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A CONTROLLED TRIAL OF LABETALOL (TRANDATE), PROPRANOLOL AND PLACEBO IN THE MANAGEMENT OF MILD TO MODERATE HYPERTENSION

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1 Labetalol, a new drug combining α- and β-adrenoceptor blocking properties, has been compared with placebo in a double-blind crossover study of a group of patients with mild to moderate essential hypertension (blood pressure 150/100 to 189/114 mmHg).

2 Labetalol and propranolol lowered blood pressure satisfactorily in the supine position, but labetalol reduced blood pressure more in the erect posture and following exercise and induced less bradycardia. Thus α- as well as β-adrenoceptor blocking actions appear to contribute to blood pressure reduction.

3 Side effects attributable to labetalol were few. The effective dose ratio labetalol : propranolol was 2.5:1 (w/w).

4 Labetalol, a new form of hypotensive agent, merits further controlled assessment of its usefulness in relation to existing drugs.

Introduction

Labetalol (Trandate, Allen & Hanbury's) is a new hypotensive drug which acts as a competitive antagonist at α- and β-adrenoceptor sites in man and animals (Farmer, Kennedy, Levy & Marshall, 1972; Boakes, Knight & Prichard, 1971; Collier, Dawnay, Nachev & Robinson, 1972; Brittain & Levy, 1976).

The drug lowers blood pressure both in normal subjects (Richards, Woodings, Stephens & Maconochie, 1974), and (in open studies) in some patients with severe hypertension, resistant to alternative therapy (Prichard, Thompson, Boakes & Joekes, 1975; Dargie, Dollery & Daniel, 1976).

We report here the findings of a double-blind crossover trial in which labetalol was compared with propranolol and placebo in the management of a group of patients with mild to moderate hypertension.

Methods

Previously untreated patients who had been referred to the Hypertension Clinic at the Radcliffe Infirmary, were recruited to the trial if their outpatient blood pressure readings fell within the range 150/100 to 189/114 mmHg (diastolic pressure = 4th phase) after three successive visits during a period of 2.5 weeks. Patients with accelerated hypertension, diabetes mellitus, obstructive airways disease and cardiac, hepatic or renal failure were excluded. All subjects entering the trial gave their informed consent.

Blood pressures were measured by a trained assistant using a London School of Hygiene sphygmomanometer. Supine blood pressure was measured after 5 min at rest, and the standing pressure after 2 min in the erect posture. During the trial blood pressure was also measured after a standard period of exercise.

The trial was double-blind, and patients were assigned to 10 week treatment periods in which they received labetalol, propranolol and placebo in a pre-arranged random sequence.

The starting daily doses of labetalol and propranolol were 75 mg and 30 mg respectively, given in three divided doses. Drug dosage was increased at weekly intervals to a maximum of 2,400 mg/day labetalol or 960 mg propranolol daily, or until the standing blood pressure fell below 130/86 mmHg, the heart rate to less than 48 beats/min, or until intolerable side effects occurred. In this way a patient could achieve maximum dosage after 6 weeks treatment. Labetalol, propranolol and placebo were prepared in identical capsules.

At each weekly visit to the clinic, blood pressures

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and heart rates were recorded and patients completed a side effects questionnaire.

The investigations carried out before treatment, and at the midpoint and end of each treatment period were: haemoglobin; packed cell volume; white cell count; platelet count; erythrocyte sedimentation rate; blood urea; serum creatinine; sodium; potassium; chloride; bicarbonate; calcium; phosphate; alkaline phosphatase; glutamic oxalic transaminase; lactic dehydrogenase; protein; albumen; urate; cholesterol; random blood sugar; mid stream urine analysis. Circulating anti-nuclear factor, LE cell examination, direct Coomb's test and electrocardiography were examined at the outset and the end of each treatment period. A chest X-ray, intravenous pyelogram and 24 h urinary vanillyl mandelic acid estimation were obtained before starting treatment.

Comparisons of blood pressures and heart rates were made between the three treatments on the basis of average values for the second to fourth, fifth to seventh and eighth to tenth weeks, after excluding readings taken during the first week. Group mean values were obtained for each of the three periods and compared by analysis of variance. Side effects during active treatment were analysed after 'subtraction' of symptoms recorded both prior to starting treatment and during the period of placebo therapy.

Results

Patient data

Eleven patients completed the trial. Three others developed severe hypertension during the first treatment period (identified as placebo therapy) and were transferred to a study of labetalol in the management of severe hypertension. A further three patients were unable to attend the clinic regularly.

The mean age of patients completing the trial was 49 years (range 23 to 57 years). Six were female. The diagnosis in each case was essential hypertension.

Blood pressures

Figure 1 shows blood pressure values in the erect and supine positions and following exercise. Each point represents the group mean systolic or diastolic pressure for consecutive 3 week periods, excluding the first week of each treatment period. Both drugs lowered blood pressure. The greatest falls in pressure are seen during the first month of treatment, but a continuing fall, most clearly seen in the erect and post-exercise readings, is evident during treatment with labetalol. Statistical analysis of the differences between groups is shown in Table 1.

The ability of labetalol, propranolol and placebo to lower individual blood pressures to the level of control

Table 1 Mean blood pressures for the eleven subjects during the trial

		Pre-Trial	Weeks 2–4			Weeks 5–7			Weeks 8–10		
			Propranolol	*Labetalol*	*Placebo*	*Propranolol*	*Labetalol*	*Placebo*	*Propranolol*	*Labetalol*	*Placebo*
Systolic Blood pressure	Supine	166.8	146.2	143.6 (1)	153.0	141.7	138.7 (1)	148.9	138.3	136.5 (1)	146.0
	Standing	169.4	142.8	137.7	148.0	137.3	134.1 (2)	147.9	137.8	126.7 (3.5)	145.9
	Exercise	169.4	144.7 (1)	141.2 (2)	159.4	137.4 (1)	132.2 (3)	150.2	135.4 (3)	124.1 (3.4)	153.2
Diastolic Blood pressure	Supine	94.2	84.1	86.3	88.8	82.7 (2)	80.9 (3)	88.9	79.4 (2)	77.8 (3)	86.6
	Standing	103	88.7	89.4	94.6	88.3 (1)	84.2 (3)	95.5	86.6 (3)	80.1 (3.4)	97.4
	Exercise	103	86.9 (1)	86.0 (1)	93.1	83.0 (3)	81.0 (3)	92.7	81.3 (3)	77.7 (3)	94.3

(1) Significantly less than placebo mean $0.05 > P > 0.02$; (2) as (1) but $0.02 > P > 0.01$, (3) as (1) but $0.01 > P$.
(4) Significantly less than propranolol mean $0.05 > P > 0.02$; (5) as (4) except $0.02 > P > 0.01$

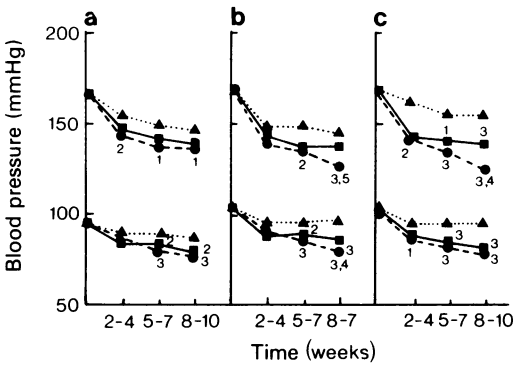

Figure 1 Group mean systolic and diastolic pressures for 2nd–4th, 5th–7th and 8th–10thweek of labetalol (●), propranolol (■) and placebo (▲) treatment according to (a) supine and (b) erect posture, and (c) following exercise.

(1) Significantly less than placebo mean value $0.05 > P > 0.02$; (2) as (1) but $0.02 > P > 0.01$; (3) as (1) except $0.01 > P$. (4) Significantly less than propranolol mean value $0.05 > P > 0.02$; (5) as (4) except $0.02 > P > 0.01$.

defined in the protocol (130/85 mmHg standing blood pressure), is illustrated in figures 11a and 11b using methods described by Dixon & Johnson (1976). The decrement in pressure during the final 3 weeks of treatment is plotted against the pretreatment standing pressure. The line represents the theoretical achievement of 'target' control for any initial blood pressure readings. Points lying on or to the left of the line represent a statisfactory response to treatment.

Viewed in this, labetalol achieved control of blood pressures in a higher proportion of patients than did propranolol. Both drugs did better than placebo.

Dosage

The final mean dose of labetalol was 1,180 mg/day (range 75 to 2,400 mg). The corresponding figure for propranolol was 480 mg/day (range 30 to 960 mg). The ratio of labetalol:propranolol was 2.45:1 (initial ratio 2.5:1). Dose ratios for individual patients ranged from 0.63 to 20.1.

Heart rate

Figure 3 depicts the mean heart rates for each treatment in the supine and erect positions and following exercise. Progressive slowing of the rate was evident throughout the trial and in the case of labetalol and propranolol. The group average rate during propranolol treatment was always slower than that due to labetalol, but these differences only achieved significance in the erect posture of following exercise.

Table 2 Side effects of therapy. To obtain the figures shown pre-treatment symptoms have been subtracted from those elicited in the symptom questionnaire during the first and last 3 weeks of each treatment period. The figures within brackets were obtained by further subtraction of symptoms present during periods of placebo therapy in the same patient.

	Weeks 1–3			*Weeks 7–10*		
	Labetalol	*Propranolol*	*Placebo*	*Labetalol*	*Propranolol*	*Placebo*
Faintness on standing			1			
Faintness on exertion	1 (0)		2		1 (1)	
Ankle swelling						
Drowsiness						1
Headaches	2 (0)		2			
Stuffy nose				1 (1)		
Difficulty in breathing	3 (0)	3(0)	3	3 (1)	1 (0)	2
Sweating		1 (0)	1	2(0)	1 (0)	2
Flushes						
Cold hands and feet		2 (2)			2 (2)	
Palpitations			1			
Depression						
Weakness	1 (0)		1		3 (3)	
Dreaming				2 (2)		
Skin rash						
Loss of sexual desire						
Failure of ejaculation				2 (2)	1 (1)	
Tiredness (loss of energy)	1 (0)	4 (1)	3	2 (2)		
Diarrhoea	1 (1)	1 (1)			1 (1)	
Nausea			1		2 (2)	
Constipation						
Totals	9(1)	11 (4)	15	12 (9)	12 (9)	5

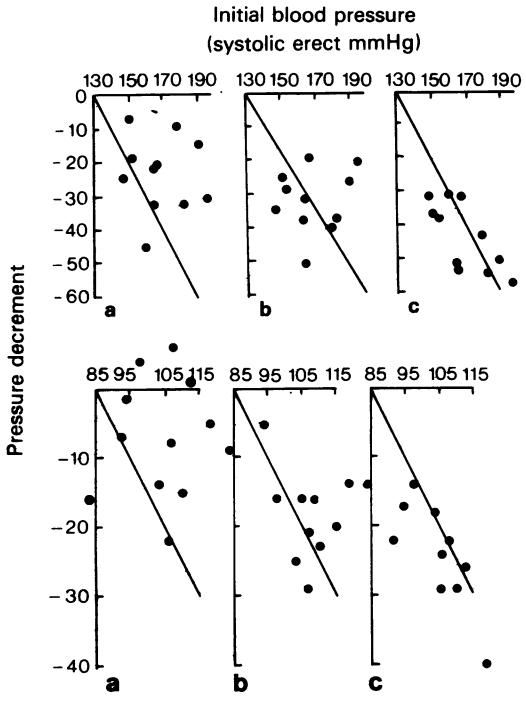

Figure 2 Upper trace: The fall in standing systolic pressure at the end of each treatment period (a) placebo; (b) propranolol; (c) labetalol) is plotted against initial standing systolic pressure. Points lying on or to the left of the line with slope unity represent achievement of the degree of control of blood pressure sought. (Standing systolic—130 mmHg.)

Lower trace: The fall in standing diastolic blood pressure at the end of each treatment period (a) placebo; (b) propranolol; (c) labetalol) is plotted against initial standing diastolic pressure. (Target standing diastolic pressure—85 mmHg.)

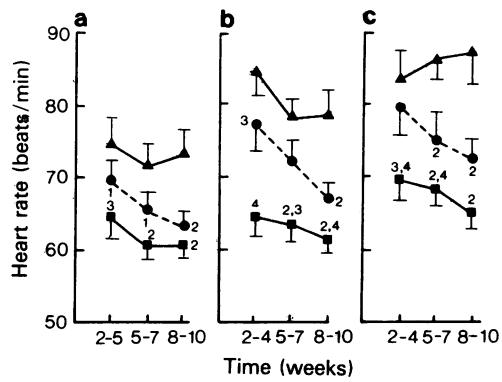

Figure 3 Group mean ± s.e. mean heart rates for labetalol (●), propranolol (■) and placebo (▲) at the 2–4, 5–7 and 8–10 weeks of each treatment period (a) supine; (b) erect; (c) post-exercise).

(1) Significantly less than placebo mean $0.05 > P > 0.02$; (2) as (1) but $0.01 > P$; (3) significantly less than labetalol mean $0.02 > P > 0.01$; (4) as (3) except $0.01 > P$.

Side effects

Pre-existing symptoms, identified by administering the questionnaire to patients before the start of treatment, were 'subtracted' from the symptoms elicited during the first and last 3 week period of exposure to the three different treatments. It was thus possible to estimate the number of early symptoms due to the drugs, and those which either developed later, or persisted throughout the treatment period. These data, and a further figure arrived at by subtracting the symptoms attributable to placebo therapy are shown in Table 2.

Fewer symptoms were attributable to both labetalol and propranolol than to placebo during the early treatment period. This trend was reversed during the last 3 weeks, but side effects due to labetalol did not occur in greater numbers than those attributable to propranolol. Modifications in therapy were not necessary as a result of side effects.

Two patients complained of difficulty with ejaculation while receiving labetalol and one volunteered postural dizziness when the dose was raised on the basis of supine pressure reading. Two patients receiving propranolol displayed Raynaud's phenomen and two had mild gastrointestinal disturbances. The three patients who complained of difficulties in breathing showed no evidence of pulmonary oedema, nor reduction in peak flow rate.

Investigations

There were no abnormalities detected in the bacteriological, immunological or biochemical investigations. Chest X-rays and ECG's showed no changes during the course of treatment. There were no differences in the white cell and platelet counts.

The average ± s.e. mean haemoglobin values (g/100 ml) at the end of each treatment period were: labetalol 12.65 ± 0.42; propranolol 13.95 ± 0.53; placebo 13.7 ± 0.42. The value for labetalol was significantly lower than both for propranolol ($P < 0.01$) and placebo ($P < 0.001$) (paired t-test).

Order of drug treatment

Labetalol was given as the first treatment on five occasions and the last (third) treatment on three occasions. Propranolol and placebo were given as the first treatment three times. Placebo was the last treatment on five occasions. On three occasions when placebo was received either as second or third course of treatment, blood pressure fell substantially. On the other hand, in three further similar instances, blood pressure remained elevated during placebo therapy.

Discussion

The results of this study show that labetalol controls the blood pressure in mild to moderate hypertension as effectively as propranolol in a dose ratio of 2.5 : 1 (w/w).

The dose response curve for labetalol was steeper than that for propranolol, in the case of standing and post-exercise blood pressure values. This trend is presumably a property of the alpha adrenoceptor blocking component of labetalol. Such differences in the behaviour of the two drugs were noted in the preliminary report of a concurrent trial (Pugsley, Armstrong, Nassim & Beilin, 1976) and the failure of increasing doses of β-receptor blocking agents to induce commensurate falls in blood pressure has been noted elsewhere (Petrie, 1976).

The importance of including a period of placebo treatment in this type of trial is emphasised by the fall in blood pressure observed during such treatment over and above that seen in the initial drug-free run-in period. On the other hand, if the patients whose blood pressure was so uncontrolled on placebo therapy, that they had to be withdrawn from the trial, had been included, it seems likely that there would have been no average fall of blood pressure during the period of placebo therapy.

The fact the labetalol was given as the first of three treatments in a majority of instances, and placebo as the last on a similar number of occasions, if anything, biases the results against labetalol, particularly as a 'wash-out' period was not included in the trial.

Labetalol induced a significantly greater effect on the blood pressure than propranolol in the standing position and following exercise. Although heart rates during labetalol treatment were slower than during placebo therapy, they were significantly quicker than with propranolol treatment, except in the supine position. Taken together, these facts suggest that peripheral α-receptor blockade contributed importantly to the hypotensive effect of labetalol, and in some patients spared the bradycardia due to β-adrenoceptor blockade exhibited alone. Abnormal dreaming in two patients on labetalol suggests this drug also penetrates the brain.

The intolerable side effects observed in an earlier study of the management of hypertension using the α-adrenoceptor blocker phenyoxybenzamine and propranolol in a fixed doxe combination (Beilin & Juel-Jensen, 1972), were not observed on this occasion. The slight excess of patients complaining of cold extremities with propranolol was probably due to more dominant α-receptor activity without the compensatory α-receptor blockade of labetalol.

The total number of side effects attributable to labetalol were small and none prevented an increase in dosage.

It is difficult to identify the cause for the lower haemoglobin value observed following labetalol therapy. The Coombs' tests were negative but depression of red cell precursors in the marrow could not be excluded. Fluid retention is unlikely in that there was no total gain in weight and no fall in plasma albumen, nor sodium concentration. An alternative explanation might be that there was a shift of fluid from the extra-vascular to the intra-vascular compartment. Support for this suggestion comes from the observations that the dose ratio of labetalol to propranolol (2.5 : 1) was higher than that required for effective lowering of the blood pressure in a controlled trial of labetalol and propranolol in the management of severe hypertension (Pugsley *et al.*, 1976) (1.6 : 1). In that trial a diuretic (Moduretic—Merck, Sharp & Dohme) was employed as adjunct therapy and no difference in haemoglobin values was seen. Other workers (D. Richards, personal communication) have shown a definite increase in the total blood volume following 3 months treatment with labetalol.

The precise role of labetalol in anti-hypertensive therapy remains to be established. Potential advantages are increased effectiveness in some cases resistant to pure beta blockade, less bradycardia and less Raynaud's phenomenon. Against this may be set an increased postural hypotension, nasal stuffiness and perhaps, difficulties in ejaculation, which are likely to be features of the α-adrenoceptor blocking actions of this drug in some patients.

We have reported elsewhere (Pugsley *et al.*, 1976), an instance of a positive ANF test developing in a patient taking labetalol. In the light of experience with practolol, the possibility of this and other allergic reactions should be monitored carefully in patients receiving the drug as long-term therapy.

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Reprint requests to Dr D.J. Pugsley.

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