THE EFFECT OF THE β -ADRENOCEPTOR ANTAGONIST PINDOLOL ON EXERCISE PERFORMANCE

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- 1 Fifty-two patients who had been treated for essential hypertension for at least 5 years with once-a-day pindolol alone or in combination with a diuretic participated in a strenuous exercise programme. The 24 h antihypertensive efficacy of once-a-day pindolol was shown in blood pressure readings made before the intake of the day's dose.
- 2 During the first stage of the study before interruption of therapy, pindolol maintained effective blood pressure control and prevented an excessive rise in blood pressure and heart rate following strenuous exercise.
- 3 Following a 6 week period of interruption of pindolol therapy, higher blood pressure and heart rate levels were reached following exercise.
- 4 After reintroduction of a single dose of pindolol, improvement in blood pressure control and lower heart rate levels were again seen following exercise.
- 5 Compared with the period without drug systolic and diastolic blood pressures were lowered to about the same extent at rest and during exercise after maintenance pindolol and after a single dose of pindolol following a 6 week interruption period, but pre-exercise levels rose considerably during the period when therapy was discontinued.

Introduction

The antihypertensive properties of the β -adrenoceptor blocking drugs are well established (British Medical Journal, 1976; Ahlquist, 1977; Prichard, 1978). Pindolol (Visken), a potent member of this group of drugs (Hill & Turner, 1969; Aellig, 1976), has been shown to be safe and effective as a single agent (Collins & King, 1972; Davies, 1976; Dhatariya, 1977; Blowers & Maclay, 1977; Dhatariya & Blowers, 1977) and also in combination (Viskaldix) with a thiazide-type diuretic, clopamide (Persson, 1977; Maetzel, 1978; Crowder & Cameron, 1979).

Comerford & Besterman (1978) expressed the view that the demonstration of hypotensive effect only at rest and not during exercise was an observation of limited value when most hypertensive patients were mobile during much of the 24 h period. Reiterer (1980) has also observed that a comprehensive evaluation of the effects of increased blood pressure on cardiovascular function should include data from quantified stress testing.

The effects of exercise on heart rate and blood pressure after a 4 week treatment period with pindolol have been reported (Bjerle *et al.*, 1980). Reiterer

(1980) has studied the effects of 12 month treatment with the pindolol/clopamide combination on exercise performance, and found that, after interruption of therapy for 24 h, no abnormal increase in the exercise blood pressure data was seen.

The present study was conducted in a group of patients who had received treatment with pindolol either alone or in combination with a diuretic for at least 5 years, with the objective of assessing the effect of this therapy on heart rate and blood pressure following periods of exercise. In addition, the interruption of pindolol therapy for 6 weeks and its subsequent resumption enabled the necessity for continued treatment to be assessed and the therapeutic efficacy of pindolol to be re-evaluated.

Methods

Patients selected for inclusion in the study had been treated for mild to moderate hypertension for a period of at least 5 years. Prior to the initiation of antihypertensive treatment their blood pressures

ranged from 150 to 260 mm Hg systolic (mean 186 mm Hg) and from 96 to 150 mm Hg diastolic (mean 117 mm Hg). They had regularly attended the hypertension clinic, and at the time of entry to the exercise study their blood pressures ranged from 120 to 160 mm Hg systolic (mean 138 mm Hg) and from 74 to 96 mm Hg diastolic (mean 82 mm Hg). They were given a full explanation of the nature of the experiment and asked if they wished to participate.

Fifty-two patients entered the study. There were twenty-one males, age range 40 to 63 years (mean 52.1 years), and thirty-one females, age range 37 to 62 years (mean 53.0 years). One patient, a male aged 49 years, was withdrawn following the appearance of chest pains after the first period of exercise.

All patients had been treated for mild to moderate essential hypertension for a minimum of 5 years with pindolol either alone or in combination with a diuretic. The mean daily dose of pindolol used throughout this period was 21.6 mg (range 10 to 45 mg), and medication had been established on a once-daily basis over the previous years. Seven patients were maintained on the pindolol/clopamide combination (Viskaldix) and three patients had required the addition of hydrallazine to their pindolol + diuretic therapy.

All patients attended the clinic 1 month prior to entering into the present study. Physical health was checked including examination of the fundi. Blood pressures were measured in the morning before the intake of the day's dose of pindolol, and all were within normal limits.

Throughout the month prior to the test programme, pindolol medication was maintained on a once-daily basis. Doses ranged during this month from 15 to 30 mg a day.

Patients then attended the clinic to commence the test programme; their blood pressures and pulse rate were recorded after 15 min in the supine position. Blood pressures were taken with a sphygmomanometer, and the figures recorded were the average of four readings. Diastolic blood pressures were measured at Korotkoff phase 5. An exercise study was then performed. A bicycle ergometer was employed. The patients sat in an upright position and the period of exercise and load were adjusted so that male patients exercised with a workload of 180 W for 5 min and female patients 125 W for 3 min. Pulse rate was checked for a period of 15 s of each minute of exercise. Supine blood pressure and pulse rate readings were taken immediately after completion of the exercise programme, and again after a 30 min period of rest. Patients were required to attend the clinic 24 h following this procedure, and their supine blood pressure and pulse rate were again recorded.

All antihypertensive therapy was then stopped for a period of 6 weeks. Weekly observation was carried out to ensure that there was no deterioration in the

patient's clinical condition, such as evidence of heart failure or oedema. During this period of interruption of antihypertensive treatment, headache and other symptoms of hypertension were reported. Patients were then required to attend the clinic and their supine blood pressure and pulse rate were again recorded.

The bicycle ergometer exercise was again undertaken with the load and period of exercise maintained at the same level as on the earlier visit. Supine blood pressure readings and pulse rate were recorded at the conclusion of this exercise session, again after 30 min and again 24 h later.

A single dose of pindolol, equivalent to the individual previous daily maintenance dose, was then administered at the same hour of day as during maintenance treatment to each patient, and 2 h later a further period of exercise was instituted of equal duration to that undertaken previously. Supine blood pressure readings and pulse rate were recorded at the conclusion of this further exercise session, again after 30 min and again 24 h later.

Antihypertensive therapy was then reinstated at the earlier dosage levels, and after a period of between 2 and 3 weeks all patients returned to the clinic for a final check during which supine blood pressure readings and pulse rate were recorded.

Results

Following treatment over a 5 year period, the mean blood pressure of the fifty-one patients who completed the present study had fallen from 186 mm Hg systolic and 117 mm Hg diastolic to 138 mm Hg systolic and 82 mm Hg diastolic.

During the period of exercise whilst antihypertensive therapy was maintained, blood pressure readings rose to 159 mm Hg systolic and 100 mm Hg diastolic, and the pulse rate rose to 97 beats/min. Thirty minutes after exercise blood pressure readings and pulse rates showed significant falls and after 24 h they had returned to the pre-exercise levels (Table 1).

During the exercise session which followed the 6 weeks of interruption of antihypertensive therapy, blood pressure readings and pulse rate rose from a higher baseline and showed a similar pattern of fall after 30 min and again at 24 h (Table 1).

After administration of the single dose of pindolol, the period of exercise increased blood pressure from 156 mm Hg systolic and 101 mm Hg diastolic to 175 mm Hg systolic and 117 mm Hg diastolic and the pulse rate increased from 78 to 95 beats/min. Thirty minutes after exercise the blood pressure and pulse rate had fallen almost to the pre-exercise level, with further improvements being observed after 24 h (Table 1).

At the clinic attendance 2 to 3 weeks after reintro-

Table 1 Blood pressure and pulse readings during exercise study periods

	Before interruption of therapy			6 weeks after therapy discontinued			24 h after reintroduction of therapy		
	Systolic (mm Hg)	Diastolic (mm Hg)	Pulse rate (beats/min)	Systolic (mm Hg)	Diastolic (mm Hg)	Pulse rate (beats/min)	Systolic (mm Hg)	Diastolic (mm Hg)	Pulse rate (beats/min)
Before exercise	Mean 138	82	74	173	113	89	156	101	78
	s.d. 8.64	4.44	4.43	19.59	8.48	4.30	13.56	7.36	4.80
Immediately after exercise	Mean 159	100	97	199	131	136	175	117	95
	s.d. 9.74	5.48	6.20	20.23	10.10	8.09	14.33	7.98	6.36
30 min after exercise	Mean 142	85	79	180	116	96	158	102	81
	s.d. 9.31	4.85	4.07	17.85	8.23	4.52	13.20	7.58	5.12
24 h after exercise	Mean 137	81	73	175	112	90	155	99	80
	s.d. 7.43	4.53	3.86	18.05	7.79	4.59	10.84	6.62	6.33

duction of antihypertensive therapy, blood pressure readings were 139 mm Hg systolic and 82 mm Hg diastolic and the pulse rate was 71 beats/min.

Discussion

The trial was carried out in hypertensive patients successfully treated with once-a-day pindolol, as shown by testing blood pressure readings made in the morning, before the intake of the day's dose. This testifies to the 24 h antihypertensive efficacy of once-a-day pindolol.

In determining the necessity for antihypertensive treatment investigation of blood pressure regulation should include measurement not only at rest but also during physical stress; in addition, a standardised ergometer test is useful in assessing the efficacy of treatment in reducing the abnormal pressure load on the cardiovascular system (Reiterer, 1980).

Compared with the period without drug, systolic and diastolic blood pressures were lowered to about the same extent at rest and during exercise after maintenance pindolol and after a single dose of pindolol following a 6 week interruption of therapy, but the levels at rest and during exercise rose considerably during the period when therapy was discontinued (Figure 1). The increase in pulse rate during exercise was greater after pindolol withdrawal. All differences between corresponding mean recordings before interruption of therapy and on the other two occasions were statistically significant by paired *t*-tests, except pulse rate immediately after exercise and 30 min later.

Following a treatment period of at least 5 years pindolol had maintained effective blood pressure control at rest and prevented an excessive rise in blood pressure following strenuous exercise. The discontinuation of β -adrenoceptor antagonist therapy for a 6 week period resulted in higher blood pressure levels following exercise, but improvement was again seen following reintroduction of pindolol therapy. The first β -adrenoceptor blocking dose when therapy was reintroduced showed the expected maximum β -adrenoceptor blocking effect measured by the reduction of exercise-induced tachycardia, whereas the full blood pressure lowering effect was reached only during chronic oral therapy.

Increases in blood pressure during physical stress (walking, standing, effort) or mental stress can be seen to coincide with elevations of noradrenaline blood levels, which also appear to be elevated under basal conditions in hypertensive patients. Brecht *et al.* (1976) found mean plasma noradrenaline levels higher in patients with essential hypertension than in control subjects under basal and orthostatic conditions. Long-term treatment of these hypertensive subjects with pindolol (32 mg daily for 16 weeks, on

Figure 1 Blood pressure and pulse readings during exercise study periods, A before exercise, B immediately after exercise, C 30 min after exercise and D 24 h after exercise. — systolic, ---- diastolic blood pressure, pulse rate.

the average) led to a significant fall in diastolic and systolic blood pressure as well as heart rate, and to a significant decrease in plasma noradrenaline concentrations under basal and orthostatic conditions. Blood pressure was reduced from a mean 163/113 to 129/91 mm Hg supine ($P < 0.001$), from 148/115 to 129/99 standing ($P < 0.05$) and from 154/110 to 129/89 walking ($P < 0.001$). Before pindolol, the change in position from supine to standing led to an increase in plasma noradrenaline from 1608 pmol/l to 2648 pmol/l; on pindolol, the increase was from 952 pmol/l to 1868 pmol/l: even though the percentage increase was higher (but not the absolute increase), the basal and the stimulated levels were significantly lower ($P < 0.001$ and $P < 0.05$ respectively) than before treatment, and they did not significantly differ from those found in normotensive control subjects — i.e. they were in the normal range. It is of interest to note that β -adrenoceptor blockade with pindolol, although it shifts values down into the normal range, does not impair the regulatory mechanisms of the

sympathetic nervous system in response to stimuli (here the stimulus of upright posture).

Reiterer (1980) found that a brief withdrawal of antihypertensive therapy for 24 h did not lead to a loss of protection against the abnormal increase in the blood pressure during physical stress. Results here would suggest that pindolol withdrawal for 6 weeks will lead to a loss of protection against baseline hypertension, but excessive responsiveness to exercise during the period of pindolol withdrawal was not seen. It is interesting to note that there is considerable similarity in the blood pressure curves (Figure 1), although pulse rate did show a greater response to exercise during the time when pindolol was discontinued.

In this study, following the discontinuation period one dose of pindolol was sufficient to reduce basal heart rate and exercise heart rate to values seen during maintenance therapy, but blood pressure takes longer to return to normal. This applied to both systolic and diastolic blood pressure whereas Reiterer

(1980) found only systolic blood pressure to be progressively lowered.

Patient reaction to the study was enthusiastic, as those who agreed to participate felt they were the subjects of special attention.

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