PAPERS AND ORIGINALS

Randomised study of six beta-blockers and a thiazide diuretic in essential hypertension

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Summary and conclusions

Atenolol was compared with five other beta-blockers and a thiazide diuretic in a randomised cross-over trial of once-daily treatment of essential hypertension. Atenolol was significantly better at reducing resting and exercise blood pressures at 24 hours than any of the other drugs and had a low incidence of side effects. Both timolol and acebutolol had a significant hypotensive effect at 24 hours and a low incidence of side effects, suggesting that further increases in dosage might be effective and well tolerated. Labetalol proved ineffective when given once daily, and the high incidence of side effects, equalled only by pindolol, would probably prohibit further increases in dosage. Bendrofluazide was equal or superior to all the beta-blockers except atenolol at reducing resting blood pressure, and its cheapness still makes it an agent of first choice in mild or moderate essential hypertension.

Introduction

Twelve beta-blockers are listed in *MIMS* for hypertension, and comparative studies are needed to determine any useful differences in effect. This is particularly relevant to once-daily treatment, where it is tempting to extrapolate data from one drug to another. Such studies, however, are hampered by trying to define equipotent doses for each agent, and until this is done the daily doses recommended by the manufacturers must be used.

I have compared the hypotensive effect of once-daily atenolol, for which there is good evidence of efficacy,[1 2] with five other beta-blockers—namely, acebutolol, labetalol, pindolol, propranolol, and timolol—and a thiazide diuretic. These beta-blockers offered various ancillary properties, such as cardioselectivity (atenolol), partial cardioselectivity (acebutolol), intrinsic sympathomimetic activity (acebutolol and pindolol), and membrane-stabilising activity (acebutolol, labetalol, propranolol, and pindolol). In addition, the effects of the alpha-blocking and beta-blocking properties of labetalol could be compared with those of the conventional beta-blockers.

The diuretic used is often regarded as the drug of first choice in hypertension; it is much cheaper than any available beta-blocker and has been used for years as a once-daily treatment of mild essential hypertension.

Patients and methods

Patients attending an outpatient clinic for uncomplicated essential hypertension gave informed consent to the trial.

At the first visit to the trial clinic any treatment was stopped, and the patients were seen again after two and four weeks. If the standing blood pressure exceeded 150/95 mm Hg at the end of this period the patients entered the trial and were seen every two weeks for the next 32 weeks. For the first four weeks they took placebo tablets, one daily for two weeks, then two tablets once daily for two weeks. This served as a run-in period, and thereafter they received in random order seven different drugs including another period on placebo. Each treatment period lasted four weeks, during which the drug was given in two doses, each for two weeks and beginning with the lower dose. All the drugs were prescribed on a once-daily basis. There were no wash-out periods between treatments. The trial was single-blind, the observer being unaware of which drug the patient was taking.

During the early stages of the trial I decided to add labetalol to the end of the randomised sequence. It was also given once daily in two different doses, each given for the same duration as the other drugs. To reduce bias during the labetalol period the order of doses was randomised.

The patients were asked to take the tablets between 0700 and 0800 but to omit the dose on the morning of each clinic visit. They were also asked to eat a standard breakfast before visits; otherwise no dietary restrictions were made. Each patient was seen at the same time every fortnight between 0830 and 1100.

Blood pressure and pulse rate were measured after resting supine for five minutes and standing for two minutes. The mean of two readings in each position was recorded. The patients then did a one-minute stepping exercise on to a 23-cm step as fast as they could

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manage. Pulse rate was recorded during the last 15 seconds of exercise and the standing blood pressure measured immediately on stopping. All blood pressures were measured by me with a Hawksley random zero sphygmomanometer, the diastolic blood pressure being taken as the point of disappearance of the Korotkoff sounds (phase V).

The patients were then asked if they wished to report any particular problems with the last treatment, but no check list or direct questions were used. Venous blood samples were then taken for measurement of serum cholesterol, triglyceride, urate, and plasma electrolyte concentrations and the patients collected their next treatment.

Drugs—The drugs used were acebutolol 200 and 400 mg; atenolol 100 and 200 mg; bendrofluazide 5 and 10 mg; labetalol 300 and 600 mg; pindolol 5 and 15 mg; propranolol 80 and 160 mg; and timolol 10 and 20 mg. When the protocol was written these doses were deemed to be clinically comparable as judged by the manufacturers' recommendations. The increments in bendrofluazide and atenolol were made to provide an identical pattern of dosage in each treatment period.

Statistical analysis was done by an analysis of variance for corrected means in the randomised study, comparing each drug against the randomised placebo, and by Student's *t* test for paired data for the labetalol-randomised placebo comparison. A P value less than 0·05 was taken as significant.

Results

Eighteen patients entered the trial and three withdrew, two because of the frequency of visits and one because of "a reaction" to his first treatment, which was placebo. Of the 15 patients who completed the trial, 13 were men and two women; their ages ranged from 24 to 62 years (mean 48), and the mean duration of known hypertension was four years. Previous treatment had been with a beta-blocker with or without a diuretic (seven patients), a diuretic only (two), and methyldopa (one); five were new patients previously untreated. Standing blood pressures at the end of the initial no-treatment period ranged from 152 to 200 mm Hg systolic and 98 to 137 mm Hg diastolic (mean ± SE of mean 173 ± 3/114 ± 2 mm Hg).

Table I shows the mean standing blood pressures and pulse rates at the end of the low-dose and high-dose treatment periods and the effect of exercise on these values at the end of the high-dose periods. The ranking and order of differences for lying blood pressures were closely similar. Although the exercise test was patient-controlled, the pulse rates achieved during the placebo run-in period (130 ± 3/min) and the two placebo randomised periods (129 ± 3/min, 128 ± 3/min) suggested a reasonable degree of consistency. None of the drugs abolished the rise in blood pressure and pulse rate produced by exercise, although the absolute levels achieved were often less in comparison with placebo.

Biochemical tests—All the beta-blockers, including labetalol, caused a small increase in serum potassium (0·2 to 0·3 mmol(mEq)/l) when compared with placebo (table II). This was not dose-related. Bendrofluazide, however, produced a decrease in potassium of 0·3 mmol/l ($P < 0·001$) when given in a dose of 5 mg/day, and 0·5 mmol/l ($P < 0·001$) when given in a dose of 10 mg/day. None of the beta-blockers at either dosage produced a significant change in urate concentrations, whereas bendrofluazide caused an increase of 60 μmol/l (10·2 μg/ml) at a dose of 5 mg/day ($P < 0·05$), and 87 μmol/l (14·8 μg/ml) at a dose of 10 mg/day ($P < 0·001$). None of the treatments had any significant effect on casual (non-fasting) concentrations of serum cholesterol or triglyceride. These two lipids remained remarkably constant in all patients during the trial, although no dietary instructions were given other than about breakfast on clinic days.

Side effects—Few side effects were reported, although there were twice as many with labetalol and pindolol as with any other drug. Seven patients complained of lethargy and nausea during the first few hours after taking labetalol, especially in the high-dose period. Five patients complained of lethargy and muscle tiredness when taking pindolol, and three reported insomnia during the high-dose period with this drug.

Discussion

Not all the drugs used here are recommended by the manufacturers for once-daily treatment of essential hypertension. The results, however, suggest that provided the dose is adequate several of them would be satisfactory on a once-a-day basis, particularly in view of the few side effects reported.

The interpretation of results in any comparative study of beta-blockers hinges on equipotency. To the pharmacologist this usually means the degree of inhibition of isoprenaline or exercise-induced tachycardia produced by the drug in comparison with propranolol. These two tests, however, may not provide comparable results for potency[3] and clearly cannot indicate the comparable doses needed to produce the same reduction in blood pressure or relief from angina pectoris. At best they may indicate approximately comparable beta-blocking doses, and with this reservation I consider that the doses used

TABLE I—*Standing blood pressures (BP) and pulse rates at end of low-dose and high-dose treatment periods and effect of exercise at end of high-dose treatment periods. Values are means ± SE of mean (15 patients)*

	Placebo period		Acebutolol		Atenolol		Bendrofluazide		Labetalol		Pindolol		Propranolol		Timolol	
	Low dose	High dose	200 mg	400 mg	100 mg	200 mg	5 mg	10 mg	300 mg	600 mg	5 mg	15 mg	80 mg	160 mg	10 mg	20 mg
Standing values at end of low-dose and high-dose periods																
BP (mm Hg):																
Systolic ..	170 ± 3	169 ± 3	164 ± 3	155 ± 3*¶	156 ± 3	148 ± 3¶	161 ± 3	154 ± 3*¶	167 ± 5	164 ± 5‡	160 ± 2	162 ± 3‡§	156 ± 2	154 ± 3*¶	161 ± 2	157 ± 3†
Diastolic ..	113 ± 2	113 ± 2	109 ± 2	105 ± 2*¶	103 ± 2	100 ± 2¶	111 ± 2	108 ± 2‡§	114 ± 3	111 ± 3‡	110 ± 2	110 ± 2‡	106 ± 2	107 ± 2†	110 ± 2	108 ± 2‡§
Pulse (beats/min)	87 ± 2	85 ± 2	82 ± 2	77 ± 2*‖	73 ± 2	71 ± 2¶	89 ± 2	90 ± 2‡	85 ± 3	83 ± 3‡	87 ± 2	86 ± 2‡	80 ± 2	74 ± 2¶	82 ± 2	77 ± 2*‖
Values after exercise at end of high-dose periods																
BP (mm Hg):																
Systolic ..		197 ± 4		183 ± 4†‖		178 ± 4¶		190 ± 4‡		181 ± 4*‖		183 ± 4*§		184 ± 4†§		187 ± 4†
Diastolic ..		101 ± 2		95 ± 2*§		90 ± 2¶		96 ± 2*		94 ± 4*§		99 ± 2‡		94 ± 2*§		96 ± 2*§
Pulse (beats/min)		128 ± 3		120 ± 3‡§		106 ± 3¶		131 ± 3‡		125 ± 5‡		121 ± 3‡		112 ± 3¶		112 ± 3¶

Versus atenolol: *$P < 0·05$; †$P < 0·01$; ‡$P < 0·001$.
Versus placebo: §$P < 0·05$; ‖$P < 0·01$; ¶$P < 0·001$.

TABLE II—*Mean biochemical values (± SE of mean) at end of high-dose treatment periods (15 patients)*

	Placebo	Acebutolol	Atenolol	Bendrofluazide	Labetalol	Pindolol	Propranolol	Timolol
Potassium (mmol/l)	4·1 ± 0·1	4·3 ± 0·1	4·3 ± 0·1	3·6* ± 0·1	4·5 ± 0·1	4·4 ± 0·1	4·3 ± 0·1	4·3 ± 0·1
Urate (μmol/l)	341 ± 15	355 ± 15	361 ± 14	428* ± 15	326 ± 21	382 ± 14	360 ± 15	362 ± 15
Cholesterol (mmol/l)	6·1 ± 0·2	5·7 ± 0·2	6·1 ± 0·2	6·1 ± 0·2	5·7 ± 0·3	5·7 ± 0·2	5·9 ± 0·2	5·8 ± 0·1
Triglyceride (mmol/l)	2·0 ± 0·2	2·0 ± 0·2	2·6 ± 0·2	2·2 ± 0·2	1·7 ± 0·1	2·0 ± 0·2	2·5 ± 0·2	2·4 ± 0·2

*$P < 0·001$ compared with placebo.
Conversion: SI to traditional units—Potassium: 1 mmol/l = 1 mEq/l. Urate: 1 μmol/l ≈ 0·17 μg/ml. Cholesterol: 1 mmol/l ≈ 38·7 mg/100 ml. Triglyceride: 1 mmol/l ≈ 88·6 mg/100 ml.

here were comparable,[3-5] with the exception of acebutolol, which was probably underestimated by some 25-50%.[6]

Owing to the design of this trial the effect of dose increments cannot be differentiated from a further period of exposure to the drugs, and this must be borne in mind when comparing the results. There was little to choose between atenolol and propranolol during the low-dose period, although in higher dosage atenolol was significantly better than all other drugs.

Pindolol proved disappointing in both its lack of hypotensive effectiveness and its high side-effect score, which might limit the use of higher doses. In an open study, however, Sedgwick and Crowder[7] reported a low incidence of side effects with doses of 5-15 mg given three times a day. Wilson *et al*,[8] who studied five patients, found that an average of 29 mg given once daily was as effective as the same amount given in divided doses. Two of their patients reported insomnia, which was abolished by taking the drug in the morning rather than at night. Pindolol has considerable intrinsic sympathomimetic activity, which was reflected in the high resting pulse rate recorded in my study.

My findings suggest that the theoretically useful combination of alpha-blockade and beta-blockade possessed by labetalol will not be competitive as a once-daily treatment. This is unfortunate, for we still lack a good peripheral vasodilator that acts for at least 24 hours and could complement a once-daily regimen of a beta-blocker with or without a diuretic. Labetalol also caused as many side effects as pindolol, both having nearly twice the side-effect score of the other drugs.

The reduction of exercise-induced peaks of blood pressure and heart rate is commonly cited as a major advantage of beta-blockers, but we do not know whether such peaks carry important risks. None of the drugs used here totally prevented significant increases in either heart rate or systolic blood pressure with exercise. Although the measurements were made at least 24 hours after the last dose of tablets, they raise the question whether it will ever be possible to inhibit such increments in blood pressure or heart rate for the whole 24-hour period after a single daily dose of a beta-blocker; and if not would it matter?

The hypotensive potential of bendrofluazide as a once-daily treatment compared with some of the beta-blockers was confirmed, and this drug is likely to remain an important contender as a first-line choice for mild and moderate essential hypertension, particularly in countries with limited budgets, since the beta-blockers are all much more expensive. The hypokalaemic and hyperuricaemic effects of bendrofluazide are rarely important.

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Need for beta-blockade in hypertension reduced with long-term minoxidil

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Summary and conclusions

Sequential changes in plasma renin activity and urinary aldosterone and noradrenaline were assessed in eight patients with severe hypertension after minoxidil had been added to their treatment. Doses of 2·5-27·5 (mean 12·5) mg/day reduced the mean blood pressure from 166/113±6/2 mm Hg to 124/88±4/2 mm Hg in one week. Plasma renin activity and urinary aldosterone and noradrenaline increased twofold to threefold initially but returned to baseline values within two to three weeks and remained unchanged during a mean follow-up of 5·1 months. Beta-blocking drugs were then withdrawn slowly in six patients without adverse effects, though blood pressure and heart rate increased in three patients, who required minimal doses of beta-blockers. Plasma renin activity and urinary aldosterone and noradrenaline did not change significantly after beta-blockade had been stopped. We conclude that the need for beta-blockade is greatly reduced with long-term minoxidil treatment and that it may be unnecessary in some patients.

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Introduction

Minoxidil[1] used in combination with beta-blocking agents has proved useful for treating hypertension resistant to other drugs.[2] It was more powerful than hydrallazine in patients already treated with diuretics and propranolol,[3] and was particularly useful in patients with hypertension and renal failure.[4] In most studies minoxidil increased plasma renin activity[1 2 5]—an effect that occurs with other vasodilator drugs.[6 7] These drugs also stimulate the secretion of catecholamines, which may oppose their antihypertensive effect[1 5] and explain why giving minoxidil without concomitant beta-blockade was unsuccessful.[1]