The treatment of hypertension with propranolol and bendrofluazide

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SUMMARY. In 101 hypertensive patients, the effects of a combination of propranolol and bendrofluazide were compared with those of each drug alone. After an introductory period with a placebo, the patients received, in a double-blind randomized trial, propranolol 80 mg twice a day, bendrofluazide 2.5 mg twice a day, or both drugs together twice daily. The combination produced significantly greater reductions in lying, standing, and post-exercise systolic and diastolic blood pressure than either drug separately. Side-effects were minimal and the combination was well accepted by patients.

Introduction

PROPRANOLOL and bendrofluazide have been used, both together and separately, for the treatment of hypertension for over 10 years (Prichard and Gillam, 1969; Zacharias *et al.*, 1972) and their antihypertensive effects have been directly compared (Berglund *et al.*, 1976; Medical Research Council Working Party, 1977). However, although the two drugs are commonly used together, no report has been published comparing the effect of combined treatment with both drugs with that of each agent separately. In this study, the doses were fixed at an optimal level of 160 mg per day propranolol (Galloway *et al.*, 1976) and 5 mg per day of bendrofluazide (Petrie *et al.*, 1975). A double-blind, cross-over study was performed to compare the antihypertensive effect of each drug alone and in combination.

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Methods

One hundred and forty patients, aged 19 to 66, from six centres entered the study. Three general practices entered 25, 25, and 23 patients respectively and three hospitals entered 31, 12, and 24* patients respectively. Patients were excluded if there was a history of recent myocardial infarction, angina, evidence of cardiac failure, airways obstruction, the presence of heart block, creatinine clearance below 50 ml/minute, diabetes mellitus requiring insulin or oral hypoglycaemic treatment, gout, grade 3 or 4 retinopathy (Keith-Wagener), or any drugs likely to interfere with antihypertensive therapy.

Patients gave their consent to take part in the trial which for each centre was designed as a randomized double-blind, within-patient, cross-over study. Routine haematological and biochemical investigations were made at the beginning and end of the trial and for many patients at the end of each treatment period.

After a placebo introductory period of two weeks in general practice or four weeks in hospital, patients were randomly allocated to treatment with either propranolol 80 mg twice a day, bendrofluazide 2·5 mg twice a day, or propranolol plus bendrofluazide twice a day, provided the diastolic blood pressure (Phase 4) was between 100 and 130 mm Hg. Matching placebo tablets were given during the single drug periods to ensure maintenance of double-blindness. At the end of each treatment period, which lasted four weeks (general practice) or six weeks (hospital), treatment was changed according to a random code. Patients were seen every two weeks throughout the trial and blood pressure was measured after lying or sitting for three minutes, standing for two minutes, and also, in most cases, after three minutes' exercise. Three recordings of systolic or diastolic (Phase 4) blood pressure were made on each visit by the same observer, with a standard mercury sphygmomanometer. Pulse rates were also measured in each position. Patients were seen, as far as possible, at

*This study is still proceeding and results from 14 patients only are included.

about the same time of day and volunteered symptoms were noted, followed by those elicited by direct questioning. Tablet counts were made at each visit.

Statistical methods

Multiple regression analysis was carried out on measurements of blood pressure, pulse rate, and weight obtained at the end of each active treatment period and the significance of patient, treatment, and period effects assessed. Treatment means were corrected to allow for the slight imbalance in the number of patients following each of the possible sequences of treatment. Comparison of the results from the treatment periods and those from the placebo period have been made by paired t-test.

Results

One hundred and forty patients satisfied the entry criteria and of these patients, 101 (45 men and 56 women) with a mean age of 51·8 years and with a mean weight of 72·1 kg (158·6 lb) (range 44·9 to 116·1 kg (98·8 to 255·4 lb)) completed the study. No patients were withdrawn because of the effects of treatment and two centres (one from general practice and one from hospital) accounted for 25 of the withdrawals, mainly for non-attendance. Tablet counts were satisfactory in patients completing the trial.

Table 1 gives placebo and adjusted treatment means and standard errors for blood pressure and pulse rate measured in the standing position for each of the six centres. All possible comparisons of means have been made and significance levels associated with them are summarized in Table 2. The results from the six centres have been pooled for convenience in Figure 1.

The figure shows the significant reduction during treatment in standing systolic and diastolic blood pressure of 21/12 mm Hg with propranolol, 21/11 mm Hg with bendrofluazide, and 34/19 mm Hg with the combination. Similar effects on blood pressure and heart rate were obtained with the patients sitting or lying and after exercise. Of patients on the combination, 80·2 per cent achieved a diastolic blood pressure $\leqslant$ 100 mm Hg; corresponding figures for propranolol and bendrofluazide were 70·4 per cent and 61·6 per cent respectively. Similarly, 67·3 per cent of patients had a final systolic blood pressure $\leqslant$ 150 mm Hg on the combination, corresponding figures for propranolol and bendrofluazide being 52·0 per cent and 46·5 per cent. The drugs, either alone or in combination, were well tolerated by the patients and the incidence of side-effects (volunteered or elicited by questioning) was no greater in the drug treatment periods than in the placebo period. There were no significant changes in any of the routine haematological or biochemical measurements. In one study, there was a significant rise in uric acid on all three treatments compared with placebo.

Discussion

The results show that the combination of 80 mg propranolol and 2·5 mg bendrofluazide is more effective than either drug alone and that this effect is independent of the order in which the drugs are given. The antihypertensive effect of the combination and propranolol

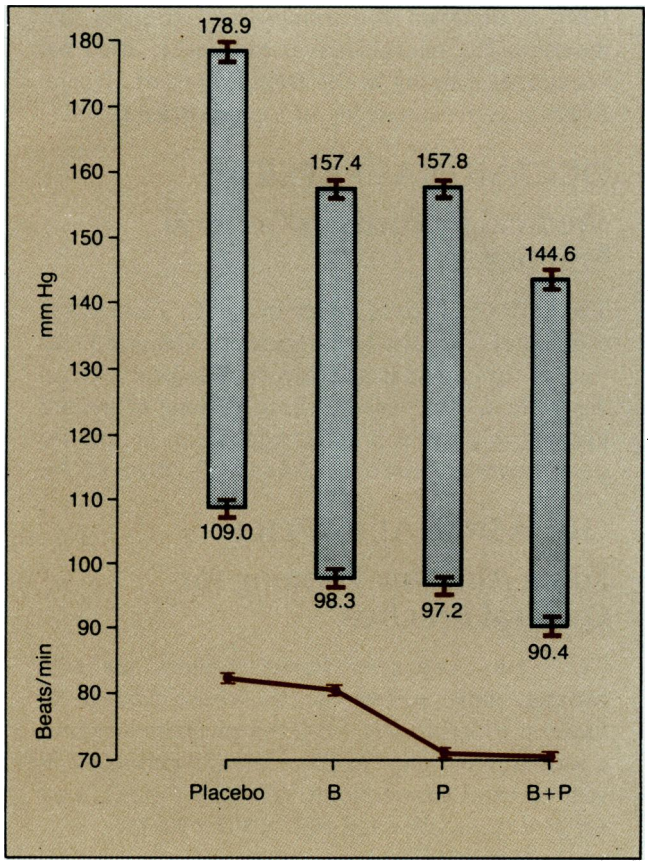
Table 1. Standing means ±1 standard error.

	Placebo	Bendrofluazide	Propranolol	Propranolol + Bendrofluazide
Systolic blood pressure				
Centre 1 n=23	183.3 ± 3.43	165.6 ± 2.71	162.9 ± 2.71	151.9 ± 2.71
Centre 2 n=23	175.8 ± 3.86	157.4 ± 2.77	153.0 ± 2.77	148.4 ± 2.77
Centre 3 n=19	172.4 ± 6.85	149.6 ± 3.61	146.8 ± 3.71	134.5 ± 3.81
Centre 4 n=10	195.7 ± 8.44	171.7 ± 6.85	189.5 ± 6.13	150.0 ± 6.13
Centre 5 n=14	177.4 ± 5.52	147.9 ± 4.90	153.3 ± 4.90	138.8 ± 4.90
Centre 6 n=12	174.2 ± 5.79	152.9 ± 4.26	153.5 ± 4.08	141.5 ± 4.08
Diastolic blood pressure				
Centre 1 n=23	104.0 ± 1.44	97.0 ± 1.16	93.9 ± 1.16	87.3 ± 1.16
Centre 2 n=23	109.4 ± 2.91	97.2 ± 1.90	95.5 ± 1.90	92.2 ± 1.90
Centre 3 n=19	114.2 ± 2.80	105.0 ± 2.21	101.7 ± 2.27	94.0 ± 2.34
Centre 4 n=10	106.4 ± 2.72	91.2 ± 3.70	96.2 ± 3.31	81.5 ± 3.31
Centre 5 n=14	107.1 ± 3.78	94.9 ± 2.89	98.5 ± 2.89	89.0 ± 2.89
Centre 6 n=12	114.3 ± 3.46	102.4 ± 3.07	99.0 ± 2.94	96.4 ± 2.94
Pulse rate				
Centre 1 n=23	73.6 ± 1.41	77.3 ± 1.64	67.9 ± 1.64	67.7 ± 1.64
Centre 2 n=23	83.4 ± 2.07	83.5 ± 1.75	76.3 ± 1.75	74.0 ± 1.75
Centre 3 n=19	90.2 ± 2.56	84.7 ± 2.37	72.9 ± 2.44	73.7 ± 2.51
Centre 4 n=10	57.8 ± 5.18	77.5 ± 2.58	70.1 ± 2.16	63.5 ± 2.16
Centre 5 n=14	91.1 ± 2.33	80.3 ± 2.11	72.2 ± 2.11	75.1 ± 2.11
Centre 6 n=12	81.7 ± 3.13	81.6 ± 1.71	67.6 ± 1.63	67.7 ± 1.63

Table 2. Significance levels attached to comparisons of means.

	Placebo v Bendrofluazide	Placebo v Propranolol	Placebo v Propranolol + Bendrofluazide	Propranolol v Bendrofluazide	Propranolol v Propranolol + Bendrofluazide	Bendrofluazide v Propranolol + Bendrofluazide
Systolic blood pressure						
Centre 1	***	***	***	NS	**	***
Centre 2	**	***	***	NS	NS	*
Centre 3	***	***	***	NS	*	**
Centre 4	*	NS	***	NS	***	*
Centre 5	***	*	***	NS	*	NS
Centre 6	***	**	***	NS	*	NS
Diastolic blood pressure						
Centre 1	***	***	***	NS	***	***
Centre 2	***	***	***	NS	NS	NS
Centre 3	**	***	***	NS	*	**
Centre 4	**	NS	***	NS	**	NS
Centre 5	*	NS	**	NS	*	NS
Centre 6	***	**	**	NS	NS	NS
Pulse rate						
Centre 1	NS	**	**	***	NS	***
Centre 2	NS	**	**	**	NS	***
Centre 3	NS	***	**	**	NS	**
Centre 4	NS	*	**	*	*	**
Centre 5	*	***	**	*	NS	NS
Centre 6	NS	***	**	***	NS	***

NS not significant
* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$



alone was fully developed within two weeks of starting treatment.

The use of a beta-adrenergic blocking agent and diuretic is established as current clinical practice. The antihypertensive effect of propranolol and bendrofluazide in the present trial compares well with that found in other studies using beta blocker/diuretic combinations. Thus, Petrie and colleagues (1975) observed falls of 33/22 mm Hg in 24 patients with atenolol and bendrofluazide and Galloway and colleagues (1976)

Figure 1. *Effect of placebo, bendrofluazide alone (B), propranolol alone (P) and bendrofluazide plus propranolol (B + P) on blood pressure (systolic: upper end of columns; diastolic: lower end of columns) and heart rate in 101 hypertensive patients.*

For both systolic and diastolic blood pressure, placebo vs B $p < 0{\cdot}001$, placebo vs P $p < 0{\cdot}001$, placebo vs B + P $p < 0{\cdot}001$, P vs B NS, P vs B + P $p < 0{\cdot}001$, B vs B + P $p < 0{\cdot}001$. For heart rate, placebo vs B NS, placebo vs P $p < 0{\cdot}001$, placebo vs B + P $p < 0{\cdot}001$, P vs B $p < 0{\cdot}001$, P vs B + P NS, B vs B + P $p < 0{\cdot}001$. (NS = not statistically significant; bars indicate ± standard error.)

reported falls of 28/13 mm Hg in lying blood pressure for practolol and bendrofluazide. Comparable figures from the current study are 31/17 mm Hg. Furthermore, the results are similar to those found when variable doses of propranolol and bendrofluazide were used (Mitchell *et al.*, 1972; Berglund *et al.*, 1976). Therefore, the fixed doses selected for this study appear to be near optimal for a satisfactory antihypertensive effect. Both propranolol and bendrofluazide are well established drugs for the treatment of hypertension and have been chosen by the Medical Research Council for a long-term study to assess the effect of treatment on morbidity and mortality in patients with mild hypertension (Medical Research Council Working Party, 1977). However, regardless of the efficacy of drug therapy, hypertensive patients, who are largely symptomless, often fail to adhere to their treatment regimen. Because of this, the advantages of fixed ratio combination therapy have received considerable attention in recent years (Dollery, 1977) and a simple treatment regimen, which is effective in the majority of patients and has minimal unwanted effects, has obvious advantages.

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