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ORIGINAL ARTICLE

Comparative effects of nebivolol and atenolol on blood pressure and insulin sensitivity in hypertensive subjects with type II diabetes

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The aim of this double-blind, parallel group study was to compare the effects of nebivolol and atenolol on blood pressure (BP) and insulin sensitivity in hypertensive patients with type II, non-insulin dependent diabetes mellitus (NIDDM). After a 4-week run-in period on placebo, 30 patients (14 males and 16 females) aged 43 to 69 years, with stable NIDDM and mild to moderate hypertension (DBP ⩾95 and <116 mm Hg) were randomised to receive either nebivolol 5 mg or atenolol 50 mg, both administered once daily for 6 months. At the end of the placebo and the active treatment periods, supine and standing BP was measured, 24-h urinary C-peptide, HbA_{1c}, plasma glucose and lipid levels were evaluated and an euglycaemic hyperinsulinaemic clamp was performed to evaluate insulin sensitivity: glucose infusion rate during the last 60 min of clamp and total glucose requirements were evaluated. Nebivolol 5 mg once daily was of an equivalent efficacy as atenolol 50 mg once daily at reducing supine and standing systolic and diastolic BP values. Neither β-blocker adversely affected carbohydrate metabolism in terms of insulin sensitivity, whole body glucose utilization, HbA_{1c} and 24-h urinary C-peptide excretion. No significant changes in cholesterol (total, high density and low density lipoprotein) and triglycerides plasma levels were observed with both β-blockers. These findings indicate that, in hypertensive patients with NIDDM, ie, in subjects who have established insulin resistance, treatment with nebivolol and atenolol neither further deteriorated insulin sensitivity nor adversely affected the lipid profile.

Keywords: nebivolol; atenolol; β-adrenergic blockers; insulin sensitivity; diabetes mellitus

Introduction

The frequent association of hypertension and type II, non-insulin-dependent diabetes mellitus (NIDDM) is well known and has been associated with a higher risk of cardiovascular complications.[1–3] Insulin resistance has been suggested to provide a common pathophysiologic link between hypertension and type II diabetes[4–6] and to contribute to associated altered plasma lipid profile that aggravates the risk of coronary heart disease (CHD) in these patients.[6,7] In addition, insulin resistance is considered to be an independent risk factor for CHD.[7–9]

The suspicion that the pharmacological treatment of hypertension may worsen the insulin resistance and associated metabolic abnormalities and contribute to the relative failure of antihypertensive treatment to reduce coronary morbidity and mortality[10] led to a series of studies[11–18] aimed at elucidating the effects of commonly used antihypertensive drugs on insulin sensitivity, by using the euglycaemic hyperinsulinaemic clamp technique.[19]

These studies showed that treatment with both β^1-selective and non-selective β-adrenergic blockers significantly increased insulin resistance and basal plasma insulin, despite effectively lowering blood pressure (BP).[11,12,14,18] These findings supported concerns about using these drugs in diabetic patients, based on previous observations that treatment with β-blockers, and particularly non-selective ones, was associated with the induction of impaired glucose tolerance, overt diabetes mellitus or exacerbation of hyperglycaemia in patients with diabetes mellitus.[20–24]

However, the studies that evaluated the influence of β-blockers on insulin sensitivity by the euglycaemic hyperinsulinaemic clamp were conducted in hypertensive subjects without diabetes mellitus, whereas, to our knowledge, no data are available about the assessment of insulin sensitivity by this technique during β-blocker therapy in subjects with NIDDM, ie, in the presence of a well established state of insulin resistance.[25,26]

The aim of this study was to compare the effect on insulin sensitivity and BP control of atenolol and

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nebivolol, a highly β^1-selective, non-intrinsic sympathomimetic activity, third generation β-blocker, provided some vasodilating properties, which have been shown to be L-arginine/nitric oxide-mediated,[27–33] in the treatment of hypertensive patients with associated NIDDM.

Patients and methods

This was a randomised, single-centre, double-blind, parallel group, actively controlled trial.

Male and female out-patients, aged 18–70 years, with stable NIDDM (average HbA_{1c} $\leqslant$8% during the previous 6 months, diet and/or oral therapy stable for at least 6 months) and mild to moderate essential hypertension (resting supine diastolic BP (DBP) $\geqslant$95 and $<$116 mm Hg at the end of a 4-week run-in period on placebo), were candidates for enrolment. Exclusion criteria included: accelerating or malignant hypertension, myocardial infarction or cerebrovascular accident within 6 months, bradycardia $<$60 b/min, atrial fibrillation or recurrent tachyarrhythmias requiring anti-arrhythmic therapy, heart failure requiring therapy, sick sinus syndrome or A-V block greater than first degree, valvular disease of haemodynamic significance, chronic obstructive lung disease, significant peripheral vascular disease, insulin dependent diabetes mellitus or incidental insulin treatment within the past 3 months, diabetic ulceration, proliferative retinopathy or previous retinal laser therapy, nephropathy (urinary protein $>$500 mg/day, serum creatinine $>$2.2 mg/dl), body mass index $>$32 kg/m^2, pregnant or nursing women, disabling or terminal illness, history of sensitivity or significant adverse reactions to β-blocker therapy.

The trial was conducted in accordance with the Declaration of Helsinki and its subsequent revisions. Ethics Committee approval was obtained and the patients gave their informed consent to participate in the trial.

After a 4-week single-blind run-in period on placebo, during which existing antihypertensive medications were withdrawn, patients who fulfilled the inclusion criteria were randomised to receive either nebivolol 5 mg or atenolol 50 mg, both administered once daily for 6 months. Each patient's diet and basic treatment with hypoglycaemic drugs were kept constant during the trial.

Before enrolment, patients provided a medical and demographic history and underwent a physical examination, which included assessment of BP, heart rate (HR), 12-lead ECG, fundoscopy, body weight, blood glucose, glycosylated haemoglobin (HbA_{1c}) and other laboratory tests (complete blood cells count, transminases, alkaline phosphatase, bilirubin, γ-GT, serum electrolytes, urea, creatinine, uric acid, urinalysis). These tests were repeated at the end of the placebo run-in (week 0) and at study completion (week 24). Visits were scheduled at weeks 2, 6, 12 and 24 throughout the double-blind treatment period; all assessments were made in the morning, after an overnight fast and at trough plasma levels (ie, approximately 24 h after previous dose of trial medications).

At each visit systolic BP (SBP), DBP and HR were evaluated. BP was measured with a standard mercury sphygmomanometer (Korotkoff I and V) by the same observer on the same arm, after the patient had been resting in supine position for 10 min. The average of three consecutive measurements, with at least a 1-min interval between them, was recorded. Standing BP values were also measured, after the patient had been upright for 2 min. HR was measured by pulse palpation for 30 s, immediately after the supine and standing BP measurements.

At the end of the placebo run-in (week 0) and at the end of active treatment (week 24) a 24-h urine collection was undertaken for the determination of protein, albumin, C-peptide and glucose excretion and the 2-h euglycaemic hyperinsulinaemic clamp test was performed according to the technique of De Fronzo *et al*[19] to measure tissue sensitivity to exogenous insulin. The following parameters were derived: whole body glucose utilization (mg) between 60 and 120 min of the test, glucose infusion velocity (mg/min) between 90 and 120 min and mean glucose infusion rate (GIR) (mg/kg/min) between 90 and 120 min, derived from the formula:

$$\text{GIR} = \frac{\text{mean}}{60} : \text{kg} \times 1000 \times 0.2$$

where mean = mean glucose infusion velocity (ml/h) between 90 and 120 min, 60 = min in an hour, 1000 = mg in 1 g, 0.2 = infusion of 20% glucose.

Plasma total cholesterol (TC), HDL-C, LDL-C and triglycerides were also determined using the enzymatic method following ultracentrifugation and precipitation of samples.

Any adverse event that occurred during the trial period and that was mentioned by the patient either spontaneously or after non-leading questioning ('did you have any unwanted effect?') was recorded. Patients' compliance to the therapy was evaluated by counting the residual tablets at each visit.

No formal sample size calculation was performed; the study population size of 30 patients was based on practical considerations of patient recruitment rates.

Data are presented as means ± standard errors. Between treatment differences were statistically analysed using the Mann–Whitney U-test. Within treatment changes were analysed using the Friedman test or the Wilcoxon matched pairs signed-rank test.

All statistical tests were two-tailed and were interpreted at the 5% significance level.

Results

Thirty patients, 14 males and 16 females, aged 43 to 69 years (mean age: 58.3 yr) were admitted to the study and none withdrew after randomisation. Fifteen were assigned to treatment with nebivolol 5 mg once daily and 15 received atenolol 50 mg once daily.

As shown in Table 1, baseline demographic and clinical characteristics were not significantly different in the two groups of patients. Changes in BP induced by treatment with nebivolol or atenolol are

Table 1 Main demographic data and baseline disease characteristics of patients recruited into the trial and randomised to either nebivolol 5 mg or atenolol 50 mg

	Nebivolol 5 mg (n = 15)	*Atenolol 50 mg (n = 15)*	*All patients (n = 30)*
Age (years)	59.2 ± 1.90	57.5 ± 1.66	58.3 ± 1.25
Sex (male/female)	8/7	6/9	14/16
Weight (kg)	69.1 ± 1.68	68.1 ± 2.23	68.6 ± 1.37
Height (cm)	168.5 ± 1.47	166.4 ± 1.71	167.5 ± 1.13
Duration of hypertension (years)	6.0	4.0	4.5
Duration of diabetes (years)	6.0	3.0	4.5

shown in Table 2. Both β-blocking agents markedly reduced BP values during the first 2 weeks of treatment and the improvements were sustained and enhanced at the end of the 24-week period assessment. None of the between treatment differences was statistically significant ($P > 0.05$ Mann–Whitney U-test).

Supine HR decreased by a mean of 10.4 and 14.4 b/min at weeks 2 and 24 in the nebivolol group and by 11.1 and 13.3 b/min in the atenolol group (Table 2). Similar reductions were seen in standing HR. In all cases the changes from baseline were statistically significant ($P < 0.001$, Friedman test). However, no significant difference was found in the reductions between the two treatment groups ($P > 0.05$ Mann–Whitney U-test).

No statistically significant changes in body weight were observed in either group of patients (Table 3).

Table 4 shows the results of the euglycaemic hyperinsulinaemic clamp test. Mean values for whole body glucose utilization decreased by a mean of 548 mg (2.6%) at the end of treatment with nebivolol compared to a mean increase of 189 (0.9%) in the atenolol group. Neither of these changes was statistically significant ($P > 0.05$, Wilcoxon matched pairs signed-ranks test). The between treatment difference was also non-significant ($P = 0.178$, Mann–Whitney U-test). The average glucose infusion rate during the last 30 min of the euglycaemic hyperinsulinaemic clamp was also virtually unchanged between the end of the placebo run-in and week 24, suggesting that neither drug altered insulin sensitivity over the period tested.

There were no newly occurring changes in HbA_{1c}, cholesterol (total, HDL, LDL) or triglycerides levels nor in mean 24-h urinary excretion of c-peptide, albumin or glucose at the end of 6 months of treatment with either β-blockers (Table 3). The between treatment differences were also non-significant. No consistent changes in blood chemistry or haematology were observed.

Adverse events were reported by three patients in the nebivolol group (nightmares, abdominal pain and headache) and by two patients receiving atenolol (abdominal pain and asthenia). In all five patients the events were of mild intensity. No serious adverse event was reported and no patient was removed from the trial due to side effects. All patients adhered to the time schedule planned for the visits and patients' compliance with drug treatment was satisfactory.

Discussion

The results of this study showed that nebivolol 5 mg once daily was of equivalent efficacy to atenolol 50 mg once daily at reducing BP in hypertensive patients with concomitant NIDDM, which is in keeping with previous results obtained with nebivolol in non-diabetic hypertensives.[34–39]

Neither nebivolol nor atenolol appeared to have any adverse effect on carbohydrate metabolism in terms of HbA_{1c} levels, 24-h excretion of glucose or C-peptide, whole body glucose utilization and insulin sensitivity. The finding of a neutral effect of both β-blockers on insulin sensitivity is in contrast with previous observations. The β^1-selective atenolol and metoprolol were found to reduce whole-body insu-

Table 2 Blood pressure and heart rate change from baseline (Week 0) after 2 and 24 weeks of treatment with nebivolol or atenolol

	Nebivolol (n = 15)			*Atenolol (n = 15)*			*P-value**		
	Wk 0	*Wk 2*	*Wk 24*	*Wk 0*	*Wk 2*	*Wk 24*	*Wk 0*	*Wk 2*	*Wk 24*
Supine									
SBP (mm Hg)	164.9	−19.2	−25.7	165.9	−18.5	−28.7	NS	NS	NS
DBP (mm Hg)	103.2	−12.9	−17.9	103.3	−11.7	−18.8	NS	NS	NS
HR (b/min)	81.1	−10.4	−14.4	80.4	−11.1	−13.3	NS	NS	NS
Standing									
SBP (mm Hg)	162.3	−19.6	−25.6	161.9	−18.3	−27.7	NS	NS	NS
DBP (mm Hg)	105.7	−13.2	−18.0	105.5	−11.9	−18.7	NS	NS	NS
HR (b/min)	85.9	−12.3	−15.6	84.1	−12.0	−13.3	NS	NS	NS

*Mann–Whitney U-test for between treatment differences in changes from end of run-in.
Note: BP and HR reductions from end of run-in to week 24 were highly significant within each treatment group ($P < 0.001$, Friedman test).

Table 3 Values of total cholesterol (TC), HDL-C, LDL-C, triglycerides (TG), glycosylated haemoglobin (HbA_{1c}), 24-h urinary C-peptide, albumin and glucose, body weight at the end of the placebo run-in (week 0) and at the end of active treatment with nebivolol and atenolol (week 24) (means ± standard error)

	Nebivolol 5 mg		*Atenolol 50 mg*		*P value*
	Week 0	*Week 24*	*Week 0*	*Week 24*	
TC (mg/dl)	222.9 ± 8.80	219.0 ± 7.87	227.0 ± 11.3	221.2 ± 10.2	NS
HDL-c (mg/dl)	45.8 ± 1.90	47.0 ± 1.62	48.5 ± 2.45	50.1 ± 2.33	NS
LDL-C (mg/dl)	145.1 ± 9.39	140.5 ± 8.14	147.2 ± 13.8	139.5 ± 12.5	NS
TG (mg/dl)	159.6 ± 8.84	157.7 ± 7.57	156.3 ± 8.44	158.0 ± 7.90	NS
HbA_{1c} (%)	7.1 ± 0.10	7.1 ± 0.08	7.5 ± 0.13	7.5 ± 0.11	NS
24-h urinary C-peptide (ng/ml)	27.5 ± 1.35	26.9 ± 1.38	29.1 ± 1.38	29.3 ± 1.29	NS
24-h urinary albumin (mg/l)	32.8 ± 17.8	19.9 ± 11.6	13.2 ± 8.98	7.9 ± 5.91	NS
24-h urinary glucose (g/l)	0.0 ± 0.03	0.0 ± 0.00	0.1 ± 0.06	0.1 ± 0.04	NS
Body weight (kg)	69.1 ± 1.68	69.2 ± 1.67	68.1 ± 2.23	68.2 ± 2.18	NS

P values referred to Mann–Whitney test for between treatment differences in changes from end of run-in.
Changes in the above parameters from end of run-in to week 24 were not statistically significant within either treatment group ($P > 0.05$).

Table 4 Main results of the euglycaemic hyperinsulinaemic clamp: whole body glucose utilization and average glucose infusion rate

Group	*Phase*	*Interval*	*No.*	*Mean*	*s.e.m.*	*(95% CI-mean)*	*P-value*[a]
Whole body glucose utilization from 60 to 120 min (mg)							
Nebivolol	Run-in	week 4	15	20444.0	2188.19	(15751; 25137)	
	Treatment	week 24	15	19896.0	2322.79	(14914; 24878)	
Atenolol	Run-in	week 4	15	21072.0	3425.57	(13725; 28419)	0.9504
	Treatment	week 24	15	21260.7	3272.91	(14241; 28280)	0.1776
Average glucose infusion rate from 90 to 120 min (mg/kg/min)							
Nebivolol	Run-in	week 4	15	4.8	0.58	(3.59; 6.08)	
	Treatment	week 24	15	4.8	0.59	(3.53; 6.04)	
Atenolol	Run-in	week 4	15	5.5	1.08	(3.17; 7.79)	0.8519
	Treatment	week 24	15	5.7	1.19	(3.13; 8.22)	0.1300

[a]Mann–Whitney U-test for between treatment differences in changes from end of run-in
Note: Changes in whole body glucose utilization and average glucose infusion rate from end of run-in to Week 24 were not statistically significant within either treatment group ($0.16 > P < 0.6$) Wilcoxon matched pairs signed ranks test.

lin-mediated glucose uptake by 13% and 20% respectively and to decrease the insulin sensitivity index by 23% and 27%, with minor but significant increases in HbA_{1c} and fasting blood glucose.[11] Although the most pronounced changes in insulin-mediated glucose uptake was observed with the non-selective propranolol,[12] the negative effect of β^1-selective β-blockers on insulin sensitivity was confirmed in another comparative study with atenolol and the calcium channel blocker diltiazem: whereas the latter did not affect insulin-mediated glucose disposal, atenolol caused a 21% reduction.[11]

All the above studies, however, regarded hypertensive patients without diabetes mellitus, whereas our findings refer to patients with NIDDM, ie, to subjects who clearly have already altered baseline insulin sensitivity. This suggests that the effect of β^1-adrenergic blockade on insulin sensitivity might be different according to the baseline characteristics of the patients, being less evident in the presence of established insulin resistance.

The lack of effect on insulin sensitivity might explain, at least in part, why neither nebivolol nor atenolol affect the lipid profile of our diabetic hypertensives. In fact, increased serum triglycerides and decreased HDL-C concentrations, ie, the most striking changes in lipid metabolism observed during β-blocker therapy,[12,40,41] are directly and inversely related to plasma insulin concentrations. Nebivolol and atenolol were both well tolerated. Only five patients (three with nebivolol and two with atenolol) reported adverse events. In each case there were mild events, that never required withdrawal from treatment.

In conclusion, the results of this study indicate that nebivolol was as effective as atenolol in controlling BP levels in hypertensive patients with NIDDM. In such patients, who clearly have insulin resistance, β^1-selective blockade did not influence insulin sensitivity nor lipid profile. Since the cardioprotective potential of β-blockers is highly desirable in diabetic hypertensives because of their enhanced cardiovascular risk, the lack of metabolic adverse effect is of obvious clinical relevance in the treatment of these patients.

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