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ORIGINAL ARTICLE / ÖZGÜN ARAŞTIRMA

Effects of valsartan and nebivolol on blood pressure, QT dispersion and left ventricular hypertrophy in hypertensive patients

Hipertansif hastalarda valsartan ve nebivololun, kan basıncı, QT dağılımı ve sol ventrikül hipertrofisi üzerine etkileri

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ABSTRACT

Objectives: The aim of this study was to analyze the antihypertensive effect of Valsartan and Nebivolol and their effects on QT dispersion and left ventricular hypertrophy (LVH) in the treatment of naive hypertensive patients.

Methods: A prospective study with a six-month follow-up was conducted on hypertensive patients with LVH and mild/ moderate essential hypertension. The patients were randomly assigned to Valsartan (80 to 160 mg/day) or Nebivolol (5 to 10 mg/day) groups. The study group consisted of 108 patients, 55 in the Valsartan group and 53 in the Nebivolol group.

Results: The range of mean systolic blood pressure (SBP) varied from 152±17 (baseline) to 132±17 mmHg (follow-up) in the Valsartan group ($p<0.001$); from 146±13 to 125±14 mmHg in the Nebivolol group ($p<0.001$). The decrease in mean diastolic blood pressure (DBP) was 9.5±2.5 mmHg in the Valsartan group and 12.3±5.0 mmHg in the Nebivolol group. A significant reduction in QT and corrected QT (Bazett's formula) dispersion was observed in both groups, with a slightly higher reduction in the Valsartan group. Echocardiography showed a decrease in the left ventricle mass (LVM) indices ($p<0.05$) in both groups with a greater reduction in the Valsartan group.

Conclusion: Valsartan treatment was as effective as Nebivolol in reducing the 24 hour- SBP after a 6 month treatment. Nebivolol treatment proved to be superior to Valsartan in reducing DBP. Both therapies were effective in reducing the LVH; Valsartan proved to be superior to Nebivolol in reducing the QT interval indexes in relation to blood pressure and LVM reduction.

Key words: Hypertension, electrocardiography, left ventricular hypertrophy, QT interval, QTc, echocardiography.

ÖZET

Amaç: Bu çalışmanın amacı valsartan ve nebivololun antihipertansif etkilerini ve bu ilaçların hipertansif hastaların tedavisinde QT dağılımı ve sol ventrikül hipertrofisi üzerine etkilerini analiz etmektir.

Yöntemler: Sol ventrikül hipertrofisi (SVH) bulunan hafif/orta hipertansiyonlu hastalarda 6 ay süreli takip içeren prospektif bir çalışma düzenlendi. Hastalar rastgele olarak Valsartan (80-160 mg/gün) veya Nebivolol (5-10 mg/gün) gruplarına alındı. Çalışma grubu 55'i Valsartan grubu, 53'ü Nebivolol grubunda olmak üzere toplam 108 hastadan oluşturuldu.

Bulgular: Valsartan grubunda ortalama sistolik kan basıncı (SKB) 152±17 mmHg (bazal)'den 132±17 mmHg (takip)'e değişti ($p<0.001$). Nebivolol grubunda ise ortalama SKB, 146±13 mmHg (bazal)'den 125±14 mmHg (takip)'e değişti ($p<0.001$). Valsartan grubunda ortalama diyastolik kan basıncı (DBP) azalması 9.5±2.5 mmHg ve Nebivolol grubunda 12.3±5.0 mmHg idi. Her iki grupta da QT ve düzeltilmiş QT (Bazett formülü) dağılımında anlamlı azalma gözlendi ve bu azalma Valsartan grubunda hafifçe daha fazla idi. Ekokardiyografi sol venrikül kitle (SVK) indekslerinde Valsartan grubunda daha fazla azalma ile birlikte her iki grupta azalmayı gösterdi ($p<0.05$).

Sonuç: Valsartan tedavisi 24 saatlik SKB'ında 6 aylık tedavi ile Nebivolol kadar etkili bulundu. Nebivolol tedavisi DKB'ını düşürmede Valsartan tedavisine üstün bulundu. Her iki tedavi SVH'sini azaltmada etkili idi. Valsartan kan basıncı ve SVK'de azalmayla birlikte QT aralık indekslerinde azaltmada Nebivolole üstün bulundu.

Anahtar kelimeler: Hipertansiyon, elektrokardiyografi, sol ventrikül hipertrofisi, QT aralığı, ekokardiyografi

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INTRODUCTION

In hypertensive patients, the left ventricular hypertrophy (LVH) predicts an increased morbidity and mortality, sudden death being up to 10 times more prevalent in individuals with LVH than those without LVH[1]. In the Framingham Study, LVH was recognized as a strong, virtually independent risk factor[2].

The QT interval is the surface Electrocardiographic (ECG) representation of the action potential duration in the ventricle and prolongation of the QT interval has been associated with an increased risk of ventricular tachycardia and sudden death[3]. Its standard clinical correction [Bazett's formula[4] QTc] is used in order to adjust this interval by the heart rate. The QT interval duration has also been found to predict all causes and cardiac mortality in hypertensive subjects with LVH[5] and QTc dispersion appears to be a valid predictor of arrhythmias[6].

An effective antihypertensive treatment, may improve the non-invasive electrocardiographic parameters in addition to the control of arrhythmias and regression of LVH[7,8].

Valsartan is part of the class of angiotensin II receptor blockers (ARBs). The benefits of ARB therapy of hypertension go beyond the reduction in blood pressure (BP). Additional advantages include a decrease in ventricular arrhythmias[9] or a reduction in the abnormal QT dispersion[10]. Valsartan has proved to have a favourable safety and efficacy profile and represents a good option for a wide range of hypertensive patients[11].

Nebivolol has proved to be as efficient as any other antihypertensive drugs (e.g. calcium channels blockers, angiotensin-converting enzyme (ACE) inhibitors, and older ß-blockers[12-14]. Nebivolol is a highly selective β1-adrenergic receptor blocker with vasodilating action through stimulation of endothelial nitric oxide (NO) bioactivity[15,16]. Nebivolol has proved to be as efficient as any other antihypertensive drugs (e.g. calcium channels blockers, angiotensin-converting enzyme (ACE) inhibitors, and older ß-blockers[12-14]. It also has a good tolerability and fewer adverse events compared with older beta-blockers[15,16].

Two therapeutic strategies (Valsartan and Nebivolol, administered once daily) were applied to treatment naive hypertensive patients, with ECG and echocardiographic evidence of LVH.

In present study, the effects of Valsartan and Nebivolol on BP, LVH and index of QT interval, corrected for heart-rate QT interval (QTc), were analyzed and compared.

PATIENTS AND METHODS

A prospective randomized, parallel-group study was conducted at the Diagnosis and Treatment Centre, Cluj-Napoca, Romania. The study was approved by the Ethics Committee of the "Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca, and all subjects gave informed consent for participation in the study.

Consecutive eligible adult outpatients of either sex with mild or moderate hypertension (office sitting SBP of 140-179 mmHg and/or office DBP 90-109 mmHg, defined according to international guidelines (18)) and echocardiographic LVH defined as left ventricular mass index ≥ 134 g/m² for men and ≥ 110 g/m² for women[19], were included in the study. Patients were enrolled between November 2004 and August 2007 and had never been treated as hypertensive patients (naive to antihypertensive drug treatment). The patients were prospectively followed-up for 6 months. Patients were excluded from the study if they had any of the following: malignant and known or suspected secondary hypertension; clinically significant heart disease (coronary heart disease, major arrhythmias, cardiac valvular defects, heart failure); concomitant cerebrovascular, renal, hepatic diseases, diabetes, haematological and malignant diseases, psychiatric disorders, obesity (BMI>30kg/m^2), pregnancy and known or suspected hypersensitivity to ARB or β blockers.

The patients that complied with the inclusion criteria were randomly assigned to one of the two treatment groups: Valsartan or Nebivolol the first patient being assigned to the Valsartan group and the second to the Nebivolol group. The study was not blind, both patient and physician were familiar with the used drugs. The starting dose was 80 mg for Valsartan and 5 mg Nebivolol, once daily in the morning (as recommended in the international guidelines[18]. The doses were doubled (160 mg for Valsartan and 10 mg for Nebivolol) in patients with inadequate BP control (office SBP ≥ 140 mmHg or

office DBP ≥ 90 mmHg, after 4 to 6 weeks of treatment with the initial doses). The medical history of each patient was recorded; physical examination, office BP measurement and 12-lead electrocardiograms were performed at the screening visit. At the study initiation and at the final visit, twenty-four-hour ambulatory BP monitoring computed LVMI[19,20], M-mode echocardiography, computed LVMI, twenty-four hour ECG recordings for computing the QT and QTc were performed.

The office BP was measured using a standard sphygmomanometer, with the patient seated for at least 10 minutes. For the office BP reference value, the mean of 3 measurements at rest in the sitting position was used.

The ambulatory blood pressure (ABPM) was monitored with ABPM-04, 99/BP411 - Medibase. Before the beginning of ABPM, blood pressure was measured with a mercury sphygmomanometer, with the patient seated for at least 10 minutes. The arm with higher BP values at sphygmomanometer evaluation was chosen for ABPM. In order to reduce errors during the day, all patients were asked to ensure that the arm was always parallel to the trunk when the cuff was inflated. Readings were obtained automatically at 15 minutes interval from 6:00 am to 10:00 pm and 30 minutes interval from 10:00 pm to 6:00 am. All the measurements were performed by the same investigator, using the same equipment, both at the beginning of the study and during the follow up.

All patients underwent 24 hour ambulatory ECG recording with a three channel (Cardiospy system Holter ECG, recorder type 3CH+PM). A single investigator, blinded to other measurements and treatment assignment, checked the automatic measurements of QT interval indexes. Appropriate corrections of cursor location were made and tracings in which the T wave was isoelectric or of too low amplitude for accurate determination of the end point, were excluded.

Echocardiography was performed with the patient in the supine left lateral decubitus position. The echocardiographic investigations were performed by the same investigator, using the same equipment (ESAOTE MyLab, 3.5-MHz transducer), both at the beginning of the study and during the follow up. The M-mode echocardiographic evaluation of the left ventricle was performed under 2-dimensional control. Measurements were taken according to the American Society of Echocardiography recommendations[20]. The following measurements were made for each patient: intraventricular septal thickness (IVSTd), posterior wall thickness (PWTd), end-diastolic diameter (LVIDd), and end-systolic diameter (LVISd). The left ventricular mass was calculated using the Devereux and Reichek formula[21]: LVM=1.04• ((IVSTd+ PWTd + LVIDd) ^{3}- (LVIDd) ^{3}) - 13.6 g. The left ventricular mass index (LVMI) was determined by dividing LV mass by body surface area.

All ABPM, ambulatory ECG and echocardiographic parameters were determined at the beginning of the study and after 6 months of Valsartan or Nebivolol therapy. All patients received regular therapy during the follow-up period.

Statistical Analysis

The values of the quantitative variables were expressed as means ± SD (standard deviation); the values of qualitative variables were expressed as a percentage with associated 95% confidence intervals [binomial distribution formula] [22,23].

Changes from baseline in QT indexes (QT dispersion, QT maxim, QTc maxim, and QTc dispersion), BP and LVMI measurements were analyzed using the Student t test after investigation of the normality distribution. When the normality was not accomplished a non-parametric test was used to compare the results (Mann-Whitney: two independent-samples test, Wilcoxon: two-related-samples test). The Z test for comparison of the equality of two proportions was applied whenever appropriate. Pearson's correlation coefficient was applied to assess the relationship between changes from baseline systolic blood pressure (SBP), diastolic blood pressure (DBP), left ventricular mass index and the change from baseline QTd and corrected QT dispersion values. A p value < 0.05 was considered statistically significant.

Statistical analyses were performed by using SPSS 12.0.

RESULTS

One hundred and eight eligible patients (48 men – 95%, CI (35.19 – 54.62), 60 women – 95% CI (45.38-64.81)) were randomized to either Valsartan

(n = 55) or Nebivolol (n = 53) once daily. The demographic and baseline clinical characteristics of the two groups are presented in Table 1. All patients included in the study completed the 6 months follow-up.

Table 1. Baseline demographic and clinical characteristics by treatment group

Variable	Treatment group		p-value
	Valsartan	Nebivolol	
Gender: absolute frequency (percentage)			
Male	20 (36.4%)	28 (52.8%)	0.0783
Female	35 (63.6%)	25(47.2%)	0.0783
Age: means±SD			
Male (years)	57.85±14.12	58.04±10.44	0.9590
Female (years)	62.11±11.94	60.07±14.94	0.5490
BMI	27.44±4.93	28.42±4.37	0.2790
Mean 24h SBP (mmHg)	152.56±16.87	145.58±13.04	0.0180
Mean 24h DBP (mmHg)	86.87±11.71	83.21±13.44	0.1330
QT dispersion (ms)	74.71±4.65	74.28±5.42	0.6620
QT max (ms)	442.35±18.13	438.09±22.21	0.2780
QT min (ms)	373.22±15.13	363.81±20.76	0.1660
QTc max(ms)	511.65±27.17	519.28±33.67	0.1960
QTc min(ms)	433.93±24.74	441.30±33.26	0.1770
QTc dispersion (ms)	77.71±6.11	77.98±6.51	0.8230
LVMI (g/m²)	173.16±25.28	165.43±25.10	0.1140

SD: Standard deviation, BMI: Body mas index, QT max: Maximal QT interval,

QT min: Minimal QT interval, QTc max: Maximal corrected QT interval, QTc min: Minimal corrected QT interval , LVMI: Left ventricular mass index

Nine characteristics, baseline vs. follow-up, were compared on each treatment group: Mean SBP, ΔSBP, Mean DBP, ΔDBP, QT max, dQT, QTc max, dQTc, and LVMI. The results expressed as mean value and associated standard deviations as well as the p-values for the mean comparisons are presented by treatment groups in Table 2.

In all 108 patients with valid ambulatory BP recordings, 24-hour SBP and DBP values were significantly ($p<0.05$) reduced by both treatments compared to baseline values. After 6 months of treatment, SBP reduction rates were significant and similar in both treatment groups but there was a higher reduction observed in DBP in the Nebivolol group (Table 2).

After 6 months of treatment, there was a statistically significant reduction in QT indexes (QT dispersion, QTc dispersion, QT max, QTc max) in the Valsartan and Nebivolol group compared to baseline values (Table 2).

The difference of the SBP mean on follow-up evaluation was revealed as significantly statistical when the Valsartan and Nebivolol groups were compared ($p= 0.034$). The same was observed also for DBP mean ($p=0.006$).

No significant differences between the investigated groups were identified in comparison of LVMI at baseline and follow-up (baseline $p=0.114$; follow-up $p=0.450$).

The correlation between the change in QT dispersion and BP and LVMI in both treatment groups are presented in Table 3.

Table 2. Treatment group comparison of mean changes from baseline parameters (mean±SD)

Parameter	Valsartan Group			Nebivolol Group		
	pre-treat	post-treat	p	pre-treat	post-treat	p
Mean SBP	152.56±16.87	131.67±17.17	< 0.001	145.58±13.04	125.25±13.64	< 0.001
ΔSBP	n.a.	20.89±4.39	n.a.	n.a.	20.34±4.53	n.a.
Mean DBP	86.87±11.71	77.36±11.74	< 0.001	83.21±13.44	70.91±12.17	< 0.001
ΔDBP	n.a.	9.50±2.48	n.a.	n.a.	12.30±4.99	n.a.
QT max	442.35±18.13	425.64±19.17	<0.001	438.09± 22.21	429.38±22.34	<0.001
QT min	373.22±15.23	359.24±16.48	<0.001	363.81±20.76	360.10±23.28	<0.001
dQT	74.71±4.65	66.38±5.13	<0.001	74.28±5.42	69.28±6.76	<0.001
QTc max	511.65±27.17	496.25±28.28	<0.001	519.28±33.67	508.40±32.26	<0.001
QTc min	433.93±24.74	429.22±26.50	<0.001	441.30±33.26	434.85±31.72	<0.001
dQTc	77.71±6.11	67.04±6.85	<0.001	77.98±6.51	73.55±7.38	<0.001
LVMI	173.16±25.28	156.51±24.68	<0.001	165.43±25.10	152.91±24.72	<0.001

n.a.: Not applicable, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, QT max: Maximal QT interval, QT min: Minimal QT interval, dQT: QT interval dispersion, QTc max: Maximal corrected QT interval, QTc min: Minimal corrected QT interval, dQTc: Corrected QT interval dispersion, LVMI: Left ventricular mass index

Table 3. Pearson correlation coefficients between change in BP, QT interval dispersion and LVMI from baseline with treatment

Parameters	Group	
	Valsartan	Nebivolol
ΔSBP-QT dispersion	0.516**	0.307*
ΔSBP-QTc dispersion	0.251*	0.542**
ΔDBP-QT dispersion	0.471**	0.368**
ΔDBP-QTc dispersion	0.309*	0.525**
LVMI-QT dispersion	0.650**	0.715**
LVMI-QTc dispersion	0.294*	0.470**
LVMI-ΔSBP	0.580**	0.435**
LVMI-ΔDBP	0.561**	0.382**

*p<0.01; ** p<0.001

DISCUSSION

Two drugs were investigated in the treatment of naive patients with mild or moderate essential hypertension by ambulatory assessment of BP; ECG and LVMI were used as primary end points.

In this study, after a 6 month treatment, mean 24h SBP, mean 24 hDBP, QT max, QTc max, QTd, QTc dispersion and LVMI were decreased compared to baseline values in both treatment groups (Valsartan 80 to 160mg/day vs. Nebivolol 5-10 mg/day) without previous antihypertensive treatment.

Both drugs were associated with comparable reductions in 24h SBP, but Nebivolol proved to reduce the DBP significantly compared to Valsartan. This result is in accordance with other studies; a greater effect of Nebivolol on DBP but not on SBP compared to Losartan was also observed[24].

Valsartan treatment proved to determine a significant reduction of QTd and QTc dispersion compared to Nebivolol in treated patients.

In hypertensive patients with no evidence of coronary disease the most important sudden cardiac death cause is ventricular arrhythmia[5,25]. In hypertensive patients an important correlation between sudden cardiac death and an increased value of QT dispersion[5] was observed and it was demonstrated that different antihypertensive treatments decrease the QT dispersion and reduce arrhythmias[10,26,27].

It is well known that antihypertensive treatments which inhibit the renin angiotensin system (RAAS) decrease also the QT dispersion in hypertension[10,28]. In the same way in the present study ARB (Valsartan) treatment, showed a significant decrease of QTd and QTc in hypertensive patients. ARB's have

been proved to reduce the LVMI this being one of the most important causes of the QTd decrease. In left ventricular hypertrophy (LVH) directly linked to myocardial fibrosis and increase of ventricular premature beats and re-entry activity, ventricular tachycardia and sudden cardiac death occur. LVH increases the action potential duration and the risk of ventricular tachycardia and sudden cardiac death[29].

In arterial hypertension and Holter ECG documented arrhythmias, the risk of sudden cardiac death increases. In a study by Galinier et al., Lown class IIb in Holter ECG, and QTd > 80 ms were significantly related to global, cardiac and sudden death ($p < 0.01$)[30]. Elevated QT interval dispersion was associated with more severe ventricular arrhythmias in hypertensive patients with LVH. The mechanism of an increased inhomogeneity of repolarization, represented by QT interval and QT dispersion, was considered to be related to anatomic modifications induced by LVH[25].

Experimental studies have demonstrated that Angiotensin II has arrhythmogenic effects on the cardiac system. Literature data supports the idea that inhibition of the rennin angiotensin system protects heart and other organs from hypertensive complications[31].

Arrhythmias can occur in LVH when the repolarization homogeneity is altered but the rennin angiotensin system (RAS) and sympathetic nervous system (SNS) are closely interrelated[32]. Thus, the inhibition of SNS could be responsible for the decrease of QTd by ARB[33]. Moreover, the β blocker therapy has proved to decrease QTd especially in patients with left ventricular systolic dysfunction[34].

The effects of Nebivolol treatment on QT dispersion in hypertensive patients with LVH were evaluated by Galetta et al.[35]. The authors observed that Nebivolol reduced QT dispersion in hypertensive subjects after four weeks of treatment. This effect occurred without any change in LVH, did not seem to be related to the lowering of the blood pressure and could contribute to reduce arrhythmias as well as sudden cardiac death in at risk hypertensive patients[36]. In contrast, in the present study Nebivolol reduced QTd from baseline values and also reduced LVMI.

Nebivolol is a highly selective ß1-adrenergic receptor blocker with vasodilating action through stimulation of endothelial nitric oxide (NO) bioactivity[37]. Nebivolol also has been shown to increase the left ventricular performance and improve the coronary flow reserve[38].

In the present study, the effects of both therapies on QT indexes were related to BP and LVMI decrease. Because the after load increases, myocardial stress is raised and can induce the risk of spontaneous depolarization. In this study the QTd decrease was related to the after load reduction, this being the possible mechanism implied. Another mechanism is that the activation on SNC is a cause of after depolarization and can increase the heterogeneous repolarization[39].

Antihypertensive treatment with Valsartan and Nebivolol reduces the heterogeneous repolarization and could help to reduce the ventricular arrhythmias risk and the risk of sudden cardiac death. Valsartan treatment proved to be superior over Nebivolol treatment in reducing the heterogeneous repolarization by BP reduction and LVH reduction.

The small sample size of subjects was the main limitation of the study. The investigation of the patients on a single centre study and also the method used for randomization could be considered also a limitation of the present study. A more extensive study is required.

Conclusion

In this study, in a small sample of treatment naive hypertensive patients, the antihypertensive effect on SBP of Valsartan 80-160 mg was not significantly different from that of Nebivolol 5-10 mg. It can be concluded based on the obtained results that Valsartan 80 to 160mg/day was as effective as 5-10 mg/day of Nebivolol in reducing the 24h systolic but not in reducing the diastolic BP during 6 months of treatment in patients with mild or moderate essential hypertension without previous antihypertensive treatment. Nebivolol provided a significantly greater reduction of DBP compared to Valsartan. The effect on LVH of both treatments was not significantly different. Valsartan proved to be superior to Nebivolol with a significantly greater reduction of QT and QTc dispersion in relation to the BP and LVMI reduction.

Conflict of Interest

The research was not financially supported by any grants or any kind of funding from any pharmaceutical company or any other possible sources. All the authors had an active involvement in data collection and analysis, writing, preparation and reviewing the manuscript.

Author contributions: LL and SLN designed the study, analyzed the data and contributed to writing of the paper. SDB statistically analyzed the data and contributed to the writing of the paper. All the authors accept the responsibility for the data and the accuracy of the data analysis.

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