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Enalapril and Hydrochlorothiazide in Hypertensive Africans

A. A. Ajayi, E. A. Oyewo, G. O. A. Ladipo, and A. Akinsola

Department of Medicine, Faculty of Health Sciences, Obafemi Awolowo University, Ile-Ife, Nigeria

Summary. The antihypertensive efficacy both of angiotensin converting enzyme (ACE) inhibitors and thiazide diuretics has been claimed to be influenced by plasma renin activity, which declines with age and is low in blacks. In a double-blind, placebo-controlled, double-dummy, randomized, parallel-group preliminary study, the antihypertensive efficacy and tolerability of the ACE inhibitor enalapril (20 mg day^{-1}) and hydrochlorothiazide (50 mg day^{-1}) were evaluated and compared for 4 weeks in 20 African patients with essential hypertension. The two groups had similar baseline clinical features and serum Na^+ and K^+ levels.

Hydrochlorothiazide caused a significant and sustained fall in erect blood pressure with a reflex tachycardia. Enalapril exerted only a modest antihypertensive action, but significantly reduced erect heart rate.

Direct comparison of hydrochlorothiazide - and enalapril - induced hypotension suggested a greater fall in subjects on the thiazide. The 95% confidence limits for the thiazide-enalapril difference in antihypertensive action at the end of the study was 39.5 to -7.5 mm Hg systolic and 22.0 to -6.6 mm Hg diastolic. The maximal blood pressure fall after hydrochlorothiazide was positively correlated with age ($r = 0.50$; $p < 0.05$), whilst that of enalapril was inversely related age to ($r = -0.57$, $p < 0.05$).

The results are compatible with the notion that ACE inhibitor monotherapy may be less effective than thiazide diuretic treatment in African and black patients with essential hypertension. The findings also support the concept that age and racial factors may influence the response to antihypertensive treatment.

Key words: enalapril, hydrochlorothiazide; hypertension, side-effects, Africans

Angiotensin converting enzyme (ACE) inhibitors and thiazide diuretics are important therapeutic modalities in the management of hypertension and heart failure. Both agents exert their pharmacodynamic action, at least in part, by modulation of the renin-angiotensin-aldosterone axis, and thus their therapeutic effect may be influenced by plasma renin activity (Lant 1987). It has been suggested that the efficacy of hypotensive agents may be influenced both by age (Buhler et al. 1982) and racial factors (Seedat and Reddy 1971; V.A. cooperative study 1982). The vasodepressor response to beta-adrenoceptor blockers and converting enzyme inhibitors has been claimed to be greater in younger hypertensives and in Caucasians (Bühler et al. 1973; Lijnen et al. 1983), whilst the efficacy of diuretics (Vaughan et al. 1973) and calcium antagonists (Bühler et al. 1982; Fadayomi et al. 1986) may be greater in the elderly and in hypertensive negro patients. These differences may reflect the biochemical heterogeneity of essential hypertension as a result of differences in plasma renin profiles (Laragh 1973), although this is a contentious issue (Zanchetti 1985). Plasma renin activity falls with age (Meade et al. 1983) and is low in unmedicated Nigerian hypertensives (Osotimehin et al. 1984), and in Africans in general (Severs et al. 1981). If, indeed, plasma renin level is predictive of antihypertensive efficacy, then it is reasonable to expect a quantitative difference in the response to a diuretic and a converting enzyme inhibitor in Nigerian hypertensive patients and possibly age related differences as well. Although several studies in North American black hypertensives revealed a poor response to ACE inhibitors (Vidt 1984), data on indigenous Africans is lacking.

The aim of the present study was to evaluate and compare the antihypertensive efficacy of enalapril and hydrochlorothiazide in Nigerian hypertensives.

Material and Methods

The study was a double-blind, placebo-controlled, double-dummy, randomized, parallel-group evaluation of enalapril 20 mg p.o. daily and hydrochlorothiazide 50 mg p.o. daily in 20 Nigerian patients with essential hypertension. After a 2-week double-placebo run-in period, the patients were randomized to receive either enalapril or hydrochlorothiazide in a double-blind fashion for 4 weeks. The inclusion criteria were Nigerian patients with supine diastolic blood pressure > 95 mm Hg (Phase V) after placebo run-in, and aged 30–75 years. All the patients were being treated with thiazides with or without methodopa prior to the study. Patient exclusion criteria were malignant hypertension, renal impairment with serum creatinine greater than 150 μmol/l, congestive heart failure, hepatic dysfunction detected clinically or by laboratory tests, and conditions requiring concomitant medication. None of the patients imbibed alcohol or smoked cigarettes. Non-compliance during the placebo run-in phase was also an exclusion criterion. The study was reviewed and approved by the Human Research Ethics Committee of the Faculty of Health Sciences, and the patients gave informed verbal or written consent to it. The patients underwent a full physical examination and biochemical screening as well as urinalysis and 12 lead electrocardiography. Patients were asked to maintain their usual salt intake. Sodium intake was judged to be adequate by finding a serum Na^+ of 134 ± 4.0 mmol/l and 138 ± 2.6 mmol/l in the two weeks before the study.

Following the placebo run-in and randomization periods, patients received either enalapril 20 mg and hydrochlorothiazide placebo, or 50 mg hydrochlorothiazide placebo plus an enalapril. The patients were studied at the end of the 2-week placebo run-in phase, and after 1, 2, and 4 weeks of active treatment. The clinical and demographic data of the patients randomized to the 2 treatment groups are summarized in Table 1.

The patients were instructed to refrain from cigarette, alcohol, coffee, tea, or kolanuts from 22.00 h of the night preceding each study day. Concomittant medication was not allowed. On arrival at the clinic at 09.00 h, supine blood pressure (in duplicate) after 30 min at rest, and erect blood pressure after standing for 2 min, were measured by sphygmomanometry, by the same observer (A.A.A.). Diastolic BP was recorded as Phase V. Supine and erect heart rates were measured at the same time by palpation of the radial pulse. Compliance was assessed by tablet counting as well as by direct questioning for recall of drug intake at each clinic attendance. An inclusion criterion for the study was evidence of compliance in the placebo run-in phase.

The adverse reaction profile was evaluated by the response to a symptom questionnaire as well as by

Table 1. Post randomization. Clinical and demographic details of the patients

	Enalapril	Hydrochlorothiazide	*p*
n	10	10	NS
Age (years)	56 (11)	50 (12)	NS
Range	35–75	33–65	NS
Sex (M/F)	5/5	4/6	NS
Weight (kg)	64 (11)	69 (16)	NS
Smokers	Nil.	Nil.	NS
Serum Creat. (μmol/l)	114 (20)	106 (26)	NS
Serum Na^+ (mmol/l)	134 (4.0)	138 (2.6)	NS
Serum K^+ (mmol/l)	4.0 (0.5)	4.0 (0.7)	NS
Erect SBP (mm Hg)	165 (25)	173 (27)	NS
Erect DBP (mm Hg)	114 (16)	109 (17)	NS
No of patients with LVH	5/10	3/10	NS

SBP = Systolic blood pressure; DBP = diastolic blood pressure; LVH = left ventricular hypertrophy determined by electrocardiography; Creat. = creatinine

Table 2. Blood pressure before and after treatment with enalapril or hydrochlorothiazide in Africans with essential hypertension ($n = 10$). Mean (SD)

A. Supine					
	Days	0	7	14	28
Enalapril	Systolic BP (mm Hg)	160 (18)	155 (21)	147 (24)	160 (24)
	Diastolic BP (mm Hg)	106 (15)	101 (17)	92 (19)	101 (15)
Hydrochlorothiazide	Systolic BP (mm Hg)	179 (28)	161 (17)	153 (18)	154 (31)
	Diastolic BP (mm Hg)	106 (13)	103 (13)	96 (13)	88 (12)
B. Erect					
Enalapril	Systolic BP (mm Hg)	165 (25)	149 (17)	161 (28)	160 (28)
	Diastolic BP (mm Hg)	114 (16)	103 (19)	105 (14)	109 (20)
Hydrochlorothiazide	Systolic BP (mm Hg)	173 (27)	156 (14)	149 (20)	150 (19)
	Diastolic BP (mm Hg)	109 (17)	102 (17)	99 (12)	96 (10)

Hydrochlorothiazide significantly reduced *supine* and *erect* systolic and diastolic BP (ANOVA, $p < 0.05$)

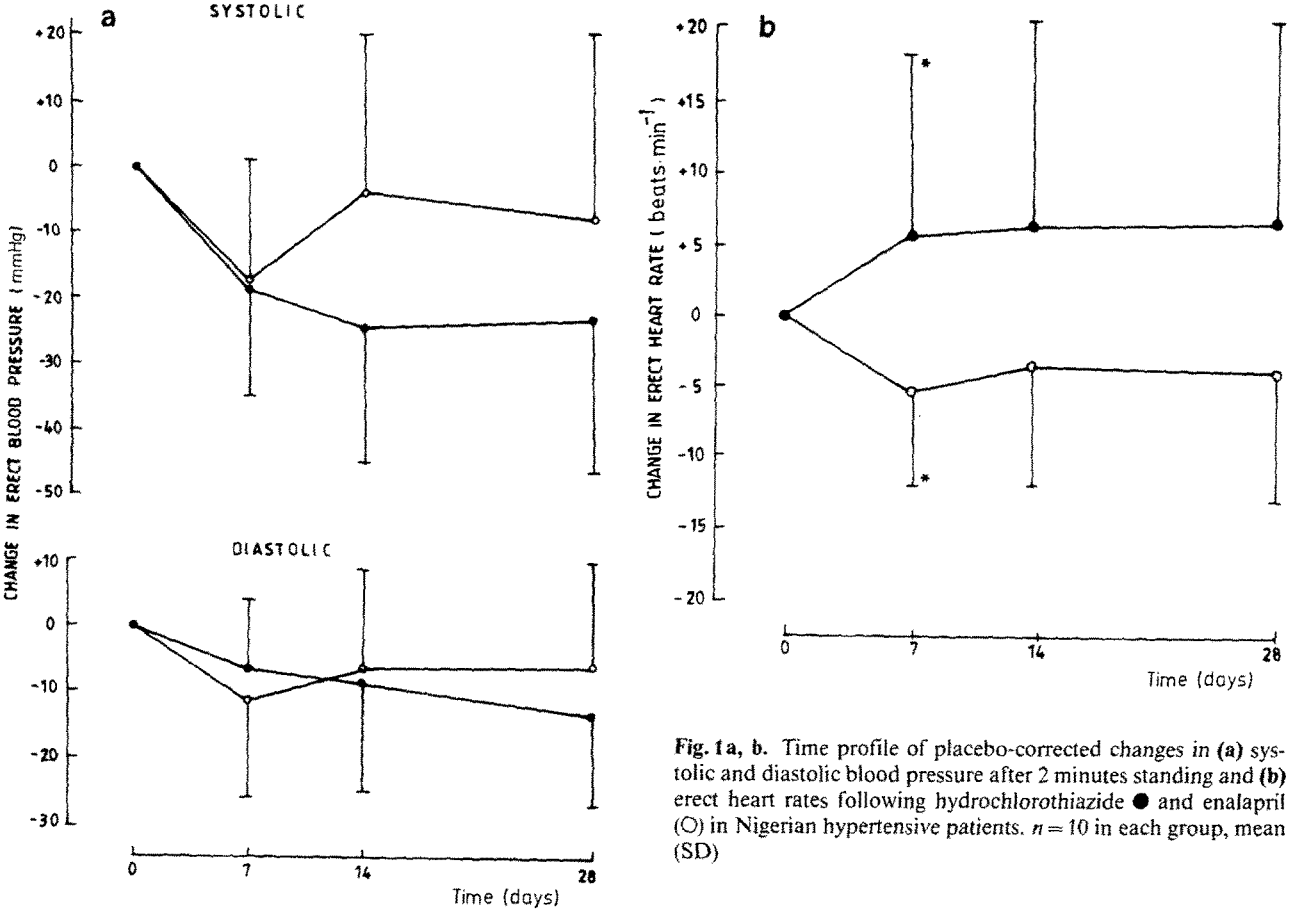

Fig. 1a, b. Time profile of placebo-corrected changes in **(a)** systolic and diastolic blood pressure after 2 minutes standing and **(b)** erect heart rates following hydrochlorothiazide ● and enalapril (○) in Nigerian hypertensive patients. $n = 10$ in each group, mean (SD)

spontaneous reporting during the placebo phase and on the active treatment days.

All results are expressed as mean (SD). Statistical evaluation was by analysis of variance (ANOVA), unpaired *t*-tests with Boneferoni correction and linear regression analysis. Results were considered significant at $p < 0.05$. 95% confidence intervals for the difference between the fall in blood pressure induced by enalapril and hydrochlorothiazide were also calculated. The Wilcoxon matched pairs signed-rank test was used to assess aggregate symptoms in the placebo, enalapril and hydrochlorothiazide groups.

Results

Enalapril and Hydrochlorothiazide Monotherapy

Patient compliance with the regimen was good as judged by the pill consumption rate and specific enquiry.

Supine blood pressure (systolic/diastolic) in the hydrochlorothiazide group after placebo run-in was 179 (28) mm Hg/106 (13) mm Hg. Treatment with hydrochlorothiazide was associated with a significant falls in supine systolic blood pressure ($f = 4.93$, $p < 0.05$, ANOVA). The time profiles of the supine and erect blood pressures after enalapril and hydrochlorothiazide are shown in Table 2. Enalapril had only a modest and in-significant hypotensive action in the supine position.

The changes in erect blood pressure and heart rate following enalapril and hydrochlorothiazide are shown in Table 2b and Fig. 1. The results are presented as changes from the placebo baseline to permit comparison of the effects of enalapril and hydrochlorothiazide, since the starting erect blood pressures were similar. Hydrochlorothiazide monotherapy caused a sustained fall in erect blood pressure, which was maximal at 4 weeks ($p < 0.05$); the mean maximal reduction was 25/13 mm Hg (Fig. 1). Enalapril exerted only a modest antihypertensive action; there was an initial vasodepressor response of 16/11 mm Hg at 1 week, which appeared to lessen on continued treatment to 4/6 mm Hg at 3 weeks, and 8/6 mm Hg at 4 weeks. Direct comparison of hydrochlorothiazide and enalapril-induced hypotension revealed a trend towards a greater effect of hydrochlorothiaze. The 95% confidence interval

of the difference in the hypotensive actions of thiazide-enalapril was:

at 3 weeks 45.4 to -3.4 mm Hg for the systolic BP and 12.8 to -18 mm Hg for the diastolic BP, and at 4 weeks it was 39.5 to -7.5 mm Hg for the systolic and 22.0 to -6.6 mm Hg for the diastolic blood pressure. Moreover, 2 patients on enalapril and 6 on hydrochlorothiazide had attained normotension at the end of the study (supine DBP less than 90 mm Hg).

The hypotensive action of hydrochlorothiazide was associated with a definite rise in heart rate, whilst there was a significant reduction in heart rate with enalapril treatment ($p < 0.05$, ANOVA, $f = 5.3$).

Relationship Between Antihypertensive Efficacy and Age

In each treatment group, the relationship between the ages of the patient and the maximum falls in the erect systolic and diastolic blood pressure corrected for placebo was investigated by linear regression analysis (Fig. 2). The antihypertensive effect of hydrochlorothiazide was positively correlated with age; the regression equation for the systolic blood pressure was $y = -7.1 + 0.86x$, $r = 0.50$, and for diastolic BP it was $y = 0.20x + 14.2$, $r = 0.54$, where y is the fall in blood pressure and x is the patient's age. On the other hand, the hypotensive action of enalapril appeared inversely related to age both for systolic and diastolic BP; the regression equation was $y = 60.2 - 0.75x$, $r = -0.57$ for the systolic and $y = 61.2 - 0.82x$, $r = -0.79$ for the diastolic BP. The results for systolic pressure are shown in Fig. 2 a, b.

Adverse Effects Profile

Enalapril and hydrochlorothiazide were generally well tolerated. There was no episode of first dose hypotension following enalapril monotherapy. Enalapril appeared better tolerated than the thiazide. Using the Wilcoxon matched-pairs signed rank, non-parametric test, it was possible to show a significant difference in the symptom profile between placebo and enalapril (4 weeks) ($T^+ = 31$, $T^- = 14$, $p < 0.05$). No such improvement was seen with hydrochlorothiazide ($T^+ = 19.5$, $T^- = 16.5$). Postural dizziness was the commonest new adverse effect of hydrochlorothiazide. Fatigue and impotence were also reported. Three patients receiving enalapril developed dry cough whilst on treatment. Two patients complained of mild dizzness on standing. No patient complained of taste disturbance. No haematological or biochemical abnormalities were detected in the post study evaluation.

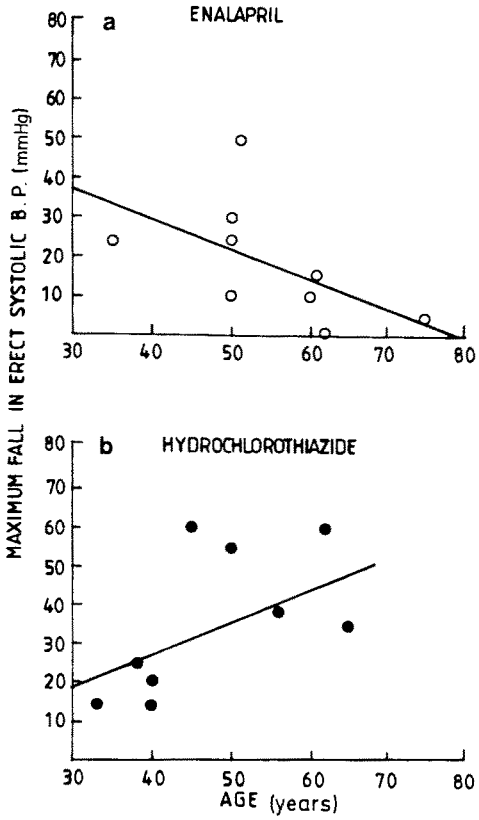

Fig. 2 a. Relationship between the placebo-corrected fall in systolic blood pressure after enalapril and age in Nigerian hypertensives. $y = 60.2 - 0.75x$, $r = -0.57$ ($p < 0.05$). **b** Relationship between the placebo-corrected fall in systolic blood pressure following hydrochlorothiazide and age in Nigerian hypertensives. $y = -7.1 + 0.86x$, $r = +0.50$ ($p < 0.05$)

Discussion

A preliminary report is presented here of an investigation of the antihypertensive efficacy of an angiotensin converting enzyme inhibitor, enalapril, and a thiazide diuretic, in a group of Nigerian mild to moderate essential hypertensives maintained on their usual salt intake. As the two treatment groups were similar in clinical and demographic features, the findings suggest a quantitative difference in the response to the two agents in this population.

The choice of dose both of enalapril and hydrochlorothiazide and the duration of the study deserve comment. Both agents have a shallow or flat dose-response curve for antihypertensive action (Lant 1987). Specifically, enalapril 10-40 mg/day shows a similar potency for inhibition of the pressor responses to angiotensin I (Davies et al. 1984) and for its hypotensive action (Wilhelmson et al. 1983). This suggests that the dose of 20 mg employed here approached the upper part of the dose-response curve. The antihypertensive action of hydrochlorothiazide is fully

expressed by 4 weeks (Lant 1987) and no further fall in BP after the 3rd week was seen in this study. Enalapril does not exhibit a triphasic response and Nadean et al. (1984) demonstrated that the full effect was attained by the third day of dosing and was maintained thereafter. These findings suggest that the dose and the duration of the study have permitted adequate comparison of their efficacy.

Hydrochlorothiazide monotherapy had a significant antihypertensive effect, which was associated with increased heart rate. The efficacy of thiazide diuretics, in Negroes is well documented, and it may be more effective therapeutically in them than in caucasian hypertensives (Bühler et al. 1982). By contrast, enalapril exerted a modest hypotensive action, although there was an initial vasodepressor effect, which appeared to become attenuated on prolonged treatment. The mechanism underlying this initial and profound response is not clear. It is possible that mechanisms other than inhibition of angiotensin II generation, or an interaction of enalapril with residual drug therapy following the washout phase, were operative. Further, the apparent fall in systolic pressure in the supine position in Week 3 of enalapril therapy may reflect spontaneous fluctuation due to the numbers studied. Direct comparison of the enalapril - and thiazide - induced falls in erect blood pressure (with similar starting values) revealed that hydrochlorothiazide tended to cause a greater fall. The 95% confidence intervals of the difference provide an estimate of the true difference between the hypotensive action of the 2 drugs. Moreover, 6 patients on hydrochlorothiazide, and only 2 on enalapril attained normotension at the end of the study. These observations are in agreement with findings in low renin hypertension in American blacks (Wilkins et al. 1983; Freier et al. 1984), who respond less well to enalapril compared to thiazides. All our patients continued their usual salt intake and it is possible that sodium restriction might have altered the response to enalapril.

After enalapril there was a reduction in heart rate concomitant with that in the blood pressure, also consistent with previous experience. Absence of a reflex tachycardia, or even a reduction in heart rate, at the same time as a fall in blood pressure is a characteristic finding with ACE inhibitors, which may be related to increased parasympathetic cardiac activity (Ajayi et al. 1985; Ajayi et al. 1986a). The lack of effect of enalapril is likely to reflect the biochemical heterogeneity in essential hypertension (Laragh 1973) with Blacks having low renin status (Sever et al. 1981). Although plasma renin was not assayed in this study, a recent report of untreated Nigerian hypertensives from this area revealed low to undetectable PRA and aldosterone using radioimmunoassay (Osotimehin et al. 1984). The pharmacodynamic response to ACE inhibitors has been claimed to be directly proportional to PRA (Case et al. 1977). Thus, the efficacy of thiazide and the ineffectiveness of enalapril may reflect the low renin status of Nigerian hypertensives.

The finding of a positive correlation between the hypotensive action of hydrochlorothiaze and age indicates that the antihypertensive effect is greater in the elderly. On the other hand, the efficacy of enalapril appeared to be inversely related to age and seemed greater in younger hypertensives, both for systolic and diastolic blood pressure. This finding is consistent with the retrospective observation of Lijnen et al. (1983) using Captopril, although several groups (Corea et al. 1984; Ajayi et al. 1986b) have shown a good response to ACE inhibitors in the elderly. Further clinical experience will be required to substantiate this possibility. However, the age relationship is consistent with the concept that age influences the response to antihypertensive agents (Bühler et al. 1982, 1984) probably on the basis of declining PRA (Meade et al. 1983). The results also accord with the experience of Vidt, who showed a negative effect of age greater than 55 years on the activity of enalapril (Vidt 1984).

Both enalapril and hydrochlorothiazide were well-tolerated, but enalapril appeared better tolerated than thiazide or placebo. There was no evidence of severe orthostatic intolerance or first dose syncope. Non-productive cough on enalapril treatment is a known adverse effect of ACE inhibitors (Sesko and Kenko 1985; Semple and Herd 1986), but its cause is uncertain.

In conclusion, the present preliminary findings suggest a superior antihypertensive effect of thiazides in comparison with ACE inhibitor monotherapy in hypertensive West Africans. The results also support the contention that age and racial factors are important determinants of the response to ACE inhibitors and thiazide diuretics. The finding of a poorer response to enalapril here contrasts with our more recent experience of its efficacy in malignant hypertension (Ajayi 1988, unpublished observations), and its improvement of treadmill exercise performance in Nigerians with heart failure (Ajayi et al. 1988, unpublished data). In both conditions plasma renin activity is known to be elevated. Further study of enalapril and diuretic combination in West Africans with hypertension and heart failure is warranted.

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A. A. Ajayi, M. D., Ph. D.
Clinical Pharmacology Unit,
Department of Medicine,
Obafemi Awolowo University,
Ile-Ife, Nigeria