlodipine 5/5 mg, then 10/10 mg or amlodipine 5 mg, and then 10 mg. This study proved that fixed combined therapy ramipril/amlodipine significantly reduced average changing of blood pressure during 24h, compared to the patients using the monotherapy approach.

Recent ESC/ESH guidelines emphasized the importance of RAAS activity inhibition in the treatment of primary hypertension (5, 6). The inhibition of RAAS activity could be achieved with ACE inhibitors or angiotensin receptor blockers (ARB). A recent meta-analysis revealed that the treatment with ACE inhibitors decreased all-cause mortality, mortality from cerebrovascular events, whereas ARB didn't show these effects. Therefore, ACE inhibitors are considered as the first-line therapy to avoid the increase in mortality and morbidity in this population. ACE inhibitors in the combination with Ca-antagonists have a synergistic antihypertensive effect, what can have an additional advantage in minimizing adverse effects of individual components (e.g., Edema with dihydropyridine CCBs). Anglo-Scandinavian cardiac outcome trials for reducing the blood pressure showed that ACE inhibitors/Ca-antagonists combination was more effective in reducing blood pressure and also decreased the risk of mortality and major cerebrovascular events, compared to the traditional combination of beta-blockers and thiazide (7, 9, 13).

Conclusion

In patients with stage I and II hypertension and with a high risk of cerebrovascular events when the previous treatment with the usage of a single antihypertensive drug failed to deliver results, the combination of the fixed does of ACE inhibitors/Ca-antagonists therapy approach was effective. Furthermore, this combination of drugs was well tolerable

with good metabolic effects. It has been shown that this fixed combination prevents huge oscillation in blood pressure during 24h, compared to mono-therapy. Patients did not forget to take therapy on time, compared to the patients who were taking combined monotherapy.

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ISPITIVANJE EFIKASNOSTI FIKSNE KOMBINACIJE ANTIHIPERTENZIVA KOD BOLESNIKA KOJI SU BILI NA ANTIHIPERTENZIVNOJ MONOTERAPIJI

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Arterijska hipertenzija je stanje u kome je krvni pritisak povišen iznad 140/90 mmHg. Ovo stanje, zajedno sa komplikacijama koje izaziva, vodeći je faktor kardiovaskularnog mortaliteta. Arterijska hipertenzija može biti sistolna, dijastolna i kombinovana. Dijagnoza arterijske hipertenzije ne može se postaviti samo na osnovu jednog merenja, već je neophodno izvršiti merenja u različitim situacijama i različitom okruženju. Cilj ove studije je da nadgleda efikasnost fiksne kombinacije antihipertenziva kod bolesnika sa hipertenzijom prvog ili drugog stepena, kod kojih se antihipertenzivnom monoterapijom nisu postigle adekvatne vrednosti krvnog pritiska. U ovom istraživanju analizirali smo podatke 395 bolesnika, starosti između 65 i 80 godina, koji boluju od hipertenzije prvog i drugog stepena i koji pomoću monoterapije nisu dostigli adekvatnu vrednost krvnog pritiska. Tokom 4 meseca ispitivanja, bolesnici su dolazili na kontrole u 3 navrata, pri čemu su im merene vrednosti krvnog pritiska i svaki od njih je primio kombinaciju fiksne doze antihipertenziva. Dobijeni podaci obrađeni su odgovarajućim statističkim analizama. Prilikom treće posete lekaru, ciljnu vrednost krvnog pritiska dostiglo je 69,8% bolesnika, a pritisak se smanjio za 16,6, odnoso za 12,3% ($p = 0,000$). Neinvazivni dvadesetčetvoročasovni holter monitoring pokazao je znatno manje oscilacije u vrednostima krvnog pritiska u toku dana, a takođe, bolesnici su u mnogo manjem procentu zaboravljali da uzimaju terapiju. Tokom ove studije dokazana je efikasnost fiksne doze antihipertenziva, s obzirom na to da je kod znatnog broja bolesnika krvni pritisak doveden na ciljne vrednosti, da nije bilo neželjenih efekata, da su bolesnici ređe zaboravljali da uzimaju lek i da su na holter monitoringu zabeležene znatno manje oscilacije krvnog pritiska.

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Ključne reči: *arterijska hipertenzija, fiksna kombinacija antihipertenziva, antihipertenzivna monoterapija*