

obtained in the final 14 days of each 21-day period. The patients' own general assessment of each treatment is based upon the whole 21-day periods and scored on a five-point scale in the following way: -1 worsening of the angina; +1, +2, and +3 indicating slight, moderate, and marked improvement respectively; and 0 showing that the condition had remained unchanged when compared with that before the start of the trial. The results are summarized in Tables I and II.

TABLE II.—*Summarized Results and Statistical Analysis of Trial*

Criterion	Propranolol	Placebo	Difference	t-Value
Days pain free .. { mean range	4.40 0-14	3.55 0-14	0.85 ± 1.08 -11 - +10	0.8 NS
No. of attacks .. { mean range	35.5 0-300	43.3 0-350	-7.8 ± 4.4 -50 - +31	1.74 0.1 > P > 0.05 NS 0.5 NS
TNT tablets .. { mean range	26.3 0-89	29.1 0-129	-2.8 ± 5.4 -41 - +62	
Average No. of days { better same worse	9.1 3.7 1.3	7.5 5.1 1.5		
Patients' general assessments of angina	+1.35	+0.75	+0.60 ± 0.37	1.61 P > 0.1 NS

* Based upon the following five-point scale for the full 21-day periods: Worse = -1, No change = 0, Slight improvement = +1, Moderate improvement = +2, Marked improvement = +3.

± Figures indicate standard errors based on within-patient comparisons.

NS = Not statistically significant.

Values not statistically significant but near the 5% or 10% level of significance are indicated as P > 0.05 and P > 0.1 respectively.

Discussion

It will be seen from Table II that, by all the criteria used, the trial failed to show any statistically significant difference between the drug and the placebo, although the reduction in the number of anginal attacks approached a 5% level of significance in favour of the drug. The patients' own general assessments showed a similar trend. Indeed, if the seven patients who failed to detect any difference between the drug and the placebo are excluded, the analysis reveals that 11 favoured the drug and only two the placebo.

The number of attacks of angina in the 14-day records varied considerably from patient to patient, and Table I shows that

those patients with the largest number of attacks (Nos. 3, 4, 16, and 20, all of whom had more than 50 attacks per 14-day period) derived no benefit at all. These were all cases with angina of long standing, and it is possible that such cases are particularly resistant to this therapy.

Propranolol appears to cause fewer side-effects than pronethalol, and when they occur they respond easily to a reduction in the dose. Whether better results could be obtained with higher doses of propranolol has not been explored in this trial, but the limiting factor in dosage is likely to be not so much toxicity as the tendency of beta-adrenergic blocking compounds to induce circulatory failure by excessive weakening of the force of contraction of heart muscle. Further observations on safe dosage are probably still needed.

It is concluded that the drug is of some value in the treatment of angina except perhaps in chronic severe cases, and a more extended trial would be fully justified.

Summary

A double-blind trial has been carried out with propranolol (I.C.I. 45520, Inderal) on 20 patients suffering from angina of effort. Although favourable results in this small series did not achieve statistical significance, they showed sufficient promise to justify a more extended trial. Symptomatic side-effects were few and transient, and no toxic effects on the urine, blood count, or liver-function were noted.

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Use of Propranolol (Inderal) in Treatment of Hypertension

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Pronethalol has a hypotensive action in man when given orally over a period of three months, though no effect was seen after acute intravenous injection. In addition, short-term administration in a double-blind trial of pronethalol in angina pectoris (Prichard, Dickinson, Alleyne, Hurst, Hill, Rosenheim, and Laurence, 1963) produced a small but significant hypotensive effect (Prichard, 1964). Fifteen patients were given pronethalol for three months; they showed an average fall of supine blood-pressure of 33/23 mm. Hg, standing 27/16 mm. Hg. This hypotensive action of pronethalol was not further investigated in view of its tumour-producing action in mice (Paget, 1963).

The animal pharmacology of pronethalol was reported by Black and Stephenson (1962). It was the first specific

adrenergic beta-receptor-blocking drug, blocking the increased rate and force of contraction of the heart and relaxation of smooth muscle that result from the administration of adrenaline or isoprenaline. The classical adrenergic blocking drugs, such as ergot and phenoxybenzamine, block the alpha effects of adrenaline and noradrenaline, preventing the vasoconstriction seen in certain vascular sites. Pronethalol has no such action and the effect in man is consistent with beta-receptor blockade. It abolishes the dilatation of the forearm blood-vessels following intra-arterial isoprenaline and it alters the response to intravenous adrenaline so that it resembles that of noradrenaline (Dornhorst and Robinson, 1962). It reduces the reflex tachycardia during Valsalva's manoeuvre and diminishes the overshoot that follows the release of effort (Prichard, 1964).

Black, Crowther, Shanks, Smith, and Dornhorst (1964) briefly described the pharmacology of the closely related drug propranolol (I.C.I. 45,520, Inderal). It was reported to have

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a beta-receptor blocking action in animals and man and to be about ten times as potent as pronethalol. It does not produce tumours in mice. The present paper concerns initial experience of the hypotensive action of propranolol in out-patients.

Patients, Methods, and Dosage

Propranolol has been given to 23 patients for two months or more. Seven were normotensive patients who received propranolol for angina pectoris; in addition, 7 of the 16 hypertensive patients also had angina. Four patients were hitherto untreated hypertensives, three were transferred from other hypotensive drugs, while in nine propranolol was added to existing therapy, to improve blood-pressure control or because of angina.

The hypertensive patients were seen by the same physicians at each visit. The first physician asked standard questions, recorded the patient's subjective symptoms, and adjusted the dose of propranolol. The second physician, unaware of the dose that the patient was receiving, took the patient's blood-pressure under the same conditions at each visit. Patients were seen fortnightly at first, then every month or six weeks. The patients with angina were seen fortnightly and assessed by the same physician at each visit.

The anginal patients were given from 80 to 400 mg. daily in divided doses, the remaining hypertensive patients from 30 to 160 mg. daily. The initial dose was 10 mg. three or four times a day, increments of 5 to 10 mg. per dose being made at each visit as required. The higher dosage that we are using in some anginal patients is a result of the trial design, which is similar to that used in the study of pronethalol (Prichard *et al.*, 1963).

One 71-year-old woman suffering from angina pectoris developed symptoms of heart failure two days after starting propranolol (10 mg. q.d.s.). The drug was stopped and the symptoms cleared within three days without other treatment. Anginal patients who were thought to be at risk of developing congestive cardiac failure have therefore received smaller increments.

Results

The effects of propranolol administration on the blood-pressure in hypertensives are summarized in Table I, in normotensives in Table II.

The seven hypertensive patients who were given propranolol alone all achieved supine and standing diastolic pressures of 100 mm. Hg or less. One of these patients who was given propranolol primarily for angina was only very mildly hypertensive with neither fundal nor E.C.G. changes. Five patients on guanethidine, or bethanidine, or methyldopa all had considerable further reduction of blood-pressure following the addition of propranolol. Four of the remaining five patients, on milder hypotensive drugs, had some reduction in blood-pressure. In only 1 of the 16 hypertensive patients on propranolol was the standing blood-pressure above 100 mm. Hg, and in only two in the supine position. A small fall of blood-pressure was recorded in five of the seven normotensive patients.

In 8 of the 11 patients who received no other hypotensive drugs pulse rates were recorded prior to propranolol administration and at the time of the most recent blood-pressure reading; in all of these there was a fall in supine and erect pulse. In the remaining patients the position is less clear owing to the concurrent administration of other drugs.

No added hypotension on exercise (two flights of stairs) has been noted in those hypertensive patients without angina on propranolol whose blood-pressure was well controlled with or without other drugs (Cases 1, 3, 4, 6, 7, 9, and 10).

Subjective Feelings and Side-effects.—In response to standard questions 20 of the 23 patients felt well on the dose listed in the Tables. Two patients felt a little tired at their last visit; one patient felt unwell because of an intercurrent illness. The sole side-effect seen at dosages below 200 mg. daily was slight tiredness in two patients; no other side-effects have been seen in any of the hypertensive patients. In normotensive patients with the larger doses used in our anginal trial the following side-effects have been recorded; (1) on 50 mg. q.d.s., one patient had transient depression, one felt giddy and unsteady; (2) on 70 mg. q.d.s. one patient felt irritable and had cramp in the chest; (3) on 80 mg. q.d.s. one patient felt nauseated, one has

TABLE II.—Normotensives

Case No.	Sex	Age	Pre-Therapy B.P.		Latest B.P.		Dose (mg./day)	Treatment Months
			Supine	Erect	Supine	Erect		
17	M	42	100/60	98/60	90/55	90/60	160	7
18	M		135/90	110/85	130/70	110/70	160	6½
19	F	66	140/80	135/80	135/70	120/70	320	5
20	M	60	174/90	—	170/80	160/90	280	5
21	M	63	155/90	170/90	125/70	110/70	280	4½
22	M	44	118/80	116/76	90/55	90/65	240	4
23	M		135/90	140/80	115/65	100/70	80	4

TABLE I.—Hypertensives

Case No.	Group	Sex	Age	Fundus	E.C.G.	Pre-Therapy B.P.		B.P. on Previous Therapy		Latest B.P.		Dose (mg./day)	Treatment Months	Reason for Administering Propranolol
						Supine	Erect	Supine	Erect	Supine	Erect			
1. <i>Previously Untreated</i>														
1		M	57	I	+	190/120	190/120	—	—	130/70	130/90	120	5	New patient
2		M	60	0	—	170/100	160/100	—	—	150/80	145/80	400	5	Angina
3		F	39	0	+	180/100	170/100	—	—	150/80	130/80	160	3	New patient
4		F	60	II	—	200/105	180/110	—	—	190/100	150/100	140	2	New patient
2. <i>Changed from Other Drugs</i>														
5	Reserpine	M	61	I	—	190/110	—	156/90	158/90	125/70	110/80	320	6½	Angina
6	Methyldopa	M	42	II	+	230/135	—	155/110	155/115	145/100	125/100	160	3	Tiredness on methyldopa
7	Guanethidine	M	52	II	+	*	—	165/100	150/110	160/80	135/85	120	2	Control not good
3. <i>Other Drugs Continued</i>														
8†	Guanethidine	M	51	I	—	190/130	—	190/120	160/110	145/85	110/90	240	4	Angina
9	Guanethidine	F	53	II	+	270/150	260/160	200/100	180/105	190/100	145/95	80	3	Fair control on guanethidine
10	Guanethidine	F	54	II	+	250/150	—	230/126	194/116	220/116	144/94	30	2½	Diarrhoea on larger doses guanethidine
11	Bethanidine	F	67	II	—	230/125	230/150	220/115	185/130	170/123	163/106	80	2½	Dizziness on larger doses bethanidine
12	Methyldopa + hydro-chlorothiazide	M	45	IV	+	250/160	—	170/115	150/120	120/80	110/85	200	2	Angina
13	Chlorothiazide + reserpine	F	58	II	—	210/120	—	140/84	132/86	155/90	150/85	120	6½	Angina
14	Chlorothiazide	F	62	II	+	190/130	—	158/98	168/100	150/90	130/85	80	5	Angina
15	Chlorothiazide	F	49	II	—	220/120	220/110	194/96	178/106	180/85	165/80	80	3½	Fair control on chlorothiazide alone
16	Reserpine	M	57	I	—	200/125	—	208/90	182/96	170/90	155/90	400	7	Angina

* Myocardial infarct since first started hypotensive therapy.

† Dose of guanethidine reduced from 30 mg. to 10 mg. daily.

felt tired, one had visual hallucinations of coloured lights on this dose. This latter side-effect also occurred after five weeks on 100 mg. q.d.s. These side-effects were all readily relieved by reducing the dose. Two of the hypertensive anginal patients on 400 mg. daily have not experienced any side-effects: we have not increased the dose above this level.

Discussion

Fifteen out of 16 hypertensive patients given propranolol for up to seven months have shown reductions of blood-pressure. Propranolol alone may prove to be useful in the treatment of mild and moderately severe cases of hypertension. In one patient experiencing marked drowsiness on methyldopa a change to propranolol resulted in improved blood-pressure control with no side-effects. Propranolol produced a considerable hypotensive effect in patients on adrenergic neurone-blocking and milder hypotensive drugs.

Propranolol has so far proved relatively free from side-effects and patients usually feel well on the drug. We have seen one case where heart failure was precipitated by propranolol; this has been reported following pronethalol (Stock and Dale, 1963). We consider that propranolol should be used with great caution, if at all, in patients with a history suggestive of heart failure, though one such patient with severe angina responded well without trouble. The only other side-effect in the dosage recommended for the treatment of hypertension, up to 200 mg. a day in divided dosage, has been slight tiredness in 2 of the 23 patients, readily relieved by reduction of the dosage. The side-effects seen with larger doses used in our angina trial have also been relieved by reducing the dose.

While a central mode of action is not excluded it is suggested that beta-receptor-blocking drugs exert their hypotensive action by blocking the sympathetic receptors in the heart. A feature of both pronethalol (Prichard, 1964) and propranolol (Tables I and II) has been the absence of postural hypotension. In all of the 14 patients (Cases 1–7, 17–23) receiving propranolol alone there is a rise or no change in the diastolic pressure on standing. This would be expected, as the response of the cardiovascular system to the effect of gravity is chiefly mediated by increasing sympathetic (alpha) vasoconstrictor tone.

Pronethalol given intravenously does not exert any significant effect on the blood-pressure (Dornhorst and Robinson, 1962; Prichard, 1964) and our preliminary results suggest that the closely related drug propranolol also has no effect (Hodge and Prichard, unpublished data). Pronethalol immediately modifies cardiovascular responses, as shown by its reduction of the cardiac response in Valsalva's manœuvre (Prichard, 1964); it

reduces the reflex tachycardia during effort and the pulse pressure in overshoot, and preliminary experiments suggest (Hodge and Prichard, unpublished data) that propranolol has a similar action. While beta-receptor-blocking drugs have no hypotensive action following intravenous administration there is a slight hypotensive effect after short-term oral use of pronethalol (two to four weeks, Prichard, 1964; one week, Schröder and Werko, 1964). A considerable response has been obtained when either pronethalol or propranolol has been given for a prolonged period.

The tentative suggestion is made that these drugs act by reducing the cardiac response to stimuli which may be responsible for transient rises in blood-pressure. This is suggested by the modification of Valsalva's manœuvre. This damping-down of pressor responses may gradually condition the baroreceptors to regulate the blood-pressure at a lower level in hypertensive and normotensive patients. However, the response to acute cardiovascular demands involving largely alterations in vascular tone is relatively unimpaired; this is manifest in the response to exercise and posture in patients receiving propranolol.

Initial studies suggest that propranolol has a useful hypotensive action, worthy of further study. It is relatively free from side-effects in the recommended dosage for hypertension.

Summary

Propranolol (Inderal) has been given to 24 patients, 16 of whom were hypertensives. Therapy was stopped in one patient after two days, as heart failure developed, otherwise it is relatively free from side-effects in the dosage recommended for hypertension.

Alone or in combination with other drugs it exerts a considerable hypotensive action in hypertensive and normotensive patients.

It is thought propranolol may exert its hypotensive action by interfering with the function of sympathetic nerves to the heart.

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Glucose-tolerance Test in Hypertensive Patients

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The association between diabetes and coronary artery disease is well recognized, and recently a high proportion of patients with coronary disease have been shown to have disturbed glucose-tolerance tests (Sowton, 1962) or increased insulin antagonism (Vallance-Owen and Ashton, 1963).

It is noteworthy also that even in the absence of glycosuria 14.5% of apparently normal subjects over the age of 50 years reported in the College of General Practitioners' survey (1963)

had abnormal glucose-tolerance curves. It would be surprising if hypertensive patients, not necessarily suffering from overt diabetes, did not also show a proportion with abnormal glucose-tolerance tests, and in view of the findings of Vallance-Owen and Ashton and of Sowton it is clearly important to establish the relationship between the two conditions.

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