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BIOCHEMICAL CHANGES DURING MODURETIC TREATMENT OF HYPERTENSION IN AFRICAN PATIENTS

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INDEXING WORDS

moduretic therapy; biochemical values; African hypertensive patients

SYNOPSIS

Twelve hypertensive patients aged between 39 and 70 years of both sex had biochemical assessment during 20 weeks (short-term) and 30 weeks (long-term) of moduretic (combination of hydrochlorothiazide and amloride) therapy. Fasting blood glucose (although within the reference range) showed significant increase from baseline value at 20 weeks of moduretic therapy. Similar significant increases were observed in the mean values of plasma total protein, albumin, urea, creatinine, calcium, bicarbonate and chloride within the short-term period. Conversely, significant reductions were recorded in the mean values of globulins, potassium, sodium and phosphate at 20 weeks of moduretic therapy.

At 30th week (long-term) moduretic therapy, the mean values of fasting blood glucose and all the other biochemical parameters showed a return to pre-treatment values, with the exception of the rise in plasma urea

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that was significant. The results suggest that the biochemical variations observed during moduretic therapy in hypertensive patients may be temporary and limited mainly to the short-term treatment period. we therefore conclude that moduretic is still acceptable for the treatment of hypertension in African patients, and recommend that fasting blood glucose and other biochemical variables should be adequately monitored during short-term moduretic therapy.

INTRODUCTION

Thiazide diuretics are usually the commonly prescribed drugs for management of hypertension in this community. Moduretic is a combination type of diuretic consisting of hydrochlorothiazide and amiloride hydrochloride. The potassium sparing effect of amiloride has long been recognised (5,19) while hypokalemia is a known side effect of thiazide type of drugs in different populations (18,22). Further evidence showed that the degree of hypokalemia is more severe in Africans using thiazide diuretic when compared with their Caucasian counterparts (23). In combination type of diuretic therapy (thiazide and potassium sparing drugs) the absence of any significant hypokalemia has been reported in different populations (4). In an earlier preliminary study Salako (24) found low but insignificant reduction in plasma potassium concentration in Nigerians treated with moduretic. This earlier study was carried out in patients treated for only 12 weeks and only one point blood collection was made after therapy.

On the other hand glucose intolerance appears to be a common metabolic side effect during thiazide therapy (8,13), but a few workers (7,21) did not confirm this. Also it has been reported that hyperglycemia may arise from prolonged state of hypokalemia in hypertensive patients (9). To our knowledge there is little information on the effect of moduretic on glucose metabolism in hypertensive patients. Recent reports from our laboratory

showed favourable biochemical variations with doxazosin treatment (3) and no alteration with amlodipine treatment in African patients (2). Meanwhile, we previously observed adverse lipid and lipoprotein changes during short and long-term treatment with moduretic in our African patients (1). It was therefore necessary to determine whether the biochemical changes during moduretic treatment would be limited to the short-term period or otherwise.

The present study was therefore designed to critically examine the effects of moduretic therapy on fasting blood glucose, electrolytes, urea, creatinine and proteins over a prolonged period of 30 weeks. A possible relationship between potassium and blood glucose changes during moduretic monotherapy was also evaluated.

PATIENTS AND METHODS

Twelve Nigerians aged between 39 and 70 years (mean ± S.E=58.0 ±5.0) attending the hypertension clinic of the University College Hospital Ibadan, Nigeria were studied. Uncomplicated essential hypertension (diastolic blood pressure DBP>95 mmHg) was established by clinical examination, chest X-ray, electrocardiography, full blood count and blood chemistry. On the first visit and subsequent visits, urine tests for reducing sugar, protein, casts and deposits were carried out. For patients previously undergoing treatment, all antihypertensive drugs were withdrawn for a "washout period" of 2 weeks and the blood pressure, biochemical parameters measured after the 2 weeks were regarded as the baseline value. Moduretic in the dose equivalent to 50mg hydrochlorothiazide and 5 mg amloride hydrochloride daily was prescribed and sufficient amounts to last till the next visit were usually dispensed to each patient and pill counts checked at each clinic visit inorder to ensure strict compliance to drug therapy. The patients were seen fortnightly at the clinic by the same physician between the hours of 8:00 and 12:00 on the appointment days. The patients maintained their usual

diets which was mainly a high-carbohydrate, low-fat, low-protein and high-vegetable diet. The female patients were neither pregnant or lactating mothers, nor on oral contraceptives.

At the beginning and at every 10 weeks during the study, 12ml of venous blood was withdrawn from each patient while fasting. 10ml of the blood withdrawn was emptied into heparinised bottles for plasma electrolytes, urea, proteins, calcium and inorganic phosphate estimation. The remaining 2ml was collected into a bottle containing sodium floride for fasting blood glucose determination. The samples were analysed immediately after collection. The biochemical estimations were as follows: fasting blood glucose was determined by the method of Trinder (26), plasma chloride by the method of Schales and Schales (25), creatinine by the modified method of Hare (16), potassium and sodium by flame photometer method (15). Inorganic phosphate was determined by the method of Delsel and Monhouri (10), calcium by the method of Baginski (6), urea by diacetyl monoxime method (12), total protein by the biuret method (14), albumin by BCG method (11) and plasma bicarbonate was determined by titration. The mean values of the variables recorded during the study were compared with baseline values using paired student t-test.

RESULTS

The fasting blood glucose showed a gradual rise from a mean baseline value of 74.0 mg/dl to a peak of about 95.0 mg/dl after 20 weeks, and the differences after 10 and 20 weeks were significant ($P<0.001$). Similarly significant increases were observed in the mean values of total protein, albumin, and creatinine at 10th and 20th weeks respectively (see table).

Calcium, urea and bicarbonate rose appreciably during the same period but the differences were significant only at the 20th week, but the rise in chloride level was significant at the 10th week of therapy. On the other

hand, significant reductions in the mean values of globulins, potassium and phosphate were recorded at the 10th and 20th weeks of moduretic treatment respectively. While the reduction in sodium level was significant at 20th week.

At 30th week (long-term), fasting blood glucose and all the other parameters tended to return to pre-treatment values except that the slight rise in plasma urea was significant (see table).

DISCUSSION

A significant incease in blood glucose level was observed during the short-term (20 weeks) administration of moduretic in our hypertensive patients, a finding similar to some earlier reports in hypertensive patients on diuretic treatment (8,13) but at variance with those of others (7,21). Interestingly, blood glucose concentration temporarily increased from baseline value and reached its peak at 20 weeks of therapy but returned to pre-treatment value at 30th week of continous moduretic therapy. The normalization of blood glucose level during long-term moduretic therapy in our patients contrasts with the persistent glucose intolerance reported in twelve of forty patients who were treated with benzothiadiazine for a period of 3 years (8). Our data probably indicate that induced diabetes may not arise from prolonged moduretic therapy in the Nigerian patients. Impairment of insulin secretion during diuretic therapy has been suggested to be responsible for the increase in blood glucose during diuretic therapy and Breckenridge et al (8) reported an increase in insulin requirement of patients on thiazide diuretics. Others have associated glucose increase with reduced potassium level in hypertensive patients (9); and the decrease of the acute hyperglycemic effect of thiazide diuretics by infusion of potassium has been reported (17). In the present study, the co-existence of glucose increase and reduction in potassium level was only limited to the short-term period of 20 weeks, as

both plasma potassium and glucose concentration tended to return to pre-treatment levels at the 30th week of treatment. An earlier report from this community (24) did not find any significant reduction in potassium level during a 3 months study of moduretic therapy. Similarly, Amery et al (4) working with a combination of hydrochlorothiazide and triameterene for 3 years in a different population reported absence of potassium decrease.

A possible mechanism for the short-term rise in fasting blood glucose level and changes in the levels of other variables may be haemoconcentration. The early stages of moduretic administration induced diuresis on the patients resulting in reductions in sodium and potassium levels, and increases in fasting blood glucose (FBG), albumin, creatinine, total protein, calcium, urea, bicarbonate and chloride levels. These variations were temporary and limited to the short-term period because FBG and the other variables normalized at 30 weeks (long-term) therapy; similar reversal of biochemical alterations have been observed by other workers (13,21). The clinical implication of the temporary changes in FBG and other variables, therefore suggest that physicians should regularly monitor the levels of FBG and other biochemical variables during moduretic therapy, especially within the first six months of therapy.

During long-term (30 weeks), the increase in plasma urea persisted while all the other biochemical variables normalised. The reason for the non-normalisation of urea level is not well understood. Meanwhile, our results indicate that it is most unlikely to be associated with renal dysfunction since all the other biochemical indices for renal assessment normalised at 30 weeks moduretic treatment..

In conclusion, hypokalemia alone has been associated with increased cardiac ectopy (18) and an increased risk of sudden death during acute myocardial infarction (20). The risk of coronary heart disease may therefore be higher if hypokalemia is present together with raised plasma

glucose. However, as potassium level normalizes and glucose level return to pre-treatment value during long-term moduretic therapy, this then removes the fear of an increased risk of coronary· heart disease during chronic moduretic adminstration in African patients. We therefore conclude that moduretic therapy is still acceptable for the treatment of hypertension in African patients, and recommend for contineous monitoring of the levels of fasting blood glucose and other variables (especially during the short-term treatment period). It is also important to realize that the variations reported here are strictly in respect to the pre-treatment values and not to the biochemical reference ranges.

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Table I. Fasting blood glucose and electrolyte changes during moduretic therapy.

	0wk	10wk	20wk	30wk	changes at		
	BFTx n=12	AFTx n=12	AFTx n=12	AFTx n=12	10wk	20wk	30wk
FBG (mg/dl)	74.0 ± 5.0	81.0 ± 6.0	95.0 ±6.6	85.0 ± 9.2	7.0 ±1.0#	21.0 ± 1.8#	10.7 ± 8.4
Total protein (g/dl)	7.4 ± 0.13	7.4 ± 0.17	7.7 ± 0.17	7.0 ± 0.32	0.20 ± 0.04+	0.30 ± 0.03*	-0.39 ± 0.39
Albumin (g/dl)	3.6 ± 0.09	4.0 ± 0.02	4.0 ± 0.15	3.7 ± 0.15	0.4 ± 0.07+	0.4 ± 0.03#	0.1 ± 0.02
Globulins (g/dl)	3.8 ± 0.09	3.4 ± 0.15	3.5 ± 0.16	3.3 ± 0.24	-0.04 ± 0.09+	-0.03 ± 0.10*	-0.49 ± 0.27
Sodium (Meq/L)	138 ± 2.6	135 ± 3.2	137 ± 2.6	145 ± 5.0	-3.0 ±0.70#	-1.0 ± 2.0	7.3 ± 5.18
Potassium (Meq/L)	3.7 ± 0.06	3.4 ± 0.84	3.2 ± 0.9	3.8 ± 0.18	-0.3 ± 0.05#	-0.5 ± 0.10+	0.08 ±0.21
Calcium (mg/dl)	8.4 ± 0.10	8.8 ± 0.32	9.5 ± 0.29	8.9 ± 0.44	0.4 ± 0.30	1.1 ± 0.28#	0.49 ± 0.41
Phosphate (mg/dl)	3.9 ± 0.06	3.4 ± 0.24	3.0 ± 0.29	3.5 ± 0.38	-0.50 ± 0.16+	-0.9 ± 2.0#	-0.42 ± 0.37
Urea (mg/dl)	16.5 ± 0.77	18.4 ± 1.17	20.9 ± 1.92	25.1 ± 2.91	1.9 ± 0.60	4.4 ± 2.0*	8.58 ± 3.26*
Creatinine (mg/dl)	1.07 ±0.04	1.82 ± 0.27	1.90 ± 0.29	1.08 ± 0.05	0.75 ± 0.21+	0.83 ± 0.20#	0.008 ± 0.05
Chloride (Meq/L)	101 ± 0.25	105 ± 0.60	102 ± 1.0	99 ± 0.70	5.0 ± 0.80#	2.0 ± 1.0	-2.0 ± 1.0
Bicarbonate (Meq/L)	25.0 ± 0.84	26.0 ± 0.96	28.0 ± 0.80	23.0 ± 1.28	1.0 ± 1.10	3.0 ± 1.7*	-2.17 ± 1.38

FBG = Fasting Blood Glucose; n= Number of patients; wk= Weeks;
BF= Before; AF= After; Tx= Treatment; *= P<0.05; += P<0.01; #= P<0.001;
values expressed as mean ± standard error.