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A DOUBLE-BLIND CROSSOVER COMPARISON OF PINDOLOL, METOPROLOL, ATENOLOL AND LABETALOL IN MILD TO MODERATE HYPERTENSION

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1 This study was designed to compare in a double-blind randomized crossover trial, atenolol, labetalol, metoprolol and pindolol.

Considerable differences in dose (atenolol 138 ± 13 mg daily; labetalol 308 ± 34 mg daily; metoprolol 234 ± 22 mg daily; and pindolol 24 ± 2 mg daily were required to produce similar antihypertensive effects.

3 The overall incidence of side-effects was similar with atenolol, metoprolol and pindolol but was slightly less with labetalol. Sleep disturbances and abnormal dreaming patterns were most frequent with pindolol.

4 There was a significantly greater fall in pulse rate during atenolol and metoprolol treatment periods.

Introduction

SINCE the first description of the antihypertensive properties of propranolol (Prichard & Gillam, 1964), β-adrenoceptor-blocking drugs have found wide acceptance in the management of hypertension (Zacharias, 1971; Morgan *et al.*, 1974). A large number of these compounds are now marketed with alterations in side-chain structure and ring substitution, modifying such properties as bioavailability, affinity for receptors, intrinsic sympathomimetic activity, and lipid solubility (Clarke, 1976). The clinical significance of these ancillary pharmocological properties has been the subject of much recent interest (Davidson *et al.*, 1976; Louis *et al.*, 1977; McNeil *et al.*, 1979).

In this study we report the results of a double-blind crossover trial comparing four agents which contrast in several of these characteristics. Pindolol is a non-specific β-adrenoceptor-blocking drug posessing a relatively high level of intrinsic sympathomimetic activity (Morgan *et al.*, 1972; Atterhog *et al.*, 1976). Metoprolol and atenolol are cardioselective agents which do not possess intrinsic sympathomimetic activity, and labetalol is a non-selective β-adrenoceptor-blocking drug without intrinsic sympathomimetic activity which in addition has α-blocking properties.

Methods

Thirty-one outpatients (10 males, 21 females, aged 33–72 yr, mean 52 y) attending the Austin Hospital Hypertension Clinic were studied. Patients with a past history of asthma, cardiac failure, heart block, diabetes, severe peripheral vascular disease, recent myocardial infarction, abnormal renal or hepatic function, or a resting pulse rate below 55 beats/min were excluded. Four patients had renal artery stenosis and in the remainder secondary forms of hypertension had been excluded by previous investigation. All had received treatment with a diuretic and a β-adrenoceptor-blocking agent for at least 3 months before the commencement of the study and were known to respond to this treatment regime.

The trial was a double-blind randomized crossover study, the design of which is shown in Table 1. For the first week of the study a placebo was given in place of the β-blocking drug. During the subsequent 10 weeks either metoprolol (50, 100, 150 or 200 mg twice daily) or pindolol (5, 10, 15 or 20 mg twice daily) were prescribed. By arrangement with the Pharmacy Department patients received one drug in the active form and the other as a placebo in a randomized sequence to achieve double-blind conditions. In addition, the diuretic cyclopenthiazide was prescribed for all patients throughout the study.

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Visits were arranged at the 2, 6 and 10 week stage of each 10 week sequence: during the first 6 weeks of each period the dosage of each drug was adjusted to bring lying and standing diastolic BPs to 90 mmHg or below. The dosage was reduced if lying and standing diastolic BPs fell below 75 mmHg or symptoms of hypotension developed.

The first 10 week period on active drug was followed by another 1 week wash-out period and a further 10 weeks, during which time the patient was carried over and the alternative preparation was given in the active form.

Following the first two active drug periods, two patients moved away from the area and were unable to continue in the study. The remaining 26 patients were again randomized into an identical double-blind crossover study comparing atenolol and labetalol.

In this study the doses of atenolol were 50, 100 and 150 mg twice daily and the doses of labetalol 100, 200 and 400 mg twice daily. BPs were measured by a single observer using a 'Bonn' automatic sphygmomanometer after 10 min supine rest and again after 2 min standing. Phase IV of the Korotkoff sounds was used to identify the diastolic BP. The pulse was measured immediately after the BP while the patient remained lying. Further recordings of pulse rate and Bp were made immediately after completion of ten brisk steps on to a 24 cm platform.

Side-effects and their severity were documented at each consultation using a check-list. Before commencement of the study (at the end of the first placebo period) and again during the final week of each treatment period, each patient underwent a number of investigations including pulmonary function measurement, electrocardiography, full blood examination, coagulation profile, Coombs, antinuclear factor and plasma biochemical screening.

Statistical comparison of blood pressures and pulse rates were made using the Student's t test for paired observations and analysis of variance. P values larger than 0.05 were considered not significant.

Results

Twenty-nine patients completed the first half of the trial. Two patients defaulted, one after developing incapacitating palpitations soon after crossing over on to pindolol at a dose of 20 mg twice daily. Another developed angina while on metoprolol. The 26 patients who entered the second half of the study all completed this part of the study.

Table 2 summarizes mean BP, pulse and drug dosage data during placebo, pindolol, metoprolol, atenolol and labetalol treatments. Supine, standing and post-exercise systolic and diastolic BPs were always lower with β-blockade than during the preceding placebo periods. However, no statistical differences in BPs were found when the various treatment periods were compared by analysis of variance (Table 2).

Mean daily dose of pindolol required to produce the antihypertensive effect was 24 $\pm$ 2 mg, metoprolol 234 $\pm$ 22 mg, atenolol 138 $\pm$ 13 mg and labetalol 308 $\pm$ 34 mg. Metoprolol and atenolol treatment produced a mean fall in supine pulse rate of 18 $\pm$ 2 and 15 $\pm$ 2 beats/min, respectively; both were significantly greater ($P < 0.05$) than the pulse rate after pindolol and labetalol (10 $\pm$ 2 and 11 $\pm$ 2 beats/min, respectively). All drugs except labetalol were equally effective in inhibiting the increase in pulse rate induced by exercise (Table 2). Five patients had pulse rates less than 55 beats/min during metoprolol treatment compared with one patient on pindolol, eight on atenolol and none on labetalol. In one of the patients metoprolol was discontinued because of severe postural dizziness when her pulse rate fell to 43 beats/min on a dose of metoprolol 50 mg twice daily. These symptoms resolved quickly when the drug was stopped; they did not occur with pindolol but recurred on atenolol. Altogether two patients ceased the atenolol part of the trial because of pulse rates of less than 50 beats/min and did not develop bradycardia on labetalol (Table 3).

Table 1 Flow chart of trial comparing non-selective and selective β-blocking drugs

Weeks		0 1 3 7 11	12 14 18 22	23 25 29 33	34 36 40 44
Consultation		X X X X X	X X X X	X X X X	X X X X
Chest X-ray		X			
Laboratory tests		X X	X	X	X
Therapy	PL	A / B	PL	PL C / D	PL

A, Metoprolol; B, pindolol; C, atenolol; D, labetalol; PL, placebo.

There was little difference in the pattern of other side-effects between the four active treatment periods, except that labetalol treatment seemed to be associated with a lesser overall burden of side-effects than the other drugs; and sleep disturbances and abnormal dreaming were common with pindolol. All drugs were well tolerated by most patients (Table 4).

Mean values in laboratory studies were statistically similar at the end of each treatment period. Parameters of pulmonary function were unchanged from the initial data taken after 1 week of placebo therapy. No abnormalities were noted in biochemical or haematological screening.

Discussion

We have previously reported a crossover study in which the antihypertensive efficacy of two non-selective β-adrenoceptor-blocking drugs without

Table 2 Comparison of pindolol, metoprolol, atenolol and labetalol after 10 weeks

	Pindolol		*Metoprolol*		*Atenolol*		*Labetalol*	
	Placebo	*Active*	*Placebo*	*Active*	*Placebo*	*Active*	*Placebo*	*Active*
Supine BP S	157 ± 4	141 ± 3	155 ± 5	136 ± 3	145 ± 4	137 ± 4	146 ± 3	137 ± 3
(mmHg) D	99 ± 2	87 ± 2	99 ± 2	88 ± 1	91 ± 2	83 ± 2	92 ± 2	85 ± 2
Standing BP S	148 ± 4	131 ± 3	145 ± 4	130 ± 3	140 ± 5	123 ± 4	141 ± 3	128 ± 4
(mmHg) D	97 ± 2	88 ± 2	99 ± 3	87 ± 2	94 ± 2	84 ± 2	96 ± 2	86 ± 2
Supine pulse (beats/min)	84 ± 2	74 ± 2	81 ± 3	63 ± 1	77 ± 3	62 ± 2	80 ± 2	69 ± 2
Pulse Increase with exercise (beats/min)	21 ± 2	13 ± 1	20 ± 2	13 ± 1	20 ± 3	13 ± 2	22 ± 3	18 ± 2
Dose (mg daily)	24 ± 2		234 ± 22		138 ± 13		308 ± 34	

S, Systolic; D, diastolic.

Table 3 Incidence of bradycardia in the individual study period

	Prindolol	*Metoprolol*	*Atenolol*	*Labetalol*
Pulse rate <50 beats/min drug discontinued	—	1	2	—
Pulse rate <55 beats/min, inadequate control	—	1	—	—
Pulse rate <55 beats/min, but adequate control	1	3	6	—
Total	1	5	8	—
No. of patients	29	29	26	26

Table 4 Incidence of side-effects in individual study period

	Pindolol	*Metoprolol*	*Atenolol*	*Labetalol*	*Total*
Lack of energy	9	10	8	6	33
Nausea	3	2	3	2	10
Insomnia	9	6	4	3	22
Abnormal dreaming	9	4	5	2	20
Diminished libido	2	2	1	1	6
Palpitations	2	2	2	2	8
Dry mouth	4	7	6	6	23
Indigestion	3	2	—	—	5
Rash	2	3	6	3	14
Wheezing	2	3	3	1	9
Cold extremities	3	6	5	4	18
Eye discomfort	3	6	6	1	16
Depression	2	3	2	4	11
Blocked nose	3	2	5	3	13
Total	56	58	56	38	208
Number of patients	29	29	26	26	

intrinsic sympathomimetic activity (propranolol and timolol) were compared with two others with intrinsic sympathomimetic activity (pindolol and alprenolol) (Morgan *et al.*, 1974). In this study all four drugs were equally effective in lowering BP provided that adequate doses were used. There were differences, however, in the patterns of side-effects. The drugs with sympathomimetic activity seemed to have a lower incidence of bradycardia and cause less interference with bronchodilator drive.

The present study compares pindolol, metoprolol, atenolol and labetalol using a twice daily regimen. As in the previous study, two of the drugs without intrinsic sympathomemetic activity (metoprolol and atenolol) produced appreciably slower pulse rates than pindolol, a non-selective β-blocking drug with intrinsic sympathomimetic activity. The incidence of bradycardia during the study (five patients during metoprolol treatment and eight patients during atenolol treatment had pulse rates less than 55 beats/min) suggests that the recommended dose of atenolol and metoprolol may be too high and our experience with atenolol in open studies supports the use of doses of 50 mg daily in many patients.

This degree of bradycardia was not seen with labetalol, a drug which also lacks intrinsic sympathomimetic activity. It is not certain whether the lack of bradycardia with labetalol reflects its associated α-blocking properties or perhaps more importantly its weaker pA_2 for the β-adrenoceptor (Drummer *et al.*, 1979). This low affinity for the β-adrenoceptor suggests that labetalol is more easily displaced from adrenoreceptors by endogenous release of catecholamines. Thus, for equal antihypertensive effect labetalol produced a smaller reduction in exercise-induced tachycardia than the other three β-blocking drugs. Its antihypertensive effectiveness in association with a lower incidence of side-effects, when used in a twice daily dosage, indicates a possible useful role in the treatment of mild hypertensives for β-blocking drugs with lower affinities for β-adrenoreceptors whether or not they in addition have α-blocking properties.

The major theoretical advantage of cardiac selectivity is a reduction of extracardiac side-effects. Abnormally vivid dreaming and insomnia appeared more common with pindolol. Three patients developed wheezing while taking metoprolol and atenolol, two while taking pindolol and one on labetalol. There was no other differences in their effects on lung function. Patients with a past history of active lung disease and peripheral vascular disease were excluded, but despite this some patients developed wheezing and cold hands and feet with the cardiac selective as well as the non-selective drugs. It has been suggested that when asthma occurs during treatment with cardioselective β-blocking drugs it is more easily reversed with selective agonists such as salbutamol and terbutaline (Horvath *et al.*, 1978). This protocol did not allow examination of this proposition.

In the group of patients as a whole there were no obvious advantages of cardioselectivity, and the high incidence of bradycardia suggests the need for care in their use and the need for cardioselective compounds with at least some degree of intrinsic sympathomimetic activity.

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