Global Journal of Pharmacology 7 (1): 45-51, 2013
ISSN 1992-0075

DOI: 10.5829/idosi.gjp.2013.7.1.718

Long-Term Effects of Amlodipine and Hydrochlorothiazide Combination Therapy on Creatinine Clearance in Hypertensive Nigerians

[1]Godfrey B.S. Iyalomhe, [2]Eric K.I. Omogbai,
[3]Osigbemhe O.B. Iyalomhe and [4]Sarah I. Iyalomhe

[1]Department of Pharmacology and Therapeutics,
College of Medicine Ambrose Alli University, Ekpoma, Nigeria
[2]Department of Pharmacology and Toxicology, Faculty of Pharmacy,
University of Benin, Benin City, Nigeria
[3]Department of Physiology, School of Medicine,
Johns Hopkins University Baltimore, MD 21205, USA
[4]Department of Public Health and Primary Health Care Central Hospital Auchi, Nigeria

Abstract: Blacks respond to therapy with amlodipine (AML) and hydrochlorothiazide (HCZ) with greater diuresis and natriuresis than whites, a situation that may lead to prerenal azotaemia and other problems. Although AML and HCZ are frequently used as antihypertensive agents in Nigeria, the effects of the combination treatment on renal function has been poorly examined. Therefore, to evaluate the effects of dual treatment with these drugs on creatinine clearance (Clcr), we enrolled 90 Nigerians of both gender 31-86 years with uncomplicated essential hypertension (blood pressure [BP] > 160/90 = 180/120 mmHg), into a randomized, open-label, prospective, two-centre, outpatient, 48-week study. Patients, who were 30 each (15 males (M) + 15 females (F)) in AML, HCZ and AML-HCZ groups, were treated, respectively, with AML 5mg for 6 weeks (wks) and the dose increased to 10mg till wk 12 (monotherapy) after which HCZ 25mg was added; HCZ 25mg till wk 6 (monotherapy) after which AML 5-10mg was added; and AML 5-10mg + HCZ 25mg. Body mass index (BMI), systolic BP (SBP) and diastolic BP (DBP), 24hrs urine volume, urine creatinine, serum creatinine and the corresponding Clcr were evaluated at baseline before treatment and at the end of wks 1, 3, 6, 12, 24, 36 and 48 during treatment. The 3 treatment regimens comparably significantly ($P < 0.05$) reduced BP. At week 48 M vs F reductions in SBP/DBP in AML, HCZ and AML-HCZ groups were, respectively, 37.88±2.46/30.86±1.45 vs 37.75±2.15/31.76±1.86, 37.66±1.50/28.67±1.56 vs 34.43±1.57/27.34±1.92 and 33.00±3.05/30.33±1.55 vs 31.67±2.86/31.33±1.95 mmHg. Diuresis was greatest and significant ($P < 0.05$) in HCZ group at week 1 with M vs F AML, HCZ and AML-HCZ levels being, respectively, 1523.33±57.34 vs 1486.00±56.09, 1621.33±36.49 vs 1586.67±37.01 and 1506.00±42.26 vs 1514.67±45.30 ml. Gender effect on Clcr was significant, for M values, respectively, in AML, HCZ and AML-HCZ groups (114.27±4.40, 108.36±4.19, 111.13±3.02 ml/min) were higher than the corresponding F values (107.20±2.30, 105.80±2.94, 104.80±2.69 mil/min, $P < 0.0001$). Duration of treatment effect was significant ($P < 0.05$) and while Clcr values appeared to increase in AML group, the reverse was the case in HCZ and AML-HCZ groups. However, changes in Clcr values were within normal range. It is concluded that long-term combination treatment with AML and HCZ does not cause clinically significant changes in Clcr; and also that it seems prudent to initiate treatment with AML to which HCZ is subsequently added instead of HCZ to which AML is later added or *ab initio* AML-HCZ combination.

Key words: Amlodipine and hydrochlorothiazide · Antihypertensive combination therapy · Creatinine clearance · Nigerians

Corresponding Author: Godfrey B.S. Iyalomhe, Department of Pharmacology and Therapeutics College of Medicine, Ambrose Alli University Ekpoma, Nigeria. Tel: +234 805 3973 990, +234 806 7500 780,

INTRODUCTION

Worldwide, renal insufficiency as defined by a reduction in the estimated glomerular filteration rate (GFR), is increasing at a worrisome rate, in part because of the greater prevalence of obesity and hypertension but in greater part because of improved longevity [1-3]. Indeed, as people age, they accumulate diseases, disabilities, doctor visits and drugs [4]. Thus, longevity increases the risk of developing diseases, such as diabetes and hypertension, that have direct adverse effects on kidney function. Accordingly, long life also increases the risk of exposure to medications such as some antihypertensive agents that may inadvertently impair renal function. But the quest is always to seek for new agents that are both effective and renoprotective [5].

Hydrochlorothiazide (HCZ) and amlodipine (AML) are frequently used in Nigeria as antihypertensive agents, both as monotherapy and as dual combination therapy. In our previous communication [6], we confirmed other reports [7-8], that HCZ monotherapy for hypertension did not have deleterious effects in patients with normal renal function. It has also been reported too that antihypertensive monotherapy with AML has salutary effects on renal haemodynamics [9-10]. It is known that blacks with their characteristic low renin, salt-sensitive, volume-dependent hypertension, respond to diuretics and CCBs with greater diuresis than whites [6, 11]. Hence, there are concerns that when AML and HCZ are co-administered, the diuretic and natriuretic properties of both drugs may synergise to precipitate prerenal azotaemia, that results from volume depletion and hence, a reduction in perfusion to the kidney, leading to renal dysfunction and an elevated serum creatinine level. Also, the severe volume depletion may induce mental changes and aggravate the orthostatic hypotension found in elderly individuals who spend most of their time in bed or in the chair [12]. Unfortunately, the effects of this combination treatment on renal function, has not been well examined in Nigerians. Consequently, we have studied the effects of dual AML and HCZ combination treatment on Clcr, which has been used for decades to estimate GFR, monitor response to drug therapy and progression of renal disease [13-14].

MATERIALS AND METHODS

Study Population: We enrolled into the study 90 Nigerians of both gender with newly diagnosed essential hypertension (stages 1 and 2) aged 31-86 years and were attending Central Hospital and Osigbemhe Hospital both in Auchi in Edo State of Nigeria between March 2008 and March 2009. The sample size was estimated based on the number of Nigerians that are believed to be hypertensive [15]; and to detect a difference of 2 units in mean change in the measured variables, between both treatment arms with a power equal to 90% using a one sample t-test at a one-sided significance level of 0.05, requires 30 patients per group.

Eligible participants had qualifying hypertension of BP > 160/90 and ≥ 180/120 mmHg measured on at least 2 occasions in lying/supine, sitting and standing positions using standardized methods [16]. Excluded were patients with identifiable cause of the hypertension, clinical evidence of cerebrovascular, cardiac, renal, hepatic, gastrointestinal or endocrinologic disease, hypersensitivity to AML and HCZ or related drugs, history of smoking, alcohol intake, substance abuse or mental illness. Also excluded were patients needing any concomitant medication eg digitalis, non-steroidal anti-inflammatory drugs, psychotropic drugs, monoamine oxidase inhibitors or oral contraceptives, that may interact with the trial drugs and pregnant or lactating females.

The research protocol was reviewed and approved by the Ethics Committees of Irrua Specialist Teaching Hospital Irrua, Nigeria (Ambrose Alli University College of Medicine Teaching Hospital) and Central Hospital Auchi, Nigeria. After suitable explanation of the study protocol in lay language, all literate patients gave informed written consent and the illiterates thumb-printed the consent form before the beginning of the study.

Study Design: Subjects were examined by a standardized pre-tested questionnaire seeking information on demographic data, the history of hypertension, current drugs if any, educational and social status, dietary habits, smoking and alcohol intake, etc. The 90 patients were randomized to three groups (AML, HCZ and AML-HCZ groups) each comprising 30 patients divided into subgroups of 15 M + 15 F using computer program-generated random numbers. AML group was treated initially with AML 5 mg and the dose was doubled after 6 weeks if BP was not controlled. Then after 12 wks (end of monotherapy), HCZ 25 mg was added if goal BP was not still achieved. HCZ group was treated initially with HCZ 25 mg for 6 weeks (end of monotherapy), after which AML 5 mg was added if BP was uncontrolled. The dose of AML was doubled after 12 wks if BP was still not normalized. AML-HCZ group was initially treated with AML 5 mg + HCZ 25 mg. If BP was not controlled after 6 weeks, the dose of AML was doubled.

The outpatient treatment lasted 48 weeks. The patients were monitored closely and outcome measures evaluated at baseline before treatment as well as at the end of wks 1, 3, 6, 12, 24, 36 and 48.

Measurements of Heights (m), Weights (wt) (kg) and BP (mmHg): A stadiometer scale (Seca model, UK) was used for measuring height, with no shoes on; and a beam balance (Hackman, UK) was used to measure wt while on light clothing. BMI was computed as wt divided by height squared. SBP and DBP were measured with a standard mercury sphygmomanometer (Riester Diplomat Presameter, Germany) using standardized methods [16] at the sitting, standing and supine positions; always between 8am and 10am. All constricting clothing on the upper arm were removed before any measurement and subjects were discouraged from talking or moving during measurements. The first phase of the Korotkov sound was regarded as the SBP while the fifth phase was regarded as the DBP. During measurement, readings were taken two consecutive times with an interval of at least one minute and the average recorded. During the study, subjects were not told the results of BP measurement.

Pharmacotherapy Intervention: AML group was treated initially with AML 5 mg and the dose was doubled after 6 weeks if BP was not controlled. Then after 12 wks (end of monotherapy), HCZ 25 mg was added if goal BP was not still achieved. HCZ group was treated initially with HCZ 25 mg for 6 weeks (end of monotherapy), after which AML 5 mg was added if BP was uncontrolled. The dose of AML was doubled after 12 wks if BP was still not normalized. AML-HCZ group was initially treated with AML 5 mg + HCZ 25 mg. If BP was not controlled after 6 weeks, the dose of AML was doubled. The outpatient treatment lasted 48 weeks. The patients were monitored closely and outcome measures evaluated at baseline before treatment as well as at the end of wks 1, 3, 6, 12, 24, 36 and 48 during treatment.

The study medications AML and HCZ are licensed for long-term treatment of hypertension so that dangerous side effects due to the medicaments were not to be expected. AML 5mg and 10mg tablets (Amlovar^{R}), were donated by Neimeth International Pharmaceuticals Ikeja, Nigeria: NAFDAC Reg No A4-0333; Manufacturing Date 07-2007 and Expiry Date 07-2010. HCZ 25mg tablets (Esidrex^{R}) were donated by Novartis Pharma SAS Nigerian Representative, NAFDAC Reg No OL-3705, Manufacturing Date 08-2007 and Expiry Date 08-2010.

Course of Study and Methods for Recording Efficacy and Safety: All patients were advised to maintain their usual diet (weight-maintaining no-salt-added diet) and regular physical activity but to avoid undue stress throughout the duration of the study. They were instructed to take their drugs every morning always between 8 am and 10 am. Each patient was observed for about 2 hours after taking medication drug for the first time. Adherence in respect of intake of medication was encouraged by interviewing patients through phone calls, sporadic visits and pill counts outside the view of patients. To preclude white-coat effect, observer bias and to accurately assess the efficacy of the drugs, patients were followed up repeatedly at weeks 1, 3,6,12, 24, 36 and 48. At each visit, volunteered or spontaneous report of adverse events were assessed for severity and association with treatment; and the attending physicians/investigators also recorded any adverse events they observed themselves or elicited from the patient through careful interrogation like "How do you feel?" No patient withdrew from the study because of adverse events.

Response to therapy as regards the BP measurement was defined as a decrease in the mean trough sitting SBP and DBP of 10 mmHg or a drop to < 90 mmHg with reduction of > 5 mmHg. BP was regarded as controlled if the DBP was < 90 mmHg and SBP < 140 mmHg. The effects of treatment on the various variables (except height) were assessed by comparing the values at each visit with the pretreatment baseline values.

Collection of Samples and Analysis

Urine: Each subject collected 24hrs urine sample into a plastic container from Sunday 7am to Monday 7am at baseline (week 0) before treatment and on the evaluation days. The need to carefully collect all urine passed was well emphasized. The volume of 24hrs urine was measured with a measuring cylinder and recorded. The creatinine concentration was determined using Jaffe's method [17].

Blood: At baseline and at the end of weeks 1, 3, 6, 12, 24, 36 and 48, 5ml of venous blood was obtained from every patient by peripheral venepuncture into a plain sterile bottle. From the prepared serum sample of each subject, serum creatinine concentration was assayed using Jaffe's method [17].

Calculation of Clcr: Clcr values corresponding to baseline, weeks 1, 3, 6, 12, 24, 36 and 48 were calculated using the formula:

$$\text{Clcr(ml/min)} = \frac{\text{mg creatinine/dl urine} \times \text{ml urine/24hrs}}{\text{mg creatinine/dl serum} \times 1440}$$

Statistical Analysis: All data are presented as mean ± SEM or mean ± SD (for age, height and weight) using the general linear model procedure (PROC GLM) of the SAS (2004). Where significant differences were noticed, mean separation was carried out using Duncan Multiple Range Test. Correlation between two sets of variables was determined using Spearman's rank correlation. $P = 0.05$ was regarded as significant.

RESULTS

Table 1 shows that at baseline (week 0), there was no statistically significant difference observed in the M vs F patients in the AML, HCZ and AML-HCZ groups, respectively, with regard to the means of ages, BMIs as well as the SBP and DBP. Most of the patients had significant (stage 2) hypertension. The analysis excluded the data for a M patient in the AML group who travelled and so could not report for evaluation at week 48; a F from AML group who became pregnant and so was withdrawn from the study between weeks 36 and 48 as well as a M patient whose week 36 serum specimen was lost in the AML-HCZ group.

Duration and treatment effect on the SBP and DBP were significant ($P < 0.05$) and gender effect was also significant ($P < 0.001$), for the differences in M values were higher than in F. The 3 treatment regimens comparably significantly ($P < 0.05$) reduced BP. At week 48 M vs F reductions in SBP/DBP in AML, HCZ and AML-HCZ groups were, respectively, 37.88±2.46/30.86±1.45 vs 37.75±2.15/31.76±1.86, 37.66±1.50/28.67±1.56 vs 34.43±1.57/27.34±1.92 and 33.00±3.05/30.33±1.55 vs 31.67±2.86/31.33±1.95 mmHg (Table 2). As shown in Table 3, diuresis was greatest and significant ($P < 0.05$) in HCZ group at week 1 with M vs F AML, HCZ and AML-HCZ levels being, respectively, 1523.33±57.34 vs 1486.00±56.09, 1621.33±36.49 vs 1586.67±37.01 and 1506.00±42.26 vs 1514.67±45.30 ml. Diuresis dovetailed soon after. As displayed in Table 4, gender effect on Clcr was significant, for M values, respectively, in AML, HCZ and AML-HCZ groups (114.27±4.40, 108.36±4.19, 111.13±3.02 ml/min) were higher than the corresponding F values (107.20±2.30, 105.80±2.94, 104.80±2.69 mil/min, $P < 0.0001$). Duration of treatment effect was significant ($P < 0.05$) and while mean Clcr values appeared to increase in AML group, the opposite was the case for HCZ and AML-HCZ groups. However, changes in Clcr values were within normal range.

Table 1: Demographic characteristics and baseline blood pressures of subjects in the AML, HCZ and AML-HCZ treatment groups

		Male		Female	
Group	Characteristics	Range	Mean±SD/SEM*	Range	Mean±SD/SEM
AML	Age (yrs)	31-80	60.80±14.03	37-80	63.60±8.02
	Height (m)	1.59-1.74	1.66±0.04	1.56-1.76	1.66±0.07
	Weight (kg)	62-88	76.77±8.94	62-90.4	79.80±8.85
	BMI (kg/m^2)	24.84-29.75	26.50±0.80	25.48-30.13	27.50±0.31
	SBP (mmHg)	150-175	162.50±2.82	150-180	165.67±3.00*
	DBP (mmHg)	100-115	103.00±1.75	90-115	105.33±2.04*
HCZ	Age (yrs)	45-86	63.80±12.02	48-80	65.47±10.15
	Height (m)	1.61-1.80	1.69±0.05	1.12-1.76	1.67±0.04
	Weight (kg)	68-89	75.37±6.27	60-80	73.44±6.30
	BMI (kg/m^2)	26.25-27.47	26.50±0.32	23.17-26.67	24.50±0.42
	SBP (mmHg)	160-180	170.33±2.09*	160-180	169.00±1.90*
	DBP (mmHg)	95-115	104.67±1.50*	90-115	104.67±1.98*
	Age (yrs)	42-78	62.13±11.89	48-87	69.93±11.60
AML –HCZ	Height (m)	1.58-1.72	1.64±0.04	1.59-1.82	1.67±0.06
	Weight (kg)	65-87.5	74.33±7.07	65-90.2	77.21±8.67
	BMI (kg/m^2)	26.10-29.66	27.50±0.38	25.79-27.33	26.00±0.56
	SBP(mmHg)	150-180	165.00±4.57*	155-180	167.50±4.44*
	DBP(mmHg)	100-115	106.00±1.48*	90-120	107.33±2.01*

Characteristics and BPs in the groups are not significantly different; AML, Amlodipine; HCZ, Hydrochlorothiazide, AML-HCZ, Amlodipine-Hydrochlorothiazide combination; BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; *, Standard error of mean; (N = 30 [15M + 15F] per group)

Table 2: Effects of AML and HCZ combination treatments on BP (mmHg) in hypertensive subjects for 48 weeks

	Treatment Subgroups (Male)				Treatment Subgroups (Female)			
Week	BP	AML	HCZ	AML-HCZ	AML	HCZ	AML-HCZ	Gender Effect
0	SBP	169.67±2.82	170.33±2.00	168.00±4.57	171.67±3.00	169.00±1.90	167.67±4.44	
	DBP	103.00±1.75	104.67±1.50	106.00±1.48	105.33±2.03	104.67±1.98	107.33±2.00	
1	SBP	$160.00\pm0.00_{A}$	$162.67\pm2.00_{A}$	$162.00\pm3.78_{A}$	$160.00\pm0.00^{b}_{A}$	$157.34\pm2.12^{b}_{A}$	165.67 ± 2.28^{a}	
	DBP	107.00 ± 1.16^{a}	102.33±1.88	$98.67\pm1.92^{b}_{A}$	102.00 ± 1.16^{a}	$99.67\pm2.01^{b}_{A}$	$100.00\pm1.95^{b}_{A}$	
3	SBP	$157.00\pm3.23_{A}$	$156.67\pm2.32_{B}$	$155.00\pm3.09_{B}$	$159.00\pm3.17_{A}$	$152.33\pm2.12_{B}$	$158.33\pm2.66_{A}$	
	DBP	$90.67\pm5.94^{b}_{A}$	$95.67\pm1.68^{a}_{A}$	$91.67\pm1.16_{B}$	$92.67\pm1.82_{A}$	$95.33\pm1.33_{A}$	$92.67\pm2.48_{B}$	
6$	SBP	$149.00\pm2.85_{B}$	$150.33\pm2.04_{C}$	$148.00\pm3.27_{C}$	$155.33\pm2.95^{a}_{B}$	$147.33\pm2.12_{C}$	$150.00\pm2.39_{B}$	
	DBP	$87.00\pm2.06_{A}$	$89.00\pm1.48_{B}$	$84.33\pm1.45_{C}$	$87.33\pm1.28_{B}$	$90.67\pm1.88_{B}$	$86.00\pm2.14_{C}$	
12$	SBP	$145.67\pm2.38_{B}$	$144.33\pm1.75_{D}$	$142.67\pm2.62_{D}$	$149.33\pm3.04^{a}_{C}$	$142.00\pm2.00^{b}_{D}$	$143.33\pm1.99^{b}_{C}$	0.198^{NS}
	DBP	$79.33\pm2.00_{B}$	$84.00\pm1.63_{C}$	$80.00\pm1.76_{D}$	$83.33\pm1.93_{C}$	$85.33\pm1.33_{C}$	$82.67\pm1.82_{D}$	0.0002^{***}
24	SBP	$140.67\pm1.75_{C}$	$138.00\pm1.48_{F}$	$136.68\pm2.05_{E}$	$140.67\pm2.00_{D}$	$139.33\pm1.53_{D}$	$139.00\pm1.63_{D}$	
	DBP	$76.33\pm1.42_{B}$	$80.00\pm1.38_{D}$	$78.67\pm1.98_{D}$	$80.00\pm1.95_{C}$	$79.67\pm1.42_{D}$	$80.33\pm1.86_{D}$	
36	SBP	$134.67\pm1.86_{D}$	$134.00\pm1.22_{F}$	$136.00\pm1.56_{E}$	$135.72\pm1.63_{E}$	$136.00\pm1.22_{D}$	$138.00\pm1.53_{D}$	
	DBP	$75.00\pm1.29_{B}$	$77.33\pm1.53_{D}$	$76.67\pm1.87_{E}$	$77.14\pm1.94_{D}$	$78.67\pm1.65_{D}$	$78.67\pm1.92_{D}$	
48	SBP	$131.79\pm2.07_{D}$	$132.67\pm1.08_{E}$	$135.00\pm1.62_{E}$	$133.92\pm1.30_{E}$	$134.67\pm1.24_{E}$	$136.00\pm1.31_{D}$	
	DBP	$72.14\pm1.14_{C}$	$76.00\pm1.63_{D}$	$75.67\pm1.61_{E}$	$73.57\pm1.69_{D}$	$77.33\pm1.82_{D}$	$76.00\pm1.90_{D}$	

Significant differences within columns are indicated by ABCDEF and within rows by ab ($P < 0.05$): Significant treatment effect occurred in weeks 1-12 and all treatment regimens significantly decreased SBP and DBP; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; AML, Amlodipine 10mg; HCZ, Hydrochlorothiazide 25mg; AML-HCZ, Amlodipine 5-10mg / Hydrochlorothiazide 25mg combination; SEM, Standard error of mean; $, Combination treatment: Weeks 24-48 (AML), Weeks 12-48 (HCZ); ***, $P < 0.001$; NS, Not Significant; (N = 15 per subgroup)

Table 3: Effects of AML and HCZ combination treatments on 24hrs urine volume (ml) in hypertensive subjects for 48 weeks

	Treatment Subgroups (Male)			Treatment Subgroups (Female)			
Week	AML	HCZ	AML-HCZ	AML	HCZ	AML-HCZ	Gender Effect
0	1437.33±53.44	1393.33±37.74	1458.00±45.11	1438.67±55.87	1390.00±41.75	1478.67±46.83	0.439^{NS}
1	1523.33±57.34	$1621.33\pm36.49_{A}$	1506.00±42.26	1486.00±56.09	$1586.67\pm37.01_{A}$	1514.67±45.30	
3	1560.67±48.37	1488.67±38.23	1520.00±42.55	1514.00±57.77	1476.00±34.79	1528.67±46.00	
6	1571.33 ± 48.37^{a}	1424.67 ± 38.16^{b}	1500.00±45.66	1559.33±58.95	1418.00±36.82	1528.00±47.99	
12$	1578.67 ± 43.62^{a}	1436.00 ± 35.18^{b}	1504.67±43.26	1535.33±55.32	1432.67±38.46	1516.67±47.43	
24$	1560.00 ± 40.05^{a}	1418.67 ± 35.66^{b}	1488.00±43.21	1500.00±50.86	1418.67±40.01	1497.33±46.33	
36	1524.00 ± 36.33^{a}	1400.00 ± 36.31^{b}	1461.33±43.19	1472.86±42.06	1390.67±42.17	1478.67±45.82	
48	1478.57 ± 32.71^{a}	1394.67 ± 36.38^{b}	1448.00 ± 42.66^{a}	1433.57±36.08	1388.00±39.59	1476.00±45.16	

Significant differences within columns are indicated by AA and within rows by ab ($P < 0.05$): Significant treatment effects are seen in HCZ male subgroups and increase diuresis in HCZ male and female subgroups; other abbreviations are as used in Table 2

Table 4: Effects of AML and HCZ combination treatments on creatinine clearance (ml/min) in hypertensive subjects for 48 weeks

	Treatment Subgroups (Male)			Treatment Subgroups (Female)			
Week	AML	HCZ	AML-HCZ	AML	HCZ	AML-HCZ	Gender Effect
0	108.47 ± 4.43^{b}	111.53 ± 4.63^{b}	119.67 ± 4.72^{a}	105.67 ± 2.27^{a}	99.13 ± 2.32^{b}	106.20 ± 4.24^{a}	0.0001^{****}
1	113.40 ± 4.72^{b}	110.40 ± 4.55^{b}	$124.93\pm5.26^{a}_{B}$	$124.53\pm2.24^{a}_{A}$	$115.52\pm1.47_{A}$	109.30 ± 4.12^{b}	
3	116.73 ± 4.43^{b}	104.07 ± 3.56^{c}	$130.47\pm5.16^{a}_{A}$	$124.33\pm2.81^{a}_{A}$	$117.00\pm2.06_{A}$	111.73 ± 4.12^{b}	
6	115.40 ± 4.08^{b}	101.73 ± 4.08^{c}	$131.13\pm4.64^{a}_{A}$	112.80 ± 2.83	$105.46\pm2.48^{b}_{B}$	$118.27\pm5.57^{a}_{A}$	
12$	116.00 ± 4.55^{b}	103.53 ± 4.34^{c}	$132.53\pm5.36^{a}_{A}$	109.53 ± 2.23^{b}	$108.33\pm2.32^{b}_{B}$	$119.93\pm7.64^{a}_{A}$	
24$	114.67±4.61	103.40±4.44	118.80±4.08	109.40 ± 2.36^{b}	$107.00\pm2.34^{b}_{B}$	$119.93\pm9.89^{a}_{A}$	
36	112.06±4.12	108.00±4.71	$111.79\pm3.49_{C}$	108.40±2.17	$105.07\pm2.42_{B}$	$104.60\pm2.80_{B}$	
48	114.27±4.40	108.36±4.19	$111.13\pm3.02_{C}$	107.20±2.30	$105.80\pm2.94_{B}$	$104.80\pm2.69_{B}$	

Significant differences within columns are indicated by ABC and within rows by ab ($P < 0.05$): Treatment is significant and mean values, which are higher in males, are increased in female AML and HCZ and male AML subgroups and decreased in other subgroups; ****, $P < 0.0001$; other abbreviations are as used in Table 2; (N = 15 per subgroup)

DISCUSSION

Apart from causing significant diuresis and BP reduction, data from the present study demonstrate that AML and HCZ combination treatment has salutary effects on renal function as observed from the Clcr in the various groups. The values of Clcr were higher in M because GFR, which is estimated by Clcr, varies according to renal mass which corresponds to body mass that is greater in M than F. GFR is conventionally corrected for body surface area (which equates with renal mass), which in normal humans is approximately 1.73m^2 and represents an average value for normal young men and women. When the GFR is corrected for body surface area, a normal range can be derived to assess renal impairment. The normal corrected GFR is 80-120 ml/min/1.73m^2, impaired renal function is 30-80 ml/min/1.73m^2 and renal failure is less than 30 ml/min/1.73m^2. The corrected GFR is approximately 8% lower in women than in men and declines with age at an annual rate of 1 ml/min/1.73m^2 from the age of 40 [12-13]. Thus, in this study, although there were significant treatment and durations effects, they were not clinically significant because they were within normal range. Interestingly, previous reports have indicated that monotherapy with AML [11, 14-15] and HCZ [6-8] has no adverse effects on renal function.

The renoprotective effects of AML combination have been confirmed in several studies. The Val-Syst trial [18] compared the risk-to-benefit profiles of valsartan and AML. To achieve target BP levels, both agents were initially titrated to 160 mg and 10 mg, respectively. After 16 weeks of treatment, 47% of the patients in the valsartan group and 35% in the AML group required the addition of low-dose HCZ (12.5 mg) to attain target systolic BP levels. The renoprotective effect of the combinations was very good. Hilleman *et al.* [19] performed a meta-analysis of 82 clinical trials that included 110 treatment groups. The combination of AML and benazepril was compared to nine monotherapies. This combination regimen displayed lower incidence of adverse effects, including renal protection, than most of the monotherapies and the lowest incidence resulting in drug discontinuance.

In the BP-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-BPLA) a large-scale clinical trial in which 19,257 patients, 40 to 79 years of age, were randomly assigned to receive either AML (5-10 mg) adding perindopril (4-8 mg) as required, or atenolol (50-100 mg) adding bendroflumethiazide (1.25-2.5 mg) and potassium as needed. At 5.5 years of follow-up, the trial was prematurely terminated because the AML/ACEI (Angiotensin Converting Enzyme Inhibitor) regimen had already prevented more CV end points, was associated with fewer cases of new-onset diabetes and had a more favourable impact on lipids, glucose and renal outcomes [20]. Furthermore, the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, [21] compared the fixed combination of AML/benazepril with HCZ/benazepril in more than 10, 000 patients. It was stopped prematurely because of a 20% reduction in cardiovascular mortality in the AML/benazepril arm. Thus, the ACCOMPLISH data, in hypertension complicated by multiple risk factors such as diabetes mellitus (DM), clearly establishes outcome superiority for a CCB/ACEI combination over a diuretic (thiazide)/ACEI combination, thereby relegating the thiazides to third-line therapy. Thus, although ACEIs or ARBs may represent the drugs of first choice in the treatment of hypertension in diabetic patients with or without incipient nephropathy, a combination of two or more drugs is often required to attain a sufficient reduction in BP with renal protection. In this regard, CCBs, such as AML, may carry an advantage over other antihypertensive drugs in combination with ACEIs [21-22].

CONCLUSION

Data from the present study has demonstrated that long-term combination treatment with AML and HCZ for 48 wks does not cause clinically significant changes in Clcr; and also that it seems prudent to initiate treatment with AML to which HCZ is subsequently added instead of HCZ to which AML is later added or *ab initio* AML-HCZ combination.

ACKNOWLEDGEMENTS

The authors are indebted to the Managements of the hospitals and patients used for this study as well as Neimeth International Pharmaceuticals, Nigeria for donation of amlodipine (Amlovar^R) tablets and the Nigerian Representative of Novartis Pharma SAS France for donation of hydrochlorothiazide (Esidrex^R) tablets for the study.

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