Original Research

Monotherapy with amlodipine or hydrochlorothiazide in patients with mild to moderate hypertension: Comparison of their efficacy and effects on electrolytes

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Abstract

Background
Amlodipine and hydrochlorothiazide (HCTZ) are commonly prescribed in Nigeria, either as a monotherapy or in combination with other drugs. The present study was designed to investigate the antihypertensive efficacy of monotherapy with amlodipine or HCTZ and their effects on electrolyte profile in patients with mild to moderate hypertension.

Methods
A single-blind randomised clinical study design was used; 50 patients newly diagnosed with mild to moderate hypertension (aged 33 to 60 years) were recruited and divided into 2 groups (each with 25 subjects): amlodipine or hydrochlorothiazide. The subjects received either 5 mg of amlodipine or 25 mg of HCTZ, in their respective group, once daily for 4 weeks. Blood pressure and serum and urine electrolytes were measured at baseline and weekly throughout the experiment.

Results
At the end of follow-up, amlodipine reduced systolic and diastolic blood pressure significantly more (P < 0.001) than HCTZ. At the end of follow-up, blood pressure was reduced to normal in 80% of the subjects in the amlodipine group, compared to 50% in the HCTZ group. Amlodipine had no significant effect on electrolyte profiles, unlike HCTZ, which significantly changed both serum and urine electrolytes.

Conclusions
Monotherapy with amlodipine was more effective than HCTZ in patients with mild to moderate hypertension and in addition maintained electrolyte balance.

Introduction
Hypertension is a globally common condition that contributes to preventable disease and death. Essential hypertension is the most common cardiovascular disease among black Africans and it is also a significant cause of adult morbidity and mortality. The recommended initial treatment for hypertension in non-black subjects may involve the administration of either angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), calcium channel blockers or thiazide-type diuretics, while the recommended treatment for black hypertensive subjects was with either the calcium channel blockers, such as amlodipine, or with the thiazide-type diuretics, such as hydrochlorothiazide (HCTZ). An earlier guideline recommended the use of thiazide diuretics in the treatment of uncomplicated hypertension, either as a monotherapy or in combination with other classes of anti-hypertensive drugs. However, a trial that evaluated this guideline found that a combination therapy with amlodipine was more efficacious at reducing blood pressure in high-risk patients than a combination therapy with HCTZ. Amlodipine and HCTZ are commonly prescribed in Nigeria as monotherapy and in combination with other antihypertensive drugs. Amlodipine monotherapy was reported to have achieved similar reduction in blood pressure in elderly patients as a combination therapy with HCTZ. Similarly, a previous study among Nigerians with essential hypertension showed that amlodipine was a more effective than HCTZ in reducing blood pressure.

HCTZ was reported to produce significant adverse effects on the potassium levels of the subjects while amlodipine was neutral. Hyponatraemia and hypokalaemia were observed during the initiation of hydrochlorothiazide therapy in type 2 diabetic hypertensive Nigerian subjects, while amlodipine caused no significant clinical biochemical abnormality in their electrolyte profiles. The effects of amlodipine and HCTZ on electrolyte profile of black patients with mild to moderate hypertension remain poorly understood. The present study investigated the efficacy and effects of monotherapy with amlodipine or hydrochlorothiazide on the electrolyte profile of Nigerians with mild to moderate hypertension.

Methods

Study location
The study was carried out in Enugu, the capital city of Enugu State, Nigeria. Enugu State is located in the South-East geopolitical zone of Nigeria. Enugu city has a population of about a million people, mostly Nigerians of the Igbo tribe. The inhabitants of the city are mostly public servants, traders and artisans. The study lasted for a period of 5 months.
Inclusion criteria

Consenting subjects newly diagnosed with mild to moderate hypertension using WHO guidelines. \[ Z_1 - \beta = 0.84 \text{ at } 80\% \text{ statistical power, } \]

Sample size

This was estimated using the method of Kadam and Bhalerao, as follows:

\[ n = \frac{2(Z\alpha + Z_1 - \beta)^2}{\sigma^2} \]  

where, 

\( Z_\alpha = 1.96 \) for 5% level of significance, 

\( Z_1 - \beta = 0.84 \) at 80% statistical power, 

\( \sigma = \text{common standard deviation}, \)

\( \Delta = \text{difference between mean values in a previous study.} \)

Fifty patients (28 males and 22 females) newly diagnosed with mild to moderate hypertension and aged between 33 and 60 years attending the medical outpatient clinic of Enugu State University Teaching Hospital, Enugu, were consecutively recruited into the study. However, 1 female subject withdrew from the study for non-medical reasons; only 49 subjects completed the study. The study was carried out in line with the guidelines of the Helsinki Declaration for human studies, as amended and approved by the Ethical Committee of the Enugu State University Teaching Hospital (EC: ESUTTH/EC/11002).

Exclusion criteria

Subjects with diabetes, chronic kidney disease, chronic heart disease, hepatic disease and cancer were excluded from the study. Pregnant women, individuals with evidence of secondary hypertension, chronic smokers and alcoholics were also excluded.

Those that met the inclusion criteria were randomly divided into 2 groups (amlodipine and HCTZ). The group and treatment given were concealed from the physicians that took the measurements.

Group 1

Patients in this group were given 5mg amlodipine (Pfizer, New York, USA) once daily before breakfast for 4 weeks.

Group 2

Patients were given 25 mg HCTZ (Esidrex®, Novarvatis, Switzerland) once daily before breakfast for 4 weeks.

Patients were given weekly appointments and a week worth of medication during each visit. Treatment adherence was monitored every 2 days via phone calls and clinical evaluation carried out weekly on their appointment day.

Blood pressure, serum and urine electrolytes were measured at baseline and weekly during treatment for 4 weeks.

Blood pressure measurement

Sitting BP was measured using Accoson® mercury sphygmomanometer. Two consecutive readings were taken from each subject at 5 minutes intervals and the average of these was calculated and taken as the mean blood pressure.
Table 1: Patient demographic characteristics and body mass index

| Characteristic | Amlodipine | Hydrochlorothiazide |
|---------------|------------|---------------------|
| Age (years)   | 48.81±12.20 | 47.68 ± 10.32       |
| Sex           |            |                     |
| Male          | 13         | 15                  |
| Female        | 12         | 10                  |
| BMI (kg/m²) ± SD | 27.44 ± 4.20 | 26.88 ± 3.40       |

SD = standard deviation

Table 2: Percentage change in blood pressure at the end of follow-up

| % change in blood pressure at week 4 | Amlodipine | Hydrochlorothiazide |
|-------------------------------------|------------|---------------------|
| Systolic blood pressure (mmHg) ± standard deviation | −17.69 ± 3.12 | −8.55 ± 1.64 |
| Diastolic blood pressure (mmHg) ± standard deviation | −12.36 ± 2.40 | −5.22 ± 1.45 |
| Mean arterial pressure (mmHg) ± standard deviation | −15.28 ± 2.31 | −8.12 ± 1.25 |

value. Readings were taken between 8.00 am and 10.00 am on their appointment. Any constrictive clothing on the arm was removed before measurement.

**Serum electrolyte measurement**

Venous blood (5 mL) was drawn from medial cubital vein into a vacutainer and allowed to coagulate for 25 minutes. The clot formed was removed by centrifuging at 2000 rpm for 10 minutes. The resulting supernatant (serum) was removed for analysis. Serum electrolyte (Na⁺, K⁺, and Cl⁻) levels were determined by ion selective electrode using Audicom automated electrolyte analyser (AC9000 series, China).

**Urine electrolyte measurement**

Urine samples were collected in clean containers and Na⁺, K⁺ and Cl⁻ measured using ion-selective electrode analyser (Audicom automated electrolyte analyser; AC9000 Series, China).

**Statistical analysis**

Results were presented as mean ± standard error of mean. Data were classified by groups and weeks of treatment and analysed using SPSS Version 20 by IBM Corp. Two-way analysis of variance (ANOVA) was used to compare differences between groups, and further analysis was carried out using Bonferroni post-test (GraphPad prism 5.0). P-values of 0.05 or less were considered significant.

**Results**

The mean age and BMI of amlodipine and HCTZ groups were not significantly different (Table 1). Amlodipine reduced SBP, DBP and MAP at the end of follow more than HCTZ group (Table 2). Amlodipine reduced SBP and DBP significantly more at week 4 compared to each other, the effect of HCTZ was significantly higher (P < 0.001) at weeks 2, 3 and 4 (Figure 4). At the end of the follow-up, amlodipine caused no change in serum K⁺ from baseline level whereas HCTZ reduced K⁺ from its baseline level. However, this difference was not significant throughout the duration of the study (Figure 5). Amlodipine had no significant effect on serum Cl⁻ while HCTZ significantly reduced it. When compared to each other, HCTZ significantly reduced serum Cl⁻ at weeks 2 (P < 0.001), 3 (P < 0.001) and 4 (P < 0.001) (Figure 6).

Amlodipine caused insignificant changes in urine electrolytes (Na⁺, K⁺ and Cl⁻) while HCTZ increased them. The changes in urine Na⁺ caused by HCTZ was significant at week 1 (P < 0.001) and weeks 2-4 (P < 0.001) when compared to amlodipine (Figure 7); changes in K⁺ also followed a similar pattern (Figure 8) while that of Cl⁻ was significant at weeks 2 (P < 0.05), 3 (P < 0.01) and 4 (P < 0.001) (Figure 9).

No adverse side effect was observed in both groups, however, polyuria was observed.

**Discussion**

Both amlodipine and HCTZ significantly reduced BP in mild to moderate hypertensive subjects. At the end of follow-up, blood pressure was reduced to normal in 80% of the subjects in amlodipine group compared to 50% in HCTZ. The efficacy of these drugs in the present study was higher than that earlier reported in a Nigerian population where monotherapy using 5 mg of amlodipine daily achieved 40% reduction to normal BP while 25mg of HCTZ daily produced 35% reduction to normal BP. The increased efficacy seen in the present study may be due to shorter duration of treatment and adequate monitoring of compliance via phone calls employed. Our study lasted for 4 weeks compared to 6 weeks in the above study and prolonged use of these drugs has been shown to produce lower antihypertensive effect; monitoring of compliance was not indicated in the

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Monotherapy with amlodipine or hydrochlorothiazide

Amlodipine caused no significant changes in serum electrolytes whereas HCTZ significantly reduced Na\(^+\), K\(^+\), and Cl\(^-\) from their baseline levels. These results agree with that from an earlier study.\(^{13}\) Our results were also similar to those obtained from an earlier study where amlodipine was also reported to maintain electrolyte balance even among diabetic hypertensive patients.\(^{7}\) The results of the present study were also similar to those reported in earlier studies.\(^{17,18}\) Treatment with HCTZ significantly increased urine electrolytes of the subjects in the present study; this similar to earlier reports where HCTZ produced increase in urine electrolytes in patients with essential hypertension.\(^{17,18}\) The corresponding increase in urine electrolytes suggests that they were lost from blood.

In conclusion, short-term monotherapy with amlodipine was more effective than hydrochlorothiazide in mild to moderate hypertensive Nigerians; it did not cause electrolyte imbalance unlike HCTZ. These results suggest that amlodipine may be safer as a monotherapy in black essential hypertensive subjects.

Conclusions
There is need to review the current management strategy in Nigeria where diuretics especially thiazide diuretics are mainly prescribed as the first line drugs in treatment of hypertension. Amlodipine should be the first line drug since it is more effective and did not cause electrolyte imbalance; it is also affordable just like hydrochlorothiazide.

Competing interests
All authors declare that they have no competing interests related to this work.

Figure 7: Urine Na\(^+\) concentration following treatment with amlodipine and hydrochlorothiazide

Each point on the graph represents the average of at least 25 independent measurements. Error bars are standard error of the mean (SEM); \(\beta\beta\beta P < 0.01\), \(\beta\beta\beta P < 0.001\) (hydrochlorothiazide versus amlodipine; 2-way ANOVA with Bonferroni post-test, using Graphpad Prism 5.0).

Figure 8: Urine K\(^+\) concentration following treatment with amlodipine and hydrochlorothiazide

Each point on the graph represents the average of at least 25 independent measurements. Error bars are standard error of the mean (SEM); \(\beta\beta\beta P < 0.01\), \(\beta\beta\beta P < 0.001\) (hydrochlorothiazide versus amlodipine; 2-way ANOVA with Bonferroni post-test, using Graphpad Prism 5.0).

Figure 9: Urine Cl\(^-\) concentration following the administration of amlodipine and hydrochlorothiazide

Each point on the graph represents the average of at least 25 independent measurements. Error bars are standard error of the mean (SEM); \(\beta P < 0.05\), \(\beta\beta P < 0.01\), \(\beta\beta\beta P < 0.001\) (hydrochlorothiazide versus amlodipine; 2-way ANOVA with Bonferroni post-test, using Graphpad prism 5.0).
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