THE EFFICACY AND TOLERABILITY OF AMLODIPINE AND HYDROCHLOROTHIAZIDE IN NIGERIANS WITH ESSENTIAL HYPERTENSION

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The efficacy and safety of the novel calcium antagonist Amlodipine (Pfizer Laboratories, New York, New York) and hydrochlorothiazide were evaluated and compared in a randomized, single-blind, parallel group study in black Africans with essential hypertension. Twenty Nigerians with newly diagnosed mild to moderate essential hypertension were randomized to receive ascending doses of Amlodipine (5 mg and 10 mg) or hydrochlorothiazide (25 mg or 50 mg), and blood pressure and heart rate were measured at baseline and at 2, 4, and 6 weeks of therapy. Both Amlodipine and hydrochlorothiazide significantly reduced supine and erect blood pressure. Supine blood pressure on Amlodipine fell from a mean of 190/104 mm Hg to 150/79 mm Hg, and on thiazide from 180/103 mm Hg to 141/84 mm Hg. There was, however, no significant difference between both drugs in antihypertensive efficacy. Neither drug induced a reflex increase in heart rate. The fall in blood pressure on both agents was associated with an increase in plasma urea. Amlodipine induced no change in plasma potassium, but hydrochlorothiazide caused hypokalemia. Both agents were well tolerated, and Amlodipine should undergo further study in the treatment of hypertension in blacks. (*J Natl Med Assoc.* 1995;87:485-488.)

Key words • essential hypertension • blacks • Nigerians • Amlodipine

Essential hypertension remains the most common cardiovascular disease among black Africans,[1] and it is also a significant cause of adult morbidity and mortality.[2] Although the benefit of antihypertensive therapy is well established, the response to individual antihypertensive drugs is known to be influenced by epidemiological variables such as age, race, and plasma renin profiles.[3] In this context, β adrenoceptor blockers[4] and angiotensin-converting enzyme inhibitors[5,6] have been reported to be of little value as monotherapeutic agents, while thiazide diuretics[6] or calcium antagonists[7] may exhibit satisfactory efficacy in black Africans. The efficacy of thiazides and calcium antagonists may relate to the low plasma renin profile of black Africans with essential hypertension.[3,8]

Amlodipine (Pfizer Laboratories, New York, New York) is a dihydropyridine, long-acting calcium channel blocker, which is of proven efficacy as monotherapy for essential hypertension in both white and black patients.[9,10] Reports of a direct comparison of thiazide diuretics and calcium-antagonist agents with proven efficacy in low renin hypertension are rare in black

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TABLE. BASELINE CLINICAL AND BIOCHEMICAL DATA*

Parameter	Amlodipine Group	Thiazide Group
No. of patients	10	9
Males	5	4
Females	5	5
Age (years)	56 ± 8	53 ± 8
Supine blood pressure (mm Hg)	190 ± 18	180 ± 13
Systolic Diastolic	104 ± 16	103 ± 7
No. of patients with left ventricular hypertrophy†	6	4
Plasma urea (mmol/L)	5.5 ± 1.6	3.9 ± 0.8
Plasma creatinine (μmol/L)	101 ± 41	110 ± 32
Plasma potassium (mmol/L)	3.9 ± 0.5	3.7 ± 0.4
Plasma sodium (mmol/L)	133 ± 5	136 ± 5
Fasting blood glucose (mmol/L)	6.1 ± 1.1	5.6 ± 0.6

*Values given as mean ± standard deviation.
†Evident on electrocardiogram.

Africans. This study evaluates and compares the efficacy and tolerability of Amlodipine and hydrochlorothiazide in Nigerian patients with mild to moderate essential hypertension.

MATERIALS AND METHODS

Twenty newly diagnosed patients with mild to moderate essential hypertension comprised the study population. The study was a randomized, single-blind, parallel group comparison of Amlodipine and hydrochlorothiazide in Nigerians with essential hypertension. The study inclusion criteria were Nigerians with supine diastolic blood pressure of 95 mm Hg or more, measured on at least two occasions. Patient exclusion criteria were malignant hypertension, renal impairment with serum creatinine levels of 150 μmol/L or more, significant comorbidity such as diabetes mellitus, or the necessity for other medications. None of the patients smoked cigarettes or imbibed alcohol.

The patients were randomized to receive 5 mg of Amlodipine or 25 mg of hydrochlorothiazide with upward dose-titration to 10 mg of Amlodipine or 50 mg of hydrochlorothiazide after 2 weeks, to a target diastolic blood pressure of 90 mm Hg supine.

The participating patients were studied at baseline and again at 2, 4, and 6 weeks after treatment. Blood pressure in the supine and erect posture (phase V, diastolic) was measured using manual sphygmomanometry and the pulse rate by radial pulse counting. Compliance was assessed by direct questioning and pill counting. Adverse reactions to the medications were assessed by spontaneous complaints or in response to a checklist.

Prior to enrollment, all of the patients underwent a complete physical examination that included biochemical and electrocardiographic screening and urinalysis. The clinical and demographic data of the patients are summarized in the Table.

Statistical Analysis

All data are given as mean ± standard deviation (SD) or standard error of the mean (SEM), as stated. The antihypertensive efficacy of both drugs was compared using two-way repeated measures analysis of variance (MANOVA) or analysis of covariance (ANCOVA). The baseline clinical or demographic data or the biochemical variables were evaluated using unpaired or paired *t*-tests, as appropriate. The null hypothesis was rejected at an α level of $P<.05$.

RESULTS

All 10 patients in the Amlodipine group completed the study protocol. Nine patients in the thiazide group completed the protocol; one was lost to follow-up. Four patients (40%) in the Amlodipine group required 5 mg/day for adequate blood pressure control. Three patients (33%) in the hydrochlorothiazide group attained normotension at 25 mg/day.

Blood Pressure and Heart Rate

Initial blood pressure in the thiazide group tended to be lower than in the Amlodipine. Both Amlodipine and hydrochlorothiazide significantly reduced supine and erect blood pressure compared with the starting basal value ($P<.0001$ ANOVA; $F=12.08$; $df=3$). Supine and erect systolic blood pressures on Amlodipine were significantly lower than on hydrochlorothiazide ($P=.006$; $F=8.24$), but this might have been a consequence of the starting blood pressure, as there was no statistically significant difference between Amlodipine and hydrochlorothiazide effects by ANCOVA using the initial blood pressure as a covariate ($F=0.97$).

Diastolic blood pressures were similarly reduced in both treatment groups ($P<.001$ ANOVA) with no significant between-treatment effects. The fall in blood pressure was apparent within 2 weeks on both Amlodipine and thiazide but appears to have reached a nadir at

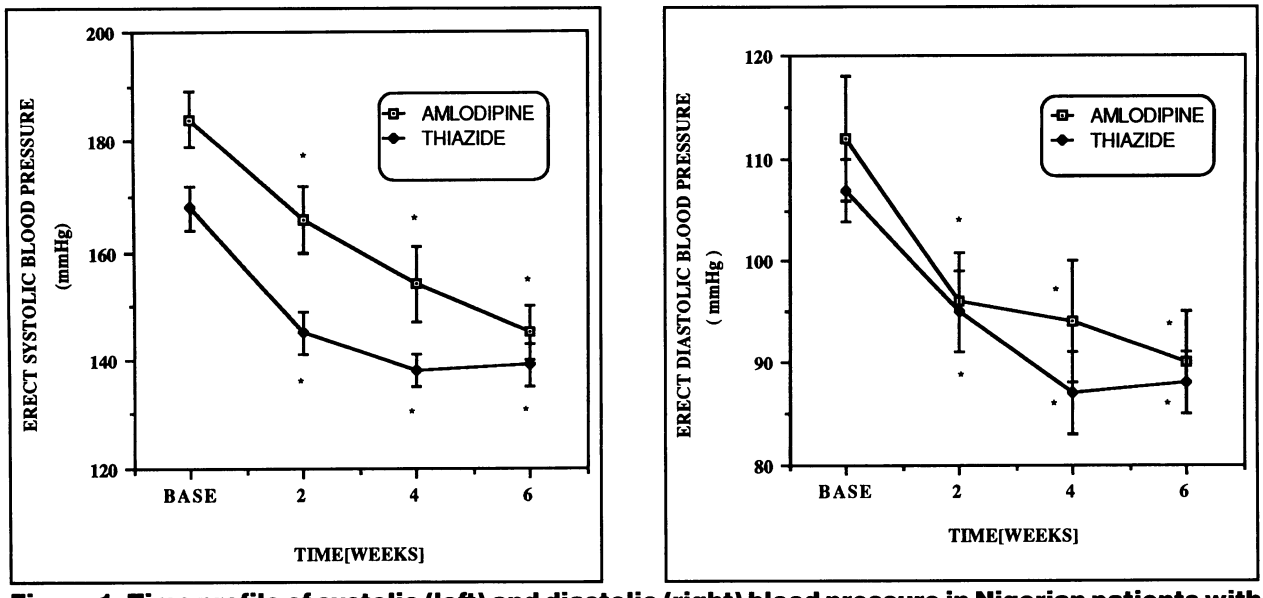

Figure 1. Time profile of systolic (left) and diastolic (right) blood pressure in Nigerian patients with essential hypertension treated with Amlodipine or hydrochlorothiazide. Values are given as mean ± SEM. Both drugs significantly reduced blood pressure compared with the baseline value ($P<.001$ repeated measures ANOVA). There was no difference between Amlodipine- or hydrochlorothiazide-induced blood pressure fall.

4 weeks on hydrochlorothiazide. The blood pressures at 6 weeks on Amlodipine-treated patients were lower than the 4-week value. These results are summarized in Figure 1.

The hypotensive action of hydrochlorothiazide and Amlodipine was unassociated with a significant increase in heart rate in both supine and erect posture ($F=0.1$; not significant). Furthermore, there was no difference in the heart rate profile between Amlodipine- or hydrochlorothiazide-treated patients (Figure 2).

Biochemical Parameters and Adverse Reactions

Both treatments were generally well tolerated. Two subjects each experienced transient postural dizziness on Amlodipine and hydrochlorothiazide treatment. One subject complained of transient headache and another of polyurea while on Amlodipine. No patients complained of palpitations. Amlodipine had no significant impact on plasma glucose or potassium. Hydrochlorothiazide, however, caused a significant hypokalemia effect in comparison to Amlodipine. The Amlodipine-induced change in plasma potassium was 0.34 ± 0.46, but was -0.18 ± 0.2 on hydrochlorothiazide treatment ($P=0.048$).

Both Amlodipine and hydrochlorothiazide caused a rise in plasma urea. In Amlodipine-treated patients, the rise was from 5.5 ± 1.5 to 6.2 ± 1.6 mmol/L ($P=0.06$), and the increase was from 3.90 ± 0.8 to 4.3 ± 0.6 mmol/L in thiazide-treated patients ($P=0.028$). There was, however, no correlation between drug-induced blood pressure fall and the concurrent rise in plasma urea concentration ($r=0.26$; $y=0.31 \pm 0.0076$ X).

DISCUSSION

This study explores the comparative efficacy, tolerability, and safety of Amlodipine and hydrochlorothiazide in newly diagnosed hypertensive Nigerians during short-term treatment. The results indicate that both drugs used as monotherapy significantly reduced blood pressure ($P<.006$ ANOVA) in this population with epidemiologically established low renin hypertension.[8] There was no significant difference between the antihypertensive efficacy of the drugs by ANCOVA. Forty percent of patients treated with 5 mg/day of Amlodipine and 33% of patients treated with 25 mg/day of hydrochlorothiazide achieved normal blood pressure. The antihypertensive effects of Amlodipine or thiazide were not associated with a significant rise in heart rate. Absence of reflex tachycardia with the vasodilator action of Amlodipine has been reported previously[10] and may be related to the slow absorption and the slow elimination of the drug.[11] Our finding on the efficacy of Amlodipine is concordant with earlier reports of the

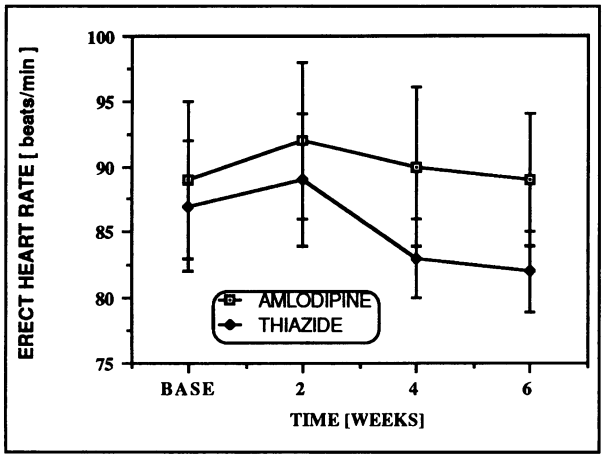

Figure 2. Time profile of erect heart rate changes in hypertensive Nigerians treated with Amlodipine or hydrochlorothiazide. Neither drug significantly changed erect heart rate, and there was no difference between the two treatments. Values are given as mean ± SEM.

efficacy of calcium-antagonist nifedepine monotherapy in Nigerians.[7] In the present study, results indicate that Amlodipine is at least as effective as hydrochlorothiazide in Nigerians. None of the patients on Amlodipine experienced palpitations, and there was no evidence of impaired cardiac function.

Both treatments were generally well tolerated with little untoward symptom side effects. Polyuria is a known adverse effect on Amlodipine therapy, and it may reflect changes in renal blood flow or increased natriuresis. The rise in plasma urea with the hypotension in both groups may reflect a slight impairment of renal function consequent on the fall in blood pressure. There was, however, no correlation between the drug-induced hypotension and the concurrent rise in plasma urea.

Hypokalemia was induced by hydrochlorothiazide, but not Amlodipine; neither Amlodipine nor the thiazide had an impact on fasting blood glucose in this short-term study. The effect of these drugs in the lipid profile was not evaluated, owing to the brevity of follow-up, but Amlodipine has been reported to have a neutral or beneficial effect on the lipid profile in hypertensive Nigerians.[12]

CONCLUSION

Amlodipine monotherapy and hydrochlorothiazide exhibited a similar significant antihypertensive effect in Nigerian hypertensives. Amlodipine was well tolerated and had no significant biochemical adverse effects over the short term. Further study of chronic Amlodipine therapy in both hypertension and heart failure in Nigerians is warranted.

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Literature Cited

1. Akinkugbe OO. World epidemiology of hypertension in blacks. In: Hall WD, Saunders E, Shulman EB. *Hypertension in Blacks.* Chicago, Ill: Yearbook; 1985:3-16.

2. Levy D, Wilson PW, Anderson KM, Castelli P. Stratifying the patient at risk from coronary disease: new insights from the Framingham Heart Study. *Am Heart J.* 1990;119:712.

3. Buhler F, Balli F, Wolfgang K, Erne P, Hulthen VL, Block LH. Renin profiling to select antihypertensive baseline drugs. *Am J Cardiol.* 1984;77(2A):36-42.

4. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Comparison of propranolol and hydrochlorothiazide for the initial treatment of hypertension, I: results of a short-term titration with emphasis on racial difference in response. *JAMA.* 1982;248:1996.

5. Goodman C, Rosendorf C, Coull A. Comparison of the antihypertensive effects of enalapril and propranolol in black South Africans. *S Afr Med J.* 1985;87:672-676.

6. Ajayi AA, Oyewo EA, Ladipo GA, Akinsola A. Enalapril and hydrochlorothiazide in hypertensive Africans. *Eur J Clin Pharmacol.* 1989;36:229-234.

7. Fadayomi MD, Akinroye KK, Ajao RO, Awosika LA. Monotherapy with nifedipine in adult blacks. *J Cardiovasc Pharmacol.* 1986;8:466-469.

8. Osotimehin B, Erasmus RT, Iyun AO, Falase AL, Akmed K. Plasma renin activity and plasma aldosterone concentrations in untreated Nigerians with essential hypertension. *Afr J Med Sci.* 1984;213:139-143.

9. Heber ME, Brigden G, Ackhawaja I, Raftery EB. Twenty-four hour blood pressure control with once daily calcium antagonists, Amlodipine. *Br J Clin Pharmacol.* 1989;27:359-365.

10. Mehta JL, Lopez LM, Vlachakis ND, Gradman AH, Nash DT, O'Connel MT, et al. Double blind evaluation of the dose-response relationship of Amlodipine in essential hypertension. *Am Heart J.* 1993;125:1704-1910.

11. Faulkner JK, McGibney D, Chasseard LF, Perry JL, Taylor IW. The pharmacokinetics of Amlodipine in health volunteers after single intravenous and oral doses, and after 14 repeated oral doses given once daily. *Br J Clin Pharmacol.* 1986;22:21-25.

12. Akaneku JE, Taylor GV, Agbedana EO, Walker O, Sowunmi A, Salako LA. Effects of Amlodipine on plasma lipids and lipoprotein levels in hypertensive patients. *J Intern Med.* 1992;232:489-492.