Afr. J. Med. med. Sci. (1990) 19, 57–61.

Assessment of a fixed-dosage combination of atenolol and chlorthalidone (Tenoretic) in hypertensive Nigerians

L. A. SALAKO, A. O. FALASE*, A. FADEKE ADEROUNMU AND OLADAPO WALKER
*Department of Pharmacology and Therapeutics and *Department of Medicine, University of Ibadan, College of Medicine, Ibadan, Nigeria*

Summary

The antihypertensive effect of a fixed dosage combination of the cardioselective beta-adrenoceptor blocker, atenolol, and the oral thiazide-like diuretic, chlorthalidone (Tenoretic) was studied in 24 hypertensive Nigerians in a double-blind, cross-over comparison with three other treatments. These were atenolol alone, 100 mg daily, chlorthalidone alone, 25 mg daily, and atenolol (100 mg) plus chlorthalidone (25 mg) daily taken as separate formulations. Tenoretic was taken as a once-daily tablet containing 100 mg atenolol plus 25 mg chlorthalidone. The order of administration of the drugs was randomized. Each drug was taken for 4 weeks. The results showed that atenolol and chlorthalidone lowered blood pressure to the same extent. Combination of the two drugs whether taken separately or in fixed-dosage combination was better than either product singly. The drugs were well tolerated.

Résumé

L'effet antihypertensif d'un dosage fixe combiné de cardiosélection du blocage du béta-adrénoceptor, aténolol, et l'orale comme thiazide, diurétique chlorthalidone (Ténorétique) a été testé sur 24 cas au Nigéria en simultanément avec trois autres traitements différents. Ceux sont aténolol uniquement, 100 mg/jour, chlorthalidone uniquement 25 mg/jour, et aténolol 100 mg plus chlorthalidone 25 mg/jour administré séparément. Ténorétique était pris à la fois en un comprimé d'aténolol (100 mg) plus chlorthalidone (25 mg). L'ordre d'administration des comprimés était au hasard. Chaque comprimé était pris pour 4 semaines. Le résultat a montré que l'aténolol et le chlorthalidone baissent la pression sanguine du même niveau. La combination des deux produits pris séparément ou en dosage combiné est meilleur à l'un d'entre eux pris uniquement. Les produits sont d'une tolérance acceptable.

Correspondence: Professor L. A. Salako, Department of Pharmacology and Therapeutics, College of Medicine, University of Ibadan, Ibadan, Nigeria.

Introduction

Since the original observation of Humphreys and Delvin [1] a large number of other studies have demonstrated the relative ineffectiveness of beta-blockers in hypertensive blacks [2–4].

On the contrary, the thiazide diuretics have been found to be effective on their own and to potentiate the effects of other antihypertensives [5–7].

In earlier studies, we have demonstrated the superiority of the antihypertensive effects of a formulation combining a diuretic, clopamide, and a beta-blocker, pindolol — Viskaldix®, over the beta-blocker alone in patients with mild–moderate hypertension [8]. However, the effect of this combination was not compared with that of the diuretic alone. Hence, while it was possible to conclude that the combination of beta-blocker and diuretic was an improvement over the beta-blocker alone, it was not possible to draw that conclusion with respect to the diuretic alone. In the present study we compared another diuretic–beta-blocker combination against the diuretic and the beta-blocker given alone.

Materials and methods

The trial was a double-blind, four-treatment, four-period, cross-over trial, each treatment period lasting 4 weeks with no washout period between treatments. The trial commenced with a 2-week run-in period during which previous treatments, if any, were withdrawn and baseline investigations, including chest X-ray, electrocardiography, haematological and biochemical tests, were carried out. This was followed by four weeks on placebo and only subjects whose diastolic blood pressure at the end of this period was between 90 and 115 mmHg were included in the trial proper, which consisted of the following four treatments administered in turn:

(a) atenolol alone, 100 mg daily;
(b) chlorthalidone alone, 25 mg daily;
(c) atenolol (100 mg) plus chlorthalidone (25 mg) daily taken as separate formulations; and
(d) Tenoretic (100 mg atenolol + 25 mg chlorthalidone), 1 tablet daily as a combined formulation.

The trial was completely double-blind, with the active tablets and matching dummies being completely alike. The subjects (n = 24) were allocated to treatment sequences according to a previously prepared randomization scheme. This scheme was based on the fact that since there are 24 possible permutations of the four different treatments, each of the 24 subjects had a different order of administration of the four treatments. Each possible treatment sequence was represented once, thereby balancing the number of treatments in each period over all subjects and balancing the number of a given treatment preceding another given treatment.

Subjects were seen at the hypertension clinic every 2 weeks. At each visit blood pressure and heart rate were recorded and adverse reactions noted. The subject was weighed and urine tested for protein, bile pigments, sugar and casts. At the end of each treatment period, haematological (packed cell volume, white cell count) and biochemical (liver function, electrolytes and urea, serum calcium, phosphorus, uric acid, sugar and creatinine) tests were done. Blood pressure was measured with an Accoson sphygmomanometer with phases I and V of the Korotkoff sounds being taken as systolic and diastolic pressures, respectively.

Comparisons between different variables were made using the appropriate statistical test and values of $P < 0.05$ were taken as significant.

Results

Twenty-four subjects completed the trial. There were 17 females and 7 males aged between 29 and 70 years. Their mean blood pressures at the end of the placebo period were 182.6 ± 23.8/107.8 ± 9.1 mmHg lying, 176.1 ± 21.4/109.7 ± 8.1 mmHg standing, and the heart rates were 80.0 ± 8.8 min^{-1} lying and 84.7 ± 12.2 min^{-1} standing. Two were newly diagnosed whilst the rest had been receiving antihypertensive treatment for between 1 and 18 years. The only abnormalities noted in preliminary investigations were in the electrocardiograms in which eight patients had left ventricular hypertrophy. Two patients had coexisting osteoarthritis for which they were being treated with piroxicam (10 mg daily) which was continued during the trial.

Analysis of variance of blood pressures and heart rate

To look for treatment, period and interaction effects, these data were fitted into the following model and analysed by computer using a commercially available program.

$$Yijkl = u + Si + Tk + Cl + eijkl,$$

where Yijkl is the overall response; u is the grand mean; Si is the effect of subjects i(i = 1 . . ., 24); Pj is the effect of period j(j = 1 . . ., 4); Tk is the effect of treatment k(k = 1 . . ., 4); Cl is the carry-over effect of treatment (l = 0, 1 . . ., 4 where 1 = 0 is the effect of no previous treatment); and eijkl is the random error normally distributed with mean 0 and variance σ^2.

Analysis of variance showed that the subject effect was highly significant in all the measured parameters indicating a high inter-individual variation. By contrast, the carry-over effect was not statistically significant in any of the parameters. Treatment effect was not statistically significant for standing systolic and diastolic blood pressure. It was, however, significant for lying systolic and diastolic blood pressure and lying and standing heart rate. Similarly, the

period effect was significant for lying and standing heart rate and standing diastolic blood pressure, but not for lying and standing systolic blood pressure and lying diastolic blood pressure.

The mean patient responses between pairs of treatment were compared using the last measurements in each treatment period and differences were analysed for significance using a paired *t*-test (Table 1), correction being made for period trends [9].

The heart rates under chlorthalidone (lying 78.6, standing 90.2 min^{-1}) were significantly higher than the rates under atenolol (difference: lying 12.3 ± 2.5; standing 21.8 ± 2.8, mean ± s.e.m.; $P < 0.001$), under Tenoretic (difference: lying 13.4 ± 2.3; standing 23.1 ± 2.9; $P < 0.001$) and under atenolol–chlorthalidone (difference: lying 13.2 ± 2.5; standing 22.0 ± 3.0; $P < 0.001$). Heart rates under atenolol, atenolol–chlorthalidone and Tenoretic were not significantly different from one another.

The means of the systolic and diastolic blood pressures in the lying and standing positions were slightly lower under Tenoretic and atenolol–chlorthalidone than under atenolol alone or chlorthalidone alone. There was little difference between atenolol alone and chlorthalidone alone, and between Tenoretic and atenolol–chlorthalidone (Table 1). There was a mean fall in all blood pressure measurements in the following treatment pairs: atenolol to Tenoretic, atenolol to atenolol–chlorthalidone, chlorthalidone to Tenoretic, and chlorthalidone to atenolol–chlorthalidone. The differences were, however, only statistically significant with lying systolic and diastolic blood pressure (atenolol to Tenoretic, atenolol to atenolol–chlorthalidone).

The blood pressures and heart rates at the ends of the four treatment periods were also compared with the pretreatment blood pressure and heart rate. This shows a significant fall in blood pressure by all four treatments whilst heart rate was significantly reduced by atenolol, Tenoretic and atenolol–chlorthalidone, but not by chlorthalidone alone.

The drugs were well tolerated. Tiredness, dizziness and insomnia were reported by three subjects, two while taking the atenolol–chlorthalidone combination, and the third whilst taking Tenoretic.

Discussion

This study has shed some more light on the blood pressure-lowering effect of two important groups of antihypertensive drugs used in this country — the diuretics and the beta-blockers, used singly or in combination. At the dosage used in this study, atenolol lowered blood pressure to approximately the same extent as chlorthalidone. This contrasts with the findings in our earlier studies in which the effect of the beta-blockers was distinctly less than that of diuretics including chlorthalidone used in this study [2–4]. The beta-blockers tested against diuretics in our earlier studies were propranolol, sotalol, pindolol, alprenolol and timolol. These are all non-cardioselective beta-blockers whereas atenolol used in this study is cardioselective. In addition to being non-cardioselective, pindolol and alprenolol also have intrinsic sympathomimetic activity. Atenolol does not possess this activity. The differences in pharmacological effects of atenolol compared with those of the earlier tested beta-blockers might make it a more effective antihypertensive drug than the others. However, in spite of the fact that in this study atenolol appears to lower blood pressure to the same extent as chlorthalidone, a similar study in South African blacks found chlorthalidone to be superior to atenolol at the same dosages as those used in this study [10]. It is therefore premature to conclude or even suggest that atenolol is more active in our subjects than the non-cardioselective beta-blockers. That conclusion must await a direct comparison of the different types of beta-blockers in the same subjects.

This study also showed that the response to the combination of atenolol and chlorthalidone, whether given separately or formulated together in the same tablet, is greater than the response to either atenolol or chlorthalidone alone. Although there is no biological difference between taking the two drugs separately and taking them in a combined formulation, compliance is easier with the fixed dosage combination and so this formulation should be preferred in the African context. One obvious disadvantage of the fixed dosage combination is the loss of flexibility of dosage adjustment for the individual components. However, this is not a major practical disadvantage in this case as both chlorthalidone and atenolol have narrow

Table 1. Blood pressure (BP; mmHg) and heart rate (min^{-1}) at the end of the control and treatment periods (n = 24)

	Control	AT	CT	AT/CT	TN	Significantly different treatment pairs ($P < 0.05$)
Lying						
Systolic BP	182.6 ± 23.8	157.0 ± 12.7	154.4 ± 16.2	148.3 ± 12.4	146.6 ± 11.4	AT vs. AT/CT; AT vs. TN
Diastolic BP	107.8 ± 9.1	91.5 ± 8.6	89.1 ± 9.3	85.4 ± 6.5	85.4 ± 6.2	AT vs. AT/CT; AT vs. TN
Heart rate	80.0 ± 8.8	66.3 ± 6.7	78.6 ± 8.9	65.4 ± 8.1	65.2 ± 7.5	CT vs. AT; CT vs. AT/CT; CT vs. TN
Standing						
Systolic BP	176.1 ± 21.4	150.8 ± 22.9	141.3 ± 21.2	138.6 ± 24.7	140.1 ± 22.8	None
Diastolic BP	109.7 ± 8.1	93.0 ± 10.2	92.9 ± 8.7	89.5 ± 10.2	88.1 ± 10.4	None
Heart rate	84.7 ± 12.2	68.4 ± 10.2	90.2 ± 16.4	68.2 ± 11.4	67.1 ± 12.6	CT vs. AT; CT vs. AT/CT; CT vs. TN

Values represent mean ± s.d.

AT = atenolol; AT/CT = atenolol + chlorthalidone; CT = chlorthalidone; TN = Tenoretic.

therapeutic windows and their effective dosages are not characterized by wide inter-individual variations.

On the basis of the findings of this study our earlier recommendation of diuretics as the drugs of first choice in the treatment of mild–moderate hypertension still appears justifiable. If, for any reason, a decision is taken to use a beta-blocker, then atenolol may be considered, although its possible superiority to propranolol and other available non-cardioselective beta-blockers requires further studies. If neither compound is individually satisfactory, a combination of a diuretic with a beta-blocker is the next logical step. The recently publicized fear that both groups of drugs might lead to an increase in the low density to high density lipoprotein ratio in the plasma and thus lead to development or worsening of coronary heart disease [11] needs to be investigated in African patients. Until such a definitive study is available this fear should not influence our use of these drugs in the treatment of hypertension since coronary heart disease is not a major complication of hypertension in the Nigerian African.

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(*Accepted* 22 *February* 1989)