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ORIGINAL ARTICLE

Effects Of Atenolol And Nebivolol On Blood Pressure And On ECG In Patients Of Stage-1 Hypertension –A Comparative Study.

SAWHNEY V ,KAPOOR B,SHARMA S,SHARMA R

ABSTRACT

Background:ß-blockers are used as first line antihypertensive drugs.
Aim: To compare the effects of atenolol and nebivolol on blood pressure and ECG in patients of Stage 1 hypertension.
Setting: This study was conducted by the departments of pharmacology and general medicine of a tertiary care teaching hospital in India.
Study Design: Prospective single blind randomized trial over 6 months.
Materials and Methods:Of the 102 patients randomized for the trial (atenolol n=50, nebivolol n=52), 26 patients were lost to follow-up. The 76 patients, who attended the three reviews at 3, 6 and 12 weeks following recruitment to the trial, were included for analysis. During each of the follow up visits, blood pressure and ECG were recorded. Corrected QT interval (QTc) was calculated using the Bazett's formula. The effect of each drug at 3, 6 and 12 weeks were compared with the baseline and were analysed using the paired 't' test, whilst the comparison between the two drugs (baseline, 3, 6 and 12 weeks) was performed using the unpaired 't'test.
Results: Both the drugs significantly reduced (P<0.001) systolic and diastolic blood pressure during the follow-up visits. QTc was significantly reduced from baseline values at 3, 6 and 12 weeks of therapy with atenolol, but only at 6 weeks with nebivolol.
Conclusion: Both atenolol and nebivolol appear to have similar antihypertensive effects in the short term. The effect of the anti-hypertensive agent on QTc appears to be more pronounced with atenolol than with nebivolol.

Keywords :Nebivolol, Atenolol, QTc.

Corresponding Author:
Dr.Rashmi Sharma MBBS.MD, DMCH(Pharmacology) Senior Demonstrator, Department of Pharmacology & Therapeutics Govt. Medical college Jammu

Introduction

Hypertension is a very common and important disease related to modern civilized life and its complications pose a major health problem in populations worldwide. Its prevalence is quite high in India, and affects both rural and urban populations [1]. Both randomized clinical trials and observational studies have confirmed the effect of uncontrolled hypertension on cardiovascular morbidity and mortality [2]. Early treatment can reverse and retard the complications associated with hypertension.

β-blockers have long been considered as first line antihypertensive drugs [3]. A

number of clinical trials such as STOP, CAPP, NORDIL and JNC 7 recommend β blockers in the initial management of hypertension [4],[5],[6],[7]. However, atenolol, a β1-blocker, is a commonly used antihypertensive agent, and has often been used as a reference drug in a number of clinical trials [8]. However, the question arises about the status of this drug as a reference drug in comparison with other antihypertensive drugs, because of its undesirable effects on lipid profile, blood sugar, and heart rate of patients [9],[10].

The newer 3rd generation β-blocker, nebivolol, is found to be more cardioselective, and has a vasodilating effect on resistance arteries [11].This drug is endowed with peripheral vasodilating properties mediated by endogenous production of nitric oxide [12]. Recently, it has been well studied that pharmacogenomics has a greater impact on the therapeutic effect of the drug [13]. Nebivolol has been recently launched in the Indian market, and as not much work has been done in our setup to compare the efficacy and safety of atenolol and nebivolol on the cardiovascular system; hence, keeping in mind the promising utility of nebivolol, it is thought of interest to elucidate the effects of nebivolol on blood pressure and ECG in patients of stage 1 hypertension.

Materials and Methods

This study was conducted in the department of pharmacology and therapeutics in collaboration with departments of general medicine and cardiology of a tertiary care teaching hospital in India, starting from 01-07-2004 to 31-1-2005, in a prospective single blind randomized design, after taking permission from the institutional review committee.

Newly diagnosed outdoor patients of both sexes, in the age group of 30-65 yrs, attending the medicine and cardiology OPDs, were screened for stage I hypertension having an SBP of 140-159 and **a** DBP of 90-99 according to the JNC report seven, for the management of hypertension **[7**]. In addition to a detailed medical history and physical examination, routine investigations including complete blood profile, renal function tests and liver function tests, were done to rule out other associated co-morbidities. All patients also underwent a full lipid profile analysis, fasting and post-prandial blood sugar analysis, as well as chest X-ray and ECG. Exclusion criteria were as follows: previously diagnosed secondary or complicated hypertension, associated ischaemic heart disease, history of stroke, abnormalities of cardiac rhythm or conduction under pharmacologic treatment, renal failure, endocrine abnormalities, obstructive airway disease, intake of any other drugs and pregnant and lactating mothers.

Initially, 122 patients were registered after taking informed consent and put on placebo therapy in the form of sugar coated tablets, and they were advised salt restriction along with dietary modifications for two weeks. After two weeks of placebo therapy, twenty patients showed improvement, and they were excluded. Finally, 102 patients were found to have stage I hypertension and they were randomized into two groups.

Randomization was done with the help of a table of random numbers, and allocation envelopes were kept with some other person in the department. Then these envelopes were opened in front of the patients.

Out of 102 patients enrolled for the study, 52 patients received tab nebivolol 5mg, and 50 patients received tab atenolol 50mg once a day, at 8A.M in the morning. 26 patients were lost during the follow up,

and only 76 patients completed the study. Thirty six patients in the atenolol group, and 40 patients in the nebivolol group, completed the study.

Each patient was followed up for a period of twelve weeks after inclusion in the study. All patients attended 3 follow up visits at 3, 6 and 12 weeks of study. During each visit, blood pressure in the sitting, standing and supine positions, was recorded using a sphygmomanometer with a gap of two minutes between each position. In each position, a mean of 3 readings, one minute apart, was taken. Before recording the blood pressure, it was seen that the patient was comfortable, and BP was recorded after giving 10 minutes of rest to the patient .Blood pressure was normal, and no patient required any increase in dose of drug or addition of any other antihypertensive drug. Postural hypotension was defined as a fall in blood pressure greater than 20/10 (SBP/DBP) mm of Hg on standing upright from a supine position within 3 minutes [14]. ECG was recorded by using a standard digital cardiomin 2K UNI-EM device.

ECGs were analyzed by calculating RR and QT intervals. It has been seen that in hypertensive patients, LVH increases the risk of sudden death, and regression of both electrocardiographic and echocardiographic LVH reduces cardiovascular events [15]. Clinical studies have also shown that reduction in LV masses is associated with shortening of QT interval and a decrease in QT dispersion [16].

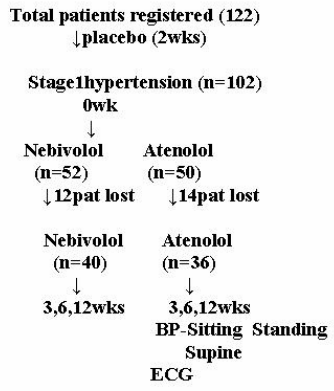
All the ECG recordings were carried out with lead 11. However; occasionally another appropriate lead was selected if lead 11 was inadequate [17]. The QT interval was measured from the onset of the QRS complex to the end of the T wave. In case of a prominent U wave, the dip or notch between the T and U wave was taken as the end of the T wave. QT interval after measurement was standardized by converting it to the QTc i.e corrected QT interval. Because the QT interval is influenced by change in heart rate, it is customary to correct the interval to such changes (QTc). QTc was calculated by using Bazett's formula [18].

$$QTc = \frac{QT\ interval}{\sqrt{R\text{-}R\ interval}}$$

QT and RR intervals were measured in seconds, and QTc was expressed in seconds. The normal QTc interval was taken as < 0.44 seconds. The average of 3 sequential QTc values was used as a single QTc value for statistical evaluation.

Statistical Analysis

Effects of the individual drug on SBP, DBP and QTc were analyzed by using paired "t"–test, and comparative analysis was done by using unpaired "t" test. Comparative analysis of the effects of each drug on sitting, standing and supine blood pressure was done by using analysis of variance test. P-values less than 0.05 were considered as statistically significant.[Table/Fig 1] Flow chart presenting the study.



(Table/Fig 1) Flow Chart Presenting The Study

Results

Both atenolol and nebivolol significantly reduced SBP and DBP at 3, 6 and 12 weeks, as compared to the baseline (P<0.001). When SBP in the sitting, supine and standing positions was compared in the atenolol group and nebivolol groups at 3, 6 and 12 weeks, no

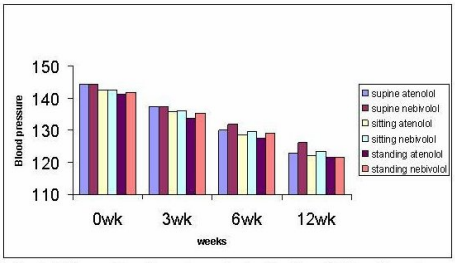
statistically significant effect was seen (P>0.05). However, a statistically significant effect was reported in DBP at three different positions in both the atenolol group and nebivolol groups at 3, 6 and 12 weeks with (P<0.01) and (P<0.001) respectively [Table/Fig 2].

(Table/Fig 2) Patient Characteristics

Characteristic	Atenolol (n = 36)		Nebivolol (n = 40)	
	Males	Females	Males	Females
Age (yrs) (Mean±SEM)	47±1.89	53.8±2.74	51.7±2.65	54.36±1.92
Sex	19	17	18	22
Weight (Kg) (Mean±SEM)	71.9±1.21	66.58±2.38	73.11±1.35	66.45±0.83
Sitting (mmHg) (Mean±SEM)				
SBP	142.5±1.48		142.3±1.91	
DBP	95.3±0.71		94.9±0.68	
Supine (mmHg) (Mean±SEM)				
SBP	144.3±1.54		144.3±1.94	
DBP	96.6±0.71		97.6±0.59	
Standing (mmHg) (Mean±SEM)				
SBP	141.2±1.39		141.8±1.88	
DBP	94.5±0.66		95.15±0.59	
ECG (Seconds) QTc	0.401±0.0017		0.404±0.0011	
Plasma Lipids (mg/dl) (Mean±SEM)				
TC	173.9±4.17		174.7±5.30	
TG	166.7±6.06		171.9±9.28	
LDL	100.3±1.01		100.3±0.91	
HDL	41.8±1.08		41.4±1.65	
VLDL	33.8±1.25		35.3±1.92	
LDL/HDL	2.41±0.06		2.55±0.10	
Blood Sugar (mg/dl) (Mean±SEM)				
Fasting	91.65±2.59		86.83±1.43	
Post Prandial	110.17±0.80		108.9±1.93	

SEM = Standard error of mean, wk = Weeks, n = number of patients

When BP in the supine, sitting and standing positions was compared between the two groups at 3, 6 and 12 weeks, it was found to be statistically insignificant [Table/Fig 3].



(Table/Fig 3) Comparitive effects of atenol and nebivolol on SBP in patients of stage -1 hypertension

Atenolol decreased the QTc significantly (P<0.001) at the end of 3, 6 and 12 weeks. However, nebivolol produced a statistically significant reduction in QTc at 6 weeks (P<0.001) [Table/Fig 4].When the effects of both the drugs on QTc were compared, it was found to be statistically insignificant. No other change in ECG alone, or in comparison, was observed.

(Table/Fig 4) Effect Of Atenolol And Nebivolol On Blood Pressure In Patients Of Stage – I Hypertension

Parameter	Supine	Sitting	Standing	'P' Value
Atenolol (n = 36) SBP (mmHg) (Mean±SEM)				
0 wk	144.3±1.54	142.5±1.48	141.2±1.39	0.33
3 wk	137.5±1.38*	135.7±1.34*	133.7±1.37*	0.15
6 wk	130.1±1.35*	128.6±1.31*	127.6±1.20*	0.39
12 wk	122.8±1.54*	121.8±1.48*	121.6±1.38*	0.82
Atenolol (n = 36) DBP(mmHg) (Mean±SEM)				
0 wk	96.6±0.71	95.3±0.71	94.5±0.66	0.100
3 wk	90.2±0.58*	88.7±0.69*	87.2±0.80*	0.01**
6 wk	82.7±0.72*	81.1±0.61*	80.4±0.59*	0.035**
12 wk	77.1±0.74*	76.05±0.75*	75.7±0.69*	0.40
Nebivolol (n = 40) SBP (mmHg) (Mean±SEM)				
0 wk	144.3±1.94	142.3±1.91	141.8±1.88	0.68
3 wk	137.5±1.79*	136±1.47*	135.4±1.84*	0.68
6 wk	131.8±1.69*	129.6±1.44*	129±1.57*	0.40
12 wk	126±1.67*	123.4±1.65*	121.6±1.59*	0.16
Nebivolol (n = 40) DBP(mmHg) (Mean±SEM)				
0 wk	97.6±0.59	94.9±0.68	95.15±0.59	0.70
3 wk	91.1±0.66*	89±0.74*	87.5±0.64*	0.001**
6 wk	86.6±0.67*	83±1.00*	83.2±1.05*	0.007**
12 wk	81±0.76*	78.5±0.02*	77.8±0.89*	0.027**

* P value >0.001 Statistically significant as compared to baseline after paired t test
** Statistically significant difference among sitting , standing and supine position after applying ANOVA SEM=Standard of Mean ,n=number of patients , Wk=Weeks

Discussion

The relationship between hypertension and cardiovascular, cerebrovascular and renovascular diseases, has long been recognized, and this relationship is strong, continuous, graded, consistent, independent, predictive and aetiologically significant for those with or without coronary heart disease [19][20]. The main goal of antihypertensive treatment is to prevent or to arrest cardiovascular damage. It has been seen that the antihypertensive treatment has proved to be effective in preventing hypertensive complications such as stroke and renal failure [21].

β-blockers are effective antihypertensive drugs, and are currently recommended as first line treatment options in patients with uncomplicated, essential hypertension .These reduce cardiac output, alter baroreceptor reflex sensitivity, block peripheral adrenoreceptors, block β1-receptors in heart and juxtaglomerular cells in kidney, and inhibit release of

norepinephrine from the sympathetic nerve terminals [22].

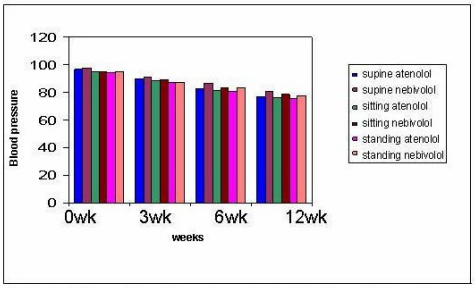
Atenolol, a β1-blocker is one of the widely and commonly used antihypertensive. Its antihypertensive efficacy is well established in a number of clinical studies [9],[10],[23],[24],[25]. The optimum antihypertensive effect of β-blocker action is seen after 10-15 days. In the present study, the effect was recorded after 3, 6 and 12 weeks. Atenolol produced a statistically significant fall in SBP and DBP throughout the study, and in all the three positions. But when the supine, sitting and standing positions were compared, the fall in SBP was not significant, whereas DBP showed a statistically significant fall at 3 and 6 weeks without any clinical signs of postural hypotension, as reported earlier [26].

Nebivolol, a new selective β1-blocker has a novel mechanism of antihypertensive activity [27]. This drug has a vasodilatory property that is attributed to an endothelium- dependent effect, which is mediated via the L-arginine / nitric oxide (NO) pathway [11]. This compound has a dl-racemic mixture. The d-enantiomer is responsible for the blockade, whereas the l- enantiomer induces vasodilation via a nitric oxide mechanism [12].As in hypertension, there is an unexplained rise in systemic vascular resistance, with an associated endothelial dysfunction ; hence, nebivolol could prove to be a better option for hypertensive therapy[28].

Because of its NO mediated peripheral vasodilatory action, nebivolol has the potential to cause orthostatic blood pressure changes. However, a few studies where nebivolol was compared with placebo and lisinopril, reported more reduction in DBP in the standing than in the supine posture, without any signs of orthostatic hypotension in the nebivolol group [29],[30].

In the present study, nebivolol produced a statistically significant fall in both SBP and DBP in all the three positions at 3, 6 and 12 weeks. When the supine, sitting and standing positions were compared, there was no statistically significant fall in SBP; whereas it produced a statistically significant fall in DBP. So, in the present study, both the drugs produced a statistically significant postural hypotension in DBP; but no clinical sign of postural hypotension was seen. Moreover, the difference in BP of 2- 3 mmHg is hardly clinically significant, and may be within the limits of measurement errors.

On comparative analysis, both drugs nebivolol and atenolol produced a similar reduction in BP at 3, 6 and 12 weeks. So, both the drugs have similar antihypertensive efficacy.[Table/Fig 5]Comparitive effect of atenol and nebivolol on DBP in patient of Stage-1 hypertension.



(Table/Fig 5)Comparitive effects of atenol and nebivolol on DBP in patients of stage -1 hypertension

EFFECT ON ECG

In the present study, atenolol decreased heart rate, which was evident by a statistically significant fall in QTc at 3, 6 and 12 weeks.

Nebivolol was also found to decrease QTc significantly at 6 weeks, but not at 12weeks.It seems that after prolonged treatment, nebivolol does not have any significant effect on heart rate, and it may be because of its NO related vasodilation resulting into tachycardia, which may counteract β-receptor mediated

bradycardia in the heart. On comparison, the drugs produced insignificant decrease in QTc. Although nebivolol affects autonomic functions and attenuates the sympathetic tone, it does not promote vagal activity more than atenolol [31].

Hence, it is quiet evident from the results of the present study that both atenolol and nebivolol should be used with caution in patients of hypertension with an associated condition like bradycardia, heart blocks and concomitent use of drugs, resulting into QT prolongation.

The results of our study clearly indicated that nebivolol is as efficacious as atenolol, as a antihypertensive drug. However, nebivolol produced reduction in QTc at 6 weeks, but there is no evidence of increased heart rate at 12 weeks. Moreover, inability of our study to compare the effect of nebivolol on lipid profile, the respiratory system, blood sugar etc with other conventional β-blockers, could be considered as lacune of the study, and further long term clinical trials are required to establish its safety and superiority in hypertensive patients.

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