Beta-adrenergic Blockade in Angina Pectoris: A Method of Treadmill Assessment

D. A. BIRKETT,* M.B., M.R.C.P.; D. A. CHAMBERLAIN,† M.B., M.R.C.P.

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The sympathetic innervation of the heart, and the cardiac effects of circulating catecholamines, are mediated through β -adrenergic receptors. The increase in heart rate, and the increased power of contraction normally produced by sympathetic stimulation, can be prevented by the recently introduced β -receptor blocking agents, which therefore modify the haemodynamic response to exercise. Pronethalol (Alderlin) was the first drug of this type without initial sympathomimetic activity, but after its introduction for clinical trial it was found to be carcinogenic to mice (Paget, 1963). Propranolol (Inderal) is a similar compound, which has replaced pronethalol because it is free from carcinogenic activity and more potent weight-for-weight than pronethalol.

Both these drugs have been used in the treatment of angina pectoris, but the reports on their value have been conflicting. In double-blind trials favourable results were obtained with pronethalol by Alleyne *et al.* (1963) and with propranolol by Keelan (1965), whereas Srivastava *et al.* (1964) found propranolol to have little advantage over placebo. Tests involving reproducible exercise have also been used to assess the value of the drugs in angina. Dornhorst and Robinson (1962) reported that pronethalol increased effort tolerance in 9 out of 14 patients, and Hamer *et al.* (1964) were able to demonstrate similar results in 12 out of 20 patients studied after propranolol. On the other hand, MacAlpin *et al.* (1965) obtained no benefit with pronethalol alone, although they found it enhanced the effect of glyceryl trinitrate.

The inherent difficulty of testing the effect of drugs in angina pectoris is undoubtedly the chief reason for the disparity in the results obtained, and also the reason for the number of drugs of doubtful value at present prescribed for this condition. Double-blind trials may be misleading for several reasons: it is difficult to find a sufficient number of patients with frequent angina whose condition is clinically stable; a high placebo response is a feature of the condition; disability varies from day to day with the level of activity, and even the environmental temperature; and, finally, the number of glyceryl trinitrate tablets used, a common yardstick in trials of this sort, may not adequately reflect changes in effort tolerance. Laboratory tests with reproducible exercise are also subject to inaccuracy; patients' performances will be affected by factors such as time of day, duration since the last meal or exercise, temperature, and above all by familiarity with the test, since effort tolerance is markedly reduced by apprehension.

We have designed an exercise technique to obviate these potential inaccuracies so far as is possible, and we have used it to determine the effect of pronethalol and propranolol on effort tolerance in angina pectoris.

Patients and Methods

Twenty patients were studied. They comprised 19 men and one woman, aged from 36 to 63 years, with a mean age of 53. The duration of symptoms varied from 10 months

to 14 years, the average being five years. All were in a stable phase, with no clinical or electrocardiographic evidence of fresh myocardial infarction within the previous three months. None had a history of heart failure, and none was receiving digitalis. Eighteen were normotensive, and two were hypertensive with diastolic pressures persistently over 100 mm. Hg. The resting electrocardiogram (E.C.G.) showed evidence of ischaemic heart disease in 13 patients, the remainder being normal.

The patients were exercised on a motor-driven treadmill with an adjustable speed and slope. The severity of exercise was varied, depending upon the effort tolerance of each patient, and the treadmill was always stopped as soon as pain occurred. The aim was to provoke angina after one and a half to two and a half minutes of walking; if it were caused sooner, the exercise involved would usually be more strenuous than the patients were accustomed to take, and this was thought to be unwise; if the level of exercise permitted a walk of longer duration the circulatory response came close to a "steady state," and only a slight change in the conditions of the experiment could cause a relatively large delay in the onset of pain.

Various precautions were taken to control factors which might influence effort tolerance. First, exercise periods were limited to two a day, about four hours after the previous meal, so that tests were performed with the patients in a semi-fasting state. Secondly, the patients were not permitted to smoke for two hours before they walked, and if glyceryl trinitrate had been taken in the same period the test was postponed. Thirdly, at least 30 minutes of rest preceded each test. Finally, practice walks on the treadmill were repeated, usually six to eight times, until the patients became completely familiar with the techniques and free from apprehension. During the earlier practice tests the degree of effort required to produce pain usually increased, but subsequently the onset of pain provided an accurate and reproducible end-point (Abrahamsen and Kiil, 1966).

When effort tolerance had become consistent to within a few seconds six tests were carried out, three being performed 90 minutes after oral pronethalol or propranolol, and three 90 minutes after identical placebo tablets. The order in which the tablets were given was varied, and was of course unknown to the patients. Ten patients were investigated with pronethalol (each dose 300 mg.), and 10 with propranolol (each dose 30 to 80 mg.). The larger doses of propranolol were used later in the series, when it became known that 30 mg. orally does not always produce an effective degree of blockade.

E.C.G.s were recorded during the tests. One electrode was placed high in the right axilla and two over the praecordium to show leads CR4 and CR6 on a twin-channel electrocardiograph. Recordings were taken at rest, and at every half-minute during exercise. In 12 subjects blood-pressure readings were taken at the same time as the E.C.G. recordings, during at least one placebo test and one drug test, by means of a sphygmomanometer, with a stethoscope held in the antecubital fossa by a crêpe bandage.

The effects of β -adrenergic blockade on seven of the present series have been briefly reported previously and compared with the results achieved by bilateral upper thoracic sympathectomy (Birkett *et al.*, 1965).

* Lately Research Assistant, Department of Cardiology, St. Bartholomew's Hospital, London.

† Senior Medical Registrar, St. Bartholomew's Hospital, London.

Results

The Table shows the average distances walked by each of the patients after pronethalol or propranolol, compared with the average distances walked after placebo and the percentage change in effort tolerance after β -adrenergic blockade. The changes observed ranged from an increase in effort tolerance of 108% to a decrease of 6%, with a mean improvement of 36% (standard error ± 7 ; $P < 0.001$). The average improvement obtained with propranolol (35%, S.E. ± 10) was similar to that obtained with pronethalol (37%, S.E. ± 10). The findings did not suggest any difference in the mechanism of action or degree of response with the two drugs, but a strict comparison cannot be made because of the small numbers tested with each and the varying doses of propranolol which were used.

The resting heart-rate was reduced in 16 patients, and the exercise heart-rate in all 20 patients after blockade. The percentage fall in heart-rate during exercise shortly before the

Average Distance Walked by Each Patient After β -Adrenergic Blockade Compared with Average Distance After Placebo

Case No.	Drug	Dose (mg.)	Distance Walked*				Percentage Change with Active Drug
			With Placebo		With β -Adrenergic Blocking Drug		
			Yards	Metres	Yards	Metres	
1	Pronethalol	300	177	162	224	204	+ 27
2	"	300	98	90	160	146	+ 63
3	"	300	268	245	395	361	+ 47
4	"	300	86	79	97	89	+ 13
5	"	300	215	196	447	409	+ 108
6	"	300	150	137	186	170	+ 24
7	"	300	203	186	220	201	+ 8
8	"	300	184	168	206	188	+ 12
9	"	300	117	107	187	171	+ 60
10	"	300	147	134	162	148	+ 10
11	Propranolol	30	184	168	195	178	+ 6
12	"	30	169	155	289	264	+ 71
13	"	30	147	134	138	126	- 6
14	"	30	171	161	236	217	+ 38
15	"	30	173	163	245	224	+ 42
16	"	30	215	196	361	330	+ 68
17	"	40	140	128	194	177	+ 39
18	"	40	110	100	103	94	- 6
19	"	50	119	109	150	137	+ 26
20	"	80	96	88	167	153	+ 74

* Mean of three tests.

Electrocardiograms (CR4) recorded during identical exercise after placebo and after pronethalol in Case 5. After pronethalol the patient was able to walk farther, and developed neither pain nor electrocardiographic abnormalities.

development of pain varied from 4 to 34%, with an average reduction of 13%. There was no close correlation between this and the degree of improvement in effort tolerance obtained. The blood-pressure was little changed, either at rest or during exercise, as a result of β -adrenergic blockade in the 12 subjects in whom measurements were made.

Subjective improvement, as shown by increased effort tolerance, was accompanied by a corresponding delay in the appearance of ischaemic ST or T changes in the effort E.C.G., indicating that the drugs acted by causing a reduction in myocardial hypoxia for a given degree of exercise rather than by suppressing anginal pain (see Fig.).

Discussion

We believe that the practical difficulties of assessing drug therapy in angina pectoris make laboratory tests with reproducible exercise of greater value than even carefully designed double-blind trials. However, laboratory evaluation can also be misleading. The method we have described involves repeated testing over a "training" period; this, together with other precautions to achieve a consistent level of effort tolerance, affords a sensitive method of comparing the effect of a drug with that of placebo. Furthermore, the use of walking as the exercise stress, together with the oral administration of drugs, provides an experimental model closely related to clinical practice.

The technique has confirmed that pronethalol and propranolol can be effective in the treatment of angina pectoris: the majority of patients studied showed an increase in effort tolerance accompanied by delay in the appearance of ischaemic changes in the exercise E.C.G. The beneficial action of these drugs is likely to be due to their blockade of β -adrenergic activity. A similar effect follows bilateral upper thoracic sympathectomy, and we have shown (Apthorp *et al.*, 1964; Birkett *et al.*, 1965) that there is some correlation between the improvement obtained in a patient after pronethalol or propranolol and the greater improvement which usually follows operation. The mechanism of action is complex: sympathectomy and β -adrenergic blockade cause slowing of the heart-rate and also a reduction in contractility, resulting in increased heart-size, increased filling-pressure, increased duration of systolic ejection, and often some decrease in cardiac output. The overall effect of these actions on coronary flow and myocardial oxygen requirement is not easily predictable at the present time, and may vary from patient to patient. Further studies are in progress to attempt to evaluate the relative importance of some of the factors involved.

The increases in effort tolerance which have been demonstrated were relatively small in most instances. This is due in part to the method of testing: with more gentle exercise, in which patients come near to attaining a "steady state," a similar degree of improvement would have a greater effect in delaying or preventing pain; the tests made no measure of the benefit resulting from the prevention of sympathetic activity on the heart due to excitement and anxiety; and, finally, the doses of propranolol used in the early part of the study were insufficient to produce full β -adrenergic blockade, so that greater increases in effort tolerance may have been possible in some patients.

The use of agents of this type is not free from risk. In addition to the important side-effects peculiar to pronethalol, β -adrenergic blockade can precipitate heart failure, and is contraindicated when myocardial function is severely impaired. Asthma may be made worse (McNeill, 1964). The long-term consequences of the metabolic effects on carbohydrate and fatty-acid metabolism (Muir *et al.*, 1964) have not yet been assessed. Nevertheless, β -adrenergic blockade should be considered in patients not adequately controlled by conventional therapy.

Summary

The value of drug treatment in angina pectoris can be accurately assessed by using reproducible treadmill exercise under controlled conditions. A "training" period to allow patients to become completely familiar with the test is of great importance, because during this period effort tolerance usually increases irrespective of drug therapy.

The change in effort tolerance after pronethalol or propranolol, compared with placebo, was measured in 20 patients. A wide variation in response was obtained, but the mean improvement of 36% was highly significant ($P < 0.001$).

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Effect of Moderate Exercise on the Fibrinolytic System in Normal Young Men and Women

J. D. CASH,* M.B., B.SC., M.R.C.P.ED

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There is considerable evidence to show that exercise increases plasma fibrinolysis (Biggs *et al.*, 1947; Truelove, 1951; Fearnley and Lackner, 1955; Sherry *et al.*, 1959; Billimoria *et al.*, 1959; Ogston and Fullerton, 1961; Jang *et al.*, 1964; Ogston and McAndrew, 1964; Burt *et al.*, 1964) and that this is due to an increased level of plasminogen activator (Sawyer *et al.*, 1960; Iatridis and Ferguson, 1963). Careful analysis of the results of all these workers reveals that some of their subjects responded poorly. Those who have commented on these poor responders have given tentative explanations. Biggs *et al.* (1947) thought increased physical fitness relevant, Sawyer *et al.* (1960) inappropriate timing of sample collection, whereas Iatridis and Ferguson (1963) suggested that the reason might be the failure to show the usual reaction to stress or to the production of a fibrinolytic inhibitor. It is not possible to make any valid conclusions from these studies, however, because of the variation of fibrinolytic assays and in the type of exercise used in different laboratories. Of no less importance is the fact that in most studies exercise to exhaustion was used and therefore no attempt was made to examine individual reproducibility of response.

In view of Astrup's (1956) hypothesis that there exists a delicately balanced dynamic equilibrium between coagulation and fibrinolysis, and that disequilibrium might result in atherosclerosis and thrombus formation, then the concept of a poorly reactive fibrinolytic system in a small proportion of apparently healthy young persons would be of considerable interest.

This paper describes a series of experiments in which the fibrinolytic system was studied before and after a standard moderate exercise procedure in a group of young healthy subjects.

Subjects

The subjects were 25 healthy male and 25 healthy female volunteers aged 18 to 30 years. All subjects undertook the

exercise procedure on more than one occasion. Most experiments were repeated at weekly intervals, but a few at intervals of several months. Nine of the women, with a history of regular and trouble-free menstrual cycles, were studied at weekly intervals throughout a menstrual cycle.

Materials

Anticoagulant.—Sodium citrate B.P. 3.8%.

Buffers.—(a) Barbiturate buffer. Modified veronal buffer of pH 7.4 and ionic strength 0.15 (Owren, 1947). (b) Tris buffer. 0.15 M solution of tris—(hydroxymethyl)—amino-methane (Koch-Light Laboratories Ltd., batch No. 11342) adjusted to pH 7.8. (c) Phosphate buffer. 0.1 M at pH 7.6.

Fibrinogen.—A Blombäck and Blombäck (1957) preparation of human fibrinogen with a clottability of 97% (supplied by Kabi Pharmaceutical Company, batch No. 83164) was used. A 1.5 g./100 ml. solution of fibrinogen in tris buffer was stored in plastic tubes at -20°C . After thawing it was diluted to 0.15 g./100 ml. in tris buffer and used for fibrin plates.

Thrombin.—Topical thrombin (Parke Davis and Co., batch No. 03179A) was used. A solution of 50 units/ml. in tris buffer was prepared for fibrin plates, one of 5 units/ml. in barbiturate buffer for euglobulin lysis time estimations, and one of 100 units/ml. in physiological saline for fibrinogen estimations. All these solutions were stored at -20°C . in plastic tubes and used immediately after thawing.

Streptokinase.—The preparation produced by Lederle Laboratories (batch No. 2201-66) was used for plasminogen assays. It was diluted to 2,000 units/ml. in phosphate buffer and stored in plastic tubes at -20°C .

Urokinase.—The standard reference preparation (2,400 Plough units) produced by Leo Pharmaceuticals, Denmark (batch No. 63062) was used. Solutions of 3 units/ml. in tris buffer were prepared and stored at -20°C . in plastic tubes.

Glassware.—All glassware was siliconized by means of a 3% solution of I.C.I. M550 silicone in trichlorethylene.

* From the South-east Scotland Regional Blood Transfusion Research Laboratories, Royal Infirmary, Edinburgh.