THE EFFECTS OF DIOVAN AND NEBILET TREATMENT ON DIASTOLIC DYSFUNCTION IN HYPERTENSIVE PATIENTS

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Abstract: *Objective: The aim of this study is to evaluate the effects of the treatment with the angiotensin receptor blocker - Diovan and of the cardioselective beta-blocker - Nebilet on the diastolic dysfunction, in grade II and III hypertensive patients, with diastolic dysfunction, echocardiographically detected. Materials and Methods: A prospective, clinical study was conducted on a six month follow–up period. The hypertensive patients were randomly assigned to either Diovan (80-160mg/day) or Nebilet (5-10mg/day). Results: 80 patients were enrolled in the study, 42 of them in Diovan group and 38 in Nebilet group. E/A ratio mean, significantly increased in both groups from baseline values (p<0,05), mean deceleration time (DT) and mean isovolumetric relaxation time (IVRT) significantly decreased from baseline values, in both treatment groups, p<0,05). Conclusions: After 6 months of treatment, both Diovan and Nebilet improved left ventricular transmitral flow, by improving transmitral flow parameters, in patients with grade II and III hypertension and diastolic dysfunction.*

Keywords: *arterial hypertension, diastolic dysfunction, Doppler echocardiography, Nebilet, Diovan*

Rezumat: *Obiective: Scopul acestui studiu a fost evaluarea efectelor tratamentului cu blocant al receptorilor de angiotensină (Diovan) si ale tratamentului cu beta blocant cardioselective (Nebilet) asupra disfuncţiei diastolice, la pacienţi cu grad II-III de hipertensiune, cu disfuncţie diastolică diagnosticată ecocardiografic. Material şi metode: S-a realizat un studiu clinic, prospectiv, pe o perioadă de 6 luni. Pacienţii hipertensivi au fost trataţi aleator fie cu Diovan (80-160mg/zi) sau cu Nebilet (5-10mg/zi). Rezultate: 80 de pacienţi au fost înrolaţi în studiu, 42 în grupul tratat cu Diovan şi 38 în grupul tratat cu Nebilet. Media raportului E/A, a crescut semnificativ în ambele grupe de tratament (p<0,05), media timpului de decelerare (TD) şi media timpului de relaxare izovolumetrică (IVRT) s-au redus semnificativ comparativ cu valorile iniţiale, la ambele grupe de tratament (p<0,05). Concluzii: După 6 luni de tratament, atât Diovanul, cât şi Nebiletul au îmbunătăţit fluxul transmitral, prin îmbunătăţirea parametrilor ecocardiografici ai fluxului transmitral, la pacienţi cu hipertensiune grad II şi III şi disfuncţie diastolică.*

Cuvinte cheie: *hipertensiune arterială, disfuncţie diastolică, ecocardiografie Doppler, Nebilet, Diovan*

INTRODUCTION

In relation to the increase of the average life, heart failure (HF) is seen as the most important pathology of the new millennium.

Hypertension is a major risk factor for heart failure and myocardial infarction in the general population. The progression of hypertensive cardiomyopathy towards HF includes different left ventricular (LV) changes-LV concentric remodeling and LVH- whose prognostic value is recognized.(1-5)

In the presence of geometrical LV abnormalities, modifications of LV diastolic properties occur. The diastolic dysfunction is defined by these modifications and represents alterations of ventricular filling and relaxation.(6,7)

Because of that, the diagnosis, prognosis and the therapeutic management of diastolic dysfunction represent attractive perspectives.

Diastolic dysfunction (DD) in hypertension has been of great interest during the past years, mainly because of the advancement of non invasive imaging tools, the Doppler echocardiography and the nuclear cardiology, and also due to the increased development of the pharmaceutical industry, in search for new therapies.

Nowadays, Doppler echocardiography is an easy and repeatable method for the identification of the left ventricle diastolic dysfunction.

The aim of the study is to evaluate the effects of the treatment with the angiotensin receptor blocker (Diovan) and of the cardioselective beta-blocker (Nebilet) on the diastolic dysfunction in grade II-III hypertensive patients, with diastolic dysfunction, echocardiographically diagnosed after 6 months of treatment.

MATERIAL AND METHODS

A prospective, clinical study was conducted and the consecutive eligible adult outpatients of either sex with grade II and III hypertension (office sitting SBP of 160-179 mmHg and/or office DBP 100-109 mmHg), defined according to the international guidelines (8) and diastolic dysfunction assessed by the echocardiographic transmitral flow (9,10) were included into the study.

The patients included into the study have never been treated as hypertensive patients (naive to antihypertensive drug treatment). The patients were prospectively followed-up for a period of 6 months.

The patients were not included into the study if they met any of the following criteria: malignant and known or suspected secondary hypertension; clinically significant heart disease (coronary heart disease, major arrhythmias, cardiac valvular defects, heart failure with decreased ejection fraction); concomitant cerebrovascular, renal, hepatic diseases, diabetes, hematological and malignant diseases, psychiatric disorders, obesity (body mass index > 30kg/m^2), pregnant women and known or suspected hypersensitivity to ARB or β blockers.

The patients who met the inclusion criteria were randomly assigned to one of the two treatment groups: Diovan (valsartan) or Nebilet (Nebivolol).

The starting dose was 80 mg for Valsartan and 5 mg for Nebivolol, once daily as recommended in the international guidelines.(8) The doses were doubled (160 mg for Valsartan and 10 mg for Nebivolol) in the patients with inadequate BP control (office SBP ≥ 140 mmHg or office DBP ≥ 90mmHg).

In all patients, the medical history was recorded, while the physical examination, the office BP measurement and the 12-lead electrocardiograms were performed at the screening visit. Upon the study initiation and at the 6 month visit, Doppler echocardiography was performed. The office BP was measured using a standard sphygmomanometer, with the patient seating for at least 10 minutes. For the office BP reference value, the mean of 3 measurements at rest, in sitting position, was used.

The Doppler echocardiographic evaluation of the diastolic dysfunction was assessed by the transmitral flow and measurements were taken according to the recommendations of the American Society of Echocardiography.(11)

The following measurements were done to each patient: early rapid ventricular filling (E-wave), atrial systolic filling (A-wave), early diastolic flow/atrial contraction signal (E/A) ratio, deceleration time (DT) and isovolumetric relaxation time (IVRT).

STATISTICAL ANALYSES

The values of the quantitative variables were expressed as means ± SD (standard deviation); Changes from baseline in Doppler indices (E/A, DT and IVRT) were analyzed using the Student t test after the investigation of the normality distribution. Whenever p-value < 0.05, the parameter was considered statistically significant. Statistical analyses were performed, by using SPSS 12.0.

RESULTS

Eighty hypertensive patients were randomized to either Diovan (n=42) or Nebilet (n=38) once daily. The demographic and clinical characteristics of the two study groups are presented in Table 1. There were no statistically significant differences in demographic and clinical baseline characteristics. All patients included into the study completed the 6-month follow-up.

Table no. 1. Demographic and clinical baseline characteristics

	LOT A (Diovan)	LOT B (Nebilet)	p value
Patients number	42	38	ns.
Men/women ratio (%)	47,6%/52,4%	47,4%/52,6%	ns.
Mean age (years) ±SD	56,76 ±14,2	56,65±13,45	ns
Clinical SBP(mmHg) ±SD	172,76 ±12,7	173,58±14,23	ns
Clinical DBP(mmHg) ±SD	106,86±13,92	107,37±16,63	ns
BP grade→grade II (%)	88,1%	81,6%	ns
→grade III (%)	11,9%	18,4%	ns
NYHA functional class→NYHA I (%)	38,1%	42,10%	ns
→NYHA II (%)	54,8%	52,63%	ns
→NYHA III (%)	7,14%	5,26	ns

SD= standard deviation, SBP=systolic blood pressure, DBP=diastolic blood pressure

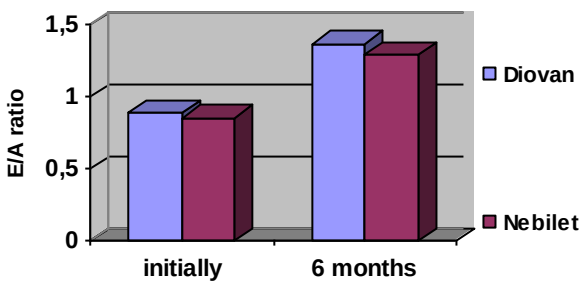
After 6 months of treatment, E/A ratio significantly increased from 0,89±0,56 to 1,37±0,23 in the Diovan group and from 0,85±0,51 to 1,29±0,25 in the Nebilet group, (p<0,05 for both groups).

After 6 months of treatment, DT significantly decreased from 206,24±43,45 msec to 190,81±41,88 in the Diovan group and from 214,53±43,78 msec to 197,61±42,04 msec in the Nebilet group, p<0,05 for both groups).

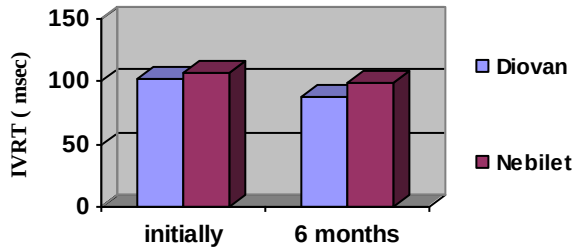
After 6 months of treatment, IVRT significantly decreased from 101,76±32,06 msec to 87,69±22,65 msec in the Diovan group and from 106,95±33,59 msec to 99,18±30,83 msec in the Nebilet group, (p<0,05 for both groups).

The evolution after 6 months of treatment with Diovan and Nebilet is presented in pictures no. 1, 2 and 3

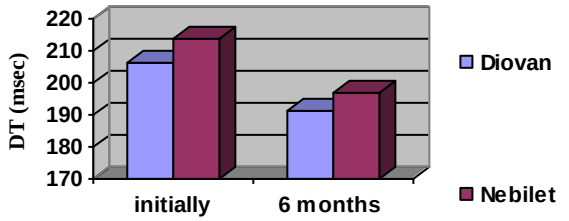
Picture no. 1. Evolution of e/a ratio per treatment group



Picture no. 2. Evolution of IVRT according to the treatment group



Picture no. 3. Evolution of DT per treatment group



DISCUSSIONS

In this study, after 6 months of treatment, E/A ratio, IVRT and DT parameters significantly improved with Diovan and Nebilet, in comparison with the baseline values. These results are in accordance with those from other previous studies.

According to Framingham study, hypertension appeared to be the most common cause of heart failure. The hypertensive patients have a two-three fold risk for heart failure.(12, 13)

Studies have shown that in 30% of the heart failure cases, the systolic function is preserved and the left ventricle diastolic function is responsible for clinical signs of the heart failure.(14,15)

Doppler ultrasonography (US) is used in conjunction with echocardiography to examine diastolic abnormalities of the left ventricle.(16,17)

No randomized, double-blind, placebo-controlled, multicentre trials have been performed in the patients with DD according to the treatment. Therefore, treatment guidelines remain empiric, based on the clinical investigations in small patient groups and underlying the pathophysiological disease.(18,19) The two main treatment goals are to reduce symptoms and improve prognosis by eliminating or reducing the underlying pathology.

Both treatments with the angiotensin receptor blockers and the cardioselective beta blockers could be used for hypertension.(8) Valsartan is a selective angiotensin receptor blocker that proved cardioprotective effects, also improving the diastolic left ventricle function.(20) Also, Nebivolol, a cardioselective beta blocker, demonstrated important effects on the diastolic function.(21)

In conclusion, after 6 months of treatment, Diovan and Nebilet improve the left ventricular transmitral flow parameters and the diastolic dysfunction in the patients with grade II and III of hypertension.

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