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Abstract

Fasting blood glucose was determined in 27 adults with essential hypertension at four different periods during a 12-month treatment with doxazosin, an alpha-adrenoceptor antagonist, and in another set of 20 adult hypertensive patients, after 3 months treatment with amlodipine, a calcium antagonist. The mean fasting blood glucose levels at various determinations during doxazosin therapy did not show any significant variation from the pre-treatment value. Similarly, mean fasting blood glucose level remained the same after 3 months of amlodipine therapy. The findings, therefore, highlights the safety of doxazosin and amlodipine antihypertensive pharmacotherapies.

KEYWORDS: blood glucose levels, essential hypertension, calcium antagonist, alpha-adrenoceptor antagonist

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Blood Glucose Levels in Hypertensive Patients During Treatment with Different Antihypertensive Agents

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Fasting blood glucose was determined in 27 adults with essential hypertension at four different periods during a 12-month treatment with doxazosin, an α-adrenoceptor antagonist, and in another set of 20 adult hypertensive patients, after 3 months treatment with amlodipine, a calcium antagonist. The mean fasting blood glucose levels at various determinations during doxazosin therapy did not show any significant variation from the pre-treatment value. Similarly, mean fasting blood glucose level remained the same after 3 months of amlodipine therapy. The findings, therefore, highlights the safety of doxazosin and amlodipine antihypertensive pharmacotherapies.

Key words: blood glucose levels, essential hypertension, calcium antagonist, alpha-adrenoceptor antagonist

In the past decade, many antihypertensive agents have been introduced clinically because of their ability to control blood pressure (1-3). However, the failure of antihypertensive agents in most clinical trials to demonstrate a reduction in the risk of coronary artery disease despite successful control of blood pressure was attributed to their adverse metabolic effect on serum glucose, lipids and potassium (4). Many reports have shown disturbances in glucose metabolism to be a common occurrence during antihypertensive therapy (5-7). Thiazide diuretics and β-adrenoceptor antagonists are the antihypertensive agents which are often implicated in blood glucose elevation (7-9). It has further been shown that patients on both drugs as combined therapy are at increased risk for hyperglycemia (9-10). Reports from our laboratory also indicated that Moduretic (MSD), a combination of hydrochlorothiazide and amloride hydrochloride showed significant elevation of blood glucose from baseline level especially during short-term treatment (11). Reports on glucose metabolism during administration with calcium antagonists and α-adrenoceptor antagonists have been scanty. Schoenberger (5) reported that prazosin and calcium antagonist (12) therapy may induce impaired glucose tolerance. On the other hand, fasting blood glucose remained unchanged between the baseline and the final visit values during doxazosin therapy (13-14).

In an attempt to identify antihypertensive agents with minimal side effects and maximal therapeutic efficacy, we recently reported lipid and lipoprotein profiles during amlodipine (15) and doxazosin (16) treatment of hypertension in our African patients. Since hyperglycemia is a well known independent risk factor for coronary heart disease and is closely associated with hypertension and disturbances in lipid metabolism, I present here the results of glucose measurements during amlodipine and doxazosin treatments in hypertensive African patients.

Patients and Methods

This report is composed of two studies. The first study consisted of 27 Nigerian men and women with a mean age of 50.3 ± 1.5 years (SEM), and essential hypertension was treated with doxazosin monotherapy for a period of 12 months. The second study consisted of 20 adult Nigerains (10 men and 10 women) mean age 52 ± 1.75 years (SEM) with essential hypertension, and these patients were treated with amlodipine for 3 months. Both studies were carried out at the hypertension clinic of the University College Hospital Ibadan, Ibadan, Nigeria. In both groups, the diagnosis of essential hypertension was based on the average of two separate blood pressure readings, no more than 2 weeks apart and laboratory

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examinations (example, complete blood counts, blood chemistry, and urine test for reducing sugars, protein, casts and sediments). All patients with hypertension secondary to other diseases such as diabetes were excluded from the study. Some patients were newly diagnosed; others who were already receiving antihypertensive agents had their drugs withdrawn for a washout period of 2 weeks. All patients gave written and oral consent before inclusion in the study. The patients maintained their usual diets which was mainly a high-carbohydrate, low-fat, low-protein and high-vegetable diet. Women who were pregnant, lactating or taking oral contraceptives were excluded from the study. Hypertension was defined as a diastolic blood pressure (DBP) between 95 and 130 mmHg in the sitting and supine positions at the end of the washout period. Sitting and supine blood pressure, heart rate and body weight at the end of the washout period were used as the baseline values. The patients in the doxazosin study were given 2 mg of doxazosin daily. Patients who showed no response after 2 weeks had their doses increased at 2-week intervals to 4 mg, 8 mg and 16 mg per day as needed. Patients that achieved DBP < 90 mmHg at the end of 2 weeks of therapy were maintained at the same dose until the end of the 12-month study. The patients in the amlodipine study were initially placed on 5 mg amlodipine after the washout period. Twelve patients whose DBP was not controlled (DBP > 90 mmHg) by 5 mg amlodipine after 4 weeks were given amlodipine 10 mg/day and they were maintained on this dose until the end of the 3-month study.

In both studies, the patients were seen at the outpatient clinic in the morning, every fortnight, by the same physician throughout the study. The sitting blood pressure and heart rate were determined after the patients had been in a sitting position for at least 3 min and readings were repeated 2 min later. Similarly, supine or standing blood pressures were taken in duplicate after 2 min supine or standing, using a mercury sphygmomanometer (Accuson (R)) throughout the study. The patient's same arm was used throughout the study. To ensure strict compliance with the dosage schedule, patients received just enough of the study drug at the clinic to last until the next visit.

In the follow-up studies, each patient was his/her own control. At the beginning (before treatment) and at every 3 months of doxazosin or amlodipine therapy, 2 ml of venous blood was withdrawn from each patient (in the morning as a fasting sample) into bottles containing sodium fluoride for fasting blood glucose determination. The samples were analysed immediately after collection by the method of Trinder (17). For each assay, a commercial quality control (Wellcomtrol II reagent) of known value was always included. The mean values of fasting blood glucose before and at every 3 months of measurement were compared using the paired t-test.

Results

As shown in Table 1, the mean diastolic and systolic blood pressures were significantly reduced ($P < 0.001$) throughout the 12 months of doxazosin therapy. Similarly, the mean diastolic and systolic blood pressures were significantly reduced after 3 months of amlodipine therapy ($P < 0.001$). The body weights of the patients did not change after either of the study periods.

In the doxazosin study group, mean fasting blood glucose levels showed irregular fluctuations but remained within the normal reference range throughout the study period, and these levels were not significantly different from the pre-treatment value (0 month) (Fig. 1). In the amlodipine treatment group, the mean fasting blood glucose level after 3 months of amlodipine therapy was not significantly different from the pre-treatment level (see Fig. 2).

Table 1 Changes in blood pressure and body weight during treatment of hypertension with doxazosin and amlodipine

Duration of treatment (months)	Diastolic BP (mmHg)	Systolic BP (mmHg)	Weight (kg)
Doxazosin			
0	110.5 ± 2.4	173.0 ± 5.0	61.3 ± 2.7
3	98.0 ± 2.3*	161.0 ± 5.3**	61.6 ± 2.8
6	90.0 ± 4.1*	150.0 ± 5.4**	60.9 ± 3.0
9	86.0 ± 3.0*	142.0 ± 5.3**	61.0 ± 3.0
12	85.0 ± 4.3*	139.0 ± 4.0**	61.8 ± 2.0
Amlodipine			
0	101.5 ± 2.6	172.0 ± 2.6	63.4 ± 3.1
3	81.0 ± 2.1*	138.5 ± 3.6*	62.8 ± 3.1

BP: Blood Pressure.
Values are expressed as mean ± standard error.
*$P < 0.001$; **$P < 0.01$.

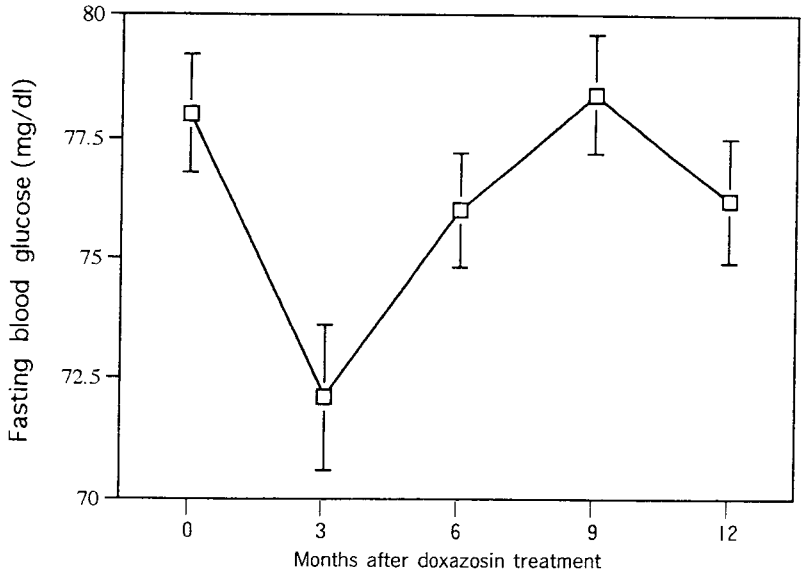

Fig. 1 Fasting blood glucose level before and during doxazosin treatment of hypertension in African patients. Data are expressed as the mean ± standard error.

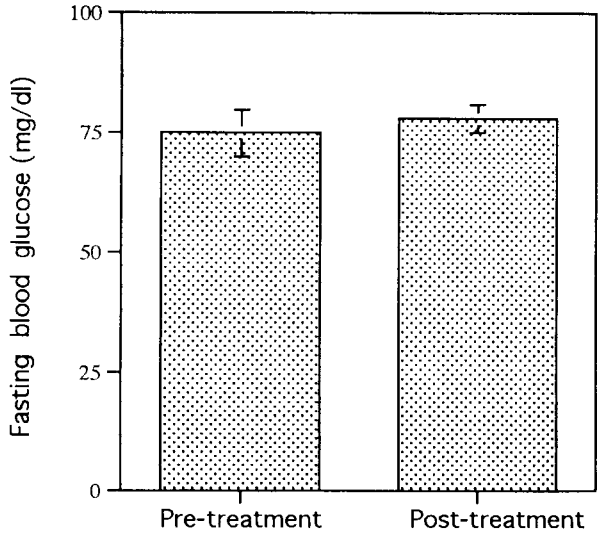

Fig. 2 Fasting blood glucose levels before and after amlodipine treatment of hypertension in African patients. Data are expressed as the mean ± standard error.

Discussion

Doxazosin and amlodipine are widely known to be efficacious in lowering diastolic and systolic blood pressures, as seen in the present study as well. The blood glucose level of the patients in this study were within the normal reference range for fasting blood glucose in Nigeria. Although many antihypertensive agents have been reported to increase blood glucose levels (5, 7–9, 12), doxazosin and amlodipine therapies lowered both diastolic and systolic blood pressures but did not alter the blood glucose levels of our patients. Furthermore, the non-significant variation in the mean value of fasting blood glucose before and during doxazosin treatment, is consistent with the previous findings by Rosenthal (13) and Castrignano *et al.* (14) in different populations. The review report by Schoenberger (5), however, indicated that prazosin (similar to doxazosin) may induce impaired glucose tolerance, but this claim was unfortunately not supported with any references. Meanwhile, prazosin has been judged to exert a favorable effect on glucose homeostasis (3); it has also been shown to increase insulin-mediated glucose disposal in obese subjects (18). The findings in the present study, therefore, complement our previous report of favorable lipid and lipoprotein changes during doxazosin therapy (16) and further supports the antiatherogenic properties and safety of doxazosin administration in hypertensive patients.

The observed insignificant change in the mean fasting

blood glucose level before and after amlodipine therapy, is in conflict with the previously reported adverse effects of calcium antagonists on glucose homeostasis (12). The inertness of amlodipine therapy on blood glucose level, which is consistent with our previous finding on lipid and lipoprotein metabolism (15) further confirms the safety of antihypertensive monotherapy with amlodipine.

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