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Ahaneku, Joseph E.

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BLOOD PRESSURE AND BLOOD GLUCOSE LEVELS DURING A CROSS-OVER TREATMENT OF DOXAZOSIN, MODURETIC AND AMLODIPINE IN HYPERTENSIVE PATIENTS.

Joseph E. AHANEKU

Department of Biochemistry,
Saga Medical School, Saga 849, Japan

Department of Chemical Pathology,
Nnamdi Azikiwe University Teaching Hospital,
Nnewi, P. B. M 5025 Nnewi, Nigeria

INDEXING WORDS

blood pressure; blood glucose; cross-over study; hypertensive patients

SYNOPSIS

A cross-over study comparing the effects of doxazosin, moduretic and amlodipine on fasting blood glucose and blood pressure levels in 9 adult hypertensive Nigerians is presented. The results showed that doxazosin, moduretic and amlodipine were effective in reducing diastolic blood pressure and thus confirmed our previous observation of blood pressure reduction during the monotherapies of these antihypertensive agents. The study further indicated the effectiveness of doxazosin in the management of severe essential hypertension in Nigerian patients. Fasting blood glucose level significantly decreased during doxazosin treatment phase and increased during moduretic phase, while amlodipine treatment did not have any effect on blood glucose level.

In conclusion, the cross-over study seem to confirm the effectiveness of doxazosin therapy and its antidiabetic effect in hypertensive patients. The

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effectiveness of amlodipine therapy in contolling blood pressure was also observed, but no effect on bloood glucose level, while moduretic therapy has hyperglycemic effect despite its effectiveness in blood pressure control in African patients.

INTRODUCTION

Researchers in the field of antihypertensive pharmacotherapeutic agents will not have any rest until the dilemma which many Clinicians now face about the choice of appropriate drug(s) with maximal therapeutic efficacy and minimal side effects is resolved. Recently, we have tackled this problem with much vigor, first by looking at the effectiveness and biochemical changes during amlodipine[1], doxazosin[2], and moduretic[6] treatment of hypertension in African patients. We also studied the antiatherogenic and atherogenic side effects of these drugs by measuring lipid and lipoprotein levels during amlodipine[4], doxazosin[3] and moduretic[4] treatments in African patients.

Doxazosin is an alpha$_1$-selective blocker and a quinazoline derivative chemically related to prazosin. It acts through selective inhibition of sympathetic stimulation of postsynaptic alpha$_1$-adrenoceptors in the vascular smooth muscle[2]. Moduretic on the other hand, is a diuretic consisting of hydrochlorothiazide (50 mg) and amloride hydrochloride (5 mg). The mode of action of hydrochlorothiazide is typical of diuretic action of thiazides, while amloride enhances the saluretic effects of hydrochlorothiazide[6]. Amlodipine is a new calcium channel blocker in the 1,4-dihydropyridine family; it is a structural analogue of nifedipine. The action of amlodipine involves a direct relaxant effect on vascular smooth muscle[5].

Hyperglycemia has long been identified as an independent risk factor for coronary heart disease[13,12]. Meanwhile, there are reports of increase in blood glucose level following different antihypertensive therapies[18].

Thiazide diuretics[7,10] and beta-adrenergic blockers[14,9] have been the most commonly studied antihypertensive agents with hyperglycemic side effects. Calcium antagonist has been shown to occasionally upset diabetic control, though without much clinical significance[21]. Recent studies have shown that the risk of raised blood glucose was higher in patients on multiple therapy than in those who received single antihypertensive therapy[11]. However, reports on blood glucose monitoring during antihypertensive therapy either as monotherapy or in combination in African patients are scanty[6].

In the present study, attempt was made to select the most effective drug with minimal side effect for treatment of hypertension in African patients. I hereby report the evaluation of blood pressure and blood glucose levels in the same hypertensive patients treated with three different classes of antihypertensive agents in a double-blind, cross-over fashion. This may further confirm the hyperglycemic side effect profile of these antihypertensive agents.

PATIENTS AND METHODS

Thirty patients aged 35 to 65 years with essential hypertension were originally selected for this study from the hypertension clinic of the University College Hospital Ibadan, Nigeria. As a result of defult nine patients were able to complete the 19 months study period. The patients were all Nigerians and the diagnosis of essential hypertension was based on the World Health Organisation (WHO) criteria for moderate to severe hypertension. Some patients were newly diagonised, others who were previously receiving antihypertensive agents had their drugs withdrawn for a washout period of 2 weeks. The patients were not subjected to any dietary restrictions or other forms of treatment throughout the study period. Women who were pregnant, lactating or taking oral contraceptives were excluded from the study. None of the nine patients showed remarkable clinical side

effects such as dizziness, headache, postural dizziness, drowsiness, edema, palpitation, dry mouth, depression, lack of energy and nasal congestion during treatment with the three antihypertensive agents. This was a double-blind, cross-over study, which comprised three phases of washout/baseline, titration and maintenance. The blood pressure (sitting and supine) pulse rate and weight at the end of the 2 weeks washout period were recorded as baseline values. An average of two diastolic blood pressure readings in the range of 105-130 mmHg in the sitting and supine positions at the end of the 2 weeks washout period was regarded as the cut-off point for the patient's inclusion in this study.

Upon selection for the study, the patients were placed on doxazosin treatment and maintained on the dosage in which the patients showed response for a period of 6 months, by which time the blood pressures were reduced in the range of mild to moderate. At the end of 6 months doxazosin therapy, the patients were switched over to one to two tablets of moduretic daily (equivalent to 50mg hydrochlorothiazide and 5mg amloride hydrochloride) for a period of 10 months. After the ten months of moduretic therapy, the blood pressure was controlled and the patients were switched over to amlodipine therapy for another 3 months. The patients were seen fortnightly at the out-patient clinic between 8 and 11 am by the same physician for full clinical assessment throughout the study period. Sitting blood pressure and heart rate were determined after patients had been in a sitting position for at least 3 minutes and readings were repeated 2 minutes later. Similarly, supine blood pressure was determined twice after 5 minutes supine and repeated 2 minutes later using a mercury sphygmomanometer (Accuson$^{(R)}$). The patients same arm was used throughout the study. Drugs were dispensed in the clinic by a co-investigator in amounts sufficient to last until the next visit to encourage compliance with the dosage schedule.

At the beginning and after every three months (in the case of doxazosin and amlodipine therapies) and two months (in the case of moduretic therapy), 2 ml of venous blood was withdrawn from each patient into a bottle containing sodium fluoride for fasting blood glucose determination. The samples were analysed immediately after collection by the method of Trinder[20]. For each assay, a commercial quality control (wellcomtrol I and II reagents) of known values were always included. The mean values of diastolic blood pressure and fasting blood glucose before and at every period of measurement were compared using the paired t-test.

RESULTS

Diastolic blood pressures (DBP) before and during cross-over of doxazosin, moduretic and amlodipine treatments are shown in figure 1. Mean DBP declined from the pre-treatment value during doxazosin treatment phase ($P<0.01$; $P<0.05$). The decrease in the mean DBP was consistent and persistent during the moduretic treatment phase (6-16 months) ($P<0.05$), when compared with the values duing doxazosin treatment phase. The lowest value of DBP (83 mmHg) was recorded at 16th month of moduretic treatment ($P<0.001$). As the patients were switched from moduretic to amlodipine treatment, the mean DBP value was maintained, so the mean value during amlodipine phase did not show any statistically significant variation when compared with the lowest value during moduretic treatment phase.

As shown in figure 2, the mean value of fasting blood glucose consistently declined during doxazosin treatment phase, and the reduction was significant ($P<0.05$) at 3rd month of doxazosin therapy when compared with the pre-treatment value. Fasting blood glucose level started to increase during moduretic treatment phase and the level of increment reached its peak at 12th month of moduretic treatment and this was statistically significant ($P<0.05$). As the patients were switched from moduretic to

amlodipine treatment, the level of fasting blood glucose tended to fall, though the mean value was not statistically different from the value of the previous measurement (16th month of moduretic phase) see fig. 2.

DISCUSSION

The significant reduction in the DBP from a mean pre-treatment value of 115 mmHg in the range mild to moderate during doxazosin treatment phase ($P<0.01$), is consistent with the previous reports on the effectiveness of doxazosin treatment in lowering blood pressure in different hypertensive populations[2,17,8]. Similarly, the observed reductions in the mean DBP during moduretic treatment phase agree with the long documented efficacy of moduretic therapy in the management of hypertension in Africans[15-16]. The minimum blood pressure recording (83 mmHg) was observed during moduretic treatment phase. At this time the patients were controlled, thus a switch to amlodipine therapy only maintained the DBP at the controlled value without further reduction. Meanwhile, our previous report on amlodipine monotherapy in hypertensive patients demonstrated the effectiveness of amlodipine in reducing blood pressure in male and female African patients[1]. The mean systolic blood pressure of the patients was simultaneously reduced during the cross-over treatment (data not shown). In general, the cross-over study seem to confirm our previous findings on blood pressure recording during the monotherapies of these antihypertensive agents[1-2,6,15] and further demonstrate that doxazosin is equally effective in the management of severe essential hypertension.

The observed reduction in the mean fasting blood glucose level ($P<0.05$) during doxazosin treatment phase further supports the antiatherogenic qualities of doxazosin therapy[5]. When the fasting blood glucose level was previously measured during doxazosin monotherapy in hypertensive patients[6], no significant variation was observed before and during treatment. However, the cross-

over study has demonstrated that doxazosin therapy could even exhibit antidiabetic properties. On the other hand, a significant rise ($P<0.05$) (though within reference range) in fasting blood glucose level observed during moduretic treatment phase demonstrates the hyperglycemic effects of moduretic therapy. This finding is consistent with the previuos observations during moduretic treatment[6,19]. The non variation in the fasting blood glucose level as the patients were switched to amlodipine treatment , showed that amlodipine therapy did not affect glucose metabolism in the hypertensive patients. This observation also is in alignment with the previously reported innertness of amlodipine therapy on biochemical variables in hypertensive patients[1,5].

In conclusion, the cross-over study seem to confirm that doxazosin therapy has antidiabetic effect among hypertensive patients and amlodipine therapy no effect on blood glucose level, while moduretic therapy has hyperglycemic effect despite its effectiveness in lowering blood pressure in African patients.

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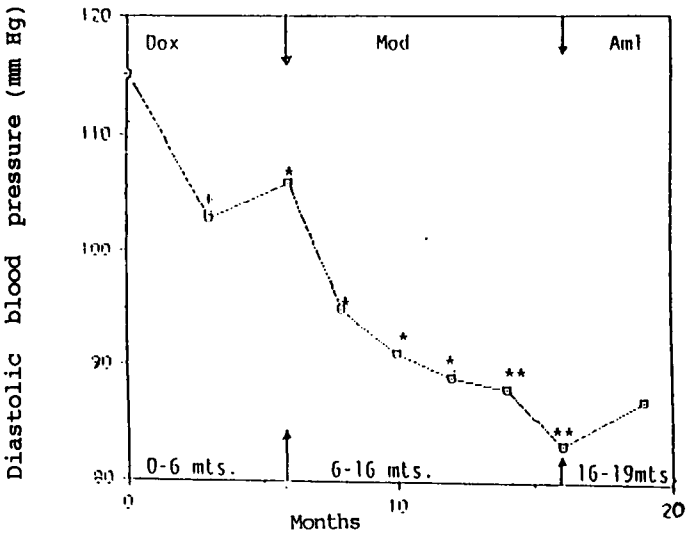

Figure 1.
Graph of diastolic blood pressure recording before and during cross-over of doxazosin, moduretic and amlodipine treatments. n = 9; where n = number of patients. * = P<0.05; + = P<o.01; ** = P<0.001.
Dox = doxazosin, Mod = moduretic, Aml = amlodipine
mts = months.

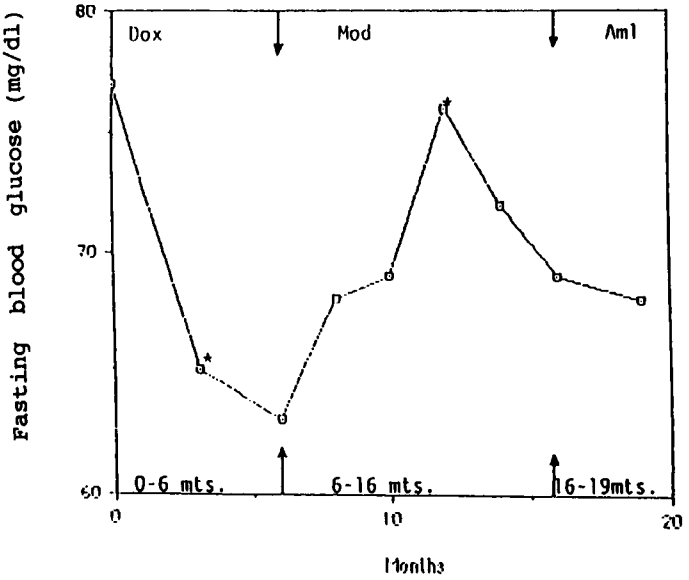

Figure 2.
Graph of fasting blood glucose levels before and during cross-over of doxazosin, moduretic and amlodipine treatments. n = 9; where n = number of patients. * = $P<0.05$. Dox = doxazosin, Mod = moduretic, Aml = amlodipine, mts = months.