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COMPARATIVE STUDY ON THE EFFICIENCY OF THE ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN II RECEPTOR ANTAGONISTS IN REDUCING SERUM C-REACTIVE PROTEIN LEVELS IN PATIENTS WITH ESSENTIAL ARTERIAL HYPERTENSION

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Abstract. Background. The past decade has shown an increase in the relevance of inflammation and its mediators in vascular biology. It is more likely that the inflammation remains one part of the complex pathophysiology linking hypertension to vascular disease. Plasma levels of circulating inflammatory molecules, such as the C-reactive protein (CRP), have been shown to be predictive of future cardiovascular disease (CVD), and drugs which modify their levels can reduce the risk of myocardial infarction and stroke. **Methods.** For the comparison of the efficiency of the angiotensin II converting enzyme inhibitors (ACEi) and the angiotensin II receptor antagonists (ARAs) on the plasma C-reactive protein (hs-CRP) we administered Enalaprilum or Candesartan for a period of 12 months to 64 patients with arterial hypertension degrees 1, 2 and 3. This was a comparative clinical study, open, randomized, non-interventional on parallel groups of subjects. **Results.** In the group treated with Candesartan (35 patients) we observed a significant decrease in the plasma level of hs-CRP from 2.29±2.39 to 1.02±0.88 mg/dl ($p<0.001$) and in the group treated with Enalaprilum (29 patients) the plasma hs-CRP level decreased from 3.04±2.12 to 1.70±1.87 mg/dl ($p<0.001$). Between the two groups we have not observed a statistically significant difference in lowering the plasma levels of hs-CRP. There were no significant correlations between hs-CRP and systolic blood pressure, diastolic blood pressure and lipoprotein levels. There was a significant correlation between initial hs-CRP and waist size ($r = 0.32$). **Conclusions.** The present results show that 12 months of Candesartan or Enalaprilum therapy improved plasmatic levels of hs-CRP. In conclusion, the angiotensin II converting enzyme inhibitors and the angiotensin II receptor antagonists have the ability to positively influence cardiovascular outcomes of essential arterial hypertension.
Keywords: hypertension, inflammatory markers, C-reactive protein, Candesartan

Introduction

Cardiovascular conditions (chronic coronary disease, cerebrovascular accident and peripheral arterial diseases) are one of the major public health issues in Romania, being responsible for 61% of the number of deaths recorded in 2002 [1]. Arterial hypertension is one of the main cardiovascular risk factors and it affects approximately 39% of the Romanian population over 18 years of age, according to the Cardio-Zone study [2]. The same study reveals the fact that the prevalence of arterial hypertension in Romania is increasing with age, from 4.5% in the population under 40 years of age, to 34% in the 40-55 age group, to 63.9% in the 55-70 age group and to 77.9% in the over-70 age group.

The risk factors responsible for the appearance and evolution of the arterial hypertension have only partially been identified. During the past decade, a low-intensity chronic inflammatory process was

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identified, which is a component of cardiovascular disease pathogenesis and is probably the connection between arterial hypertension and its cardiovascular complications. For example, the experimental studies of arteriosclerosis on animal models confirmed the importance of the chronic inflammatory process for the appearance and evolution of atheromatous plaques [3,4], and some prospective clinical trials demonstrated that the chronic, systemic, low-intensity inflammatory process is associated with the increase in the incidence of cardiovascular diseases and mortality because of this [5,6,7,8].

Clinical trials which included hypertensive patients demonstrated the increase in the plasmatic levels of the inflammatory markers, such as the high sensitive C-reactive protein (hs-CRP) [9]. Other clinical trials demonstrated that the high plasmatic levels of the hs-CRP were predictive for the development of arterial hypertension in pre-hypertensive and normotensive subjects [10,11]. The pathophysiological mechanisms which lead to the appearance of this low-intensity chronic, systemic inflammatory process, in arterial hypertension, have not been elucidated and probably include both the intervention of mechanical stress in the arterial wall and the intervention of certain humoral factors such as angiotensin II, which also has certain pro-inflammatory features in addition to its intervention in the regulation of vascular tone.

There are few data in the literature to demonstrate the existence of a connection between the inflammatory process and arterial hypertension. Probably, they are based on common pathophysiological mechanisms. Within this context, a question of particular interest is: the treatment of which of the two diseases might positively influence the other?

The purpose of the present research was to comparatively assess the capacity of the angiotensin II-converting enzyme inhibitors and of the angiotensin II receptor antagonists in the reduction of the hs-CRP plasmatic level.

Material and Method

For the comparison of the efficiency of the angiotensin II-converting enzyme inhibitors (ACEi) and the angiotensin II receptor antagonists (ARAs) in the reduction of the hs-CRP plasmatic level in hypertensive subjects we have conducted a comparative, open, randomized, non-interventional clinical trial on parallel groups of subjects with essential arterial hypertension degrees 1, 2 and 3 [12]. The Protocol was endorsed by the Medicine Committee in the Emergency County Hospital of Sibiu where the trial was conducted. The subjects 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. All subjects had signed the participation agreement. They were monitored for 12 months. Medical exams were performed every 3 months during the trial.

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

The exclusion criteria were: (a) subject with secondary AHT, (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 ACEi and/or ARAs, (d) hs-CRP plasmatic concentration higher than 10 mg/dl; (e) subject known to consume abusively medicine and other substances, (f) female patients who were pregnant, lactating or planning to have a baby during the trial, (g) subjects who intended to travel abroad extensively during the trial.

Considering the inclusion and exclusion criteria above, 64 hypertensive subjects were selected. They were randomly divided into two groups: Group 1 (35 subjects) treated with Candesartan and Group 2 (29 subjects) treated with Enalaprilum. They underwent an anamnesis on the first and last day of the trial, a general clinical examination and paraclinical investigations.

The paraclinical investigations consisted of: (a) electrocardiogram, (b) determining the hs-CRP plasmatic concentration, (c) biochemical determinations: total cholesterol, triglycerides, HDL-cholesterol, creatinine, glycemia, transaminases.

In the morning when the clinical and paraclinical investigations were performed, the subjects were not administered anti-hypertensive medication. Blood samples were taken in the morning before breakfast and after an alimentary pause of 12 hours.

The hs-CRP plasmatic concentration was determined by means of IMMULITE. The IMMULITE Automated Immunoassay Analyzer is a continuous, random access instrument which performs automated chemiluminescent immunoassays. The measurement range is 0.01-98 mg/dl.

For the statistical processing of the data obtained we used MATLAB.

Results

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

Both in Group 1 and in Group 2 there is a statistically significant decrease in diastolic and systolic arterial tension, after 12 months of treatment (see table 1).

Candesartan determined a statistically significant decrease in the level of hs-CRP from 2.29 ± 2.39 to 1.02 ± 0.88 mg/dl (p<0.001), and Enalaprilum decreased hs-CRP from 3.04 ± 2.12 to 1.70 ± 1.87 mg/dl (p= 0005) (table II).

Because the distribution of the hs-CRP is not normal, for the comparison of the efficiency of the two treatments, in the decrease in hs-CRP plasmatic concentration, we compared the medians corresponding to the two treatments with the test of the Wilcoxon rank sum. We verified the null hypothesis that the difference medians for the two treatments are equal in relation to the bilateral alternative (different medians). Because p=0.4706 the null hypothesis was accepted, and thus the treatments are equivalent considering their capacity to decrease the hs-CRP plasmatic concentration (fig. 1).

Our study reveals the fact that hs-CRP is positively correlated with the waist size (r=0.32), but it is not significantly statistically correlated with the

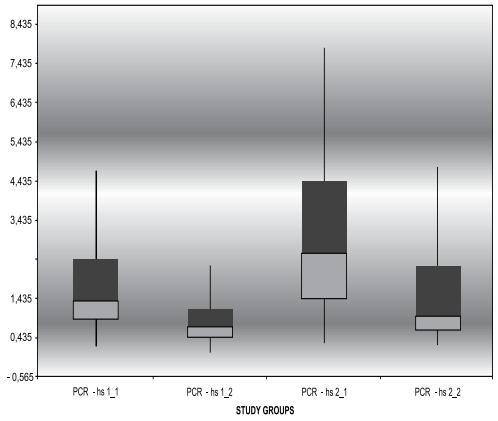

Figure 1. The initial and final values of the hs-CRP in the groups subjected to the trial
Legend: hs-CRP 1_1 – group 1 initial, hs-CRP 1_2 – group 1 final, hs-CRP 2_1 - group 2 initial, hs-CRP 2_2 – group 2 final.

	Variable*	Initial	Final
Group 1 (n=35)	Age (years)	49.65 ± 7.48	49.65 ± 7.48
	Men/Women	28/7	28/7
	BMI (kg/m^2)	27.58 ± 3.4	27.64 ± 3.39
	Waist (cm)	98.37 ± 12.32	98.02 ± 12.11
	CF (beats/min.)	73.7 ± 13.7	70.03 ± 6.79
	DAT (mmHg)	100.4 ± 11.01	82.43 ± 7.21
	SAT (mmHg)	168.7±10.39	133.6 ± 11.6
	MAT (mmHg)	123.47 ± 9.41	99.47± 7.2
	Glycemia (mg/dl)	100.88 ± 11.38	92.2 ± 12.7
	Creatinine (mg/dl)	0.94 ± 0.16	0.84 ± 0.16
	Total Cholesterol (mg/dl)	213.17 ± 43.62	220.65 ± 54.60
	HDL - cholesterol (mg/dl)	52.37 ± 14.78	45.62 ± 8.87
	Triglyceride (mg/dl)	148.00 ± 105.10	164.5 ± 138.6
	LDL- cholesterol (mg/dl)	131.21 ± 43.408	142.13 ± 44.52
	Variable*	**Initial**	**Final**
Group 2 (n=29)	Age (years)	49.96 ± 4.27	49.96 ± 4.27
	Men/Women	22/7	22/7
	BMI (kg/m^2)	28.97 ± 2.86	28.89 ± 2.91
	Waist (cm)	100.96 ± 8.02	100.68 ± 8.21
	CF (beats/min.)	76.30 ± 11.00	72.7 ± 4.7
	DAT (mmHg)	102.40 ± 8.82	83.1 ± 11.05
	SAT (mmHg)	173.40 ± 14.02	140. 00 ± 14.58
	MAT (mmHg)	126.78 ± 8.41	102.06 ± 11.09
	Glycemia (mg/dl)	104.48 ± 12.42	95.17 ± 9.55
	Creatinine (mg/dl)	0.99 ± 0.18	0.83 ± 0.14
	Total Cholesterol (mg/dl)	220.06 ± 33.08	217.82 ± 31.94
	HDL - cholesterol (mg/dl)	50.10 ± 9.51	45.89 ± 9.1
	Triglyceride (mg/dl)	136.60 ± 68.07	167.9 ± 210.5
	LDL- cholesterol (mg/dl)	142.72 ± 33.07	137.45 ± 36.59

Table I. Comparative characteristics of the subjects (initial and final)
Legend: BMI- Body Mass Index, CF- cardiac frequency, DAT- Diastolic Arterial Tension, SAT- Systolic Arterial Tension, MAT- Median *Arterial Tension*

hs-CRP	Statistical Indicator	Group 1	Group 2
Initial	number	35	29
	average	2.2906	3.0400
	Standard error	0.4056	0.3944
	Average square deviation	2.3997	2.1241
	median	1.3800	2.5800
Final	average	1.0220	1.7048
	Standard error	0.1492	0.3474
	Average square deviation	0.8825	1.8708
	median	0.7100	0.9700

Table II. Initial and final values of hs-CRP in the groups subjected to the trial

systolic, diastolic and median arterial tension, cardiac frequency, total cholesterol, HDL-cholesterol, triglycerides, LDL-cholesterol, glycemia.

Discussion

Arterial hypertension is associated with the development of a process of resistance vessels remodeling, which leads to an increase in the ratio average/lumen [13,14]. On a cellular level, vascular remodeling includes changes in the growth of smooth muscle cells, in cellular migration, inflammation and fibrosis, processes which are mediated by multiple factors, among which angiotensin II seems to play an important part [15,16].

Angiotensin II, produced both through traditional and alternative means, both systemically and locally, in the vascular wall, plays a crucial role in controlling arterial pressure through stimulating the contraction of the vascular smooth muscle, producing aldosterone, and stimulating the reabsorption of sodium in the renal tube [17,18]. Moreover, angiotensin II stimulates, at the level of endothelial cells, the synthesis of reactive oxygen species, pro-inflammatory mediators such as IL-6, MCP-1, and causes the activation of the kB and alpha nuclear factor [19].

In the literature, there is enough evidence to prove the existence of a connection between arterial hypertension and inflammatory markers [9]. The C-reactive protein is considered the most robust and reproducible marker for the vascular inflammation [20,21].

The present research proved that both the angiotensin II conversion enzyme inhibitors (Enalaprilum) and the angiotensin II receptor antagonists (Candesartan) significantly statistically reduce the plasmatic level of the hs-CRP in the hypertensive patients included in the trial. These data are in concordance with the published results of other trials which demonstrated that the decrease in the production of angiotensin II through ACEi and using ARAs to block the AT1 receptors significantly ameliorates the vascular microinflammation but also the endothelial function in hypertensive patients [22,23].

Because reduction of the hs-CRP plasmatic level was not correlated with the changes in the values of arterial tension, in the two groups included in the trial, we might state that the vascular microinflammation is partly influenced by the renin-angiotensin-aldosterone system independently from arterial pressure.

In conclusion, the angiotensin II converting enzyme inhibitors and the angiotensin II receptor antagonists have the ability to positively influence cardiovascular outcomes of essential arterial hypertension.

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