A COMPARATIVE TRIAL OF CLONIDINE, PROPRANOLOL AND PLACEBO IN THE TREATMENT OF MODERATE HYPERTENSION

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- 1 A double-blind cross over trial between clonidine, propranolol and a placebo in patients with moderate hypertension has been performed.
- 2 Thirty-two patients completed the study which consisted of three treatment periods in random order of 3 months each. Patients had their blood pressure recorded by an unbiased observer using a random-zero machine.
- 3 Both clonidine and propranolol produced a significant reduction in blood pressure ($P < 0.01$), which was apparent by the second week of therapy. Propranolol gave a greater reduction in pulse rate than clonidine ($P < 0.01$) but clonidine also reduced the pulse rate significantly ($P < 0.05$). There was no evidence of postural hypotension on either drug. Side-effects were more common with clonidine but these tended to wear off after several weeks of therapy.
- 4 Clonidine and propranolol were equipotent in reducing blood pressure, but clonidine has more initial side-effects than propranolol.

Introduction

Clonidine, an imidazoline derivative, has been shown to have a useful place in the therapy of all grades of hypertension (Davidov, Kakaviatos & Finnerly, 1967; Smet, Hobler, Sanbar & Julius, 1969; Raftos, 1969; MacDougal, Addis, Mackay, Dymock, Turpie, Ballingall, MacLennan, Whiting & MacArthur, 1970).

Clonidine appears to act both on the peripheral vasculature, making the smooth muscle less responsive to sympathetic stimulation (Zaimis & Hanington, 1969), and on the central nervous system. The central effects are thought to be due to an agonist action on noradrenaline receptors in the brain (Dollery & Reid, 1973).

Whilst it has a marked hypotensive action in both short and long-term administration (Reubi, Vorburger & Butikloler, 1969), the place of this drug in the spectrum of anti-hypertensive agents is not clear because there have been few trials comparing clonidine with other commonly used hypotensive agents (Kellet & Hamilton, 1970; Becker-Christenson, Bang & Ditzel, 1971). We have therefore performed a double-blind cross-over study comparing clonidine, propranolol and a placebo in the treatment of moderate hypertension.

Methods

Thirty-five patients who were referred by their general practitioners to a hypertension clinic were selected for the study by the following criteria:

1. Age 25-70 years.
2. Resting supine diastolic pressure between 105-129 mm Hg on at least three separate occasions over a period of one month.
3. Previously untreated or unsatisfactory control on other medication.
4. Informed consent.

Patients excluded were those with malignant hypertension, renal failure, obstructive airways disease, heart failure, peripheral vascular disease and those with myocardial infarction in the previous year. At each clinic visit the blood pressure was taken by a trained observer using a Hawksley random-zero sphygmomanometer. The diastolic pressure was taken at Korotkow phase 4 (muffling) and the blood pressure was measured after lying supine for 2 min, standing for 1 min, and after exercise for 1 min on an 8-inch two-step block. The pulse rate was also taken, and the patient weighed.

If hypotensive drugs that were not controlling the blood pressure satisfactorily were being taken,

these were stopped and the patients were seen again after 2 weeks.

All patients who satisfied the entry requirements were admitted for a 5-day period of investigation to exclude secondary hypertension. These investigations included blood urea and electrolytes, 12-lead electrocardiogram (at rest and after exercise), chest X-ray, midstream urine for microscopy and culture, 24 h urine for vanillyl mandelic acid determination and isotope renography.

Trial design

Patients were seen in the hypertension clinic where their blood pressure, pulse rate and weight were measured as described. They were then allocated randomly to a sequence of clonidine, propranolol and a placebo by a 'blind' observer.

Drug dosage for the first 2 weeks was as follows:

clonidine 50 µg three times a day for 1 week then 100 µg three times a day;
propranolol 40 mg three times a day for 1 week then 80 mg three times a day;
placebo one tablet three times a day for 1 week, then two tablets three times a day.

The patients were reviewed after 2 weeks and the number of tablets adjusted according to the level of blood pressure and the presence of side effects. Symptoms were assessed by a questionnaire at the start of the trial and at the end of each treatment period, and by an open question at each visit. Symptoms were graded from 1-3 (1 = mild symptoms of nuisance value only; 2 = moderate symptoms interfering with the patient's life; 3 = severe symptoms leading to the doctor or the patient stopping treatment).

Follow-up visits were at 2, 4, 8 and 12 weeks after the start of therapy, with a 2-week washout period. Each patient crossed over to each of the three treatment periods. Treatment was terminated if the patient complained of intolerable side-effects, or the diastolic pressure rose above 129 mm Hg. At the end of each treatment period the following investigations were performed:

1. Blood urea and electrolytes.
2. Chest X-ray.
3. Electrocardiogram.

At each clinic visit, a tablet count was performed on the returned bottles.

Results

Of the thirty-five patients entering the trial, three dropped out; one because he left the country, one

because of an acute lumbar disc lesion which required an operation and a third after poor attendance at the clinic. Of the thirty-two patients completing the study, seventeen were male and fifteen were female. Their median age was 54 years (range 37-66). The median known duration of hypertension at presentation was 2 years (range 1 week-20 years). Twelve of the patients had not received prior antihypertensive treatment, whereas twenty had received other agents (including α -methyldopa, oxprenolol, bethanidine, guanethidine and thiazides).

Seven patients had electrocardiographic evidence of left ventricular hypertrophy and two patients showed a left bundle branch block pattern. All but one of the patients had a diagnosis of essential hypertension made by exclusion. This patient had had radiation therapy to his left loin as a child for a skin tumour, and the left kidney was seen to be contracted on an intravenous pyelogram.

Blood pressure

In assessing the results, means and standard deviations for the whole group were calculated from the final clinic blood pressures at the end of each period of active treatment. These were compared with the mean blood-pressure at the end of the placebo period (Table 1; Figure 1). Both clonidine and propranolol produced a significant reduction in blood pressure ($P < 0.01$), compared with placebo, but there was no significant difference between the effects of the active drugs.

The fall in blood pressure appeared to take place mainly in the first 2 weeks of therapy after which, in spite of increasing drug dosage, there was no further significant change in the group mean pressures.

In most patients it was not considered necessary to increase the dose of active drug after the second week, but eleven patients during the propranolol period had their dose increased at each visit, and seven patients on clonidine likewise. Figure 2 emphasizes the point that the fall in diastolic pressure was mainly in the first 2 weeks with these patients and shows that at one point when the clonidine dose was increased, the diastolic pressure showed a temporary rise. There was no significant postural or exercise hypotension during either clonidine or propranolol treatment.

Thirteen of the patients achieved a supine diastolic pressure of less than 95 mm Hg on clonidine, whilst nineteen patients achieved a supine diastolic pressure of less than 100 mm Hg; with propranolol the numbers were thirteen and eighteen respectively. There were eight patients in whom the diastolic pressure could not be reduced

Figure 1 Group means $\pm$ s.d. of supine systolic and diastolic blood pressures at each clinic visit. Note that the effects of active treatment are fully apparent at the 2-week visit. $\bullet$ placebo; $\blacksquare$ clonidine; $\circ$ propranolol.

below 105 mm Hg with either propranolol or clonidine, but all these patients had diastolic pressures above 115 mm Hg at the start of their treatment periods.

Four patients on placebo developed a diastolic pressure greater than 129 mm Hg and were changed to active therapy. Five patients had a diastolic pressure of 100 mm Hg or less after thirteen weeks on placebo, despite their diastolic blood pressure being greater than 105 mm Hg on at least three separate occasions before admission to the trial.

Pulse rate

Clonidine (Table 1) reduced the resting pulse rate significantly compared with placebo ($P < 0.05$) as did propranolol ($P < 0.01$) which gave a significantly greater reduction than clonidine ($P < 0.01$). Eight patients on propranolol (40 mg three times a day) and two patients on clonidine (50 μ g three

Figure 2 Mean $\pm$ s.d. of group diastolic blood pressures in those patients in whom the dose of active drug therapy had to be increased during the trial period. There was little change in the pressures after the first clinic visit despite steady increases in the dosage of drug. $\blacksquare$ clonidine, $n = 7$; $\circ$ propranolol, $n = 11$.

times a day) developed a bradycardia of less than 50 beats/min. During treatment with propranolol one patient developed a pulse rate of 44 beats/min, and although he remained asymptomatic, it was felt advisable to stop the drug.

Drug dosage

Drug dosage was increased over each 3 month period in the group as a whole (Table 2). As might be expected, those patients with high initial blood pressures required higher dosages of the two active agents.

Of interest are five patients who at some time

Table 1 Mean $\pm$ s.d. ($n = 32$) supine resting blood pressure and pulse rates during treatment with clonidine, propranolol and placebo

	Clonidine			Propranolol			Placebo		
	Blood pressure (mm Hg)			Blood pressure (mm Hg)			Blood pressure (mm Hg)		
	Systolic	Diastolic	Pulse (beats/min)	Systolic	Diastolic	Pulse (beats/min)	Systolic	Diastolic	Pulse (beats/min)
Pre-treatment	185 $\pm$ 25	116 $\pm$ 12	81 $\pm$ 12	190 $\pm$ 20	116 $\pm$ 10	80 $\pm$ 10	189 $\pm$ 22	115 $\pm$ 10	86 $\pm$ 15
Week 2	167 $\pm$ 27	101 $\pm$ 11	73 $\pm$ 12	171 $\pm$ 29	103 $\pm$ 14	65 $\pm$ 8	181 $\pm$ 23	112 $\pm$ 12	83 $\pm$ 15
Week 4	167 $\pm$ 23	102 $\pm$ 11	74 $\pm$ 10	170 $\pm$ 18	101 $\pm$ 12	67 $\pm$ 9	184 $\pm$ 22	114 $\pm$ 12	83 $\pm$ 13
Week 8	173 $\pm$ 28	104 $\pm$ 12	75 $\pm$ 12	166 $\pm$ 29	101 $\pm$ 12	67 $\pm$ 9	188 $\pm$ 22	113 $\pm$ 11	81 $\pm$ 14
Week 12	167 $\pm$ 23	101 $\pm$ 12	74 $\pm$ 12	168 $\pm$ 29	101 $\pm$ 12	66 $\pm$ 8	185 $\pm$ 24	114 $\pm$ 11	80 $\pm$ 11

during the active treatment period experienced a rise in blood pressure after the dose of either clonidine or propranolol had been increased. This was a temporary rise in all but one patient and after a further dose increase the blood pressure fell.

Side effects

Side effects (Table 3) were initially commoner with clonidine than propranolol. The dry mouth that many patients developed with clonidine showed a tendency to decrease after several weeks of therapy and patients could then tolerate higher doses. Drowsiness and dry mouth were noted at some time by two-thirds of the patients whilst on clonidine, the drowsiness being described as a feeling of tiredness coupled with a tendency to drop off to sleep during the day. Three patients found that the drowsiness during the day made it difficult for them to sleep at night and two patients found the drowsiness intolerable, although they were on the lowest dose level (150 µg/day). Three patients complained of cold extremities.

Propranolol gave rise to few initial side effects, but more appeared as the dose was increased. Drowsiness was noted by one-third of the patients and one patient found this severe enough to warrant stopping the drug. Nine patients complained of gastrointestinal symptoms, these being mainly diarrhoea and abdominal pains. Two patients found these side effects intolerable and the drug had to be stopped. Six patients complained of coldness of the hands and feet whilst on propranolol and eight patients noted vague musculoskeletal aches.

Of interest was the smaller number of patients complaining of headache with propranolol, and particularly with clonidine. Two patients with regular migraine noted immediate relief of symptoms on starting clonidine, and one patient found some relief with propranolol although this was only after several weeks of therapy.

Weight and biochemical data

There was no significant weight change during any of the treatment periods, nor was any change noted in blood urea and electrolytes, chest X-ray or ECG.

Table 2 Mean and range of group doses of drug at each clinic visit

Drug	Weeks of treatment			
	2	4	8	12
Clonidine (µg)	270 (150-300)	360 (150-900)	460 (150-1200)	540 (150-1500)
Propranolol (mg)	224 (120-240)	372 (120-480)	476 (120-960)	576 (120-1200)
Placebo (tablets)	6 (3-9)	5.8 (3-9)	6.2 (3-12)	6 (3-12)

Table 3 Number of patients volunteering specific symptoms at each clinic visit

Symptoms	Weeks of treatment											
	Clonidine				Propranolol				Placebo			
	2	4	8	12	2	4	8	12	2	4	8	12
Dry mouth	11	10	9	8	1		1					
Diarrhoea					1	4	2	1				1
Constipation	3	2	2								1	
Drowsiness	11	13	15	6	3	6	3	8	5	3	2	3
Headache	2	3	2		4	5	2	1	6	4	5	2
Dizziness			1	1	1		1	4	1	1		4
Muscle aches	3	5	2		2		4	2	1	1	2	
Reduced libido			1					1				
Cold extremities		2		3	2		2	2				

Discussion

With the growing awareness of the large number of hypertensives in the community, the search for more acceptable and efficacious therapy continues. Propranolol has been shown to be both effective and relatively free from side effects in the treatment of hypertension (Zacharias, Cowen, Prest, Vickers & Wall, 1972) and is therefore a useful standard against which to compare other drugs.

Conolly, Briant, George & Dollery (1972) found that clonidine was effective in lowering blood pressure but that its side effects were similar in character and more frequent than those associated with α -methyldopa. Mroczek, Liebel & Finnerty (1972) felt that clonidine and α -methyldopa were equivalent in their hypotensive effect and in the frequency of side effects, whilst Becker-Christenson *et al.* (1971) found that α -methyldopa gave more side effects.

We have shown clonidine to have a similar hypotensive effect to propranolol in treating patients with moderate hypertension but without producing the same degree of bradycardia. Most of the hypotensive effect appeared in the first two weeks of therapy, and it seems that a judgement can be made at this stage as to whether it is worthwhile continuing either medication. Neither drug caused postural or exercise hypotension. Side effects were commoner with clonidine, but some tolerance to these developed after several weeks of treatment. We were able to confirm the previously described effect of clonidine in alleviating the

symptoms of migraine (Wall & Wilkinson, 1973).

One of the problems associated with clonidine is the rapid rise in blood pressure following cessation of therapy. Several patients at the end of their clonidine period were studied in detail with intra-arterial blood pressure recording during withdrawal and the results have been reported elsewhere (Goldberg, Wilkinson & Raftery, 1976). Of the remaining patients, two complained of an immediate recurrence of migraine and four developed headaches which persisted for about 24 h. We feel that patients should be advised not to stop clonidine suddenly, and withdrawal from therapy should be made under medical supervision.

The use of propranolol is restricted to patients without cardiac failure, obstructive airways disease or peripheral arterial disease, and potentially dangerous situations may arise if these restrictions are ignored (Boston Collaborative Programme, 1973). Clonidine however, can be given to patients with all grades of hypertension, no matter what other coincidental disease processes they may have. We feel that clonidine compares favourably with propranolol on its hypotensive effect but the higher incidence of side effects associated with clonidine will restrict its use. A starting dose of 50 μ g three times a day is suitable, the dose being increased at weekly intervals until control is achieved or side effects become a problem.

This work was supported by a generous grant from Boehringer Ingelheim Ltd.

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(Received June 20, 1976)