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The Effects of Nebivolol Therapy on QT Dispersion in Patients with Congestive Heart Failure

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Abstract: Nebivolol results in a significant improvement in Left Ventricular (LV) systolic function and prognosis in patients with Congestive Heart Failure (CHF) but it is unknown whether nebivolol effects QT dispersion (QTd), which is related with sudden cardiac death. Aim of this study was to investigate the effects of nebivolol on QTd in heart failure patients. Fifty CHF patients (age 65±11 years, 31 male) with a LV ejection fraction ≤35% and in New York Heart Association (NYHA) class II-III were included in this study. After the 1 month standard heart failure therapy; nebivolol was added on standard therapy at an initial dose of 2.5 mg and up titrated to the maximum tolerated dose. At baseline and at the 3rd month of nebivolol treatment all patients were assessed by clinical, laboratory, electrocardiographic and echocardiographic examinations. From 12-lead standard ECG maximum and minimum QT intervals (QTmax, QTmin), QTd, corrected QT intervals (QTcmax, QTcmin) and corrected QTd (QTcd) values were calculated at baseline and at the end of follow-up period. Mean nebivolol dose was 4.5±0.49 mg. QTd and QTcd values significantly decreased with nebivolol therapy (QTd: 81±25 vs. 71±22 ms, $p<0.0001$; QTcd: 86±27 vs 70±16 ms, $p<0.0001$). While QTcmax decreased significantly ($p<0.001$), there was no statistically significant changes in QTcmin value. A significant reduction was noted in the resting heart rate (94±26 vs 75±12 bpm, $p<0.0001$), systolic and diastolic blood pressures ($p<0.0001$). Left ventricular systolic functions also had significant improvement that Ejection Fraction (EF) increased from 28.8±3.4-31.4±4%, ($p<0.0001$). As a conclusion, added-on nebivolol therapy for 3 months was associated with a significant decrease in QTd and QTcd values and improvement in systolic functions in heart failure patients. This effect of nebivolol, which is due to the improvement in myocardial repolarization properties and special vasodilatory effects, may contribute to a possible reduction in sudden cardiac death in congestive heart failure patients.

Key words: Nebivolol, heart failure, QT dispersion, patient, congestive, left ventricular

INTRODUCTION

Chronic heart failure is a common disease with restrictive symptoms and pure prognosis due to high mortality (Ho *et al*., 1993). The 1-year mortality rate is 5-10% in patients with mild symptoms, but 30-50% in patients with a more advanced stage of disease (Peterson *et al*., 1997). And about 30-50% of these are sudden death due to lethal ventricular arrhythmias (Parmley and Chatterjee, 1986; Bigger, 1987; Narang *et al*., 1996).

Clinical and electrophysiological studies have shown that the most important mechanism of malignant ventricular arrhythmia is impaired homogeneity of myocardial repolarization (Periomaki *et al*., 1995; Vasallo *et al*., 1988). The present electrical inhomogeneity reflects directly on QT in the standard 12 lead surface ECG and QTd is defined as the interlead QT interval variability. QTd reflects regional differences in myocardial repolarization and can give indirect clues due to arrhythmogenicity (Kuo *et al*., 1983). It was reported that Qtd and Qtcd values increased in CHF patients when compared with control population (Bonnar *et al*., 1999).

Recent studies that were planned to investigate the high risk arrhythmic unexpected deaths have reported that QTd has a high predictive value due to sudden cardiac death in patients with ischemic cardiac diseases (Periomaki *et al*., 1995; Higham *et al*., 1992; Pye *et al*., 1994) hypertrophic cardiomyopathy (Buja *et al*., 1993) and congestive heart failure patients (Bonnar *et al*., 1999; Yee and Struthers, 1997; Barr *et al*., 1994; Brooksby *et al*., 1990). For this reason, QTd may be an important parameter to follow up the CHF patients.

β-blocker drug therapy results in a significant improvement in left ventricular systolic function and

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prognosis in patients with chronic heart failure (Lombardo *et al*., 2006). Recently nebivolol that is a highly β-1 selective blocker is used in clinical practice (Bundkirchen *et al*., 2003). And with extensive clinical studies it has been shown that nebivolol, has additional vasodilator effects mediated by Nitric Oxide (NO) different from other β blockers (Dawes *et al*., 1999; Broeders *et al*., 2000). It has been also recently shown that nebivolol treatment decreased mortality and hospitalization rates in older chronic heart failure patients (Shibata *et al*., 2002; Istvan *et al*., 2005). This benefit may be due to increase in left ventricular ejection fraction but it is unclear if it has any effect on sudden cardiac death (Istvan *et al*., 2005; Fu *et al*., 1997). There are many studies that examined the effects of several drugs on QT dispersion in congestive heart failure patients (Jepson *et al*., 1999; Akbulut *et al*., 2003; Lechat *et al*., 1998; Falciani *et al*., 2001; Barr *et al*., 1997). However, there is limited data about the effects of nebivolol on QTd in CHF patients. Therefore, in the present study we aimed to evaluate the effects of nebivolol, a selective β-1 receptor blocker on QTd in congestive heart failure patients.

MATERIALS AND METHODS

Population: Patients who admitted to our cardiology clinic were screened and 50 of the congestive heart failure patients who have the inclusion criteria were selected. Selected CHF patients were clinically stable, in the NYHA II-III classes; EF ≤35%. Patients with primary uncorrected severe regurgitative and obstructive valvular disease, restrictive or hyperthrophic cardiomyopathy, uncontrolled ventricular arrhythmias, obstructive pulmonary disease, unstable angina, active myocarditis, peripheral vascular disease, atrial fibrillation, bradycardia <60 bpm, sick sinus syndrome, second or third degree heart block, hypotension (<90 mmHg), patients taking any medication influencing QT dispersion (antihistaminic and antipsychotic drugs), patients who have abnormalities on ECG that interfere with QT measurement were excluded from the study. After inclusion to the study, standard congestive heart failure treatment which included Angiotensin Converting Enzyme Inhibitors (ACE-I), digoxin and diuretics were given at a stable dose for at least one-1 month to all patients to eliminate the known effects of ACE-I and diuretics. At the end of 1 month of standard treatment basal QT measurements and laboratory tests were applied to all patients to compare with added on nebivolol therapy. Added initial nebivolol dose was 2.5 mg and was titrated at 2 weeks intervals if tolerated. All the patients were followed for 3 months with added-on nebivolol on conventional CHF treatment including ACE-I, diuretics and/or digoxin.

QT analysis: All patients had standard ECG recordings obtained at the same time interval of the day (10:00-11:00 am) with same study speed and gain settings (25 mm ms^{-1} and 0.1 mm mv^{-1}, respectively) at baseline with standard therapy and after 3rd month of follow-up period with added-on nebivolol. QT intervals were measured in all patients manually by trained investigators who were blinded to the clinical status and therapy. QT intervals were measured from the beginning of the QRS complex to the end of T wave where returned to baseline. When U waves were present the QT intervals were measured from the beginning to the bottom of T and U wave junction. QT intervals were measured in all leads if technically available. A minimum of 9 leads with measurable QT intervals was needed for determination of QT dispersion. Three consecutive cycles were measured in each lead and arithmetic mean was used for QT dispersion calculations. QT dispersion was defined as the difference between the minimum and maximum measured QT intervals. With use of Bazett's Formula (QTc: QT/square root of RR interval), QT dispersion was corrected (QTc) for heart rate.

Echocardiographic measurements: Echocardiography was performed using a VIVID 3 instrument with M-mode, 2 dimensional and pulsed, continuous and color-flow Doppler capabilities. All echocardiographic measurements were performed at baseline with conventional CHF treatment and after the end of added 3 months nebivolol therapy. EF was measured by modified Simpson's method.

Statistical analysis: Continuous variables are reported as the mean±standard deviation. Comparisons between groups were performed using Mann Whitney U test. For analysis of continuous variables and for comparisons before and after treatment period Wilcoxon's signed rank test was used. Spearmann's test was used to asses the correlations, $p<0.05$ was considered as statistically significant.

RESULTS

The mean age of study population was 65±11 years (range 38-84) and 31 of them (62%) were male. Twenty-six (52%) patients were class II; 24 patients (48%) were class III. Thirty-three (66%) of the patients were hypertensive and 23 patients (46%) were ischemic. All the patients had the same standard treatment including ACE-I, diuretic and/or digoxin. With added-on nebivolol therapy there was no change on biochemical values and blood count values at the end of 3rd month. The mean daily nebivolol dose was 4.5±0.49 mg (range 2.5-10) and the general clinical characteristics are all shown in the Table 1.

Table 1: Clinical characteristics of study population

Characteristics	Values
Total No.	50
Age (years)	65±11
Sex (M/F) (n)	31/19
Hypertensive (%)	66
Coronary artery disease (%)	46
Functional class (n)	
II	26
III	24
Drug dose(mg)	4.5±0.49
Medications	
ACE inhibitors/ARB (%)	92
Diuretics (%)	89
Digoxin (%)	78

Table 2: Clinical, echocardiographic and ECG characteristics of congestive heart failure patients basally and after the therapy

Characteristics	With standard therapy	Nebivolol therapy	p-value
Heart rate (bpm)	94±26	75±12	<0.0001*
Systolic BP (mmHg)	145±28	120±20	<0.0001*
Diastolic BP (mmHg)	87±12	76±9	<0.0001*
LV ejection fraction (%)	28.8±3.4	31.4±4	<0.0001*
QTmax (ms)	434±62	436±54	>0.05
QTmin (ms)	353±50	369±48	<0.001*
QT cmax (ms)	462±54	450±37	<0.001*
QTcmin (ms)	390±38	392±41	>0.05
QT dispersion (ms)	81±25	71±22	<0.0001*
QTcdispersion (ms)	86±27	70±16	<0.0001*

Values were reported as±standart deviation and the statistically significance limit was *p<0.05; BP: Blood Pressure; LV: Left Ventricle

The mean heart rate was significantly reduced by added nebivolol (94±26 vs 75±12 bpm, p<0.001). The mean baseline QTd value 81±25 ms were higher than normal range seen in normal population (which is between 20-50 ms). A significant decrease was observed in QTd values such as (81±25-71±22 ms, p<0.0001) and QTcd values (86±27-70±16 ms, p<0.0001). While the QTcmax value significantly decreased (p<0.001), there was no statistically significant changes in QTcmin value. There was no correlation between the dose and the percent decrease in QTd and QTcd. Like the change in QTd, nebivolol treatment also improved the left ventricular systolic functions and EF measurements increased significantly from 28.8±3.4-31. 4±4% (p<0.0001). The QTd and QTcd values before and after the treatment period are shown briefly in the Table 2.

Clinical status of the patients also improved with treatment and 8 patients in class III improved to class II, 1 patient in class II improved to class I at the end of 3 months. When the study population is subdivided into hypertensive and normotensive groups, QTd in hypertensive group decreased from 82±31-68±24 ms at 3rd month and Qtd in normotensives decreased from 79±27-69±6 ms (p<0.001). Similarly in ischemic and nonischemic patients nebivolol treatment improved QT dispersion from 83±33-72±24 ms (p<0.001) and from 77±37-70±26 ms, respectively (p<0.001). Reduction in QTd and QTcd was not related to age, gender, baseline left ventricular EF, presence of hypertension or coronary artery disease (p = 0.49).

DISCUSSION

This study first demonstrated that add-on nebivolol treatment in congestive heart failure patients decreased QT and corrected QT dispersion. QT dispersion is a noninvasive marker of inhomogeneity of myocardial repolarization, which is important in the genesis of lethal ventricular arrhythmias and many studies support that increased QTd may predict sudden cardiac death in coronary artery disease, hypertrophic cardiomyopathy and long QT syndrome (Barr *et al*., 1994; Brooksby *et al*., 1990; Fu *et al*., 1997; Galinier *et al*., 1997; Day *et al*., 1990). Besides these diseases Bonnar *et al.* (1997) reported that QTd values significantly increased in CHF patients. In CHF patients, it was noted that the regional variations in ventricular myocardial repolarization period mostly caused by sympathetic over activity, alterations in excitation and contraction coupling and myocardial fibrosis (Fu *et al*.,1997; Bonnar *et al*., 1997). Although, there are some doubts due to the limitations in its methodology; QTd is still accepted as a valuable marker of arrythmogenic diseases.

In a retrospective case control study Bonnar *et al.* (1997) compared a group of 25 CHF patients with 100 control subjects and they reported that there was a significant decrease in QTd and QTcd values in heart failure patients with β-blocker therapy. And like this some other studies also reported that β blocker users had significantly lower QTd and QTcd values; may be due to antiarrythmic effects of β blockers (Fesmire *et al*., 1999; Hjalmarson, 1999; Yildirir *et al*., 2001; Akbulut *et al*., 2003). But they did not evaluate the effect of one drug especially on the same patient. Jephson *et al*. (1999) administered 25 mg carvedilol bid as add-on drug on conventional therapy for 4 weeks and QTd and QTcd values were evaluated at the entry of study with conventional therapy and after 4 weeks of add on carvedilol therapy. They reported significant decrease in heart rates, QTd and QTcd values at the end of 4 weeks. Yildirir *et al*. (2001), also investigated effects of 16 months add-on carvediolol therapy on QTd and QTcd in 19 CHF patients and every patient were his/her own control subject.

Nebivolol was reported to be safe and improved systolic function in elderly CHF patients in SENIORS and ENECA study (Shibata *et al*., 2002; Istvan *et al*., 2005). In SENIORS study all cause mortality and hospitalisations

significantly decreased. But there are limited data about effects of nebivolol on QTd and QTcd in heart diseases. Even though in a study planned in hypertensive patients Galeta *et al.* (2005), investigated a significant reduction in QTd and QTcd with nebivolol that was free from antihypertensive effect but there is limited data about effects of nebivolol on QTd and QTcd in CHF patients.

Our study for the, 1st time showed that QTd and QTcd values significantly decreased with 3 months nebivolol add-on therapy and this effect was not related with dose, age, gender and etiology of the disease such as coronary artery disease or hypertension. We compared values on conventional treatment with add-on nebivolol so this effect is not related to ACE-I and diuretics. QTmin increased with treatment but QT max and QTcmin did not change and QTcmax decreased with treatment. Nebivolol is a highly selective β-1 receptor antagonist with an additional vasodilatory effect. It has the ability to modulate NO and consequently to reduce the pressure of veins and arteries (Lechat *et al.*, 1998; Cockcroff, 1995). Several mechanisms may be responsible for prolonged Qtd in CHF and its reduction with nebivolol. This reduction in QTd and QTcd under nebivolol treatment may be partly related to adrenergic blocking effects in heart failure patients. We know that sympathetic over activity, which is found in CHF patients modifies myocardial membrane properties and produces early afterdepolarizations and inhomogeneity of repolarization (Pagani and Lucini, 2001; Abildskov, 1976). Although, chronic ACE-I therapy also was shown to reduce sympathetic overactivitiy and reduced QTd in CHF patients (Barr *et al.*, 1997), in our study we investigated reduction in Qtd and Qtcd with nebivolol despite pre-existing ACE-I and diuretic therapy (Akbulut *et al.*, 2003). Diuretics was also shown to reduce QTd in CHF (Akbulut *et al.*, 2003) but we think that it's unlikely that reduction in QTd in our study is due to the effect of diuretic or ACE-I because we administered nebivolol in addition to conventional CHF therapy and we didn't change dose during the study period. Also the effect of nebivolol on protection from oxygen free radicals, beneficial effects on endothelial functions such as ability of modulating Nitric Oxide (NO) and effects on proliferation and apoptosis of human coronary artery smooth muscle and endothelial cells (Brehm *et al.*, 2001) may be important in reduction of repolarization inhomogeneity of heart failure patients (Cockcroff, 1995; Janssen *et al.*, 1999). In spite of these many reasons the exact mechanism of reduction of QTd is unknown. Antiaggregant action (Falciani *et al.*, 2001), anti-ischemic action, β-blocker class effect (Fesmire *et al.*, 1999) may all contribute to this useful effect. Besides effects on Qtd and QTcd nebivolol consequently reduces arterial and venous pressure by modulating NO (Lechat *et al.*, 1998) and this may contribute to the significant improvement in EF and systolic functions that we have found.

The limitation of our study may be thought as lack of a control group but every patient served as his or her control with ongoing stable standard heart failure treatment with this design of study.

CONCLUSION

This study shows that nebivolol significantly reduced QTd, which is a predictor of susceptibility to lethal ventricular arrhythmias and improved left ventricular systolic functions in congestive heart failure patients after 3 months treatment. Therefore, these effects may contribute to decrease in mortality and sudden cardiac deaths in CHF patients. But more studies including large number of patients are needed to show the exact mechanism underlying the effect of nebivolol on QT dispersion in heart failure patients.

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