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ESSENTIAL HYPERTENSION

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ABSTRACT... drrriz72@yahoo.com. **Background:** Hypertension and type 2 diabetes mellitus also tend to coexist. The goal of antihypertensive therapy should consist of reducing cardiovascular morbidity and mortality associated with hypertension by a strategy focused on lowering blood pressure while minimizing the impact on other associated cardiovascular risk factors like diabetes mellitus. **Objectives:** To observe and compare any change in serum glucose in patients with newly diagnosed essential hypertension with Atenolol and Amlodipine. **Setting:** Department of Pharmacology and Therapeutics, Basic Medical Science Institute (BMSI), Jinnah Post Graduate Medical Centre (JPMC), Karachi. **Period:** 12 weeks (90 days) **Methods:** Patients with newly diagnosed essential hypertension (N=70) were enrolled in this study and were divided into two groups, each comprised of 35 patients and were given tablet Atenolol 50/100mg once daily and tablet Amlodipine 5/10 mg once daily respectively for 90 days. Fasting Blood glucose was measured on day of inclusion i.e. day 0, day 45 and day 90. At each fortnightly visit, blood pressure was recorded. **Results:** Atenolol raised mean blood glucose levels from baseline levels of 91.82±1.34 mg/dl to 99.73±1.33 mg/dl on day 90 (P<0.001) while Amlodipine had no significant effect on blood glucose level (P= N.S). **Conclusion:** Atenolol may not be a good choice for essential hypertensive patient with type 2 diabetes mellitus as it is found to impair the

normal glucose metabolism. Long term clinical trials in diabetic patients are needed to confirm the observation of the present study.

Key words: Essential hypertension, Atenolol, Amlodipine, Blood glucose

INTRODUCTION

For years doctors have referred to hypertension as a silent killer, because it can exist with no obvious symptoms. Uncontrolled and prolonged elevation of blood pressure can lead to a variety of changes in the myocardial structure, coronary vasculature and conduction system of the heart[1]. Hypertension and type 2 diabetes mellitus also tend to coexist. Hypertension is approximately twice as common in persons with diabetes as in persons without diabetes. Diabetes places hypertensive patients automatically in the highest risk category because of the enhancement of vascular and renal injury and its consequences[2,3,4,5].

In the past half century, the importance of aggressively treating hypertension particularly in patients with concomitant cardiovascular risk factors, has been increasingly recognized. There is now evidence that several major antihypertensive drug classes decrease cardiovascular morbidity and mortality. Therefore the choice of antihypertensive therapy is largely dependent upon additional factors such as age, the presence of comorbid medical conditions and drug cost. One additional factor that may potentially influence the choice of antihypertensive therapy is the possibility that certain antihypertensive drug classes may accelerate or delay the development of type 2 diabetes. However the results of previous studies[6,7,8,9,10,11] have been inconsistent, with some showing no difference between major antihypertensive drug classes and others suggesting a potentially protective effect of ACE inhibitors, angiotensin receptor blockers, or calcium channel blockers and a potentially harmful effect of beta blockers or thiazide diuretics[12,13].

The question of whether we have thoroughly explored the capacity of Angiotensin Converting Enzyme Inhibitors, Calcium Channel Blockers, and, Adrenergic Receptor Blockers for primary and secondary prevention of cardiovascular events and death in hypertension remains a matter of debate[6]. The initial use of b-blockers in other patient groups, including patients with diabetes mellitus and the elderly is less well established[14].

The goal of antihypertensive therapy should consists of reducing cardiovascular morbidity and mortality associated with arterial hypertension by a strategy focused on lowering blood pressure while minimizing the impact on other associated cardiovascular risk factors.

Purpose of study

The purpose of present study was to observe and compare any significant change in serum glucose in patients with newly diagnosed essential hypertension with Atenolol (cardio-selective beta blocker) and Amlodipine (Calcium channel blocker).

MATERIAL AND METHOD

This study was conducted in the Department of Pharmacology and Therapeutics, Basic Medical Science Institute (BMSI), Jinnah Post Graduate Medical Centre (JPMC), Karachi. Patients with newly diagnosed essential hypertension (N=70) were initially enrolled in this study after taking informed and written consent, selected from Medical OPD of Jinnah Post Graduate Medical Centre (JPMC) Karachi, were divided into 2 groups each comprised of 35 patients were given Tab Atenolol 50mg (Max:100mg) and Amlodipine 5 mg (Max:10 mg) respectively . Out of these, 60 patients were associated through out the study period. Out of remaining 10 patients, 5 has not come for follow up in Atenolol group, 3 due to unknown reason and 2 patients has complained of weakness, lethargy and refused to continue the study, 5 patients were dropped in Amlodipine group, 2 due to gastric upset and diarrhea while 3 has not come for follow-up due to unknown

reason. All patients in the study were selected according to following criteria.

Inclusion criteria

Patients of either sex with newly diagnosed essential hypertension with stage I hypertension (systolic 140-159 & diastolic 90-99)[2], Patients aged between 20-70 years, Patients having no previous history of using antihypertensive drug.

Exclusion criteria

Patients having history of allergy to β-Blockers or Calcium Channel blockers, Patients with uncontrolled diabetes mellitus or diabetic complications or Hyperlipidemia, Pregnant or lactating women, Patients having history of myocardial infarction, coronary artery bypass grafting, proven coronary artery disease, unstable angina, clinically manifest heart failure, Patients with acute liver disease or hepatic dysfunction, Patients with impaired renal function, Patients who were on systemic steroids, androgens, cyclosporine, immunosuppressant drugs or any other drug with reported interaction with antihypertensive drugs, any other concurrent medical illness.

The study period consist of 12 weeks (90 days) with fortnightly follow up visits of patients. The required information such as name, age, sex, occupation, address, previous medication, date of follow up visit and laboratory investigations etc of each patient were recorded on proforma, especially designed for this study

Initially a detailed medical history and physical examination of all patients were carried out. 12-14 hour fasting Lipid profile and fasting blood sugar was done on the day of inclusion i.e. day 0 and on day 45 and day 90.

Blood pressure

At each fortnightly visit, blood pressure readings were taken after giving 10 minute rest to the patient. The blood pressure was measured with a mercury sphygmomanometer having cuff size of 14 × 54 cms.

Statistical Analyses

All data was fed in SPSS version10.0 and analyzed. Descriptive statistics were calculated. Mean±SEM of FBS for each group was calculated. Paired t test was used to compare the mean values of each group separately. P value of less than 0.05 was considered statistically significant.

RESULTS

The demographic characteristics of the study population are shown in table I. The two treatment groups are fairly comparable for the listed variable. The patients were male (45%) and females (55%). The mean age was 59 years (range 20-70 years).

Table-I. Demographic data of atenolol and amlodipine group

	Atenolol (n=35)	Amlodipine (n=35)
Male	15	17
Female	20	18
Age (years)	60±5.04	58±5.8
Body weight (Kg)	62.2±10.45	63±9.80
Height (cm)	165.2±8.8	17.60±9.20

Out of 35 patients on Atenolol (DR1) on day 0, 30 patients were treated till day 90. Mean fasting blood glucose level increased from 91.82±1.34 mg/dl on day 0 to 94.97±1.33 mg/dl on day 45 and to 99.73±1.64 mg/dl on day 90. This increase was statistically significant when compared between day 0 to day 45 ($P < 0.01$) and become highly significant between day 45 to day 90 and significant between day 0 to day 90. The percentage increase from day 0 to day 90 was 8.61 percent. Out of 35 patients on day 0 of Amlodipine (DR2), 30 patients were treated till day 90. The mean fasting blood glucose level remain unchanged from 90.22±1.85 mg/dl on day 0 to 90.26±1.67 mg/dl on day 45 and to 89.20±1.70 mg/dl on day 90. This reduction was statistically non significant between day 0 to day 45 between day 45 to day 90 and between day 0 and day 90. The percentage reduction from day 0 to day 90 was only 1.13%.

Table-II. Changes in mean fasting blood glucose from Day 0 –day45, day 45 – day 90, day 0 –day 90 of treatment with dr1, dr2 in patients with Essential hypertension

Groups	at day 0 mg/dl	At day 45 mg/dl	At day 90 mg/dl	P value			%age change day0-90
				day 0-day45	day45-day90	day0-day90	
DR1	91.82±1.34 (35)	94.97±1.33 (30)	99.73±1.64 (30)	<0.01	<0.001	<0.001	0.0861
DR2	90.22±1.85 (35)	90.26±1.67 (30)	89.20±1.70 (30)	N.S	N.S	N.S	-1.13%

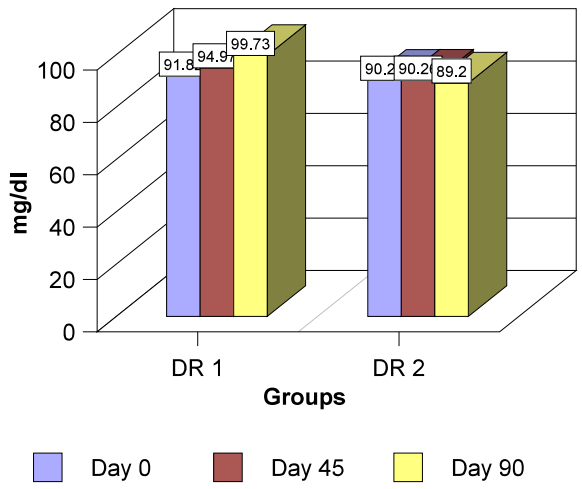
Key:DR1=AtenololDR2= Amlodipine
Figures are in (mean ± SEM)
(–) Indicates decrease in percentage.
(+) Indicates increase in percentage.
All Observations were measured in 'mg/dl'
Figures in parenthesis indicate number of patients.

Table-III. Comparison of DR1 and DR2 for Fasting Blood Glucose at Day 0, Day 45 & Day 90 (table III)

Group	Day 0	Day 45	Day 90
DR1	91.82±1.32 (35)	94.97±1.33 (30)	99.73±1.64 (30)
DR2	90.22±1.85 (35)	90.26±1.67 (30)	89.20±1.70 (30)
P value	N.S	<0.02	<0.001

Key:DR1=AtenololDR2= Amlodipine
Figures are in (mean±SEM
Figures in parenthesis indicate number of patients.
FBS= Fasting blood sugar

Fig-1. Changes in mean fasting blood glucose on Day 0, Day 45, and Day 90 with DR1 & DR2 in patients with essential hypertension.



Key: DR1 = Atenolol DR2 = Amlodipine

On day 0, the difference in fasting blood glucose on the average showed very slightly different values of DR1 and DR2 , however when tested statistically it was difference was found to be non significant.

On day 45, the difference in FBS showed an increase in fasting blood sugar with DR1 as compared to DR2 which showed slight decrease in blood sugar. This difference was statistically significant with a P Value of (< 0.02).

On day 90, fasting blood sugar with DR1 showed greater increase as compared to DR2 with statistically highly significant difference between DR1 and DR2 in relation to FBS (<0.001).

DISCUSSION

Previous randomized controlled trials have inconsistently demonstrated that the incidence of type 2 diabetes may be potentially lowered with ACE inhibitors or calcium channel blockers therapy and raised with beta-blocker therapy or thiazide therapy[6].

The present study demonstrates significant changes in blood pressure with both Atenolol and Amlodipine but showed an increase fasting blood glucose levels with Atenolol but no significant change in fasting blood glucose levels with Amlodipine.

The results observed in present study are in accordance with a previous clinical trial[8] who have reported 28 percent greater risk of developing diabetes in patients who were given beta blocker than among those who took no medicine, but calcium channel antagonist was not associated with a significant increase in the risk of diabetes. They stated that in subjects who were taking a thiazide diuretic, ACE inhibitor, or a calcium channel antagonist were not at greater risk for the subsequent development of diabetes mellitus than were their untreated counterparts. This observation may have some limitations regarding effects of beta blockers on glucose metabolism as they have not mentioned the differences between. cardio-selective or non-selective beta blockers.

The Veterans Administration Cooperative Study Group on Antihypertensive Agents[15]found that propranolol had a hyperglycemic effect that persisted for one month after the discontinuation of drug treatment that had lasted one year. In the Oslo study, the fasting serum glucose concentration in the group treated with propranolol in combination with a thiazide diuretic was specifically higher than that in the placebo group whereas there was no difference in serum glucose concentrations between a group treated only with a thiazide diuretic alone[16].

Groop L et al[17] studied the effects of non selective propranolol and beta 1- selective metoprolol on glucose metabolism in hypertensive non diabetic patients reported a small but significant increase in basal blood glucose values at pharmacological doses of propranolol and metoprolol. This was in accordance with the changes in blood glucose observed in present study except that atenolol was used instead of metoprolol although both are selective beta blockers.

The reason for finding the increase in blood glucose levels in present study can be explained by statement that treatment with beta blockers has been associated with weight gain and with attenuation of the beta receptor mediated attenuation of insulin by the pancreatic beta cells[18] both of which may be risk factor for diabetes.

In contrast, in a previous clinical trial[19] atenolol did not significantly affect any of the metabolic parameters studied, thus indicating that beta-selective β-adrenoceptors blockers have less impact on plasma glucose and lipids than non selective ones. They also mentioned the neutral effects of Amlodipine on lipids and glucose levels. This is in contrast with our study in which blood glucose were altered significantly with a rise in serum glucose levels of 3.20 percent with atenolol after 12 weeks of study while there was no significant changes observed in blood glucose with Amlodipine.

Our study also is in accordance with the statement of Abernethy DR & Schwartz JB[20] who stated that calcium antagonists are an option for the treatment of hypertension associated with diabetes mellitus because they do not adversely affect glucose metabolism, lipid metabolism, or renal function. In our study calcium antagonist are well tolerated and showed no significant changes in lipid profile and blood sugar as well.
In another previous clinical trial[21] the authors conclude that in non obese, normolipidemic, glucose tolerant hypertensive patients, blood pressure normalization with combined therapy is feasible at no cost in terms of undesired effects on glucose and lipid metabolism and insulin sensitivity. The combination regime used in that study was (Verapamil 180 mg/day + trandolapril 2mg/day or Atenolol 50mg/day + nifedipine 20 mg/day). This is in contrast with the present study in which we have observed a significant increase in blood glucose levels with atenolol but not with Amlodipine.

In neither the treatment of Mild Hypertension study[22] nor the Systolic Hypertension in the Elderly Program[23] was an increased risk of hyperglycemia or diabetes found for subjects taking beta-blockers; however acebutolol was used in the former study and atenolol was used in combination with a thiazide diuretic in the latter. Both of these studies are in opposition to the changes found in present study.

In a recent clinical trial[12], beta blocker therapy was associated with a non statistically significant reduction in the incidence of diabetes. This was in contrast to the present study, though the patient in present study are non diabetic and also the primary end point was not development of diabetes but we found a statistically significant increase in fasting blood glucose with atenolol that may contribute to development of diabetes.

CONCLUSION

Comparing the two drugs Amlodipine had no effect on blood glucose as observed in this study and proved its merit over atenolol in not altering one of the most important cardiovascular risk factors in patients with essential hypertension.

Therefore we suggest that long term clinical trials should be conducted to evaluate the effect of cardio selective beta blockers on blood glucose in both diabetic and non diabetic hypertensive patients to assess their role in the treatment of hypertension associated with diabetes.

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THE MAN IS RICHEST WHOSE PLEASURES ARE THE CHEAPEST

Thoreau