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Antihypertensive and Some Biochemical Effects of Hydrochlorothiazide and Furosemide in Some Nigerians

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The objective of this prospective, randomised, open, single-centre study was, therefore, to determine the antihypertensive and biochemical effects of 25 mg oral hydrochlorothiazide and 40 mg oral furosemide given once daily for 21 days to 40 patients with mild to moderate uncomplicated essential hypertension aged between 32 and 80 years and 40 age and sex-matched normotensive controls while on their usual diet. Urine volume, systolic and diastolic BP evaluated as Mean Arterial Pressure (MAP) as well as urine and serum sodium (Na^+), potassium (K^+) and chloride (Cl^-) were assessed before and during treatment. Both drugs significantly increased diuresis ($p<0.0001$); lowered MAP ($p<0.0001$) and increased urine K^+ ($p<0.001$) in the hypertensive subjects compared to controls. It is concluded that once daily 25 mg of hydrochlorothiazide and 40 mg of furosemide are effective in lowering BP as monotheraphy in Nigerians with mild to moderate hypertension and they are associated with some adverse biochemical effects including K^+ depletion.

Key words: Antihypertensive and biochemical effects, hydrochlorothiazide, furosemide, Nigerians

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INTRODUCTION

Hypertension poses serious health risks particularly among blacks (Akinkugbe, 1985, 2003; Kaplan, 1994) because this population presents with earlier onset and more severe forms of the disease than nonblacks. Although diuretics, especially thiazides and loop diuretics, are the cornerstone of antihypertensive therapy among black patients (Weir and Saunders, 1988; JNC, 1993; Freis, 1995), investigators like Kaplan (1990) Izzo and Case (2001) have expressed concern over increasing evidence of adverse effects including electrolyte derangement such as hyponatremia, disproportionate hypochloremia, alkalosis and hypokalemia, produced during diuretic monotherapy especially when high doses of the drugs are used. According to the reports of McKibbin *et al.* (1984) and Siscovick *et al.* (1994), this condition predisposes to increase cardiovascular risk and lack of protection against coronary mortality.

Clinical studies to date (Hoes and Grobbees, 1996; Ramsay, 1999) indicate that low dose diuretics such as 25 mg hydrochlorothiazide and 40 mg furosemide are efficacious and associated with minimal side effects, especially in those patients with salt-sensitive hypertension (Svetkey *et al.*, 1996; Weinberger, 1996), majority of whom are blacks, the elderly, the obese and others with low renin status (Channick *et al.*, 1969). This research examines the beneficial and side effects of these diuretics in the treatment of mild to moderate hypertension in Nigerians. It is hoped that more research will be done in this direction and that the findings will be given adequate consideration in the evolution of a detailed country-wide hypertension control program in Nigeria.

MATERIALS AND METHODS

Patients (20 males and 20 females) between the ages of 32 and 80 years with untreated mild to moderate essential hypertension (BP > 160/95 mmHg and > 180/110 mmHg) who attended Osigbemhe Hospital Auchi, Edo State of Nigeria were eligible for inclusion into this prospective, randomized, nonblind and single centre study to determine the effects of hydrochlorothiazide and furosemide on BP, urine and serum electrolytes in mild to moderate hypertensives.

A standardised pretested questionnaire was used to elicit background information such as demographic data, family history of hypertension, current drug use if any, educational and social status as well as dietary habits. Pregnant women were excluded from the study, as well as patients with concurrent medical conditions including cardiac, renal, hepatic, gastrointestinal or endocrinologic (e.g., diabetes) diseases, following clinical examination and urinalysis. Also excluded were patients with known hypersensitivity to hydrochlorothiazide and furosemide or related drugs, a recent history of smoking, drug or alcohol abuse or clinically relevant mental disorder and use of concomitant medications that might interfer with BP or renal function within 4 weeks before entering the study. These medications included monoamine oxidase inhibitors, antiarrhythmic drugs, digitalis, sedative-hypnotics, minor tranquilizers, psychotropic drugs or non-steroidal anti-inflammatory drugs. Additionally, patients were excluded if they needed concomitant medication apart from the study drugs. Control subjects were 40 age and sex-matched healthy normotensives.

All the patients signed an informed-consent form according to the protocol approved by the Medical Ethics Committee of Ambrose Alli University College of Medicine. The entire study was conducted in an outpatient setting and none defaulted. All subjects were advised to maintain their usual diet but to avoid foods excessively high in salt and undue stress.

Height and weight: In all the participants, a standard scale (Seca model, UK) was used to determine height (no shoes on) and a beam balance (Hackman, UK) was used for measuring weight (on light clothing) by the same trained observed.

BP measurements: Maintaining standardized procedures, all BP (systolic and diastolic) readings were taken by the same observer with a standard mercury sphygmomanometer (Riester Diplomat Presameter, Germany) using the subject's left arm (any constricting clothing on the arm was removed) while seating comfortably on a chair always between 8 and 10 am. Readings were taken two consecutive times with an interval of one minute and the average recorded. The MAP was calculated using the formula MAP = Diastolic BP +1/3 Pulse Pressure. BPs were measured at baseline and at 7, 14 and 21 days during pharmacotherapy intervention. Results were not disclosed to subjects.

Sample collection and analysis: The forty nomotensives were divided into two sub-groups of 20 (10 males and 10 females) identified as sub-groups A and B and so were the 40 hypertensives. Each subject was given a 4 L plastic container to collect a 24 h urine sample at baseline i.e., day 0 (24 h before pharmacotherapy intervention) and on days 7, 14 and 21. The importance of carefully collecting all urine passed during the period was emphasized. The volume of urine was recorded each day as well as urine

Na^+ K^+ and Cl^- which were measured with an ion-selective electrolyte analyzer branded Biolyte 2000 (BioCare Corporation, Hsinchu 300, Taiwan). Venous blood was sampled at baseline and at days 7, 14 and 21 to determine serum Na^+ K^+ and Cl^- concentrations using ion-selective electrolyte analyzer.

Pharmacotherapy intervention: Subgroups A in controls and hypertensives individually took every morning for 21 days hydrochlorothiazide (Esidrex^R) 25 mg tablet (National Food and Drug Administration and Control, NAFDAC) Reg. No. 04-3705 with expiry date of August 2007 and manufactured by Novartis Pharma SAS, France). Subgroups B in controls and hypertensives individually took furosemide (Frumed^R) 40 mg tablet (NAFDAC Reg. No. 04-3275 and expiry date November 2007, Fidson Drugs Ltd. Lagos, Nigeria) for the same period. The participants collected 3 successive 24 h urine samples which were analysed together with serum as earlier described. Compliance was assessed by sporadic visits and pill counts as well as urine volume measurement.

Data analysis: All data are presented as mean±SEM, or mean±SD (for age, weight and height). Comparative statistics (GraphPad Prism Software UK) were done using the Students' t-test or One-way ANOVA with Turkey *post hoc* test. Correlation between two sets of variables was determined using Spearman's rank correlation and statistical significance was set as $p<0.05$.

RESULTS

Baseline characteristics of subjects: The youngest hypertensive was 32 years (female) and the oldest 80 years (male) (Table 1). There was no statistically significant difference between the means of ages (58.10±7.84 and 57.10±11.58 years) as well as the body mass index (26.96±4.53 and 25.15±2.34 kg m^{-2}) in the normotensives and hypertensives, respectively. There was a significantly higher MAP in hypertensives (127.20±4.20 mmHg) than in controls (92.97±6.25 mmHg) with $p<0.0001$.

The baseline serum Na^+ and Cl^- (152.8±2.14 and 115.4±2.62) in the hypertensives were significantly higher than the values (136.0±3.23 and 102.2±2.52) in normotensives ($p<0.0001$) (Table 2). The serum K^+ (4.01±0.08) in hypertensives was significantly lower than the value (4.82±0.03) in controls ($p<0.0006$). The pretreatment 24 h urine volume in hypertensives (1410.0±41.30 mL) was also significantly higher than in the normotensives (1253.0±14.33 mL) with $p<0.0006$.

Effects of pharmacotherapy intervention: Treatment with hydrochlorothiazide and furosemide caused a significant reduction in the MAP in hypertensives but not in normotensives (Table 3). On day 21, hydrochlorothiazide reduced MAP by 15.30±1.05 mmHg in hypertensives and 7.12±1.39 mmHg in normotensives, $p<0.0001$. Furosemide decreased MAP by 16.40 ±0.97 mmHg in hypertensives and 5.76±1.33 mmHg in controls, a significantly lower value ($p<0.0001$).

With hydrochlorothiazide, diuresis was maximal on day 14 in both normotensives and hypertensives with the urine volume being 2028±64.33 mL in hypertensives and 1455±19.83 mL in normotensives-two significantly different values ($p<0.0001$) (Table 4). There was maximal diuresis on day 7 during treatment with furosemide urine volume being 2048±64.63 mL in hypertensives and this was significantly different from 1505±22.03 mL in normotensives ($p<0.0001$). Diuresis gradually decreased after the peak.

Time-dependent hyponatremic changes were observed during treatment with both drugs (Table 5). Within the first week, the decrease in serum Na^+ concentration was more marked in hypertensives ($p<0.0001$) after which the changes were no longer significantly different.

In the therapy with both drugs, urine Na^+ was significantly higher in hypertensives than in normotensives ($p<0.0001$) (Table 6). After day 14, urine Na^+ decreased in both groups of subjects but the decrease caused by furosemide was more pronounced and it was more so in hypertensives than in normotensives ($p<0.0001$).

Table 1: Demographic characteristics of subjects

	Normotensives		Hypertensives	
Characteristics	Range	Mean±SD	Range	Mean±SD
Age (years)	33-80	58.10±7.84	32-80	57.10±11.58
Height (m)	1.56-1.72	1.63±0.04	1.50-1.80	1.65±0.07
Weight (kg)	56-98	71.74±9.02	52-85	68.41±6.86
BMI (kg m^{-2})	23.01-33.13	26.96±4.53	23.11-26.23	25.15±2.34
MAP	83.30-106.70	92.27±6.25	118.30-136.70	127.20±4.20*
Male (n)	20		20	
Female (n)	20		20	

Normotensive and hypertensive values are indicated with a significantly higher MAP for the hypertensives, *$p<0.0001$; n = 40 per group; BMI = Body Mass Index; MAP = Mean Arterial Pressure

Table 2: Baseline serum and urine parameters

	Normotensives		Hypertensives	
Parameters	Serum	Urine	Serum	Urine
Na^+ (mmol L^-)	136.00±3.23	147.10±1.10	152.800±2.14**	300.90±41.3**
K^+ (mmol L^-)	4.82±0.03	55.60±0.63	4.010±0.08**	73.70±0.73***
Cl^- (mmol L^-)	102.20±2.52	126.40±1.51	115.40±2.62*	278.60±4.39***
Creatinine (mg dL^{-1})	0.74±0.03	89.73±3.41	0.94±0.02	101.80±4.68*
Creatinine clearance (mL min^{-1})	107.90±1.69		103.70±3.81	
Urine volume (mL 24 h)	1253.00±14.33		1410.00±41.30**	

*p<0.01; **p<0.0006; ***p<0.0001 when hypertensives are compared with corresponding normotensive values. n = 40 per group

Table 3: Effects of hydrochlorothiazide and furosemide on MAP

	Hydrochlorothiazide MAP (mmHg)		Furosemide MAP (mmHg)	
Days	Normotensives	Hypertensives	Normotensives	Hypertensives
0	93.13±1.37	128.50±1.08**	91.43±1.44	125.90±0.68**
7	91.60±1.43	119.20±1.50*	88.41±1.64	115.70±1.31*
14	87.92±1.50	115.70±1.28*	85.67±1.22	113.50±1.67*
21	86.01±1.40	113.20±1.01*	85.25±1.18	109.50±1.26*

Values are in mmHg (mean±SEM). MAP = Mean Arterial Pressure (*p<0.001; **p>0.0001). n = 40 per group

Table 4: Effects of hydrochlorothiazide and furosemide on urine volume

	Hydrochlorothiazide Urine volume (mL)		Furosemide Urine volume (mL)	
Days	Normotensives	Hypertensives	Normotensives	Hypertensives
0	1253±23.36	1413±64.37*	1253±17.20	408±53.59*
7	1385±23.25	1.926±50.39*	1428±19.01	2220±78.00**
14	1455±19.83	2028±64.33 *	1505±22.03	2048±64.63*
21	1410±20.71	1963±66.08 *	1415±21.49	1933±66.91*

Hypertensives have significantly higher values when compared with baseline at each point and when compared with the corresponding control (*p<0.001; **p<0.0001). Values: mL 24 h. n = 40 per group

Table 5: Effects of hydrochlorothaizide and furosemide on serum Na^+ (mmol L^{-1})

	Hydrochlorothiazide		Furosemide	
Days	Normotensives	Hypertensives	Normotensives	Hypertensives
0	139.60±1.01	152.10±3.58*	132.50±6.38	153.60±2.45*
7	136.50±0.87	136.50±1.81	134.70±0.85	135.60±1.65
14	133.20±0.77	132.60±1.95	131.90±0.68	132.10±1.46
21	131.50±0.73	129.00±2.13	129.20±0.57	132.80±3.17

Only baseline values are significantly different (* p<0.0001); values are in (mean±SEM), n = 40 per group

Table 6: Effects of hydrochlorothiazide and furosemide on urine Na^+ (mmol L^{-1})

	Hydrochlorothiazide		Furosemide	
Days	Normotensives	Hypertensives	Normotensives	Hypertensives
0	147.80±1.35	290.50±6.51*	146.40±1.76	311.30±6.33*
7	147.80±5.07	310.00±6.67*	152.00±2.04	336.20±6.08*
14	157.70±1.52	314.70±6.74*	157.60±2.26	328.50±5.93*
21	160.90±1.47	312.00±5.97*	159.00±2.29	318.10±5.72

On each day, values of Na^+ excretion are significantly higher in hypertensives (*p<0.0001) when compared with the baseline and with the corresponding controls; values: mmol L^{-1} (mean±SEM) n = 40 per group

Table 7: Effects of hydrochlorothiazide and furosemide on serum potassium

	Hydrochlorothiazid serum K^+ (mmol L^{-1})		Furosemide serum K^+ (mmol L^{-1})	
Days	Normotensives	Hypertensives	Normotensives	Hypertensives
0	4.87±0.04	3.91±0.12*	4.78±0.05	4.12±0.09*
7	4.77±0.04	3.88±0.10*	4.78±0.03	3.92±0.09*
14	4.67±0.04	3.70±0.09*	4.66±0.02	3.82±0.10*
21	4.61±0.04	3.63±0.03*	4.62±0.02	3.71±0.09*

Serum potassium levels are significantly lower in hypertensives than in normotensives (*p<0.001). Values are in mmol L^{-1} (mean±SEM). n = 40 per group

Table 8: Effects of hydrochlorothiazide and furosemide on urine potassium

	Hydrochlorothiazide urine K^+ (mmol L^{-1})		Furosemide urine K^+ (mmol L^{-1})	
Days	Normotensives	Hypertensives	Normotensives	Hypertensives
0	55.30±0.95	72.95±0.86*	55.90±0.84	74.45±1.18*
7	58.60±1.07	79.80±0.91*	58.10±0.86	82.40±1.40*
14	62.55±1.07	83.90±0.97*	61.45±0.99	88.20±1.14
21	62.55±1.07	86.15±0.97	63.20±1.07	89.90±1.19

Urinary potassium excretion is significantly higher in hypertensives both at baseline and during treatment (*p<0.0001) compared with baseline and the corresponding values in controls. Values in mmol L^{-1} (mean±SEM). n = 40 per group

Table 9: Effects of hydrochlorothiazide and furosemide on serum Cl^-

	Hydrochlorothiazide		Furosemide	
Days	Normotensives	Hypertensives	Normotensives	Hypertensives
0	105.60±4.89	112.70±4.20	98.80±0.95	118.00±3.08*
7	98.10±0.96	99.20±3.56	95.65±0.88	102.10±2.55*
14	95.60±0.86	93.50±3.58	94.15±1.13	98.50±2.46
21	93.80±0.78	92.45±6.15	91.10±0.83	95.05±2.75

Values for hypertensives treated with furosemide were significantly higher at baseline and on day 7 (*p<0.02); values in mmol/L (Mean±SEM); n = 40 per group

Table 10: Effects of hydrochlorothiazide and furosemide on urine Cl^- (mmol L^{-1})

	Hydrochlorothiazide		Furosemide	
Days	Normotensives	Hypertensives	Normotensives	Hypertensives
0	129.70±1.68	271.80±6.61*	123.20±2.33	285.50±5.53*
7	134.60±2.02	288.80±6.49*	127.10±2.64	210.60±6.05*
14	138.20±1.96	288.40±7.24*	134.30±2.87	293.60±6.55*
21	140.90±1.89	286.20±6.82*	136.60±2.97	287.00±8.31*

Cl^- excretion values are significantly higher in hypertensives (*p<0.0001) when compared with the baseline values and the corresponding values in controls; values are mean±SEM; n = 40 per group

As a result of the baseline hypokalemia earlier observed in hypertensives, throughout the treatment period K^+ levels in hypertensives were significantly lower than in the normotensives (p<0.0001) (Table 7).

There was a significantly higher urine K^+ excretion in hypertensives than in normotensives (p<0.0001) during treatment with both drugs (Table 8).

A time-dependent hypochloremic changes were observed during treatment with both drugs (Table 9). Within the first week, the decrease in serum Cl^- concentration was more marked in hypertensives than normotensives (p<0.0001). After that the changes were no longer significantly different. During treatment with both drugs, urine it was significantly higher in hypertensives than normotersives (p<0.0001, Table 10).

DISCUSSION

The means of age and the body mass index in normotensive controls and hypertensives were not significantly different, thus indicating a balanced sampling. We observed that baseline as well as treatment serum and urine Na^+ and Cl^- levels were significantly higher in hypertensives, confirming the important role of these ions in the pathogenesis of essential hypertension in many populations consuming salt. These observations are consistent with results of studies by many workers including Ukoh and Obasohan (1992) and Elliot *et al.* (1997).

Hypertensives are known to have greater blood volume and higher cardiac output than normotensives. It is not surprising, therefore, that the 24 h urine volume was higher at baseline and during treatment in the group. Present finding support many others (Ukoh and Obasohan, 1992; Elliot *et al.*, 1997; Freis *et al.*, 1998). On day 14, there was a positive correlation between urine volume and urine Na^+ in hypertensives, explaining the observed increased diuresis in this group. The negative correlation between urine volume and MAP (days 7 and 14) and not after justifies the use of low doses of these diuretics as increasing doses may not lead to increased diuresis but increased side effects.

We observed an interesting difference in pharmacodynamics between furosemide and hydrochlorothiazide. Furosemide had peak diuresis on day 7 while hydrochlorothiazide peaked on day 14. This feature may be accounted for by the shorter duration of action of furosemide. Its fast and robust diuresis easily provokes physiological compensatory mechanisms thus making the drug especially useful in hypertensive crises, volume-dependant hypertension commonly accompanying chronic renal disease, coexisting refractory congestive cardiac failure, resistance to combination regimens containing a thiazide or marked fluid retention

due to the use of potent vasodilators (Akinkugbe, 1985; Ives, 2004).

Although a less potent diuretic, hydrochlorothiazide is preferred as an antihypertensive agent (used as monotherapy or with a potassium-sparing diuretic or in combination with other agent/s), because apart from having a longer duration of action, Brater (1998) reported that it also has an important intrinsic vasodilating effect on vascular smooth muscle.

The sharp decrease in serum Na^+ concentration in hypertensives in the first week demonstrates that the patients were salt (Na^+) sensitive and the fact that the level stabilized even though urine Na^+ excretion continued implies a physiological adaptation and influence of uncontrolled dietary salt intake. The kidneys are the main players in salt sensitivity and the mechanisms causing the trait are still conjectural. Svetkey *et al.* (1996) defined salt sensitivity as a change in BP in response to changes in salt and water homeostasis and its higher prevalence in blacks compared with whites strongly suggests a heritable component. Found in 73% of hypertensive and 36% of normotensive blacks, it is generally considered a hallmark of hypertension in blacks (Weinberger, 1996).

In contrast to the findings of Ukoh and Obasohan (1992) in urban Benin City that there was no significant difference in baseline plasma or serum K^+ concentration in hypertensives and normotensives, a relative baseline hypokalemia negatively correlated with MAP and which could cause compromised vascular function, was observed in hypertensives even before drug treatment. This could well be a vital factor in the pathogenesis of hypertension in the rural population in this study. It is known that in various human populations, hypertension is correlated more closely with low K^+ intake than with Na^+ and hypertensives have been reported to have lower plasma (serum) and total body K^+ levels (Krishna *et al.*, 1989; Whelton *et al.*, 2002). Majority of the rural populace, from which this study population was drawn, are the poor (particularly the elderly with lower K^+ intake) and so become susceptible to hypokalemia.

Treatment did not significantly affect the serum K^+ in hypertensives most probably because of the relatively low pretreatment level which could make the body minimize losses and prevent hypokalaemia with its risk of increased BP and development of ventricular arrhythmias (Hoes and Grobbee, 1996). The baseline and treatment urine K^+ were significantly higher in hypertensives. This probably reflects increased K^+ secretion in exchange for the high Na^+ Cl^- load that reaches the renal distal tubules and this again may be due to uncontrolled dietary salt intake. The presence of a high urine K^+ in the absence of increased serum K^+ further emphasizes this possibility.

In a review, Morgan and Davidson (1980) showed that the fall in serum K^+ with diuretic therapy of hypertension was found to average 0.67 mmol L^{-1} and the percentage of diuretic-treated patients who develop hypokalemia varies from 0 to 40%, the differences reflecting variable dietary Na^+ and K^+ intakes, the degree of secondary aldosteronism invoked by diuretics and the concomitant use of other interacting drugs. In this study, however, the K^+ loss approximated to 0.41±0.09 mmol L^{-1} in hypertensives and normotensives.

Moderate restriction of dietary Na^+ intake (60-100 mmol day^{-1}), high K^+ diet in form of fresh fruits and vegetables or the use of K^+ - sparing diuretics have been shown to potentiate the effects of diuretics in essential hypertension and to lessen renal K^+ -wasting (Ives, 2004).

Unlike the normotensive controls whose BPs were not significantly affected, both drugs caused a significant reduction in the MAP by day 14 in 85% of the hypertensives towards the normal level. This is similar to the findings of Stein *et al.* (1992). Maroko *et al.* (1989), reporting the results of a large multicenter, randomized, placebo-controlled, double-blind trial using 25 mg dose of hydrochlorothiazide, showed that approximately 80% of the antihypertensive effect occurred within 2 weeks and after 4 weeks, there was no further significant reduction.

CONCLUSION

In conclusion, to present knowledge, we have made a debut report of a relative basal hypokalemia among hypertensives in the studied population. By examining the effects of hydrochlorothiazide 25 mg day^{-1} and furosemide 40 mg day^{-1}, this investigation has demonstrated the effectiveness of low doses of these diuretics in short-term antihypertensive monotherapy. Present results also showed that though these doses seem prudent, they are however associated with biochemical changes-Na^+, K^+ and Cl^- depletion, thus making serum electrolyte investigation clinically imperative in this population before diuretic therapy.

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