

Original Article

Long Term Effects of Hydrochlorothiazide on Diabetic Control and Blood Pressure in Nigerians

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ABSTRACT

Objective: We determined the long term effects of hydrochlorothiazide (HCTZ) on fasting blood glucose (FBG), serum K⁺, serum creatinine, body weight and blood pressure (BP) in individuals with controlled type two diabetes and hypertension (HBP).

Subjects/Method: Adults attending a university based diabetic clinic with type two diabetes and FBG consistently 7.00 mmol for at least three months and BP 160/85 were approached to volunteer. Eligible individuals received 75 mg aspirin by mouth daily and dietary advice, i.e., not to add table salt to meals four weeks prior to exposure to HCTZ. Thereafter, only those whose BP remained 165/85, received in addition, doses of HCTZ 12.5 mg - 50 mg titrated to a target BP 150/85. At each visit, clinical and laboratory measurements were made.

Results: Mean systolic blood pressure (SBP) fell to 143.1, 137.3 and 145.4 mmHg at three, six and 12 months respectively from a baseline value of 170.4 mmHg. The

sitting diastolic blood pressure (DBP) was 78.7, 84.9 and 89.4 mmHg at three, six and 12 months respectively compared to a baseline value of 85.3 mmHg. The corresponding values for fasting blood glucose (FBG) at these times were comparable to each other; being 7.9, 6.7, 7.1 mmol and 5.8 mmol (at baseline). Also, the serum K⁺ values were 3.5, 3.9 and 3.6 mmol at three, six and 12 months respectively compared to a baseline value of 3.9 mmol. The fall in serum K⁺ at the end of three months, but not at six and 12 months was significant compared to baseline. There were no drop-outs, hospitalization or morbidity related to either diabetes or hypertension during the period of observation.

Conclusion: The data suggest that this therapy was tolerated and associated with a sustained fall in systolic but not diastolic blood pressure at the end of 12 months without any clinically relevant changes in diabetic control or serum K⁺ value.

KEYWORDS: hydrochlorothiazide, hypertension, Nigerians, type II diabetes.

INTRODUCTION

Many individuals with type two diabetes also have hypertension^[1-4]. Incidentally, several studies^[5-12] show that effective control of blood pressure in type two diabetes achieves more dramatic results in preventing premature deaths and complications related to diabetes than did better glycaemic control. While effective glycaemic control can reduce the incidence and retard the progression of diabetic microangiopathy^[13], the practical difficulties often associated with maintaining tight blood glucose control in this part (Nigeria) of the world, makes control of BP appear a cheaper and clinically more feasible method to reduce the worrisome high mortality and morbidity still associated with type two diabetes in Nigeria^[14,15].

Unfortunately, cost of medication remains a major obstacle in optimizing blood pressure control; as majority of our patient population can hardly afford even the cheapest of drugs. Besides, angiotensin converting enzyme inhibitors (ACEIs) and β -blockers which are considered antihypertensives of choice in type two diabetes are

often ineffective and expensive when compared to thiazides which are cheaper and effective in Nigerians^[16-19]. However, safety concerns have been raised about the use of thiazides based on observations in a sample of non-diabetic hypertensives^[20,21]. These concerns have been largely exaggerated and derive mainly from earlier studies^[20-24] using far higher doses of thiazides than is now known to effectively and safely lower BP^[25-27].

For these reasons and based on our initial observations^[11], we studied the long term effects of hydrochlorothiazide (HCTZ) on diabetic control, serum electrolytes, renal function and blood pressure in individuals with type two diabetes and hypertension. This report therefore supplements data which have appeared in studies cited above.

METHOD

The location, experimental design, patient population and procedures have been extensively detailed elsewhere^[1]. Specifically, this study involved a cohort of middle aged individuals (n =

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11) with controlled type two diabetes (defined as FBG 7.00 mmol/L) and hypertension (defined as SBP averaging 160 mmHg and or diastolic blood pressure (DBP) of 85-120 mmHg on at least three different occasions). Essentially and as previously reported^[1], all eleven subjects (five females) were Nigerians with a mean age of 58.2 years and a BMI of 28.3 kg/m²; mean duration of hypertension and diabetes were 8.06 years and 13.8 years respectively. Diabetic control was achieved by diet alone (one patient), diet and glibenclamide (four subjects) and a combination of diet, glibenclamide and metformin (six subjects). Prior to enrolment, all subjects receive information and advice on life-style adjustments such as weight reduction, physical activity etc. tailored to individual needs. Thereafter, those individuals meeting these and other criteria were exposed to HCTZ beginning with 12.5 mg daily in conjunction with 75 mg aspirin and a dietary advice not to add table salt while eating regular diet, commenced four weeks prior to the introduction of HCTZ. Subsequently, the dose of HCTZ was titrated (doubled) monthly to a sitting BP target of SBP 150 mmHg and DBP of < 85 mmHg and a maximum of 50 mg daily. During each visit blood was sampled for measurements of serum K⁺, Na⁺, creatinine and fasting blood glucose (FBG). BP was taken in triplicate after a five minutes rest in the sitting position and then, two minutes after standing as extensively described previously^[1,28]. Adverse events were assessed in response to the question. "Have you had any problem or feeling of being unwell since the last visit?" and on specific questioning using a structured questionnaire. Compliance was defined and assessed by pill counting of unused medications and attendance at scheduled visit as reported earlier^[1]. The blinding procedure adopted was such that dose-adjustment, compliance assessment etc. were done by another investigator after evaluating clinical measurements of BP, weight etc. gathered in specific format by a trained observer who was unaware of the types and doses of medication each subject was on. Criteria for premature termination as previously reported^[1] were a DBP 120 mmHg on any visit, diabetic ketoacidosis or any illness requiring hospitalisation.

Dropouts, dosage and concomitant medications: All eleven patients that completed the 12-week phase^[1] were available for evaluation at the end of 12 months. Two patients, however, agreed to do only FBG testing at the end of 12 months because of the cost. Also the daily dose of HCTZ was doubled to 25 mg in two patients originally on 12.5 mg at the end of three months; while another three patients initially on 25 mg had their dose

doubled to 50 mg at the end of six months because their BP fell outside the set target of either sitting SBP of 150 and/ or DBP of 85 mmHg. Thus, at the end of 12 months, four patients were on daily HCTZ of 12.5 mg, four were on 25 mg while three were on 50 mg HCTZ daily as against six subjects who were on 12.5 mg of HCTZ daily and five on 25 mg at the end of three months as previously reported^[1]. In this arm of the study, scheduled clinic visits were deliberately reduced to a minimum to keep down cost; but, patients were informed to contact the principal investigator or one of the senior residents should they feel unwell or have concerns in between scheduled visits. For these reasons, five patients received chloroquine for acute fever and aches thought to be due to acute malaria. Two other patients received Fansidar® at various times. Another patient was given oral cotrimoxazole because of sore throat. All patients took paracetamol as over the counter medications for aches and pains at various times.

Statistical procedures: Results presented as means and comparison between treatment periods was by split-plot analysis of variance (of repeated measures) using *Genstat software package version 5.3*. A difference between means was identified using the 5% level of significance. The sample size has a minimum power of 80% in detecting a real change of 11.7 mmHg in sitting SBP, 7.95 mmHg in sitting DBP, 0.34 mmol in serum K⁺ and 2.71 mmol in FBG during the 12-month period of exposure to HCTZ.

RESULTS

a. Biochemical parameters: There was no significant change in serum creatinine, FBS and body weight. Similarly, the serum K⁺ was stable except at the 12 week point after exposure to HCTZ, when it fell significantly compared to the initial value (week 0) prior to exposure to HCTZ. Also there was no measurable variation in serum Na⁺ except at week 28 when it rose significantly compared to baseline value (week 0). Of note, both these changes were transient and within the normal range for the wider population (Table 1)

b. Blood pressure: In contrast, the systolic BP fell significantly within four weeks of exposure to HCTZ and remained so subsequently (see protocol). On the other hand, beyond the initial fall in DBP observed after exposure to aspirin and dietary advice (see Table 1: weeks- 4 and 0), addition of HCTZ did not result in any further fall in DBP. Rather, there was a perceptible rise in DBP which became significant at weeks 28 and 52 compared to the values at weeks four, eight and 12 (Table 1).

Table 1
Mean values of selected variables over time

Variables	Months								Normal Range (mmol)
	-1	0	1	2	3	6	12	LSD	
Serum K ⁺	-	3.9	3.9	3.8	3.5*	3.9	3.6	0.3	2.9-5.0
FBG	-	5.8	6.4	7.5	7.9	6.7	7.2	2.7	2.5-5.0
Serum creatinine	-	99.5	95.3	105.1	102.9	103.7	91.0	16.6	53-106
Serum Na ⁺	-	133.2	137.8	134.3	136.2	139.8*	134.3	2.3	135-145
Body weight	74.77	75.5	75.6	75.1	76.4	76.2	73.6	6.2	-
Sitting SBP mmHg	171.6	170.2	148.2*	137.8*	143.1*	137.3	145.4*	11.6	-
Sitting DBP	95.27	85.3	81.5	79.7	78.7	84.9	89.8	7.9	-
Standing SBP	173.4	164.3	145.7*	134.0*	135.8	124.1*	140.8*	14.2	-
Standing DBP	95.5	85.5	81.0	78.0	79.0	86.1 ^c	92.1	9.7	-

LSD indicates least difference expected between means that are significantly different from each other at $\alpha = 0.05$

* indicates significant difference from value at 0 week

+ indicates significant difference from value at - 4 week

DISCUSSION

Before discussing these results, a number of issues must be addressed. First, conducting clinical studies in Nigeria that involve repeated measurements and visits is extremely difficult for reasons previously indicated^[1, 29] when compared to the situation in countries with advanced health care systems. Second, the present sample size is higher than similar pioneering studies in the US^[30] and much higher than those of another Nigerian study^[2] comparing the combined effects of lisinopril (ACEI) and HCTZ (50 mg) in diabetes. Third, both the studies cited above went on for less than six weeks, unlike the present study with a 52 week period of observation. In addition, the study is exploratory and our sample size had a power of 80%.

For these reasons, we believe the following conclusions are possible based on the present findings. Specifically, Table 1 shows that there were no significant changes in glucose homeostasis, electrolytes, renal function and body weight over a 12 month period even with some patients on doses of HCTZ as high as 50 mg daily. Of note, the serum electrolytes and creatinine remained within the normal range of the wider general population from which this subset was drawn^[1]. In this regard, although we lack facilities for measuring glycosolated haemoglobin, the final average value of FBG of 7.2 mmol/L after 12 months of HCTZ was much lower than the mean value of 8.6 mmol/L of the intensive group in the DCCT study and comparable to the level of glycaemic control of the intensive group in the UKPDS study^[8, 31]. Of note, there were no dropouts and neither was there any hospitalization, cardiovascular or diabetes related morbidity during this period. This safety profile is

no different from observations in non-diabetic Nigerians with hypertension^[18-19, 32].

However, there was a perceptible rise in DBP at six months which became significant at 12 months compared to that observed at three months, thus, necessitating dose increment of HCTZ to 50 mg (see methods) in some patients whose BP fell outside the set target. This could suggest a blunting of the antihypertensive effects of HCTZ in a number of individuals over this time period. This is consistent with reports^[5-12, 25] from Europe and US that over time many type two diabetics would require more than one antihypertensive medication to achieve optimal BP control. Nevertheless, the fall (Table 1) in SBP that became evident within four weeks of exposure to HCTZ as previously reported^[1] remained sustained after one year of treatment.

Specifically, the sustained reduction of systolic blood pressure averaging 15-20 mmHg observed in this study is far higher than the 2-6 mmHg fall in systolic BP reported in the HDFEP, SHEP, HOT, UKPDS, SYST-EUR AND MICRO-HOPE trials^[5-12, 27] which showed that the risk of premature deaths and diabetes related complications in type two diabetes was substantially reduced. Therefore, contrary to recommendations^[20-21], based on extrapolations from non-diabetics, we find no evidence to preclude the use of thiazides in Nigerians with diabetes and hypertension and conclude that HCTZ at the doses studied can cause a fall in systolic blood pressure in some type two diabetics without any relevant change in diabetic control, electrolyte or renal function.

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