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# Atenolol and bendrofluazide in hypertension

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## Summary

**The effect of atenolol, a new beta-1-adrenergic receptor blocking agent, was studied in a double-blind cross-over trial in 24 carefully selected hypertensive outpatients. After a four-week run-in period on matching placebo each patient received atenolol 200 mg/day, atenolol 400 mg/day, a combination of atenolol 200/mg day with bendrofluazide 5 mg/day, and bendrofluazide 5 mg/day alone, according to a random sequence.**

**Atenolol at either dose produced a significantly greater reduction in all blood pressure levels except standing systolic pressure than bendrofluazide alone. There was no statistically significant difference between the effects of the two atenolol doses on either blood pressure or pulse rate. The addition of bendrofluazide to atenolol resulted in a further significant lowering of the blood pressure. A significant effect of thiazide on weight was noted.**

**The study shows that atenolol, a cardioselective beta-blocker of similar potency to propranolol in animals but without membrane-stabilizing or partial agonist activity, is an effective and well-tolerated hypotensive agent.**


## Introduction

Atenolol (Tenormin, I.C.I. 66082) is a new cardioselective adrenoceptor beta-blocking agent of similar potency to propranolol in animals that lacks partial agonist activity and membrane stabilizing effects. We report here the findings of a study that was designed to compare the efficacy of atenolol, bendrofluazide, and combined treatment with atenolol and bendrofluazide in a carefully selected group of hypertensive outpatients.

## Patients and methods

### SELECTION OF PATIENTS

Patients, aged 21-65 years, referred for investigation of raised blood pressure were assessed in hospital after at least 14 days off any drug treatment. Patients were excluded if there was a history of recent myocardial infarction, evidence of cardiac failure, heart block, or gross ischaemia, grade III or IV retinopathy (Keith-Wagener), diabetes mellitus, gout, impaired liver function, creatinine clearance less than 60 ml/min, or if they were on any other drug treatment.

During a 36-48 hour hospital admission routine haematological, bacteriological, and biochemical investigations and chest *x*-ray examination, intravenous pyelography, and electrocardiography were performed. Lying and standing blood pressures were recorded every four hours. The observers in the trial (D.B.G. or J.C.P.) also measured the blood pressures with Hawksley random-zero sphygmomanometers on two separate occasions on the evening of admission (20.00-21.00 hours) and after a 10-hour overnight rest (08.00-09.00 hours). On both these occasions the number of 12 in steps required to produce an increment of standing pulse of 30 beats/minute was determined using electrocardiographic control. Patients were invited to participate in the trial if the morning lying diastolic pressures were over 90 mm Hg and under 105 mm Hg, and all other outpatient and ward blood pressures confirmed persistent readings above 90 mm Hg. The nature of the trial was explained and all suitable patients gave their consent.

Before discharge from hospital the patients were familiarized with a standard questionnaire about general health and the occurrence and severity of several symptoms. The methods of access to the doctors conducting the study were outlined.

### CONDUCT OF TRIAL

After discharge from hospital the patients were seen at the hypertension clinic within two weeks. The protocol excluded patients from further participation in the trial if the lying diastolic blood pressure fell below 90 mm Hg after a four-week outpatient run-in period on a matching placebo. After the run-in period a double-blind cross-over method was used to assess the effects on lying, standing, and post-exercise blood pressure of the following four treatments, each provided by two identical-looking tablets and given twice daily:

(*a*) Atenolol 100 mg; (*b*) atenolol 200 mg; (*c*) bendrofluazide 2·5 mg; (*d*) atenolol 100 mg and bendrofluazide 2·5 mg; each treatment was given for four weeks and each patient received the four treatments. Open pilot work had shown that no further hypotensive effect of atenolol occurred after two weeks, but we chose a four-week period to confirm this with a double-blind technique. The order of administration was determined by a random code which ensured that each of the 24 possible permutations of four treatments was given to one of the 24 patients. Thus each treatment period followed or preceded any other treatment period on six occasions. Two-week supplies of drugs were supplied to each patient in prepacked and paired containers.

The patients were seen every two weeks and the blood pressure of each patient was recorded using Hawksley random-zero sphygmomanometers under standard conditions at the same time of day by the same observer (D.B.G. or J.C.P.), except on a few occasions when a deputy substituted (J.W.). The mean of two or three blood pressure readings (same arm) after three to five minutes lying and two to three minutes standing was recorded. A single reading was taken after performance of the predetermined exercise load specified for each patient. The diastolic end point was taken as the phase-4 muffle. Between-observer comparisons of the blood pressure readings were made at intervals throughout the trial.

The observer not recording the blood pressure completed the questionnaire on symptoms in another room. Separate forms were


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TABLE I—*Mean Blood Pressure, Pulse Rate, and Weight (±S.E.) during Run-in Period and Treatment in 24 Patients*

| | Run-in | | | A. | | B. | | C. | | D. | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Visit 0 | Visit 1 | Visit 2 | 2 Weeks | 4 Weeks | 2 Weeks | 4 Weeks | 2 Weeks | 4 Weeks | 2 Weeks | 4 Weeks |
| *Blood Pressure (mm Hg)* | | | | | | | | | | | |
| Lying systolic | 171·4 (2·1) | 169·6 (2·1) | 169·8 (2·1) | 145·4 (2·5) | 146·3 (3·0) | 146·8 (2·5) | 145·0 (3·0) | 135·5 (2·5) | 136·5 (3·0) | 151·3 (2·5) | 159·6 (3·0) |
| Lying diastolic | 106·4 (1·4) | 107·5 (1·4) | 107·4 (1·4) | 89·5 (2·1) | 88·0 (1·7) | 92·1 (2·1) | 87·3 (1·7) | 84·9 (2·1) | 84·8 (1·7) | 97·3 (2·1) | 100·4 (1·7) |
| Standing systolic | 165·4 (2·6) | 163·9 (2·6) | 163·0 (2·6) | 142·6 (3·1) | 142·9 (2·5) | 144·9 (3·1) | 141·9 (2·5) | 123·7 (3·1) | 126·7 (2·5) | 144·9 (3·1) | 145·5 (2·5) |
| Standing diastolic | 112·0 (1·2) | 112·3 (1·2) | 111·8 (1·2) | 96·2 (1·9) | 96·7 (1·5) | 96·2 (1·9) | 95·2 (1·5) | 88·2 (1·9) | 91·8 (1·5) | 106·1 (1·9) | 107·4 (1·5) |
| Postexercise systolic | 176·0 (3·4) | 179·3 (3·4) | 178·8 (3·4) | 148·4 (3·2) | 154·4 (2·9) | 153·1 (3·2) | 148·5 (2·9) | 135·6 (3·2) | 137·7 (2·9) | 160·8 (3·2) | 163·9 (2·9) |
| Postexercise diastolic | 107·7 (1·8) | 105·3 (1·8) | 107·7 (1·8) | 93·5 (2·1) | 96·0 (1·7) | 96·3 (2·1) | 93·1 (1·7) | 87·7 (2·1) | 88·6 (1·7) | 101·3 (2·1) | 102·7 (1·7) |
| *Pulse Rate (beats/min)* | | | | | | | | | | | |
| Lying | 82·5 (1·4) | 78·6 (1·4) | 80·3 (1·4) | 63·7 (1·8) | 61·0 (1·6) | 62·5 (1·8) | 61·3 (1·6) | 62·5 (1·8) | 62·8 (1·6) | 82·6 (1·8) | 80·8 (1·7) |
| Standing | 91·6 (1·8) | 89·2 (1·8) | 91·7 (1·8) | 68·3 (2·0) | 63·2 (1·8) | 65·1 (2·0) | 63·9 (1·8) | 66·6 (2·0) | 65·9 (1·8) | 92·7 (2·0) | 91·3 (1·8) |
| Postexercise | 117·0 (2·1) | 117·3 (2·1) | 117·0 (2·1) | 82·9 (2·4) | 80·9 (2·5) | 80·4 (2·4) | 78·8 (2·5) | 82·2 (2·4) | 82·1 (2·5) | 119·5 (2·4) | 117·6 (2·5) |
| *Weight (Kg)* | | | | | | | | | | | |
| | 68·5 (0·1) | 68·0 (0·1) | 67·8 (0·1) | 68·1 (0·2) | 68·2 (0·2) | 68·2 (0·2) | 68·2 (0·2) | 67·3 (0·2) | 67·4 (0·2) | 67·3 (0·2) | 67·4 (0·2) |

A. = Atenolol 200 mg/d. B. = Atenolol 400 mg/d. C. = Atenolol 200 mg/d and bendrofluazide 5 mg/d. D. = Bendrofluazide 5 mg/d.

completed for every patient at each of the 11 visits. Questions covered volunteered information and included specific items about general wellbeing, dizziness, headache, energy, tiredness, mood, sleep, dreams, and bowel habit. At each visit blood samples were also taken for monitoring biochemical and haematological function. Tablet counts and weights were recorded.

All information was then analysed statistically with the help of a computer.

## Results

Twenty-four patients (12 men, 12 women) aged 31-64 years (mean 47 years) with a mean weight of 68·5 kg (51-94 kg) satisfied the selection criteria. No patient was excluded after the one-month run-in period on placebo. A complete set of results was available for each patient. There were no defaulters. Tablet counts were satisfactory throughout (>90%).

The run-in and treatment means (±S.E.) of blood pressure, pulse, and weight are shown in table I. The same results are expressed graphically in figs. 1, 2, and 3. Twenty-two of the patients achieved a lying diastolic blood pressure of under 90 mm Hg on the most effective treatment—combined therapy.

Overall tests of significance (F test) showed that highly significant differences existed between treatments in terms of their effects on blood pressure, pulse, and weight both after one fortnight of treatment and after one month of treatment (table II).

The results show that atenolol 200 mg/day was not significantly different in effect from atenolol 400 mg/day. After four weeks' treatment both regimens produced significantly greater reductions in all pressures except standing systolic blood pressure than bendrofluazide alone. The addition of bendrofluazide to the lower dose of atenolol produced a further significant lowering of blood pressure. The reduction in lying blood pressure obtained with combined treatment was 33/22 mm Hg from an initial level of 170/107 mm Hg.

All three treatment regimens containing atenolol had a highly significant effect on pulse rate when compared with thiazide alone (table I and fig. 2).

The statistical significance of the treatment effect on weight seemed to be due solely to the contrast between those regimens containing thiazide and those not containing thiazide, the former being associated with a statistically significant weight loss (table I and fig. 3).

Detailed analysis of the questionnaires on side effects showed that all treatments (including placebo) were associated with similar side effects. The patients felt just as well on treatment as they did while receiving placebo. No complaints relating to dry eyes, skin lesions, or sclerosing peritonitis were noted.

Detailed fortnightly liver function tests (alkaline phosphatase, aspartate aminotransferase, and bilirubin) showed few abnormalities. A small reduction in serum potassium was noted in a few patients while on bendrofluazide but other electrolytes were unaffected. Blood urea showed a tendency to rise slightly with treatment in most patients; with the most effective treatment (combined therapy) the mean values were just outside the laboratory normal range but not significantly so. Treatment seemed to have no adverse effects, on haemoglobin red cells, white cell and differential counts, or platelets.

## Discussion

Our results show that atenolol is an effective hypotensive agent at a dose of 200 mg/day. The hypotensive effect was well developed after two weeks of treatment. The addition of a thiazide diuretic resulted in a further significant lowering of blood pressure. There was no evidence of undue postural or

TABLE II—*Comparison of Treatments (P Values) after Two and Four Weeks of Treatment in 24 Patients*

| Comparison of Treatments* | Weeks | Lying | | | Standing | | | Post Exercise | | | Weight |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Systolic B.P. | Diastolic B.P. | Pulse | Systolic B.P. | Diastolic B.P. | Pulse | Systolic B.P. | Diastolic B.P. | Pulse | |
| A. *v.* B. | 2 | N.S. | N.S. | N.S. | N.S. | N.S. | N.S. | N.S. | N.S. | N.S. | N.S. |
| | 4 | N.S. | N.S. | N.S. | N.S. | N.S. | N.S. | N.S. | N.S. | N.S. | N.S. |
| A. *v.* C. | 2 | <·01 | N.S. | N.S. | <·01 | <·01 | N.S. | <·01 | N.S. | N.S. | <·01 |
| | 4 | <·05 | N.S. | N.S. | <·01 | <·05 | N.S. | <·01 | <·01 | N.S. | <·01 |
| B. *v.* C. | 2 | <·01 | <·05 | N.S. | <·01 | <·01 | N.S. | <·01 | <·01 | N.S. | <·01 |
| | 4 | N.S. | N.S. | N.S. | <·01 | N.S. | N.S. | <·01 | N.S. | N.S. | <·01 |
| A. *v.* D. | 2 | N.S. | <·05 | <·01 | N.S. | <·01 | <·01 | <·01 | <·05 | <·01 | <·05 |
| | 4 | <·01 | <·01 | <·01 | N.S. | <·01 | <·01 | <·05 | <·01 | <·01 | < 01 |
| B. *v.* D. | 2 | N.S. | N.S. | <·01 | N.S. | <·01 | <·01 | N.S. | N.S. | <·01 | <·01 |
| | 4 | <·01 | <·01 | <·01 | N.S. | <·01 | <·01 | <·01 | <·01 | <·01 | <·01 |
| C. *v.* D. | 2 | <·01 | <·01 | <·01 | <·01 | <·01 | <·01 | <·01 | <·01 | <·01 | N.S. |
| | 4 | <·01 | <·01 | <·01 | <·01 | <·01 | <·01 | <·01 | <·01 | <·01 | N.S. |

*See table I for key to treatments.
B.P. = Blood pressure. N.S. = Not significant.

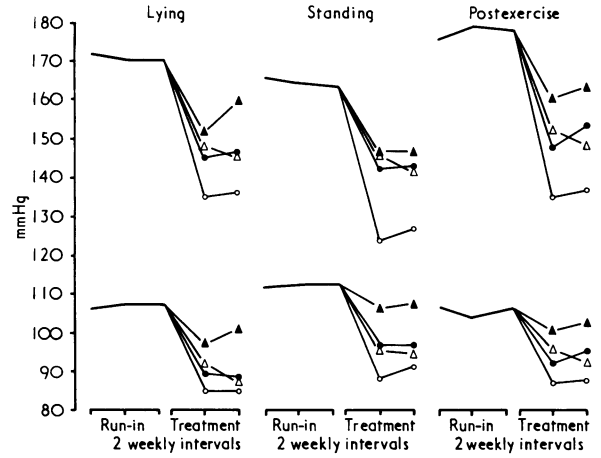


FIG. 1—Run-in and treatment means of blood pressure. ● = Atenolol 200 mg/d. △ = Atenolol 400 mg/d. ○ = Atenolol 200 mg/d and bendrofluazide 5 mg/d. ▲ = Bendrofluazide 5 mg/d.

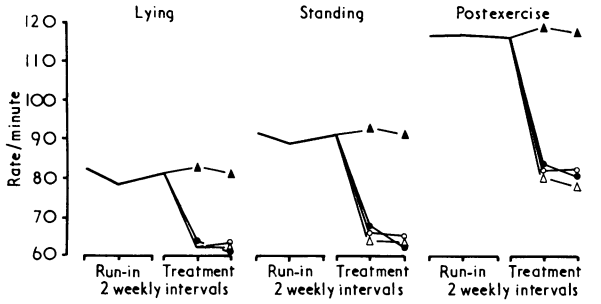


FIG. 2—Run-in and treatment means of pulse rate. See legend to fig. 1 for key to treatments.

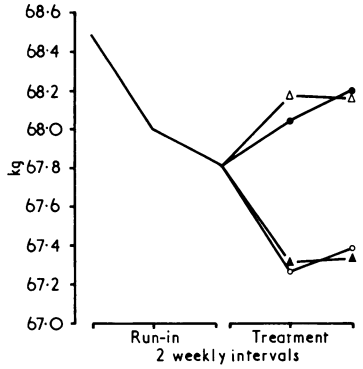


FIG. 3—Run-in and treatment means of weight. See legend to fig. 1 for key to treatments.

postexercise hypotension and all treatments were as well tolerated as placebo. The findings support the conclusions of a clinical evaluation and of a multicentre double-blind study without cross-over of atenolol.[12]

The double-blind cross-over within-patient design was chosen to allow each patient to act as his own control for the different drugs and doses. All 24 patients completed the five-month study, in which each of the treatments followed or preceded any other on six occasions. An elaboration of the balanced design to include "washout" periods between treatment periods would have been of additional value in attempting to reduce further any effects due to the order of administration of the treatments, though a further three months (seven visits) without treatment would have been required for each of the 24 hypertensive patients.

The dose of 200 mg/day of atenolol was chosen on the basis that near maximal blockade of cardiac beta-receptors, as measured by inhibition of exercise tachycardia, should occur.[3] A higher dose, 400 mg/day, was also included in the study as the relationship between cardiac beta-blockade and the antihypertensive effect of beta-blocking agents is not clear. Some investigators, using agents such as propranolol, have recommended doses greater than those needed for maximal beta-blockade.[4,5] It is of interest that doubling the dose of atenolol, a cardioselective agent without membrane-stabilizing effect or partial agonist activity, resulted in no further reduction in blood pressure.

The dose of bendrofluazide selected (5 mg/day) and the treatment period on combined beta-blocker and diuretic reflects current clinical practice. Some comparisons may also be attempted with our findings in a similar study of practolol and bendrofluazide.[6] Identical selection criteria and blood pressure measurement methods were used. Combined treatment with atenolol and bendrofluazide seems to reduce lying blood pressure (−33/22 mm Hg from 170/107 mm Hg) more than combined treatment with practolol and bendrofluazide (−28/13 mm Hg from 167/104 mm Hg).

There was no evidence of any influence of atenolol on the haematological or biochemical indices, with the exception of blood urea. Sporadic rises above normal were noted during active treatment periods, and during administration of the most effective treatment, atenolol 200 mg and bendrofluazide 5 mg, the mean blood urea levels just exceeded the upper limit of normal. Since effective treatment of hypertension with most drugs, including propranolol, may be associated with a slight reduction in renal function we do not think that this finding has any sinister significance.

The formulae of atenolol (4-(2-hydroxy-3-isopropylaminopropoxy) phenylacetamide) and practolol (4-(2-hydroxy-3-isopropylaminopropoxy) acetanilide) look similar but differ chemically in the side chain and in their theoretical metabolites. It is thought that the acetanilide side chain may cause the adverse effects on skin, eyes, or peritoneum that have been reported in association with practolol treatment. Similar effects have not been seen in treatment with atenolol, but long-term observation is required with this drug, as it is for all beta-blockers, until the aetiology of the practolol-induced reaction has been elucidated. Further studies on this new cardioselective beta-blocker are awaited with interest.

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