Oral Phentolamine in Angina Pectoris

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SUMMARY

Twelve patients with stable angina pectoris received a placebo for 7 days and then oral phentolamine for an additional 7 days. Exercise was performed at the conclusion of the 2 drug periods. All of the patients developed angina with the stress of exercise while taking placebos. The average time to develop angina was 208 sec. In comparison, 9 of the 12 patients were able to exercise longer after phentolamine. The mean increment in exercise capacity was 95 sec. Four of the patients were limited by fatigue rather than by angina following phentolamine. None of the patients exercised less after phentolamine than after placebo. Phentolamine can be an effective agent in the treatment of angina pectoris.

Additional Indexing Words :

Coronary blood flow Adrenergic nervous system Coronary artery disease Exercise

THE administration of phentolamine at an infusion rate of 0.3 mg/min to patients in congestive heart failure produces a striking hemodynamic improvement. The cardiac output, cardiac rate, systemic pressure and stroke index increase while the pulmonary artery pressure, systemic peripheral resistance, left ventricular end diastolic pressure, and left ventricular end diastolic volume fall.¹⁾ Evidence was presented demonstrating that phentolamine has a positive inotropic action upon the heart.

Taylor and his associates^{2),3)} studied the cardiac performance in normal and hypertensive patients before and after the acute intravenous injection of 5 mg phentolamine. The drug caused a prompt reduction in the right atrial, pulmonary arterial, systemic arterial and wedge pressures. The cardiac output was invariably increased while the systemic vascular resistance was decreased. They concluded that the predominant vascular activity of the drug was to cause a direct relaxation of the vascular smooth muscle.

These observations led us to consider the use of phentolamine in angina. We now report the effects of orally administered phentolamine in patients with coronary artery disease and angina.

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METHODS

Twelve patients exercised until the onset of angina before and 7 days after the administration of placebo or phentolamine. The patients ranged in age from 38 to 71 years (average 58 years). Each patient had stable angina pectoris for at least 6 months prior to the study. Seven had electrocardiographic evidence of a previous myocardial infarction. All of the patients participating in this study were members of a special clinic formed for the evaluation and therapy of angina.

Six of the patients exercised in the upright position on a Quinton uniwork bicycle ergometer until the onset of angina. The other 6 patients exercised on a treadmill until angina was produced. This mode of exercise was utilized in the latter 6 patients because leg fatigue occurred prior to angina on the bicycle ergometer and precluded further exercise. The consistency of patient performance was confirmed in each instance by preliminary trials on the ergometer or treadmill in the absence of any drug.

The patients took a placebo, 1 pill 4 times a day, for 7 days prior to the definitive study. Phentolamine, 1 pill or 50 mg, was then administered 4 times a day to the patients for an additional week. The study was performed utilizing the identical settings on the ergometer or treadmill. All studies were performed 3 or more hours after meals or cigarette smoking. Lead II of the electrocardiogram was recorded prior to and at the conclusion of the exercise. No patient received propranolol or long acting nitrates at the time of the study. The placebo physically appeared different from the active drug. Therefore, the patients were told that the placebo was an agent different from phentolamine. However, they were not informed that this agent was pharmacologically inert. It would have been desirable to alternate the sequence of placebo and phentolamine. However, administration of the drug prior to placebo was not feasible because the delay required for the effects of phentolamine to dissipate would have prolonged the study excessively.

RESULTS

The results of the study are listed in Table I.

Effects of No Medication: The average resting cardiac rate was 79 beats/min. With the stress of exercise the average rate increased to 102 beats/min. All of the patients developed angina with exercise. The average time to develop angina was 186 sec.

Effects of Placebo: Comparison of the exercise capacity after no medication and after placebo revealed no significant changes. All of the patients developed angina with the stress of exercise while taking placebos. The average time to develop angina was 208 sec. The average resting cardiac rate was 83 beats/min and with exercise the rate increased to 103 beats/min.

Effects of Phentolamine on Exercise Capacity: Comparison of exercise capacity after phentolamine and after placebo showed that 9 out of 12 patients were able to exercise longer after phentolamine. The mean increment in exercise

Table I

Patient No.	Mode of Exercise	Placebo				Phentolamine			
		Control Cardiac Rate	Exercise Cardiac Rate	Time to Angina	ST Segment Depression and Lead	Control Cardiac Rate	Exercise Cardiac Rate	Time to Angina or Fatigue	ST Segment Depression and Lead
1	Ergometer 600 work-load 24 cycles/min	66/min (66)	72/min (72)	270 sec (180)	1.25 mm V ₄	90/min	95/min	330 sec- Angina	3.25 mm V ₄
2	Ergometer 1,000 W.L. 25 cycles/min	63/min (64)	95/min (97)	245 sec (230)	0.5 mm V ₅	70/min	112/min	1,450 sec- Fatigue	1.5 mm V ₅
3	Ergometer 1,000 W.L. 10 cycles/min	75/min (78)	78/min (80)	120 sec (120)	0.25 mm V ₅	80/min	85/min	120 sec- Fatigue	0.25 mm V ₅
4	Ergometer 1,000 W.L. 25 cycles/min	100/min (95)	110/min (115)	120 sec (120)	0.75 mm V ₅	100/min	135/min	240 sec- Angina	2.75 mm V ₆
5	Ergometer 1,000 W.L. 25 cycles/min	85/min (82)	90/min (88)	180 sec (180)	2.0 mm V ₆	95/min	95/min	180 sec- Fatigue	1.0 mm V ₆
6	Ergometer 1,000 W.L. 25 cycles/min	84/min (86)	110/min (105)	180 sec (170)	0.5 mm V ₆	100/min	140/min	240 sec- Fatigue	0.5 mm V ₆
7	Tread Mill 10% incline 2 miles hr.	70/min (66)	78/min (75)	60 sec (80)	1.0 mm V ₅	75/min	85/min	165 sec- Angina	1.5 mm V ₅
8	Tread Mill 10% incline 2 miles hr.	69/min (70)	112/min (110)	120 sec (120)	1.0 mm V ₅	80/min	135/min	120 sec- Angina	1.0 mm V ₅
9	Tread Mill 10% incline 1 miles hr.	110/min (90)	130/min (120)	130 sec (115)	2.5 mm V ₆	95/min	120/min	180 sec- Angina	2.0 mm V ₆
10	Tread Mill 10% incline 1 miles hr.	100/min (90)	120/min (120)	780 sec (600)	1.75 mm V ₆	100/min	120/min	1,200 sec- Angina	1.0 mm V ₆
11	Tread Mill 20% incline 1 miles hr.	75/min (72)	116/min (115)	105 sec (100)	2.0 mm V ₆	90/min	130/min	165 sec- Angina	1.25 mm V ₆
12	Tread Mill 10% incline 1 miles hr.	100/min (98)	135/min (130)	180 sec (170)	2.0 mm V ₆	100/min	135/min	210 sec- Angina	0.75 mm V ₆
Mean		83/min (79)	103/min (102)	208 sec (186)		90/min	116/min	303 sec	

Numbers in parentheses () = The values observed before the placebo period.

capacity was 95 sec. Four of the patients were limited by fatigue rather than by angina following phentolamine. None of the patients exercised less after phentolamine than after placebo. The average resting cardiac rate was 90 beats/min and after exercise the rate increased to 116 beats/min. Comparison of the exercise ST segment depression before and after phentolamine revealed no changes in 3 patients and a diminution of the ST segment depressions in additional 5 patients. The remaining 4 patients showed an increase in the ST segment depression after phentolamine. The increased rate may, in part, explain the greater ST segment depression.

DISCUSSION

Our studies indicate that orally administered phentolamine, produced an increase in exercise capacity in almost all patients. Further phentolamine prevented the appearance of angina in 4 subjects. These changes were associated with a consistent alteration in the circulatory response to upright exercise. A given amount of exercise, after phentolamine administrations, resulted in a more rapid heart rate.

Knowledge of the circulatory changes associated with phentolamine administration permits an evaluation of the possible mechanisms of this drug in augmenting exercise capacity. It is well established that oxygen consumption of the myocardium is a primary factor regulating coronary blood flow, and in general an increase in oxygen requirement increases the coronary blood flow. The various factors that effect myocardial oxygen consumption have recently been delineated.⁴⁾ These include the intra myocardial tension, heart rate and the contractile state of the heart. Of lesser importance quantitatively are the resting metabolism of the myocardium and the external work of the heart. The increased velocity of contraction and the improvement in contractility produced by phentolamine would be associated with an increase in the myocardial oxygen consumption. Similarly, the increased cardiac rate observed in our study would also augment the oxygen requirements. Phentolamine's effect on the shape of the heart has been investigated and the intra myocardial tension, as defined by the law of La Place could presumably play a major role in the oxygen requirements of the heart. The administration of phentolamine, intravenously, to patients with cardiac disease produces a decrease in the left ventricular end diastolic volume and left ventricular end systolic volume.¹⁾ Further, during the stress of exercise a striking fall in the left ventricular end diastolic pressure and a rise in the cardiac output will be observed.⁵⁾ This decrease in cardiac size would therefore lead to a fall in the myocardial oxygen requirements. The oxygen requirements of the heart

that are produced by phentolamine, would therefore depend on the interplay of these various factors.

Phentolamine's beneficial effect in angina may also be due to coronary artery dilatation with a resultant increase in coronary blood flow. In support of this concept Taylor and his associates^{8), 9)} have established that the predominant vascular activity of the drug is to cause a direct relaxation of the vascular smooth muscle.

Phentolamine has other pharmacologic actions which undoubtedly contribute to the patient's improved performance. In the failing heart, insulin and glucose are important for the maintenance of pumping function.⁶⁾ Severe pumping failure of the heart is associated with suppression of insulin secretion whatever the etiology of the heart failure.⁷⁾ It has recently been demonstrated that phentolamine can produce an immediate reversal of this insulin suppression.⁸⁾ Thus the effects of the drug in supporting myocardial metabolism by release of insulin suppression may play an important role in these circumstances.

Breathlessness may limit exercise performance in patients with cardiac disease. Phentolamine may relieve this symptom by reducing the left ventricular end diastolic pressure, pulmonary arterial pressure and pulmonary blood volume. However, some of the relief in breathlessness following phentolamine may be due to its bronchodilator effects. This drug is completely effective in preventing experimental histaminic and allergic bronchoconstriction in the guinea pig⁹⁾ and can produce bronchodilatation in man.¹⁰⁾

Thus the definitive answer to explain how phentolamine can improve the exercise capacity in patients with angina is still conjectural. However it would appear that phentolamine can be an effective agent in the treatment of this disorder. Further investigation of this new application of the drug is therefore warranted.

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