Biochemical Changes During a Cross-Over Treatment of Doxazosin, Moduretic and Amlodipine in Hypertensive Patients

Pages with reference to book, From 71 To 73

J. E. Ahaneku (Department of Chemical Pathology, Nnamdi Azikiwe University Teaching Hospital Nnewi, Nigeria.)
G. O. Taylor, E. O. Agbedana (Departments of Chemical Pathology, College of Medicine, University of Ibadan, Nigeria.)
O. Walker, A. Sowunmi, L.A. Salako (Pharmacology & Therapeutics, College of Medicine, University of Ibadan, Nigeria.)

Abstract

A cross-over study was done to compare the effects of doxazosin, moduretic and amlodipine on biochemical values in 9 hypertensive Nigerians aged 35 to 65 years. Doxazosin therapy was characterized by significant increase in the levels of mean plasma total protein and albumin, while moduretic therapy showed significant reduction in the mean values of plasma creatinine and calcium. All other parameters did not show any significant variation during doxazosin and moduretic treatment phases; and amlodipine therapy did not have any effect on the biochemical values of the hypertensive patients. (JPMA 46:71,1996).

Introduction

Biochemical variations are common findings during anti- hypertensive pharmacotherapy and many previous workers have provided data during the use of different anti-hypertensive agents in various populations[1-3]. We described the effectiveness and biochemical changes during doxazosin[1] and amlodipine[5] monotherapies in hypertension as well as forthe long used diuretic “moduretic"[6,7]. . The results of our monotherapy studies revealed beneficial biochemical changes during doxazosin treatment[4] and adverse changes during moduretic therapy especially at the short term period[6], while anilodipine treatment did not alter biochemical levels in hypertensive patients[5]. Thus inorderto confirm thebiochemical profile during the use of these anti-hypertensive drugs, the same hypertensive patients treated with the three different classes of anti-hypertensive agents in a double-blind cross over fashion were studied. Apart from our previous study which was used to confirm the lipid and lipoprotein atherogenic and antiatherogeriic properties of the above drugs[8], similarthree way cross-over studies are lacking. In the present study, the biochemical results during a three way cross-over anti-hypertensive therapy are presented. The findings are expected to help physicians better their knowledge of choice of drugs and management of hypertension.

Patients and Methods

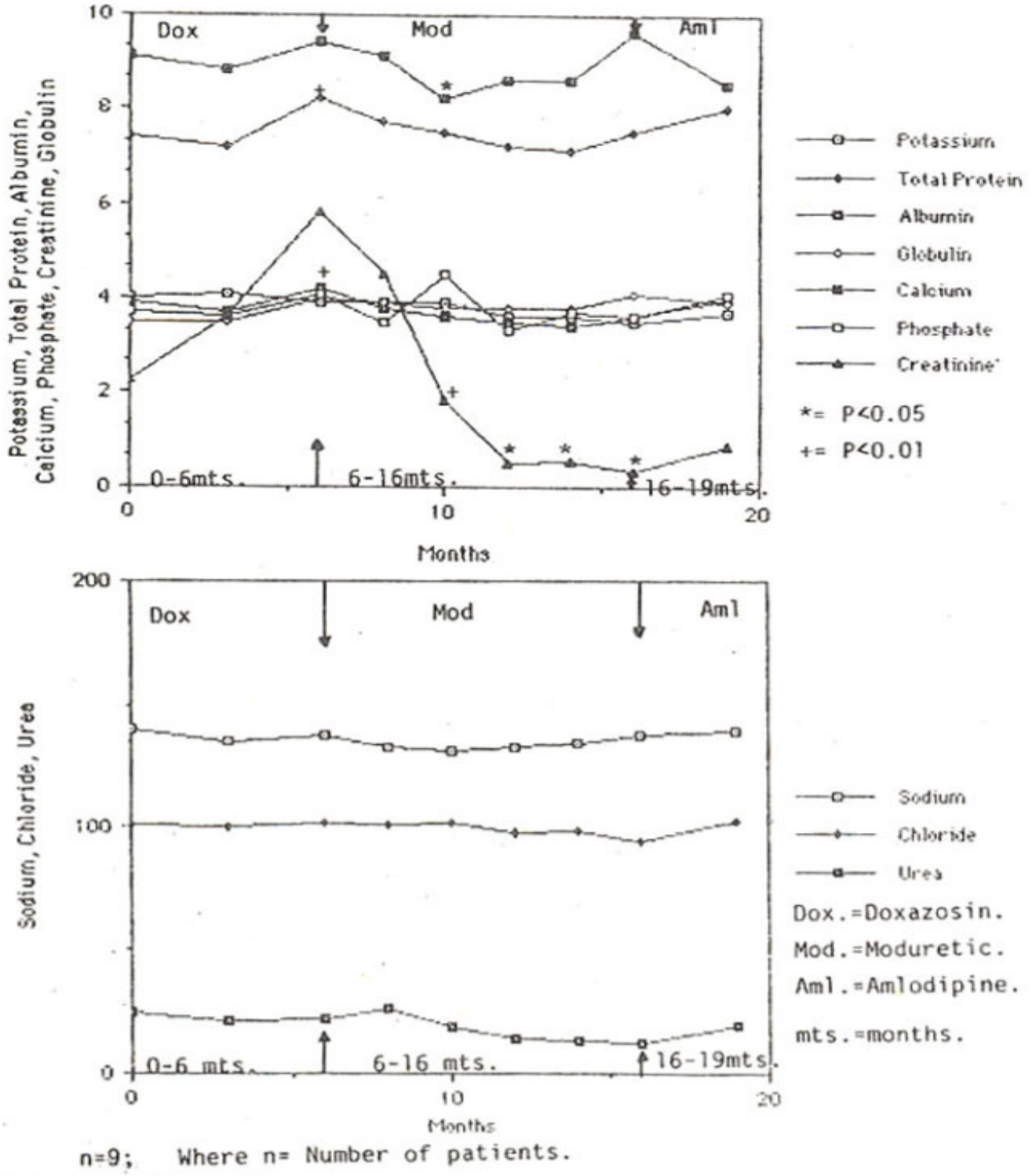
Thirty patients aged 35 to 65 years with essential hypertension attending the hypertension clinic of the University College Hospital, Ibadan, Nigeria were studied, Because of non-compliance only nine patients completed the 19 months study period. All patients were Nigerians and the diagnosis of essential hypertension was based on two separate blood pressure readings withinaminimum of 2weeks interval and laboratory examinations (complete blood count, blood chemistry, urine tests for reducing sugar, protein, casts and deposits). All patients with hypertension secondary to other diseases, pregnant and lactating women and those on oral contraceptives were excluded. Some patients were newly diagnosed; others who were on anti- hypertensive agents had their drugs withdrawn for a washout period of 2 weeks. Patients were not subjected to any dietar restrictions. This was a double-blind, cross-over study, which consisted three phases of washout/baseline, titration and maintenance. Moderate to

severe hypertensionwas defined by an average of two diastolic blood pressure (DBP) between 105 and 130 minHg in the sitting and supine positions at the end of the washout period. Sitting and supine blood pressure, heart rate and body weight at the end of the washout period were regarded as the baseline values. After the washout period, patients were placed on doxazosin treatment and maintained on the dosage in which they showed response for a period of 6 months, by which time the blood pressure were reduced in the range of mild to moderate levels. At the end of 6 months doxazosin therapy, patients were switched over to one to two tablets of moduretic daily (equivalent to 50mg hydrochiorothiazide and 5 mg amloride hydrochloride) for a period of 10 months after which, blood pressure was controlled and the patients were switched overto amlodipine therapy for another 3 months.

Patients were seen at the out-patient clinic between 8 and 11 A.M. every 2 weeks by the same physician throughout the study. Sitting blood pressure and heart rate were determinedafterthe patients hadbeenina siftingpositionforafleast 3 •minutes and readings were repeated 2 minutes later. Similarly, supine blood pressure was determined twice after 5 minutes supine and repeated 2 minutes later using a mercury sphygmomanometer (Accuson^{R}). The patients same arm was used throughout the study. To ensure strict compliance with the dosage schedule, patients received just enough study drugs dispensed by aco-investigatorat the clinic to last until the next clinic visit.

At the beginning and after every three months (in the case of doxazosin and amlodipine therapies and two months in the case of moduretic therapy), 10 ml of hepannised venous blood was withdrawn from each patient and plasma obtained after centrifugation was immediately used for biochemical analysis. Plasma creatinine levels were determined using the modified method of Hare[9], chlonde levels usingthe method of Schales and Schales[10], potassium and sodium levels using the flame photometer method[11], inorganic phosphate levels using the method of Delsel and Manhouri[12], calcium levels using the method of Baginski et al[13], urea levels using the diacetyl monoxime method[14], total protein levels using the Biuret method[15], and albumin levels using bromocresol green method[16]. For each assay, a commercial quality control (wellcomtrol I and II reagents) of known values were always included. The mean values of thebiochemical variables before and at every period of measurement were compared using the paired t-test.

Results



Figures 1a and 1b. Graph of plasma electrolytes, urea and protein before and during a cross-over of doxazosin/moduretic/amlodipine treatments.

In figures a and b, the mean values of plasma total protein and albumin showed gradual increments duling doxazosin treatment phase and this was significant at 6th month of therapy (p

Discussion

The pattern of biochemical variation characterized by increments in protein and albumin levels

observed during doxazosin treatment phase is not consistent with the changes observed during the monotherapy of doxazosin in the same population[4]. In the previous report, plasma total protein and albumin levels remained unchanged after 12 months of doxazosin monotherapy, instead significant reductions in plasma urea, calcium and creatinine were observed. Another report from a different population[17] observed reduction in seruim globulin level in one patient after doxazosin therapy, but no information was given for total protein and albumin. Judging from the normal distnbution of globulin, albumin and total protein, one would expect that an increase in albumin level would correspond with a reduction in globulin and vice versa. However, the clinical implication of the observed variation in protein metabolism during doxazosin treatment phase is not well understood, but may probably be of no significance. The mean plasma total protein and albumin remained the same during moduretic treatment phase. These parameters were found to be raised during short-term mono-therapy of moduretic but returned to normal after prolonged treatment[7]. In the cross-over study the few observed biochemical variations during moduretic treatment phase were reductions in mean plasma calcium and creatinine levels. A previous report from our laboratory during moduretic mono-therapy showed that calcium and creatinine were increased during short-term treatment period and subsequently normalized on prolonged therapy[7]. The otherbiochemical parameters remained unchanged during doxazosin and moduretic treatment phases of the cross-over study. Amlodipine treatment phase did not show any significant variation in all the measured biochemical parameters. This observation is consistent and confirms the previously reported innertness of amlodipine therapy on biochemical variables[5]. In conclusion, the cross-over study seem to confirm that doxazosin therapy does not have adverse effects on biochemical parameters and thatmoduretic therapy thoughreportedto have adverse effects on biochemical levels (especially during short-term treatment) in many studies, this study has confinnedthatprolonged moduretic therapy. may not be associated with adverse biochemical changes, instead favourable renal function indices could be found. The cross-over study also confirmed the Innertness of amlodipine treatment on biochemical parameters of African hypertensive patients.

Acknowledgement

We are grateful to Pfizer Pharmaceuticals (Nigeria) PLC for the supply of the drugs used in this study. The study was supported in part by a University of Ibadan senate research grant.

References

1. Aderounmu, A.F. and Salako, L.A. Abnormal cation composition and transport in erythrocytes from hypertensive patients. Eur. J. Clin. Phatmacol., 1979;9:369-375.
2. Mitas, J.A., Hofle, R., Levy, SB. et al. Racial analysis of the volume-renin relationship in human hypertension. Arch. Intern. Med., 1979;139:157-160.
3. Saruta, T. Effects of Nicardipine on blood pressure and renal fimction in elderly hypertensive patients with renal dysfunction. Am. Heart J., 1989; 117:234-45.
4. Ahaneku, J.E., Taylor, GO., Walker, 0. et al. Blood pressure and biochemical changes during doxazosin monotherapy in Nigerian hypertensive patients. Curr. Ther. Res., 1994;55: 1067-1074.
5. Ahaneku, J.E., Taylor. GO. Walker, 0. et al. Biochemical changes during amlodipine treatment in hypertensive patients. Eur. J. Clin. Pharrnacol., 1994;46:249-251.
6. Salako, L.A. Serum electrolytes in hypertension in Nigerians. Chin. Chim. Acts., 1971,34:105-106.
7. Ahaneku, J.E. Plasma lipids, lipoproteins and other biochemical variables in Nigerian bypertensives during treatmentwith different antihypertensive agents. Doctoral thesis, Ibadan, Nigeria, University of Ibadan, 1991.

8. Ahaneku, J.E., Taylor, GO., Agbedana, E.O. et al. Changes in lipid and lipoprotein values during .a cross-over treatment of doxazosin, moduretic and amlodipine in hypertensive patients. J. Pak. Med. Assoc., 1994;44: 166-169.
9. Hare, R.S. Endogenous creatinine in serum and urine. Proc. Soc. Exp. Biol. Med., 1950;74:148-151.
10. Schales, 0. and Schales, S.S. A simple and accurate method for determination of chloride in biological fluids. J. Biol. Chem., 1941; 140:879-880.
11. Hald, P.M. Determinations with flame photometer. In: VisscherMB, ed. Methods in Medical Research. Vol. 4 Chicago; year book; 1951 ;79:105.
12. Delsel, M. and Monhouri, H. Estimation of inorganic phosphate. In: King, EJ; Wooton, IDP, eds. Micoanslysis in Medical Biochemistry. 3rd ed., London, J and A Churchill Ltd., 1958.
13. Baginski, SE., Marie, $.S., Clark, W.L. et al. Direct microdetermination of serum calcium. Clin. Chim. Acta., 1973 ;46:49-54.
14. Evans, R.T. Manual and automated methods for measuring urea based on a modification of its reaction with diacetyl rnonoxime and thiosemicar bazide. J. Clin. Pathol., 196.8;21 :527-532.
15. Gornall, A.G., Bardwill, C.J. and David, M.M. Determination of serum proteins by means of the biuret reaction. J. Biol. Chem., 1949;117:751-766.
16. Doumas, B.T., Watson, W.A. and Briggs, HG. Albumin standards and the measurement of serum albumin with bromocresol green. Clin. Chim. Acta., 1971;31:87-92.
17. Van der Hogen, A.L.C.J. Doxazosin in the treatment of mild and moderate essential hypertension in general medical practice. Am. Heart. S., 1988;116:1757-1762.