STANDARDIZED STRESS AND HYPERTENSION: COMPARISON OF EFFECT OF PROPRANOLOL AND METHYLDOPA

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- 1 Using a standardized form of mental stress, 21 patients with idiopathic hypertension were investigated before and after treatment with placebo ($n=8$), propranolol ($n=7$) or methyldopa ($n=6$).
- 2 Blood pressure was satisfactorily controlled in the propranolol and methyldopa groups but only the propranolol group showed modification of the pressor response to stress testing.
- 3 These results suggest that propranolol may provide more uniform control of blood pressure than methyldopa in patients with essential hypertension

Introduction

Despite considerable improvement in the effectiveness and acceptability of antihypertensive agents, many patients continue to have poorly controlled blood pressure throughout the day. A recent study of 24 h arterial pressure recordings in hypertensive patients on adrenergic neurone blocking agents has shown both continued significant hypertension at rest and marked fluctuations in pressure with daily activities (Goldberg & Raftery, 1976). Exposure to stress of various kinds has been reported to cause a greater increase in systemic arterial pressure in hypertensive than in normotensive subjects (Shapiro, Moutsos & Krifcher, 1963; Nestel, 1969; Lorimer, MacFarlane, Provan, Duffy & Lawrie, 1971). Modification of these excessive pressor responses to stress would be likely to lead to more constant control of arterial pressure. This study was therefore designed to compare the effect of the β -adrenoceptor blocking agent propranolol with methyldopa on the blood pressure response to a standardized form of mental stress in patients with mild and moderate idiopathic hypertension.

Methods

Twenty-one patients with idiopathic hypertension were investigated. All gave informed consent to the studies and approval for the project was given by the hospital ethical committee. Prior investigations confirmed that these patients had idiopathic hypertension; none had received any antihypertensive therapy for the preceding 4 weeks. All patients had a basal systolic arterial pressure greater than 150 mm Hg and/or a diastolic pressure of greater than 90 mm Hg. Patients were instructed to refrain from coffee, cigarettes and other stimulants on the day of the test.

The stress test was performed as previously described (Lorimer *et al.*, 1971) and involved a monotonous but attention-demanding task in which 250 mixed steel ball bearings (13, 12, 11 and 10 mm in diameter) had to be sorted by size into appropriate groups. Concentration was interrupted by discordant noise received through headphones from a tape recorder and by variations in light intensity. The investigation was in three parts, the pre-stress, stress and post-stress periods of 1 h each. The pre-stress hour was spent sitting quietly. The stress was given during the second hour with post-stress hour being again spent sitting quietly. Systolic and diastolic blood pressures were recorded at 5 min intervals using a Roche arteriosonde blood pressure recorder.

All patients were initially stressed before treatment. The patients were then allocated to receive placebo ($n=8$), propranolol ($n=7$) or methyldopa ($n=6$) for a period of at least 6 weeks. The patients were seen at regular intervals and therapy was adjusted until satisfactory control of blood pressure was achieved. Thus, before restressing, all patients in the propranolol and methyldopa groups had systolic pressures of 140 mm Hg or less and diastolic pressures of 85 mm Hg or less. The second stress test was performed in a similar manner to the first and with the same observer. The data was analysed using a paired *t*-test within each group.

Results

Table 1 provides clinical details of patients and dosage of propranolol and methyldopa required to control blood pressure. Systolic, diastolic and mean arterial pressure responses to stress before and after therapy

are shown in Table 2. All groups showed significant elevations ($P < 0.01$) of pressure and of similar magnitude in response to stress before therapy. The placebo group showed no significant alteration in baseline pressure and no modification of the stress response when the study was repeated. Both active treatment groups showed an equivalent and significant fall in baseline pressure (Table 2: $P < 0.01$). The difference between the groups is shown in Table 3

which summarizes the percentage rise in mean arterial pressure during stress. The percentage rise was significantly modified only by propranolol (8.7% to 1.6%), the rises in the methyldopa group being 8.3% and 9.2% and in the placebo group 8.7% and 8.6% before and after treatment respectively. The reduction in mean blood pressure response to stress in patients treated with propranolol was associated with both lowered systolic and diastolic pressure responses.

Table 1 Clinical details and dosages given in each group

	<i>Propranolol</i>	<i>Placebo</i>	<i>Methyldopa</i>
Number of patients	7	8	6
Mean age years (range)	44.6 (27–54)	40.6 (33–50)	40.7 (35–45)
Sex (male : female)	4 : 3	4 : 4	3 : 3
Mean dosage: mg (range)	120 (40–160)	—	1083 (1000–1500)

Table 2 Systolic, diastolic and mean arterial pressure (mean $\pm$ s.d.) before and after therapy in the three study groups

	<i>Pre-stress</i>	<i>No therapy Stress</i>	<i>Post-stress</i>	<i>Pre-stress</i>	<i>Therapy Stress</i>	<i>Post-stress</i>
Propranolol						
Systolic (mmHg)	168 $\pm$ 22	179 $\pm$ 27*	169 $\pm$ 30	124 $\pm$ 11	126 $\pm$ 14	123 $\pm$ 14
Diastolic (mmHg)	111 $\pm$ 13	121 $\pm$ 10†	112 $\pm$ 14	85 $\pm$ 8	86 $\pm$ 9	85 $\pm$ 8
Mean (mmHg)	130 $\pm$ 14	140 $\pm$ 15†	131 $\pm$ 15	98 $\pm$ 8	99 $\pm$ 10	98 $\pm$ 9
Placebo						
Systolic (mmHg)	161 $\pm$ 17	176 $\pm$ 20†	164 $\pm$ 21	156 $\pm$ 22	170 $\pm$ 25†	165 $\pm$ 27
Diastolic (mmHg)	101 $\pm$ 12	110 $\pm$ 11†	104 $\pm$ 12	98 $\pm$ 16	107 $\pm$ 12†	101 $\pm$ 15
Mean (mmHg)	121 $\pm$ 13	132 $\pm$ 13†	124 $\pm$ 13	118 $\pm$ 16	128 $\pm$ 15†	123 $\pm$ 15
Methyldopa						
Systolic (mmHg)	153 $\pm$ 13	165 $\pm$ 13†	158 $\pm$ 12	120 $\pm$ 8	128 $\pm$ 12	124 $\pm$ 10
Diastolic (mmHg)	102 $\pm$ 10	111 $\pm$ 11†	108 $\pm$ 13	83 $\pm$ 6	92 $\pm$ 9†	89 $\pm$ 9
Mean (mmHg)	118 $\pm$ 10	128 $\pm$ 10†	124 $\pm$ 10	95 $\pm$ 6	108 $\pm$ 10*	100 $\pm$ 7

* $P < 0.05$; † $P < 0.01$ over preceding pre-stress period.

Table 3 Percentage change in rise of mean arterial pressure before and after stress with propranolol, placebo and methyldopa (mean $\pm$ s.d.)

	<i>No therapy</i>	<i>Therapy</i>
Propranolol	8.7 $\pm$ 4.4†	1.6 $\pm$ 3.0
Placebo	8.7 $\pm$ 4.5†	8.6 $\pm$ 7.2†
Methyldopa	8.3 $\pm$ 1.9†	9.2 $\pm$ 5.9*

* $P < 0.02$; † $P < 0.01$.

Discussion

Although it has been previously suggested that different forms of stress are associated with hypertension (Cobb & Rose, 1973; Jonsson & Hanson, 1977), the exact nature and importance of this relationship has not been clearly defined. This is at least in part due to difficulties in quantifying stress and in the application of a standardized stress stimulus to hypertensive patients. In this study the similar responses in all three groups before treatment support the view that an acceptable degree of standardization was probably achieved. Furthermore, the validity of repeating the procedure was confirmed in the placebo group with similar blood pressure responses before and after treatment.

Previous studies have demonstrated that beta adrenergic blocking compounds can modify heart rate and arterial pressure responses to different types of stress. A reduced heart rate response to the stress of motor car driving has been shown in normal subjects (Taggart & Carruthers, 1972) and to public speaking in both normal subjects and patients with coronary heart disease (Taylor & Meeran, 1973).

It has also been shown that the fluctuations in arterial pressure which occur throughout the day can be at least partially controlled by β -adrenoceptor blocking agents (West, Sleight & Honour, 1976) and that these agents can modify the rise in arterial pressure occurring during exercise (Shinebourne, Fleming & Hamer, 1967). Our results show that propranolol modifies the arterial pressure rise produced by a standardized form of stress in patients with mild idiopathic hypertension. This does not occur in patients whose hypertension has been controlled by methyldopa. Thus it appears that the modification of the stress response is a feature of the β -adrenoceptor blocking compound and not merely of a lower resting arterial pressure during therapy.

Several studies using different forms of stress have been unable to show a modification of the pressor response in hypertensive patients with β -adrenoceptor blocking agents (Nicotero, Beamer, Moutsos & Shapiro, 1968; Ulrych, 1969; Tarazi & Dustan, 1972). Nicotero *et al.* (1968) could not demonstrate any change in rise in arterial pressure in response to noxious stimuli with propranolol but resting arterial pressure was also unaffected by propranolol and this represents a fundamental difference from our study. Ulrych (1969) used the intravenous route for administration of oxprenolol and since it is known that intravenous β -adrenoceptor blocking agents do not change resting arterial pressure comparisons with our findings cannot be made. Tarazi & Dustan (1972) found that the transient increases in blood pressure which occurred during office visits were not affected by propranolol. However, these findings were based on demonstrating a higher blood pressure level in the office compared to levels recorded in the same patient

at home. Since more detailed and standardized studies of stress were not undertaken, it is difficult to draw conclusions from that study on the effect of β -adrenoceptor blocking drugs on the pressor response during stress.

In this study both propranolol and methyldopa afforded good control of resting arterial pressure and both agents reduced the height to which systolic and diastolic pressures rose in response to stress. However only propranolol modified the percentage increase in arterial pressure. The importance of these findings in man remains to be determined but experimental animal studies suggest that elevations of blood pressure produced by emotional stress may be related to the subsequent development of sustained hypertension (Henry, Meehan & Stephens, 1967) and that the arterial pressure response to acute stress in spontaneously hypertensive rats can be modified by treatment with propranolol from an early age (Weiss, Lundgren & Folkow, 1974) resulting in a delay in onset and decrease in severity of the hypertension (Weiss, 1974). It may be therefore that β -adrenoceptor blocking agents, besides affording good control of resting blood pressure may also be of added benefit by limiting the surges in arterial pressure which occur with daily activities.

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(Received March 28, 1977)