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## **A Comparison of the effects of fixed dose Valsartan/Hydrochlorothiazide and Atenolol/Chlorthalidone on Blood Lipid Profile in Hypertensive Patients**

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# A Comparison of the effects of fixed dose Valsartan/Hydrochlorothiazide and Atenolol/Chlorthalidone on Blood Lipid Profile in Hypertensive Patients

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## ABSTRACT

**Background:** Hypertension is the commonest non-communicable disease and the leading cause of cardiovascular disease in the world. Antihypertensive therapy often produces plasma lipid and glucose derangements. This study, therefore, was designed to find antihypertensive combinations that do not adversely affect plasma lipid and glucose profiles. **Method:** 240 carefully selected hypertensive patients of both sexes aged between 35-64 years were divided into two groups A and B. Baseline values of systolic and diastolic blood pressure, fasting blood sugar, serum total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglyceride and reduced glutathione (GSH) were recorded. Fixed dose combinations of valsartan 80mg +hydrochlorothiazide 12.5mg (Diovan-HCT) and atenolol 50mg +chlorthalidone 12.5mg ( Diovan-50) were administered orally once daily to group A and group B subjects respectively. Post-treatment values were recorded at the end of six weeks. **Results:** The valsartan+hydrochlorothiazide combination produced a statistically significant higher reduction in diastolic blood pressure, plasma LDL-C, HDL-C, and triglyceride and a minimal increase in fasting blood compared with atenolol + chlorthalidone combination ( $p = 0.0001$  for all variables). **Conclusion:** Valsartan + hydrochlorothiazide combination produced a better control of diastolic blood pressure with a favourable effect on FBS, plasma total cholesterol, LDL-C, HDL-C, and GSH.

**Keywords:** Blood pressure, valsartan/hydrochlorothiazide, atenolol/chlorthalidone, lipid profile, blood sugar, glutathione.

## INTRODUCTION

Hypertension is defined as a sustained increase in systolic blood pressure above 140mmHg and/ or diastolic blood pressure above 90mmHg. It is the commonest non-communicable disease and the leading cause of cardiovascular disease in the world (Chobaman et al., 2003). Worldwide prevalence for hypertension is about one billion persons (Burt, 2000). This is expected to hit 1.5 billion persons by 2025 (Kearney et al., 2005). In Nigeria, the prevalence is put at 32.8% of the adult population (Ejike et al., 2008). Ahaneku et al. (2011) reported a prevalence of 44.4% among the adult population in Nnewi, Eastern Nigeria.

Major organ complications of hypertension include left ventricular hypertrophy, congestive cardiac failure, cerebrovascular accidents, and renal failure, resulting in 7.1million death per year worldwide (WHO, 2002). Luckily, effective management of hypertension is associated with considerable reduction in its morbidity and mortality (NIH, 2004).

The ultimate goal of antihypertensive therapy is the reduction of cardiovascular and renal complications. However, many of the antihypertensive agents have been found to influence serum lipid profile negatively, thereby contributing to cardiovascular complications. For instance, atenolol, one of the common anti-hypertensive agents, is known to adversely affect lipid profile (Kuster et al., 2002). Also, Gotto and Antonio (2005) observed that whereas

antihypertensive therapy reduced the incidence of cerebrovascular accidents, it did not reduce that of coronary heart diseases in many cases.

Combination therapy in the treatment of hypertension has been found to improve efficacy and reduce unwanted adverse effects, especially the negative effect on lipid profile. The most common combination product comprises a thiazide diuretic and a  $\beta$ -adrenergic blocker. Combination therapy using either chlorthalidone or hydrochlorothiazide and other agents improves treatment outcome. Reports indicate that chlorthalidone is superior to hydrochlorothiazide in this respect (Roush et al., 2012). Both drugs increase total serum cholesterol and triglycerides, but Dorsch et al. (2011) found that chlorthalidone displayed lower serum total cholesterol and lower LDL, compared with hydrochlorothiazide. To further reduce the incidence of unwanted adverse effects, low dose combinations of drugs are recommended. For example, chlorthalidone 6.25mg + atenolol 25mg was found to be more effective and safer for the treatment of uncomplicated hypertension than the high dose combination of these drugs (Pareek et al., 2008).

The main objective of the study is to compare the effect of fixed dose valsartan/hydrochlorothiazide and atenolol/chlorthalidone combinations on blood pressure, blood glucose and lipid profiles. Specific objectives include:

- (a) To compare the effect of these agents on blood pressure in hypertensive patients.
- (b) To compare the effect of these agents on fasting blood sugar in hypertensive patients.
- (c) To compare the effects of these agents on plasma lipids (total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides).
- (d) To compare the effect of these agents on serum reduced glutathione (GSH) in hypertensive patients.

## MATERIALS AND METHODS

**Study area/population:** This study was done in Umuahia North Local Government Area of Abia State, Nigeria. Umuahia North LG has a population of 345,342 based on the 2007 National Population Census. Inhabitants are mainly Nigerians from the Igbo ethnic group and are mainly farmers, traders and civil servants.

**Study design:** The study was randomized clinical study. The subjects were randomly divided into 2 groups A and B. Fixed dose combinations of valsartan 80mg + hydrochlorothiazide 12.5mg (Diovan – HCT) were given to group A; while combinations of atenolol 50mg + chlorthalidone 12.5mg (Tenoric -50) were given to group B.

Baseline parameters were recorded from members of each group. Drug administration lasted for six weeks, at the end of which post-treatment parameters were measured and the differences recorded.

**Inclusion criteria:** Hypertensive patients with abnormal plasma lipid levels aged between 35 – 64yrs who access health care at FMC, Umuahia.

**Exclusion criteria:** Obese patients ( $BMI \geq 30\text{kg/m}^2$ )

- Patients with history of stroke, heart attack or heart failure
- Patients less than 35yrs of age or more than 64yrs of age
- Patients treated with lipid lowering drugs in the last six weeks.

**Sample size determination:** The sample size was determined using Statistical Software GraphPad StatMate 2. A sample size of 140 in each group was chosen at 95% power to detect a difference between means of 0.75 at a significant level (alpha) of 0.05 (two tailed).

### Drug source:

- (1). Valsartan 50mg + hydrochlorothiazide 12.5mg (Diovan – HCT, Novartis, NAFDAC NO. 04-5471).
- (2). Atenolol 50mg + chlorthalidone 12.5mg (Tenoric – 50, IPCA Pharmaceuticals, NAFDAC NO 04-7866).

**Reagents:** All the reagents for the determination of fasting blood sugar, reduced glutathione, and plasma lipid profile were obtained from Randox Laboratories Ltd, UK. They were stored in the refrigerator at 2-8<sup>o</sup>c.

**Collection of blood samples:** 5.0mls of venous blood was collected from each subject in both groups in the morning following an overnight fast by clean venopuncture from the antecubital vein and distributed in specimen bottles as follows: 2mls in EDTA bottle for reduced glutathione estimation; 1 ml in fluoride bottle for fasting blood

sugar estimation; 1ml in plain bottle for lipid profile analysis. All plasma samples were stored at -4<sup>0</sup>c and assayed within one week of collection.

**Laboratory analysis:** All laboratory analyses were carried out at the Chemical Pathology Laboratory, Federal Medical Centre, Umuahia, Abia State, Nigeria.

**Measurement of blood pressure:** Arterial blood pressure was measured in the subjects using adult sphygmomanometer (Accoson, mercury type), with the subject sitting on a chair and resting his/her feet on the floor for a minimum of five minutes prior to the measurement. Systolic BP was recorded to the nearest 2mmHg.

**Biochemical analyses:** Fasting blood glucose concentration was measured in accordance with instructions in Randox GOD/PAP manual (Barham and Trinder, 1972). The total cholesterol was measured using the enzymatic end point method (Allain et al., 1974). The low density lipoprotein cholesterol (LDL-C) was measured using the enzymatic (colorimetric) method of Weiland and Seidel (1983).

High Density Lipoprotein cholesterol (HDL-C) was measured using the precipitant method (Lopez-Virella et al., 1977).

Triglyceride was estimated using the method of Tietz (1986) while the plasma reduced glutathione (GSH) concentration was estimated using the method of Beutler et al. (1963).

## SATISTICAL ANALYSIS

The data generated for all the variables passed the D'Augustino and Pearson omnibus normality test. Thereafter, the figures were expressed as mean ( $\pm$ S.E.M) and the test of statistical significance between the mean values was calculated for each variable using GraphPad Prism 5 statistical soft ware. The results were taken as statistically significant if the p values were less than 0.05.

## RESULTS

Out of 140 subjects randomized into group A, 122 (87%) completed the study while 118 (84%) completed the study out of 140 subjects randomized into group B.

The mean ( $\pm$  S.E.M) of the baseline (pre-treatment) and end point (post-treatment) values for group A subjects are shown in Table I, while the values for group B subjects are recorded in Table II. Table III compares the values in group A and B.

Valsartan + hydrochlorothiazide and atenolol + chlorthalidone drug combinations both reduced systolic and diastolic blood pressure, but there was statistically significant difference in the antihypertensive action of both combinations only on diastolic blood pressure. However, there were statistically significant differences on the effects of the two drug combinations on fasting blood sugar, total cholesterol, LDL-C, HDL-C, Triglyceride and GSH (Table III).

**Table I: Mean ( $\pm$ S.E.M) pre-treatment and post-treatment values of the clinical and biochemical parameters of hypertensive patients treated with valsartan 80mg+hydrochlorothiazide 12.5mg combination (Group A)**

Parameter	Pre-treatment value	Post-treatment value	Change in value
Systolic BP (mmHg)	154.25 $\pm$ 12.40	130.75 $\pm$ 6.93	23.50 $\pm$ 5.47
Diastolic BP (mmHg)	96.50 $\pm$ 5.85	83.50 $\pm$ 1.31	13.00 $\pm$ 4.54
Fasting blood sugar (mg/dl)	85.00 $\pm$ 2.50	87.41 $\pm$ 3.00	2.75 $\pm$ 0.50
Total cholesterol (mg/dl)	215.05 $\pm$ 15.97	212.30 $\pm$ 10.74	2.75 $\pm$ 5.23
LDL-cholesterol (mg/dl)	139.20 $\pm$ 17.28	104.20 $\pm$ 11.36	35.00 $\pm$ 5.84
HDL-cholesterol (mg/dl)	44.15 $\pm$ 6.10	48.70 $\pm$ 6.10	4.55 $\pm$ 0.00
Triglyceride (mg/dl)	153.55 $\pm$ 9.03	144.35 $\pm$ 9.24	9.20 $\pm$ 0.21
(Glutathione (GSH) (mg/dL)	1.22 $\pm$ 0.42	1.66 $\pm$ 0.46	0.44 $\pm$ 0.04

**Table II: Mean ( $\pm$ S.E.M) pre-treatment and post-treatment values of the clinical and biochemical parameters of hypertensive patients treated with atenolol 50mg+chlorthalidone 12.5mg combination (Group B)**

Parameter	Pretreatment value	Post treatment value	Change in value
Systolic BP (mmHg)	158.25 $\pm$ 13.40	134.50 $\pm$ 8.56	23.75 $\pm$ 4.84
Diastolic BP (mmHg)	93.25 $\pm$ 5.74	84.25 $\pm$ 5.44	9.00 $\pm$ 0.30
Fasting blood sugar (mg/dl)	85.20 $\pm$ 2.40	90.12 $\pm$ 4.02	6.92 $\pm$ 1.62
Total cholesterol (mg/dl)	212.15 $\pm$ 9.17	214.15 $\pm$ 16.02	2.00 $\pm$ 6.85
LDL-cholesterol (mg/dl)	135.10 $\pm$ 14.25	151.65 $\pm$ 21.37	16.55 $\pm$ 7.12
HDL-cholesterol (mg/dl)	45.95 $\pm$ 5.43	41.90 $\pm$ 5.14	- 4.05 $\pm$ 0.29
Triglyceride (mg/dl)	150.95 $\pm$ 11.13	156.55 $\pm$ 11.49	5.60 $\pm$ 0.36
(Glutathione (GSH) (mg/dl)	1.34 $\pm$ 0.40	1.49 $\pm$ 0.04	0.15 $\pm$ 0.36

**Table III: Pre-and post-treatment differences in clinical and biochemical parameters in group A & B hypertensive patients compared**

Parameter	GROUP A	GROUP B	P-value
Systolic BP (mmHg)	23.50 $\pm$ 5.47	23.75 $\pm$ 4.84	P > 0.05 (0.99)
Diastolic BP (mmHg)	13.00 $\pm$ 4.54	9.00 $\pm$ 0.30	P < 0.05 (0.0001)
Fasting blood sugar (mg/dl)	2.75 $\pm$ 0.50	6.92 $\pm$ 1.62	P < 0.05 (0.0001)
Total cholesterol (mg/dl)	2.75 $\pm$ 5.23	2.00 $\pm$ 6.85	P < 0.05 (0.0001)
LDL-cholesterol (mg/dl)	35.00 $\pm$ 5.84	16.55 $\pm$ 7.12	P < 0.05 (0.0001)
HDL-cholesterol (mg/dl)	4.55 $\pm$ 0.00	-4.05 $\pm$ 0.29	P < 0.05 (0.0001)
Triglyceride (mg/dl)	9.20 $\pm$ 0.21	5.60 $\pm$ 0.36	P < 0.05 (0.0001)
(Glutathione (GSH) (mmol/L)	0.44 $\pm$ 0.04	0.15 $\pm$ 0.36	P < 0.05 (0.0001)

## DISCUSSION

The drug combinations (group A and B) produced significant changes in blood pressure and plasma lipid profile. For example, both groups caused reductions in both systolic and diastolic blood pressures (Tables I and II).

Valsartan, an angiotensin II receptor antagonist causes vascular smooth muscle relaxation and inhibits aldosterone secretion while hydrochlorothiazide causes plasma volume reduction and moderate natriuresis, all of which contribute to reduction in blood pressure. Similarly, atenolol, a  $\beta$ -adrenergic blocker, causes reduction in blood pressure by its negative inotropic effect on the heart while chlorthalidone have antihypertensive properties similar to hydrochlorothiazide.

However, valsartan/hydrochlorothiazide combination produced a statistically significant higher reduction in diastolic BP when compared with atenolol/chlorthalidone combination ( $p = 0.0001$ ) as shown in Table III. The better diastolic BP control achieved with valsartan/ hydrochlorothiazide combination could be as a result of reflex increase in sympathetic activity produced by atenolol. Also, atenolol, unlike valsartan, does not improve peripheral vascular resistance, an important contributory factor to systemic hypertension (Cruickshank, 2007; Poirier and Lacourciere, 2012).

Both drug combinations also produced an increase in fasting blood sugar, but the atenolol/chlorthalidone combination produced a statistically significant higher increase ( $6.92 \pm 1.62$ mg/d/ and  $2.75 \pm 0.50$ mg/d/ respectively) as shown in Table III ( $p = 0.0001$ ). This could be explained by the fact that both thiazides and  $\beta$ -blockers decrease glucose tolerance in normal individuals and potential diabetics (Stears et al., 2012). Barzilay et al. (2006) had earlier found that treatment of adult hypertensive patients with chlorthalidone increased fasting blood sugar more than with calcium channel blockers and ACE inhibitors.

On the other hand, valsartan/ hydrochlorothiazide combination caused only a marginal increase in fasting blood sugar ( $2.75$ mg/d/) as shown in Table I. This could be because valsartan improves pancreatic  $\beta$ -cell function. This is supported by the findings of van der Zijl et al. (2011) who demonstrated that this drug increased glucose stimulated insulin release and sensitivity in normotensive patients with impaired glucose metabolism.

Both drug combinations produced a minimal change in plasma total cholesterol (Tables I, II), but valsartan/ hydrochlorothiazide significantly reduced LDL-C from  $139.20 \pm 17.28$  to  $104.20 \pm 11.36$ mg (Table I) when compared with atenolol/chlorthalidone combination which increased LDL-C from  $135.10 \pm 14.25$ mg to  $151.65 \pm 21.37$ mg/d/ (Table II). The beneficial reduction in LDL-C produced by the valsartan/hydrochlorothiazide combination could be as a result of the presence of valsartan. This is in keeping with results from earlier studies (Ott et al., 2003; Kwelou et al., 2006; Fujiwara et al., 2012). Valsartan is known to activate peroxisome proliferators – activated receptor gamma

(PPAR- $\alpha$ ) which regulates lipid metabolism (Benson et al, 2004). The fact that atenolol/chlorthalidone combination increased LDL-C and reduced HDL-C could be attributed to the presence of atenolol since this  $\beta$ -blocker is known to adversely affect lipid profile. This was despite the fact that this combination contained chlorthalidone, a more plasma lipid friendly thiazide than hydrochlorothiazide (Dorsch et al, 2011).

The valsartan/hydrochlorothiazide combination caused a reduction of plasma triglyceride from  $153.55 \pm 9.03$ mg to  $144.35 \pm 9.24$ mg compared with atenolol/chlorthalidone combination which increased plasma triglyceride from  $150.15 \pm 11.13$ mg/d/ to  $156.55 \pm 11.45$ mg/d/ (Tables I, II). These changes in plasma triglyceride were statistically significant when subjected to students t-test ( $p = 0.0001$ ) as shown in Table III. This was in keeping with reports from earlier studies which showed that angiotensin II receptor blockers reduced plasma triglyceride and glucose through activation of the peroxisome proliferators – activated receptor gamma involved in carbohydrate and lipid metabolism (Benson et al, 2004).

Both drug combinations increased plasma reduced glutathione concentration. However, the valsartan/hydrochlorothiazide combination produced a more significant increase ( $p = 0.0001$ ). Earlier animal and clinical studies had observed a possible antioxidant role of valsartan (Silva et al, 1998; Bolterman et al, 2005). Angiotensin II stimulates the production of reactive oxygen species through membrane bound NADP/NADPH oxidase. Valsartan, by inhibiting the action of angiotensin II receptors inhibits the action of this oxidase thereby increasing reduced glutathione (GSH) production (Rabin et al., 2005). GSH maintains a reduced cellular environment by mopping up reactive oxygen species (ROS) which are implicated in the pathogenesis of cancers, Parkinson's disease, cystic fibrosis and aging (Townsend et al., 2003). Therefore these agents help in maintaining a cleaner cellular environment in addition to their antihypertensive properties.

## CONCLUSION

The valsartan/hydrochlorothiazide combination produced a statistically higher reduction in diastolic blood pressure, plasma LDL-C, and triglyceride. It also caused only a minimal increase in fasting blood sugar, and significantly reduced plasma reduced glutathione concentration compared with the atenolol/chlorthalidone combination. From this study, it could be observed that valsartan/hydrochlorothiazide combination produced a more favourable plasma lipid, glucose and antioxidant profile than the atenolol/chlorthalidone combination. The use of valsartan/hydrochlorothiazide combination for the treatment of hypertension should be encouraged especially in older hypertensive patients whose plasma glucose, lipid and antioxidant profiles are more likely to be negatively affected by atenolol-containing drug combinations.

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