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Propranolol and polythiazide in treatment of hypertension

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Twenty-seven patients with severe hypertension were treated initially with propranolol alone and polythiazide was later added. The mean pretreatment blood pressure was 205/124 mmHg. Propranolol alone achieved good blood pressure control in 22 per cent of patients and, after the addition of polythiazide, the combination was successful in 43 per cent of patients. It is concluded that propranolol alone is only effective in a small proportion of patients with severe hypertension, but that in combination with a diuretic it may be an effective hypotensive agent.

Several workers have claimed that propranolol is an effective hypotensive drug (Prichard and Gillam, 1969; Zacharias and Cowen, 1970; Axford and Gilchrist, 1971). Though diuretics have been used in combination with propranolol in a number of trials (Richardson *et al.*, 1968; Zacharias, 1971), it has never been emphasized that a diuretic enhances the effect of propranolol, and it is the purpose of this study to demonstrate this potentiation.

Patients and methods

Selection of patients Patients with essential hypertension and a persistent diastolic blood pressure of 110 mmHg or greater were included in this study. The majority of patients had not received previous treatment and were admitted to hospital for assessment and investigation, to exclude a primary cause for the hypertension. Patients with labile hypertension, a history of bronchitis, cardiac failure, grade 3 to 4 retinopathy, or a blood urea greater than 50 mg/100 ml were not included.

Blood pressure recordings Blood pressure recordings before treatment were obtained in the majority of patients in hospital. After discharge, patients were seen at weekly intervals until blood pressure control had been achieved and thereafter fortnightly or monthly. Blood pressure was recorded to the nearest 5 mmHg in the supine and standing positions, the average of at least three readings being taken. All recordings were made after 30 minutes' rest and under the same conditions at each visit. The pulse rate was recorded at each visit.

Treatment Initially, 27 patients were treated with propranolol alone until control of hypertension was achieved, or side effects prevented a further increase in dosage, or a maximum dosage of 960 mg daily had been reached, whereupon polythiazide 1 mg daily was added; potassium supplements were not prescribed. Propranolol was always started cautiously in a low dosage of 40 mg daily and then increased weekly if possible by increments of 80 mg daily until the maximum daily dosage of 960 mg had been reached. At low dose ranges 10 mg and 40 mg tablets were used, but for higher dose ranges 80 mg tablets were prescribed.

Criteria for control Blood pressure control was assessed as follows.

Good – diastolic blood pressure of 100 mmHg or less, without serious side effects.
Fair – diastolic blood pressure greater than 100 mmHg but with a fall in diastolic pressure greater than 10 per cent without serious side effects.
Poor – diastolic blood pressure greater than 100 mmHg, without a sustained fall in diastolic pressure

Only patients with 'good' control were considered as 'successes' in the final analysis. Those with 'fair' or 'poor' control or those who had to be withdrawn because of side effects were classified as 'failures'. To assess control, the mean lying and standing diastolic pressures obtained on three consecutive visits have been employed. All patients were left on the maximum dosage of propranolol for 4 weeks before failure was accepted and an alternative hypotensive agent used.

P values were obtained by applying the paired t test.

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Results

Thirty-one patients were admitted to the trial, but 3 were excluded because of labile hypertension, and 1 patient was withdrawn in the early stages because of failure to obtain rapid control of his hypertension. Of the remaining 27 patients, there were 17 men and 10 women, of whom 10 were West Indian and 17 were European. The ages of the patients ranged from 34 years to 64 years, with an average age of 53 years.

Tables 1 and 2 summarize the results of therapy in 27 patients. The mean blood pressure before treatment ranged from 183/110 mmHg to 253/144 mmHg, with an average of 205/124 mmHg. After treatment with propranolol alone, there was a significant mean fall in the diastolic blood pressure from 124 mmHg to 111 mmHg ($P = 0.02$–0.01), and the overall success rate (Table 2) was 22 per cent. After the addition of polythiazide, there was a further significant reduction in the diastolic blood pressure to 100 mmHg ($P < 0.001$) and the overall success rate was 43 per cent. Six patients were withdrawn because of serious side effects. The average daily dose of propranolol was 879 mg, and the average duration of therapy was 31 weeks.

The dosage of propranolol ranged from 240 mg daily to 1920 mg daily. In 6 patients, the maximum dosage of 960 mg daily was exceeded because it was thought that control might be achieved; in none of these cases was good control in fact achieved.

The pulse rate was reduced in all patients after treatment with propranolol, but this did not correlate with blood pressure control. Five patients developed pulse rates below 55 a minute, which temporarily prevented further increase in the dosage of propranolol.

The following side effects occurred – dyspepsia (6), coldness of extremities (5), tiredness and somnolence (5), feeling of 'drunkenness' (4), dizziness (4), hallucinations (4), bronchospasm (3), impotence (3), withdrawal symptoms (3), constipation (2), insomnia (1), rash (1), anxiety (1), left ventricular failure (1). Six patients were withdrawn because of side effects – bronchospasm (3), somnolence (1), impotence (1), and rash (1). Two patients developed gout due to polythiazide, and this drug had to be stopped.

TABLE 1 *Mean blood pressure levels before and after treatment*

	Blood pressure (mmHg)			*Per cent change in diastolic pressure*
	Supine	*Standing*	*Mean*	
Before therapy	216/125	202/124	205/124	—
Propranolol alone	198/109 $P < 0.001$	193/115 $P = 0.02$–0.01	195/111	−10
Propranolol + polythiazide	172/100 $P < 0.001$	159/100 $P < 0.001$	165/100	−19

Discussion

Zacharias (1971) regards a sitting diastolic pressure averaging less than 100 mmHg as good control. As propranolol does not cause postural hypotension (Prichard and Gillam, 1969), we regarded a mean standing and supine diastolic pressure of 100 mmHg or less as evidence of good control. This is, of course, a stricter assessment of a drug than that usually employed for other hypotensive agents with a postural effect, in which a standing diastolic blood pressure of 100 mmHg or less is regarded as satisfactory without reference to the supine pressure.

There are conflicting reports concerning the effectiveness of propranolol as a hypotensive agent. Several authors (Tewari and Grant, 1968; Zacharias and Cowen, 1970; Zacharias, 1971; Axford and Gilchrist, 1971) claim that it is effective, and Prichard and Gillam (1969) state that propranolol is of at least similar potency to bethanidine, guanethidine, and methyldopa. However, there have also been reports in which it has been shown to have only a mild hypotensive effect (Paterson and Dollery, 1966; Richards, 1966; Richardson *et al.*, 1968; Humphreys and Delvin, 1968), but these authors have been criticized for using small doses of propranolol or administering it for too short a time (Prichard and Gillam, 1969; Zacharias and Cowen, 1970). In this study, though the series is small, the dosage and duration of therapy are acceptable and yet the results (a success rate of 43%) do not compare favourably with those who claim a success rate of 86 per cent

TABLE 2 *Response to treatment with propranolol alone and propranolol with polythiazide*

Degree of control		*Propranolol alone*		*Propranolol + polythiazide*	
Success		6	22%	10	43%
Failure	Fair	5	78%	6	57%
	Poor	12		5	
	Side effects	4		2	
Total		27		23	

(Zacharias, 1971) and 84 per cent (Prichard and Gillam, 1969).

Another factor that might possibly account for our results is that 10 patients (37%) were West Indian. Humphreys and Delvin (1968) showed that there was no significant difference between the effect of propranolol and a placebo in 18 Jamaican patients. There was no significant difference in the severity of hypertension, nor in the degree of control achieved between the West Indian and European patients in this study, and this suggests that a racial difference was not responsible for our results. The most likely explanation for our comparatively poor results is the severity of hypertension in our patients. The mean pretreatment blood pressure was 205/124 mmHg, a level that appears to be higher than in most previous series.

The incidence of side effects was high. It is noteworthy that of the three patients withdrawn because of bronchospasm, none gave a previous history of chest symptoms. Tiredness and somnolence were troublesome in a number of patients, and in one patient it was necessary to stop therapy. Impotence is not considered to be a side effect of propranolol, though Zacharias (1971) cautions that it may be commoner than suspected. Two male patients developed impotence and one woman demanded a change of therapy as she was unable to achieve any satisfaction from coitus; after cessation of therapy, her sexual responses were normal. Withdrawal symptoms occurred in 3 patients after the sudden cessation of propranolol, the clinical picture being similar to that of thyrotoxicosis, with tachycardia, anxiety, tremulousness, perspiration, and general malaise. These symptoms were abolished with as little as one-quarter of the original dose.

The average blood pressure after treatment with propranolol alone was 195/111 mmHg and after the addition of polythiazide was 165/100 mmHg; the 'success' rate was increased from 22 per cent to 43 per cent (Table 2) after the addition of polythiazide. These results suggest that propranolol alone is not an effective hypotensive agent in the treatment of most cases of severe hypertension, but that when used in combination with a diuretic it may be an effective method of treating severe hypertension.

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