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COMPARATIVE STUDY ON THE EFFICIENCY OF THE INHIBITORS OF THE ANGIOTENSIN CONVERSION ENZYME AND RECEPTOR ANTAGONISTS FOR ANGIOTENSIN II ON THE ENDOTHELIAL DYSFUNCTION IN PATIENTS WITH ESSENTIAL ARTERIAL HYPERTENSION

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Abstract. The endothelial function is a "barometer" of the health of the cardiovascular system, and its quantification in patients suffering from a cardiovascular disorder, particularly arterial hypertension, represents a useful method for the evaluation of cardiovascular risk, of the severity of the disease and a useful method for the quantification of the effectiveness of several therapeutic strategies. We have performed a comparative clinical study, open, randomized, non-interventional on parallel groups of subjects with essential arterial hypertension degrees 1, 2 and 3 for the comparison of the efficiency of the angiotensin II conversion enzyme inhibitors (IECA) and the receptor antagonists for angiotensin II (ARA) on the endothelial dysfunction evaluated through the flow-mediated vasodilatation (FMD). Comparing the average of the FMD increase after 12 months of treatment for the two treatments we concluded that there are no statistically significant differences.
Keywords: angiotensin II, endothelial dysfunction, candesartan

Introduction

During the last decades, as a result of the experimental and clinical studies performed, it has become more and more obvious that the vascular endothelium is not an inert, single-layered barrier located on the inner surface of the sanguine vessels, but an "organ" crucially involved in maintaining the normal structure and function of the cardiovascular system. Within this framework, we may state that the endothelial function is a "barometer" of the health of the cardiovascular system, and its quantification in patients suffering from a cardiovascular disorder, particularly arterial hypertension, represents a useful method for the evaluation of cardiovascular risk, of the severity of the disease and a useful method for the quantification of the effectiveness of several therapeutic strategies (15).

Risk factors such as arterial hypertension, age, smoking, hyper-cholesterolemy, the metabolic syndrome, diabetes mellitus are associated to the diminishing of the endothelium-dependent vasodilatation capacity in both adults and children. These determine, at the level of the vascular endothelium, a decrease in the synthesis of vasodilatation and antithrombotic factors and an increase in the vaso-

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constrictor and pro-coagulant factors (8, 11).

A non-invasive method which measures endothelium-dependent vasodilatation capacity is ***flow-mediated vasodilatation- FMD***. In this ultrasound method, vasodilatation is induced by the increase in the sanguine flow through the vessel, stimulated by the reactive hyperemia produced as a result of the occlusion of the brachial artery with the cuff of a blood pressure monitor.

The purpose of the study was to establish the efficiency of the therapy with inhibitors of the angiotensin II conversion enzyme inhibitors in comparison to the therapy with AT1 receptor antagonists in the rehabilitation of the endothelial function in subjects considered.

Material and method

For the comparison of the efficiency of the angiotensin II conversion enzyme inhibitors (IECA) and the receptor antagonists for angiotensin II (ARA) on the endothelial dysfunction of the evaluated through the flow-mediated vasodilatation (FMD) in hypertensive subjects we have performed a comparative clinical study, open, randomized, non-interventional on parallel groups of subjects with essential arterial hypertension degrees 1, 2 and 3 (5). The subjects were monitored for 12 months. The Protocol was endorsed by the Medicine Committee in the Emergency Clinical County Hospital, Sibiu where the research was conducted. All subjects had signed the participation agreement. They were selected from employees of SC COMPA SA Sibiu, as a result of the collaboration with the Occupational Medicine Unit within the "Paltinu" Clinic, Sibiu.

The inclusion criteria were: (a) man and women older than 18 years of age, able to freely express their agreement to participate in the research, (b) diagnosed with essential essential arterial hypertension (TAS≤200 mmHg, TAD≤110 mmHg) at least one year ago, (c) who were not previously treated with IECA and/or ARA.

The exclusion criteria were: (a) subject with secondary essential arterial hypertension, (b) subject suffering from severe cardiovascular disease (acute or chronic coronary disorder, arrhythmia, cardiac, renal, hepatic insufficiency and diabetes mellitus), (c) subject with hypersensitivity to IECA and/or ARA, (d) subject known to consume abusively medicine and other substances, (e) female patients who are pregnant, lactating or plan to have a baby during the development of the study, (f) subjects who plan to travel abroad extensively during the development of the study.

Considering the criteria above, 61 hypertensive subjects were selected. They underwent an anamnesis on the first and last day of the study, a general clinical examination and paraclinical investigations.

The paraclinical investigations consisted of: (a) electrocardiogram, (b) ultrasound and Doppler test of the brachial artery in order to determine flow-mediated vasodilatation (FMD), (c) biochemical determinations: total cholesterol, triglycerides, HDL-cholesterol, creatinine, glycemia, transaminase.

In the morning when the clinical and paraclinical investigations were performed the subjects were not administered anti-hypertensive medication. The blood samples were taken in the morning before breakfast.

The flow-mediated vasodilatation was determined in compliance with the requirements in "Guidelines for the ultrasound assessment of endothelial-dependent flow- mediated vasodilatation of the brachial artery: A report of the International brachial artery reactivity Task Force" (2).

The ultrasound assessment was performed in a quiet room with constant temperature (21±1°C), the subjects having been advised to refrain from eating high-fat food, to avoid physical labor, smoking (for at least 12 hours before the trials) and vasoactive medication (this having been interrupted 24 hours before the trials). Before the trials, the patient rested for at least 20 minutes.

The evaluation of the endothelial vasodilator function through the FMD method was performed by means of Sonoline Versa Plus and a software program able to produce color vascular 2D images and Doppler. We used linear transducers of 7.5 MHz which helped us obtain high resolution images.

The diameters where recorded: the initial diameter (D_1) and the final diameter (D_2) at the end-diastolic moment, i.e. at exactly 60 seconds from the deflation of the blood pressure monitor cuff. The trials were performed on recorded pictures twice or by two examiners who were not informed on the examined subjects and not on the results obtained by the other observer.

FMD was expressed as the variation in percentages of the diameter of the brachial artery against the base value one minute after the deflation of the blood pressure monitor cuff. The formula utilized was:

$$FMD = \frac{D2 - D1}{D1} x100$$

Variable*	Group 1 (n=31)	Group 2 (n=30)
Age (years)	50.3871 ± 5.7253	49.9000 ± 4.2047
Men/Women	25/6	20/10
Smokers (%)	22.58	26.66
Alcohol consumers (%):	83.87	86.66
a. occasionally (%)	88.46	96.15
b. daily (%)	11.53	3.84
Body mass index (kg/m2)	28.1290 ± 4.3080	29.2403 ± 2.8378
Waist (cm)	100 ± 12.48	101.2 ± 7.87
Cardiac Frequency (beats/min.)	75.9677 ± 13.9248	76.3000 ± 10.5672
Diastolic arterial tension (mmHg)	100.4839 ± 1.4277	102.6667 ± 9.1664
Systolic arterial tension (mmHg)	169.6774±10.9495	170.8333 ± 13.5877
Average arterial tension (TAS-TAD mmHg)	123.2206 ± 9.8877	125.3840 ± 8.5629
Glycemia (mg/dl)	103.4839 ± 11.1172	103.0000 ± 13.6154
Creatinine (mg/dl)	0.94 ± 0.15	0.98 ± 0.18
Total Cholesterol (mg/dl)	216.3226 ± 40.6533	227.9333 ± 38.2775
HDL- cholesterol (mg/dl)	52.6129 ± 15.4352	49.4667 ± 9.5366
Triglyceride (mg/dl)	163.3226 ± 106.0856	135.4667 ± 68.8956
LDL- cholesterol (mg/dl)	131.0581 ± 41.8907	1.4400 7.1683

Table I. Comparative characteristics of the subjects in the groups on the first examination:
**P > 0.05 – the two groups are equivalent.*

FMD	Statistical Indicator	Group 1	Group 2
V1	average	5.2321	4.8776
	Standard error	0.7853	0.6174
	Average square deviation	4.2288	3.0869
	median	5.2600	4.7600
V2	average	13.4566	13.7660
	Standard error	0.7592	1.3300
	Average square deviation	4.0885	6.6499
	median	12.5000	12.5000

Table II. FMD values: initial values (V1) and after one year (V2)

The values FMD≥10% were considered normal.

For the statistical processing of the data obtained we used MATLAB 2007B and t test (Student) for paired information, equivalent to a t test on the difference (10, 13, 14).

Results

The subjects included in the study were divided into two groups: the subjects in group 1 were treated with Candesartanum 8-16 mg/daily, and those in group 2 with enalaprilum 10-20 mg/daily, depending

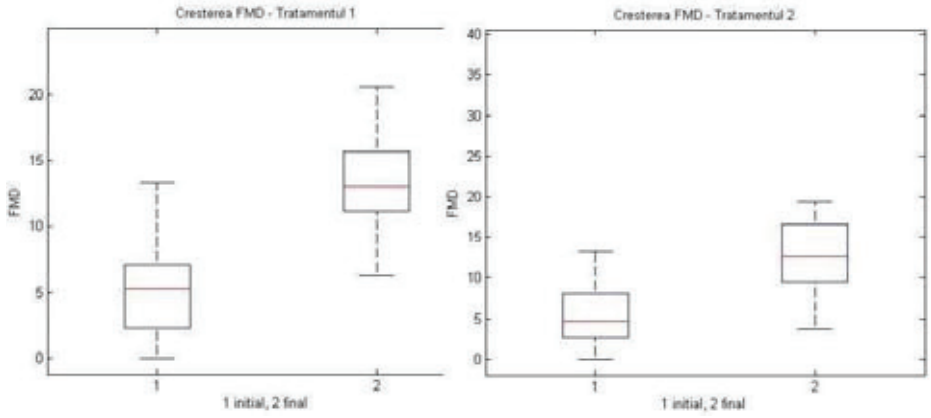

Figure 1. Increase in the FMD value after 12 month of treatment for the two groups

on the blood pressure values, for 12 months.

The characteristics of the groups studied are presented in table I.

As a result of the ultrasound assessment of the diameter of the brachial artery the following average values were obtained: initial value (V1) and after one year (V2) (table II).

Of the 61 patients 90,16% (55) have FMD<10%, and 9,83% (6) have FMD ≥ 10.

Both group 1 and 2 had a significant increase of the FMD value (approximately 9%) after 12 month of treatment. (Figure 1)

Comparing the average of the FMD increase after 12 months of treatment for the two treatments we concluded that there are no statistically significant differences (p=0.67) (table II and figure 2).

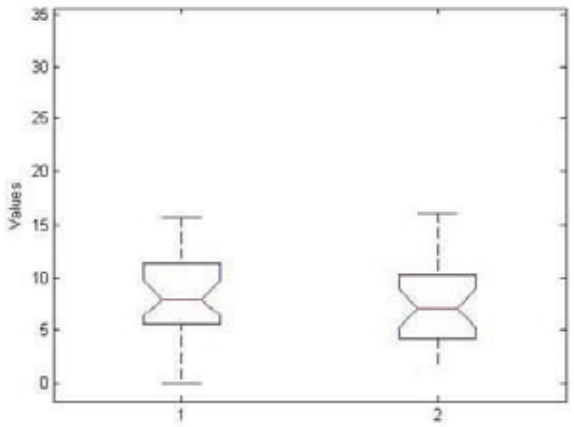

Figure 2. Comparison of the FMD averages of group 1 (1) and group 2 (2), after 12 months of treatment

Interpretation of results

The endothelial disorder is the initial vent in the development of atherogenesis (4, 6). Chronologically, it appears before the development of coronary disease detected through coronography (3).

Angiotensin II is an important factor in the physiopathology of the cardiovascular disorders and thus the inhibition of the rennin-angiotensin-aldosterone system is an important goal in the therapeutic strategy of these disorders.

The study shows that patients suffering from essential arterial hypertension present a decrease in endothelial vasodilatation capacity, demonstrated through the FMD ultrasound method, which corresponds to the data found in the literature (12).

It is a known fact that the inhibitors of the angiotensin conversion enzyme (IECA) exert a positive effect upon the endothelium-dependant vasodilatation, which was demonstrated through the experimental and clinical trials conducted (1, 9). The antagonists of the AT1 receptors (ARA) have a cardio-protective effect in patients suffering from arterial hypertension as demonstrated in the LIFE clinical trials (Losartan Intervention for Endpoint reduction in Hypertension), SCOPE (Study Of Cognition and Prognosis in the Elderly) and VALUE (Valsartan Antihypertensive Long-Term Use Evaluation).

Through this study, we compared the ARA effect to the IECA effect on flow-mediated dilatation as indicator of endothelial function. After 12 months of treatment and after statistical processing of the data obtained we came to the conclusion that ARA ameliorates endothelial disorder, its effect being comparable to that of IECA.

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