PAPERS AND ORIGINALS

Comparison of antihypertensive activity of beta-blocking drugs during chronic treatment

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Summary

The hypotensive activity of five beta-adrenoceptor antagonists with different ancillary pharmacological properties was compared in a randomised double-blind factorial trial in 25 untreated patients with stable, uncomplicated, essential hypertension. In doses that produced similar reductions in exercise tachycardia all drugs had similar blood-pressure lowering activity, greater on systolic than diastolic pressure and greatest during exercise. With the exception of vasodilator activity the possession of any particular combination of ancillary pharmacological properties did not significantly influence the specific antihypertensive activity of these compounds.

Introduction

Clinical acceptance of beta-adrenoceptor antagonists in the treatment of hypertension has led to a proliferation of compounds for which various theoretical advantages have been claimed without valid therapeutic confirmation. The study reported here was therefore designed to compare the antihypertensive activity of five beta-adrenoceptor antagonists with different ancillary pharmacological properties.

Methods

Twenty-five patients, including ten women with untreated, stable, uncomplicated, essential hypertension were studied; their average

age was 51 years (range 38-63 years) and average weight 72 kg (range 59-80 kg). At the end of the eight week run-in period, during which outpatient diagnostic investigations were undertaken, systolic and diastolic (phase 4) pressures measured standing at rest were 152-210 mm Hg and 106-139 mm Hg, respectively. All were in sinus rhythm. Electrocardiography (ECG) showed left ventricular hypertrophy in seven; the radiographic cardiothoracic ratio was under 55% in all. None had cardiac failure, renal insufficiency, or retinopathy. Studies were undertaken as part of the long-term treatment with these drugs. Informed consent was obtained from all patients^{1 2}; the study was approved by the hospital ethical committee.

DESIGN OF INVESTIGATION

As the study was particularly concerned with the comparative antihypertensive activity of different beta-adrenoceptor antagonists, six patients who showed no reduction in resting blood pressure after the highest dose of drug were replaced. The trial was organised on an outpatient basis. During the eight-week run-in period blood pressure was measured every week; at these times patients got used to walking on a treadmill at 1½-3 mph (2.4-4.8 kph) for two minutes (heart rate 100-115 beats/min), followed by two minutes at the same speed on an incline of 10-15° (heart-rate 130-145 beats/min).

Drugs were administered in similar capsules, each containing either propranolol 40 mg, oxprenolol 40 mg, practolol 100 mg, tolamolol 50 mg, metoprolol 50 mg, or placebo. These drugs were chosen for their different spectra of ancillary pharmacological properties (table 1). Comparative doses were selected on the basis of their similar attenuation of exercise tachycardia.³⁻⁵ The bioavailability of the capsules used was similar to that of tablets clinically available.

An initial dose-finding period was followed by a randomised cross-

TABLE 1—Ancillary pharmacological properties of beta-adrenoceptor antagonists

Drug	Relative cardio-selectivity	Intrinsic stimulating activity	Membrane stabilising effect	Single dose range (mg)
Propranolol	—	—	+	40-320
Oxprenolol	—	+	+	40-320
Practolol	+	+	—	100-800
Tolamolol*	+	—	—	50-400
Metoprolol	+	—	—	50-400

*Tolamolol also has weak intrinsic vasodilator activity.
+ = Present
— = Absent } symbols indicate qualitative properties.

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over factorial comparison. Patients were randomly allocated to treatment with one of the five drugs. Treatment was started with a dose of two capsules twice a day, which was doubled at monthly intervals until the standing diastolic pressure at rest was 100 mm Hg or less one hour after the morning dose, or a maximum of 16 capsules twice daily were being consumed; the final dose was continued unchanged for eight weeks to measure habituation. Patients on one drug then transferred to the same number of capsules of the other five drugs or placebo in random order every two months. Patients were reviewed every two weeks, and heart rate and blood-pressure were measured every month lying, standing, and at two levels of treadmill walking. Throughout the study measurements were made one hour after the morning dose of drug had been seen to be taken.

LABORATORY TECHNIQUES, MEASUREMENTS, AND STATISTICS

Precautions were taken to control factors that may have caused erroneous changes in blood pressure. Laboratory temperature was maintained at 20–22.2°C, patients were familiar with staff and procedure, studies were carried out not earlier than two hours after breakfast, and smoking was forbidden during the test period.

Heart rate and blood pressure were measured every minute. To ensure double-blind conditions the ECG was recorded for 10 seconds in each minute and counted only in the final analysis. Blood pressure was measured over the right brachial artery using a random-zero sphygmomanometer (Hawkesley-Gelman Ltd). Lying and standing measurements were made in triplicate; a single reading was taken at the end of each exercise period.

Changes in heart rate and blood pressure were evaluated by analysis of variance and the significance of results determined using a multiple range test.⁶ Probability of statistical significance of changes was accepted at the 5% level of confidence.

Results

Clinical observations—All studies were accomplished without untoward incident. No symptoms of hypotension related to posture or exercise occurred with any drug. At the end of the dose-finding period patients were taking the following doses (average and range): propranolol 540 (160–1280) mg/day, oxprenolol 580 (160–1280) mg/day, practolol 720 (400–1600) mg/day, tolamolol 480 (200–800) mg/day, and metoprolol 380 (100–800) mg/day. During the crossover study no abrupt increase in blood pressure was observed during the eight-week placebo period, and blood pressure never exceeded pretreatment values. No adverse effects of treatment with any drug were observed in any patient.

Blood pressure after eight weeks' treatment—During the placebo period changing from lying to standing was associated with a reduction in systolic ($P < 0.05$) and an increase in diastolic ($P < 0.05$) pressure in all subjects. Compared with measurements standing at rest, treadmill walking was associated with significant increases in systolic pressure (exercise 1 $P < 0.01$; exercise 2 $P < 0.001$) and significant decreases in diastolic pressure (exercise 1 $P < 0.05$; exercise 2 $P < 0.01$). Compared with values on placebo, all drugs produced similar reductions in systolic and diastolic pressures lying, standing at rest, and at both levels of exercise; all differences were statistically significant at the 99.9% level of confidence (fig 1; table II). Reduc-

FIG 1—Blood pressure lowering activity during sustained treatment with beta-adrenoceptor antagonists possessing different ancillary pharmacological properties compared in double-blind randomised crossover studying 25 patients with stable, uncomplicated, essential hypertension. Diagram shows blood pressures after eight weeks' treatment.

FIG 2—Effects on heart rate of same drugs in same patients as in fig 1. Diagram shows heart rates after eight weeks treatment.

tions were greater for systolic than diastolic pressure and greatest during the highest level of exertion. There were no significant differences between the blood-pressure lowering activities of the five drugs, with the exception of tolamolol: systolic ($P < 0.05$) and diastolic ($P < 0.01$) pressures were more reduced on standing after tolamolol than after any of the other five drugs.

Heart rate after eight weeks' treatment—Compared with values on placebo, all drugs reduced the heart rate lying, standing, and during both slow and fast walking; all differences were statistically significant at the 99.9% level of confidence (fig 2; table II). The reduction in heart rate was greater on propranolol and metoprolol than on the other three drugs lying ($P < 0.001$), standing ($P < 0.001$), and during slow walking ($P < 0.001$), but not at the highest level of exertion ($P > 0.05$). Differences between propranolol and metoprolol were not statistically significant.

TABLE II—Mean ($\pm$ SE of mean) blood pressure (BP; mm Hg) and heart rate (beats/min) measured one hour after morning dose after four and eight weeks of continuous treatment

Variable	Placebo		Propranolol		Practolol		Oxprenolol		Tolamolol		Metoprolol	
	4 weeks	8 weeks	4 weeks	8 weeks	4 weeks	8 weeks	4 weeks	8 weeks	4 weeks	8 weeks	4 weeks	8 weeks
Lying												
Systolic BP	171 $\pm$ 6	175 $\pm$ 5	151 $\pm$ 3	157 $\pm$ 4	157 $\pm$ 3	156 $\pm$ 4	149 $\pm$ 4	154 $\pm$ 4	152 $\pm$ 3	149 $\pm$ 4	143 $\pm$ 4	148 $\pm$ 4
Diastolic BP	110 $\pm$ 2	111 $\pm$ 2	98 $\pm$ 2	100 $\pm$ 2	100 $\pm$ 2	101 $\pm$ 2	98 $\pm$ 2	101 $\pm$ 2	94 $\pm$ 3	97 $\pm$ 3	93 $\pm$ 2	95 $\pm$ 1
Heart rate	77 $\pm$ 2	77 $\pm$ 2	61 $\pm$ 1	62 $\pm$ 1	66 $\pm$ 3	68 $\pm$ 2	67 $\pm$ 1	66 $\pm$ 2	69 $\pm$ 2	67 $\pm$ 1	62 $\pm$ 1	64 $\pm$ 3
Standing												
Systolic BP	169 $\pm$ 4	170 $\pm$ 3	145 $\pm$ 4	147 $\pm$ 4	144 $\pm$ 3	146 $\pm$ 4	145 $\pm$ 3	147 $\pm$ 4	137 $\pm$ 4	134 $\pm$ 3	139 $\pm$ 3	143 $\pm$ 3
Diastolic BP	113 $\pm$ 2	115 $\pm$ 2	98 $\pm$ 2	99 $\pm$ 2	99 $\pm$ 2	100 $\pm$ 2	99 $\pm$ 1	99 $\pm$ 2	91 $\pm$ 3	94 $\pm$ 3	95 $\pm$ 2	99 $\pm$ 1
Heart rate	83 $\pm$ 2	84 $\pm$ 2	63 $\pm$ 2	64 $\pm$ 2	71 $\pm$ 3	72 $\pm$ 2	71 $\pm$ 1	70 $\pm$ 2	74 $\pm$ 2	72 $\pm$ 2	64 $\pm$ 2	66 $\pm$ 3
Exercise 1												
Systolic BP	178 $\pm$ 5	181 $\pm$ 4	151 $\pm$ 3	152 $\pm$ 4	152 $\pm$ 3	151 $\pm$ 3	150 $\pm$ 3	153 $\pm$ 4	146 $\pm$ 4	147 $\pm$ 4	145 $\pm$ 3	150 $\pm$ 4
Diastolic BP	105 $\pm$ 3	109 $\pm$ 2	94 $\pm$ 2	96 $\pm$ 2	94 $\pm$ 2	96 $\pm$ 2	93 $\pm$ 2	95 $\pm$ 2	85 $\pm$ 3	92 $\pm$ 3	92 $\pm$ 2	96 $\pm$ 1
Heart rate	105 $\pm$ 2	107 $\pm$ 2	80 $\pm$ 3	79 $\pm$ 2	87 $\pm$ 2	87 $\pm$ 2	87 $\pm$ 1	86 $\pm$ 2	86 $\pm$ 2	87 $\pm$ 2	83 $\pm$ 3	86 $\pm$ 2
Exercise 2												
Systolic BP	186 $\pm$ 4	198 $\pm$ 4	153 $\pm$ 4	150 $\pm$ 4	156 $\pm$ 2	154 $\pm$ 3	149 $\pm$ 5	152 $\pm$ 5	147 $\pm$ 4	150 $\pm$ 4	150 $\pm$ 3	154 $\pm$ 4
Diastolic BP	100 $\pm$ 2	105 $\pm$ 2	89 $\pm$ 2	89 $\pm$ 2	93 $\pm$ 2	92 $\pm$ 2	91 $\pm$ 2	90 $\pm$ 2	87 $\pm$ 3	89 $\pm$ 3	89 $\pm$ 2	91 $\pm$ 2
Heart rate	134 $\pm$ 2	136 $\pm$ 2	97 $\pm$ 3	96 $\pm$ 3	99 $\pm$ 2	101 $\pm$ 2	98 $\pm$ 3	99 $\pm$ 2	99 $\pm$ 2	98 $\pm$ 2	97 $\pm$ 2	98 $\pm$ 3

Habituation to continuous treatment—There was no further reduction in heart rate or blood pressure at rest or during exercise with any drug after eight weeks compared with the results after four weeks' treatment (table II).

Specificity of antihypertensive activity—After transfer to placebo heart rate and blood pressure returned to the pretreatment range in all patients within four weeks. There was no significant change in either variable during the subsequent four weeks with the exception of the systolic pressure at the highest level of exertion ($P < 0.05$) (table II).

Discussion

These studies clarify some of the debate that has arisen about the comparative antihypertensive effectiveness of different beta-adrenoceptor antagonists. During sustained treatment, in doses which produced comparable reductions in exercise tachycardia, all drugs had similar specific blood-pressure lowering activity, greater on systolic than on diastolic pressure, greatest during exercise, and unassociated with habituation.

Therapeutic benefits and disadvantages have been claimed for some of the ancillary pharmacological properties of these drugs. Our studies indicate that such properties are of little importance in relation to their blood-pressure lowering activity in hypertensive patients. Although intrinsic stimulating effects on heart rate were observed with oxprenolol, practolol, and tolamolol, these drugs were equal in antihypertensive effectiveness to those without this property. Cardioreslectivity (practolol and metoprolol) likewise did not seem to enhance blood-pressure lowering activity. Tolamolol possesses weak vasodilator activity,⁷ which probably accounted for the postural drop in blood pressure on this drug compared with the lack of such effect with drugs without this property. Nevertheless, this augmented blood-pressure lowering activity on standing did not persist during walking. Hence the antihypertensive activity of all these drugs is predominantly related to their common property of blockade of cardiac sympathetic beta-adrenoceptors, and their ancillary pharmacological properties, with the possible exception of intrinsic vasodilator activity, play little part in this response. These observations confirm other less comprehensive comparisons.^{8,9}

Our results also give information on prescribing. The reduction in blood pressure was directly related to the dose of beta-blocking drug—that is, the higher the dose the greater the reduction in blood pressure. A similar dose-response relation-

ship was also observed when these drugs were first administered to hypertensive patients.¹⁰ In our study the final dose of each drug was arbitrarily fixed at the dose which induced a reduction in standing diastolic pressure to 100 mm Hg or at a maximum of 16 capsules twice daily. Given these dosage end-points the final comparative doses were relatively narrow, ranging from 5–7 mg/kg body weight (with the exception of practolol, 10 mg/kg).

A point of possible therapeutic importance was that these drugs had a greater hypotensive effect on systolic than on diastolic pressure and the greatest effect was during exertion. Direct correlation between the height of the systolic pressure and morbidity and mortality from cardiovascular events is now firmly established.¹¹ The relation is even closer if exercise and other daily events are taken into account,¹² and there are feasible biological links to establish a cause-effect relationship between these correlates.¹³ Lowering of resting pressure and the suppression of the pressor response to exercise may therefore be important in preventing vascular complications during long-term treatment of hypertension with these drugs. This, together with the protection of the myocardium from sympathetic stimulation, may be an important therapeutic advantage possessed by these drugs over other antihypertensive agents in preventing the cardiac consequences of hypertensive vascular disease.

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References

- 1 Medical Research Council Annual Report, *British Medical Journal*, 1963, 2, 178.
- 2 Ormrod, R, *British Medical Journal*, 1968, 2, 7.
- 3 Thadani, U, *et al*, *British Medical Journal*, 1973, 1, 138.
- 4 Taylor, S H, *et al*, *International Journal of Clinical Pharmacology*, 1974, 10, 136.
- 5 Davidson, C, *et al*, *Circulation*, in press.
- 6 Duncan, D B, *Biometrics*, 1955, 11, 1.
- 7 Taylor, S H, Singleton, W, and McGibney, D, in preparation.
- 8 Leishman, A W D, *et al*, *British Medical Journal*, 1970, 4, 342.
- 9 Morgan, T O, *et al*, *Postgraduate Medical Journal*, 1974, 50, 253.
- 10 Singleton, W, *et al*, *Clinical Science and Molecular Medicine*, 1975, 48, 18.
- 11 Kannel, W B, and Dawber, T B, *British Journal of Hospital Practice*, 1974, 11, 508.
- 12 Sokolow, M, *et al*, *Circulation*, 1966, 34, 279.
- 13 Taylor, S H, in *Hypertension—Its Nature and Treatment*, ed D M Burley, *et al*. Horsham, Ciba Laboratory Publications, 1975.

Blood pressure survey in a population of newborn infants

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Summary

Systolic blood pressure in the arm was measured in infants at the ages of 4 to 6 days and 5 to 7 weeks by the

Doppler ultrasound technique. At the age of 4 to 6 days the mean blood pressure ($\pm$ SE of mean) in 469 sleeping infants was 70.7 ± 0.3 mm Hg, rising at 5 to 7 weeks to 89.7 ± 0.9 mm Hg (in 144 infants). In 252 infants awake at 5 to 7 weeks blood pressure was 96.8 ± 0.6 mm Hg. In 391 infants in whom measurements were made on both occasions blood pressure at 4 to 6 days was significantly related to blood pressure at 5 to 7 weeks. Thus those infants with relatively high blood pressures at 4 to 6 days showed a weak tendency to have relatively high blood pressures at 5 to 7 weeks. If this trend continues with age it would suggest that the tendency to develop hypertension may already be demonstrable at the age of 4 to 6 days.

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