THE EFFECTS OF ANGIOTENSIN RECEPTOR BLOCKERS ON LEFT VENTRICULAR MASS IN HYPERTENSIVE PATIENTS

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***Abstract**: The aim of the study was to investigate the effects of Diovan on the Left Ventricular Hypertrophy in hypertensive patients. A prospective study, from Cluj-Napoca Diagnosis and Treatment Centre was designed between 2007 and 2008 and included patients with essential arterial hypertension. A sample of forty patients has been investigated. Diovan (Valsartan) in a single dose of 80-160 mg/day reduced the systolic blood pressure and the diastolic blood pressure over 24 hours, with no influence on the lipid or glucide metabolism. Diovan proved to improve the echocardiographic left ventricular hypertrophy parameters in hypertensive patients. ARB's as monotherapy are efficiently first line antihypertensive therapy.*

***Keywords**: Diovan, essential hypertension, left ventricular remodelling, left ventricular mass, renine angiotensine aldosteron system*

***Rezumat**: Scopul acestui studiu a fost urmărirea efectelor Diovanului asupra hipetrofiei ventriculare stângi la pacienţii hipertensivi. S-a efectuat un studiu prospectiv, la Centrul de Diagnostic si Tratament din Cluj-Napoca, între 2007-2008. S-a luat în considerare un lot de 40 de pacienţi cu hipertensiune arterială esenţială. Diovanul (alsartan) în doză unică de 80-160mg/zi a determinat reducerea valorilor sistolice şi diastolice a TA, pe parcursul a 24 de ore, fără a influenţa metabolismul glucidic sau lipidic. Diovanul a îmbunătăţit semnificativ parametrii echocardiografici ai HVS, la pacienţii hipertensivi. Blocanţii receptorilor de angiotensină ca monoterapie reprezintă agenţi antihipertensivi eficienţi şi reprezintă o terapie antihipertensivă de primă intenţie.*

***Cuvinte cheie:** Diovan, hipertensiunea arterială, remodelarea ventriculară stângă, masa ventriculară stângă, sistemul renină angiotensină aldosteron*

INTRODUCTION

Hypertension is still a major health problem all over the world and is frequently associated with other cardiovascular risk factors. Hypertension plays a key role in global cardiovascular risk concept which permits to estimate the probable incidence of major cardiovascular events: stroke, acute coronarian syndromes, heart failure, aneurism and aortic dissection, heart sudden death.

Essential hypertension is one of the most common diseases, affecting about 800 million people—or about 20% of the Earth's adult population.

In Romania, the prevalence of hypertension according to SEPHAR study is about 40.1%, which means that 4 from 10 persons are known as hypertensive or newly discovered hypertensive.

PURPOSES OF THE STUDY

The purpose of the study was to investigate the effects of Angiotensin Receptor Blockers (ARBS) on left ventricular remodelling in a group of hypertensive patients, by evaluating the left ventricular mass before ARBs treatment and 3,6,12 months after ARBs treatment.

MATERIAL AND METHODS

The study was conducted at the Diagnosis and Treatment Centre from Cluj- Napoca, over a period of 12 months. The characteristics of the design were as follows:

- Prospective study over a six month period: (January 2007 – and January 2008);
- The study population consisted of 40 patients with essential hypertension;
- The mean age of the patients included in the study was 60 ±6.5 years;
- The sample was divided into two groups:
  - Group I – 20 hypertensive patients treated with Diovan 80mg -160mg/day with normal left ventricle geometry;
  - Group II – 20 patients treated with other hypertensive drugs and with left ventricular geometric remodelling;

Patients with secondary hypertension were excluded from the study. All patients diagnosed with essential hypertension were diagnosed by: physical examination, chest X-ray, 12 lead EKG and echocardiography and biochemical examination. All demographical, clinical and paraclinical data were recorded and visits were scheduled at 3 months, 6 months and 12 months. Patients with secondary hypertension, hypertensive patients with aortic stenosis, aortic regurgitation, mitral regurgitation, hypertrophic cardiomiopathy were excluded from the study

Before and after ARBs treatment the following measurements and parameters were established:

- BP was measured by 24hours AMBP (Ambulatory Blood Pressure Monitoring)

- Mean BP value
- Mean Systolic blood pressure value
- Mean Diastolic blood pressure value
- Mean pulse pressure value

- Glucose and Lipid Metabolism:
  - blood samples obtained in the morning after and ≥12h fast
- Echocardiography
  - M-mode 2 dimensional echocardiography and Doppler recordings echocardiograms – using standard parasternal, short axis and apical views
    - LV mass (g) calculated by method Devereux:

LV mass= 0.8{1,04(LVIDd+IVSTd+PWTd)3 – LVIDd3}+0.6g

LVIDd-left ventricular internal dimension at end-diastole

IVSTd- interventricular septal thickness at end-diastole

PWTd- posterior wall thickness at end-diastole

LV mass was divided by body surface area to calculate LVMI. Left ventricular hypertrophy was defined according to the American Society of Echocardiography as follows:

- LVH → LVMI > 131g/m2 for men
  → LVMI > 100g/m2 for women

LV end-diastolic diameter and wall thickness were used to calculate relative wall thickness. Using relative wall thickness and LV mass echocardiographically, 4 left ventricular (LV) remodelling types were defined:

1. normal geometry (both parameters in normal limits)
2. concentric remodelling (LV mass is normal and wall thickness in increased)
3. eccentric hypertrophy (increased LV mass and normal wall thickness)
4. concentric hypertrophy (both LV mass and wall thickness are increased

- Electrocardiography was used to diagnose the left ventricular hypertrophy (LVH; ECG-LVH) using: the Romhilt – Estes scoring system for ECG-LVH and the Cornell Voltage Criteria.

The following risk factors were considered:

- Diabetes mellitus diagnosed as FPG ≥120 mg/dl.
- Dislypidemia diagnosed as low-density lipoprotein cholesterol (LDL-C) levels >130mg/dl
- low-density lipoprotein cholesterol (LDL-C) levels > 100mg/dl in diabetic patients
- High-density lipoprotein cholesterol [HDL-C] levels <40mg/dl
- Triglyceride levels >200mg /dl and levels >150mg /dl in diabetics
- Obesity diagnosed as BMI (body mass index) > 30 kg/m², BMI = weight in kilograms / (height in meters) ²
- Smoking and sedentarism.

For statistical analyses, we used the SPSS programme for Windows.

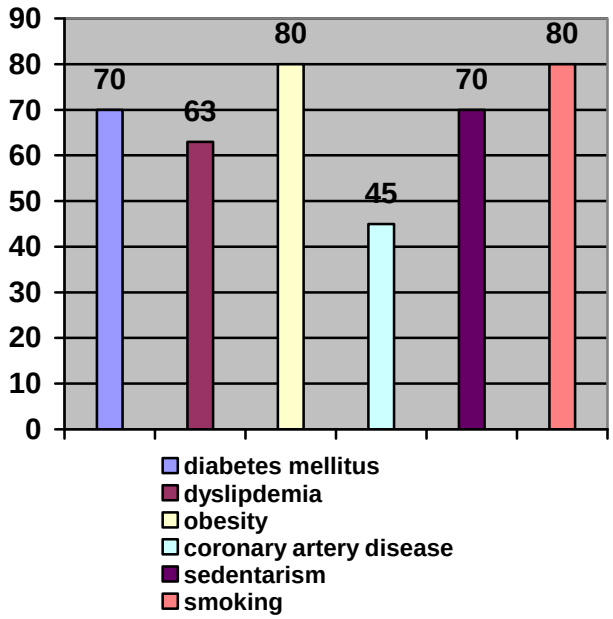
Results:

The patients were divided in two groups: group I – 12 patients (30%) with normal left ventricle geometry and group II 28 patients (70%) with geometric left ventricle remodelling. The patients from group II were divided into 3 subgroups: 8 patients with concentric left ventricle remodelling, 14 patients with concentric left ventricular hypertrophy and 6 patients with excentric left ventricular hypertrophy.

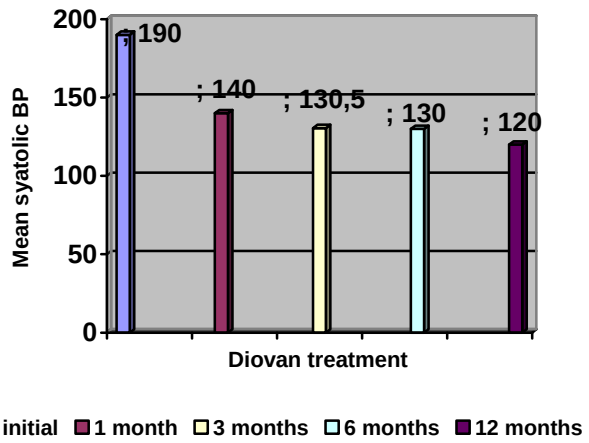
The mean age of the patients included in the study was 60 ±6.5 years. A comparative analyse of the risk factors was made, from the two groups of patients before and after Diovan treatment in a 80-160 mg/ day dose.

There was an increase prevalence of diabetes mellitus (70%), dislypidemia (63%0. obesity (80%), sedentarism (70%), coronary artery disease (45%).

Picture no. 1.The risk factors prevalence

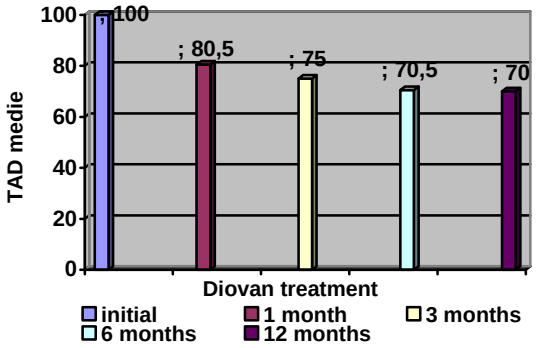


Picture no. 2. The Mean Systolic Blood Pressure and Diovan treatment



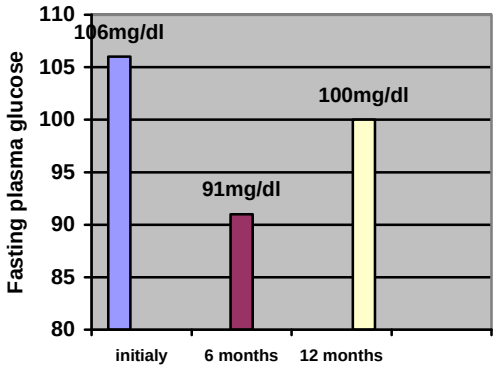
The ambulatory blood pressure monitoring (ABPM) in patients treated with Diovan, after 3 months of treatment shows an efficient control of the blood pressure over 24 hours. The mean arterial blood pressure values were significantly decreased after 3 month of Diovan treatment, the mean systolic BP decreased from 170.5 mmHg to 130 mmHg, and the diastolic blood pressure decreased from 100 mmHg to 75 mmHg. After 12 months, the mean systolic BP decreased to 120 mmHg and the mean diastolic BP decreased to 70mmHg.

Picture no. 3. The mean diastolic blood pressure and Diovan treatment



Diovan treatment did not interfere with lipid and glucide metabolism. The analyse of the bioumoral parameters evaluated at the beginning of the treatment with Diovan and then 3, 6, 12 months after showed that Diovan had no effect on fasting plasma glucose level in hypertensive patients without diabetes mellitus. Diovan had no negative effects on glucide metabolism in hypertensive patients with diabetes mellitus, with no influence on the fasting plasma glucose level or random plasma glucose.

Picture no. 4. The fasting plasma levels evolution after Diovan treatment



Diovan had no negative effect on the lipid metabolism. 6 and 12 months after the Diovan treatment in a 80-160mg/ day dose, the triglycerides and total cholesterol levels remained the same. Diovan proved to be metabolically neutral and this places it into the modern antihypertensive therapies.

The patients with more associated risk factors proved to have an increased left ventricular mass compared to the patients without associated risk factors. Concentric left ventricular hypertrophy is correlated with the extension of coronary artery disease and with the presence of cardio-vascular risk factors as diabetes mellitus, dislypidemia, obesity.

After 3 months of Diovan treatment in a dose of 80-160mg/day, the - interventricular septal thickness, posterior wall thickness, left ventricular mass were significantly decreased, as shown in the table below.

Table1. Left ventricular hypertrophy reduction after Diovan treatment

	Before Diovan treatment	3 months of Diovan treatment	12 months of Diovan treatment	P value
IVSTd	13 mm	11.04 mm	10.3 mm	P<0.05
PWTd	12	11.02	10.5	P<0.05
LV mass	240.5	110.5	105.3	P<0.05

DISCUSSIONS

Hypertension is characterized by a sustained elevation of resting systolic BP, diastolic BP, or both and hemodynamic anomalies of cardiac output (CO) and total peripheral vascular resistance (TPR), and arterial compliance.

An increase in left ventricular mass represents a compensatory response of hypertensive heart to augmented loading conditions.

The renin-angiotensin-aldosterone system (RAAS) and angiotensin II plays a pivotal part in the pathogenesis of hypertension. In the early phase of ventricular dysfunction, in myocardium, the RAAS activates and levels of angiotensin II increase and the stimulus for this activation is the wall stress (1,2). The effects of angiotensin II excess are represented by an inotropic effect directly on human cardiac muscle an arithmogenic effect and coronary vasoconstriction. The expression of protooncogenes like c-fos, c-myc, c-jun contributes to the hypertrophy of myocytes, fibroblast proliferation and stimulates collagen production. (3)

The vascular RAAS plays an important role, smooth muscle cells produces contraction and also vascular proliferation and remodelling. The rennin is secreted by kidneys. The enzyme circulates in the blood stream and hydrolyzes angiotensinogen into peptide angiotensin I.Angiotensinogen is localised in smooth muscle cell and adventicia. Angiotensin – converting enzyme is localized on the membrane of the endothelial cells where it is synthesized. The vascular angiotensin II synthesis is probably in extracelular space.

Angiotensin–converting enzyme participates in circulating angiotensin I convertion to angiotensin II, and in local production of angiotensin II. It is known that 90% of angiotensin converting enzyme is produced in the endothelial, cardiac, kidneys, suprarenals and brain tissue) and only 10% can be found in blood (4).Vascular

remodelling is represented by wall thickness increase because of an increased level of water and sodium, muscular hypertrophy and collagen proliferation.

In endothelial dysfunction, a great quantity of angiotensin converting enzyme is released from endothelium and the effect is the increase of angiotensin II production with all its effects, including the cardiac and vascular remodelling.

Angiotensin II acts by its specific receptors on different organs and tissues by specific cellular receptors and the main receptors are AT1 and AT2 type. There are two subtypes of AT1 receptors: AT1a and AT1b. The AT1 and AT2 angiotensin receptors contain about 360 amino acids. The gene for AT1 receptor is located on chromosome 3, and that for AT2 receptor on chromosome X. AT 1 receptors are localized on the heart, vessels, brain, kidneys, having a main role in the mechanism of action of angiotensin II.

By AT1 receptors modulate the main functions of angiotensin II:

- constricting arteries and veins and increasing blood pressure
- acts on the adrenal cortex, causing it to release aldosterone
- induces cell proliferation
- increases the release of endothelin
- induces PAI-1 (plasminogen activator inhibitor-1) expression (5,6).

The AT1a receptors are probably implied in vasoconstriction and AT1b receptors are implied in hormone regulation and osmosis control. (7).

Angiotensin receptor blockers (ARB), also named Sartans are recommended by the new ESH.ESC 2007 arterial hypertension guideline as first line therapy.

All ARB's have a long half life and a 24 hour action, this is why they can be used in a once - daily regimen. Most of ARB's specifically antagonize the action of angiotensin II in 80-100 % during the first 24 hours after the administration of a therapeutic dose, and the inhibition is maintained at more than 60% for 24 hours. The angiotensin receptor blockade by ARB's is very good for ARB's and can be done either by an increase of the drug concentration or by a greater affinity for ARB's receptors(8).

The clinical efficacy was demonstrated by the reduction of the blood pressure (BP) for 24 hours and peak (T:P) ratio (the average BP reduction during the last 2 h of the dosing interval compared to the average of the maximal reduction in BP over two consecutive hours, which is a parameter approved by FDA for the antihypertensive therapies (9). All ARB's have T:P ratio>50%.

The ARBs act by selectively binding and blocking the angiotensin II type 1 (AT_1) receptor. The pharmacologic basis for interrupting the RAAS with ARB therapy is threefold. Selective AT_1 blockade with an ARB inhibits the negative cardiovascular consequences of AT_1 receptor activation. Circulating angiotensin II (whose levels undergo a compensatory rise during ARB therapy) can act only at unopposed AT_2 receptors. This should preserve (or even augment) the favourable effects of angiotensin II, potentially producing benefits above and beyond those due to blood pressure. Because they act at the final step of the RAAS, ARBs block the effects of angiotensin II regardless of whether it is generated systemically by ACE or within tissues by ACE-independent pathways (10,11,12).

ARB's do not interfere with bradikinine metabolism. Bradikinine has vasodilatatory effects, stimulates the nitric oxide production and of prostacyclin, but also produces side effects like (cough and bronchospasm). Unlike angiotensin-converting enzyme inhibitors, they do not inhibit bradykinin metabolism or enhance prostaglandin synthesis. ARB's do not increase blood levels of bradikinine, having a better tolerance than ACE inhibitors and don't have the ACE inhibitors side effects (13). Clinical studies have demonstrated that ARB's are well tolerated, a single dose provides effective BP control along the day, with a very good tolerance similarly to placebo. A synthesis of 18 clinical studies with Valsartan in hypertensive patients, administrated in a mean dose of 80mg/day for a period of 6 months in 2 years, demonstrated the antihypertensive effect independently of age, gender or race.

The tolerance of ARB's is very good and the incidence of side effects is lower; they do not adversely affect lipid or glucide profiles or cause rebound hypertension after discontinuation. In experimental studies on animals ARB's reduced the myocardial hypertrophy and fibrosis, the vascular hypertrophy and hyperplasia from hypertension (14).

The left ventricular hypertrophy is associated to a normal cardiac phenotype for atrial natriuretic peptide (ANP), a marker of myocyte hypertrophy.

The ARB's cardioprotection was demonstrated in clinical studies in hypertensive patients treated with ARB's, the result being the regression of left ventricular mass, with no modification of left ventricular endiastolic stress and stroke index.

The ARB's have a renoprotective effect: they reduce the microalbuminuria in old patients with essential hypertension and diabetes mellitus.

In experimental studies ARB's inhibits the gene implicated in the synthesis of ARNm implicated in the synthesis of TGF beta (transforming growth factor) and of the extracellular matrix (fibronectine, collagen type I, III and IV, laminin.

ARB's directly inhibits the hypertrophy or proliferation of the cardiomyocites and non myocites cells (fibroblasts), mesangial cultures and smooth muscle cells (which are stimulated by angiotensin II) (15,16) .

ARB's are recommended in the treatment of hypertension and left ventricular hypertrophy, hypertension and diabetes mellitus, hypertension and heart failure, hypertension in elderly. ARB's are recommended in all patients with ACEI intolerance. (17,18).

CONCLUSIONS

1. After 3 months of Diovan treatment the left ventricle mass significantly reduced.
2. ARB's play an important part in the regression of myocardial remodelling by decreasing the left ventricular mass.
3. Angiotensin receptor blockers as monotherapy are very efficient and represent a first line antihypertensive therapy.
4. Diovan therapy in a single dose efficiently controlled the BP levels in the majority of the treated patients.
5. ARB's do not produce cough and this is why this antihypertensive therapy is an alternative to ACEI intolerance.

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