Comparison of Adrenergic Beta-receptor Antagonists in Angina Pectoris

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Summary

The symptomatic, electrocardiographic, and circulatory effects of intravenous and oral preparations of propranolol, oxprenolol, and practolol were compared in 16 patients with uncomplicated angina pectoris precipitated by exertion. The method of study included treadmill exercise, double-blind assessment, single-blind analysis, with placebo control and randomized serial comparison of each drug in each patient. The doses used were selected to give the same near-maximum suppression of the heart rate response to exercise. The symptomatic, electrocardiographic, and circulatory response of each patient to both preparations of each of the three drugs was similar. Exercise tolerance was increased in two-thirds, unchanged in one-sixth, and significantly worsened in one-sixth of the studies. Electrocardiographic evidence of myocardial ischaemia was conspicuously reduced by all three drugs in most studies irrespective of their symptomatic effects. Though the exclusive choice of patients, the single dose design of the trial, and the treadmill method of assessment limit the general application of these results, they do clearly indicate that in doses that induce equal suppression of the exercise heart rate these three drugs have similar distinct anti-anginal activity. Their ancillary pharmacological properties are probably of little importance in this respect. Equally, the similarity in the symptomatic, circulatory, and electrocardiographic response to the intravenous and oral preparations suggests that metabolic breakdown products are probably of therapeutic importance only in so far as they antagonize beta-receptor activity.

Introduction

The beneficial symptomatic effects of the adrenergic beta-receptor antagonists in angina pectoris are well known, but there is little information on the comparative effectiveness of different preparations. This is of particular clinical interest, as the most common drugs used—propranolol, oxprenolol, and practolol—differ conspicuously in their secondary pharmacological properties. In addition, the ingestion of these drugs is followed by the formation of metabolic degradation products with potentially different anti-anginal activities to those of the unchanged intravenous preparation. In view of the possible clinical importance of these differences the following study was undertaken to evaluate the comparative therapeutic effectiveness of the intravenous and oral preparations of the three drugs in patients with angina pectoris.

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Patients and Methods

The design of the trial involved the serial evaluation in each patient of the effect of placebo, propranolol, oxprenolol, and practolol, and to achieve a balanced analysis 16 men, average age 52 years (range 38-60) and average weight 75 kg (range 67-82), were studied. All were suffering from uncomplicated exercise-induced angina pectoris. None were obese, hypertensive, or diabetic, none had hypercholesterolaemia and none had had a previous myocardial infarction or any other history of heart disease. The history of angina extended from four months to eight years (average 23 months) and in all patients was induced solely and repeatably by walking. In all cases the angina was judged to be stable by the historical evidence of relative constancy of the number of attacks and daily glyceryl trinitrate consumption, the repeatable time of onset during objective exercise testing, and the rapid relief afforded by subsequent rest. None suffered from nocturnal or emotionally-induced angina, and none had received previous treatment other than glyceryl trinitrate.

The resting electrocardiogram was normal in all patients, but during treadmill exercise all developed ischaemic changes at the onset of pain. The diagnostic criteria of ischaemic electrocardiographic response used was a flat or downward sloping depression of the S-T segment in chest lead V_5 of at least 1 mm (0·1 mV) persisting for 0·08 seconds or longer and present in five successive beats with a stable isoelectric baseline. A positive response is illustrated in fig. 1. A standard six-foot (1·8 m) standing chest radiograph showed no cardiac enlargement, and radiographic screening showed no abnormality of left ventricular contraction. There was no auscultatory or angiographic evidence of mitral incompetence in any patient and all had angiographic evidence of multiple coronary artery disease. Objective evidence of the presence of exercise-induced left ventricular myocardial ischaemia was also furnished by the fact that in all patients the left ventricular end-diastolic pressure was less than 12 mm Hg at rest, rose abruptly to more than 25 mm Hg during angina, and returned rapidly and completely to normal in parallel with the resolution of the electrocardiographic S-T segment depression, as previously described (Sharma and Taylor, 1970).

The patients selected for this trial formed part of a medical control population of a randomized trial for the evaluation of the results of coronary artery bypass surgery. The purpose and nature of the investigative programme, the possible clinical

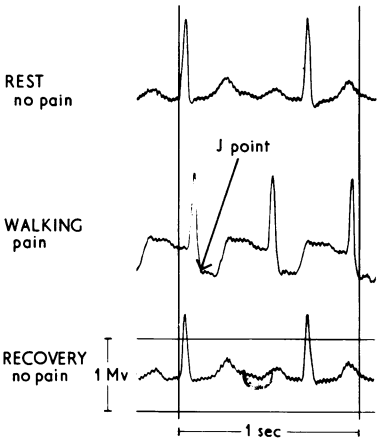

FIG. 1—Diagnostic changes in exercise electrocardiogram.

benefits, and the scientific aspects of the study were explained in detail to each patient; without inducement all consented willingly to the studies (Medical Research Council Annual Report, 1964; Ormrod, 1968).

DESIGN OF INVESTIGATION

Each patient was trained on a motor-driven treadmill, the speed (1-2 m.p.h., 1·6-3·2 k.p.h.) and slope (10-15°) of which were individually adjusted to the exercise tolerance of each patient so that anginal pain did not occur before the second minute of exercise, and all were able to complete six minutes of continuous walking at constant speed and slope. This level of exercise was selected as most closely approximating to that normally inducing angina and yet allowing sufficient sensitivity to discriminate changes in time of onset and pain induced by drug therapy. The patients were trained spontaneously to indicate the point at which definite pain occurred without observer questioning. Training was continued until the onset of pain was consistent to within 20 seconds in three consecutive tests.

Precautions were taken to control factors which might have induced erroneous changes in exercise tolerance. The laboratory temperature was 68-72°F (20-22·2°C), patient apprehension was reduced by familiarization with the technique and staff, the studies were carried out at the same time each day—not earlier than one hour after a light carbohydrate meal and only if the patient had not had an attack of angina during the previous four hours. Patients were not allowed to smoke before any exercise test and only a single exercise test was carried out each day. When exercise tests had become consistent the definitive trial was started. Each study consisted of contiguous six-minute periods of sitting, standing, walking, standing, and sitting. Studies were carried out every third day and begun five minutes after the intravenous infusion of normal saline, propranolol (0·2 mg/kg), oxprenolol (0·2 mg/kg), or practolol (2·0 mg/kg) administered in random order by a motor driven pump in a dilution of 80 ml over five minutes. The oral studies were then carried out every third day starting one hour after oral placebo (10 mg ascorbic acid), propranolol (80 mg), oxprenolol (80 mg), or practolol (500 mg), again administered in random order.

The intravenous and oral doses of the three beta-adrenoreceptor antagonists were chosen after pilot studies in normal volunteers had shown that these doses resulted in a comparable degree of blockade of the heart rate response to intravenous isoprenaline and a near-maximum reduction in the heart rate response to supine leg exercise (Taylor *et al.*, 1973).

The order of administration of placebo and the three drugs was decided by a series of random numbers. The content of the injection or the tablets was not known to the patient or doctor in charge of the investigation. The electrocardiogram and heart rate were monitored continuously on an oscilloscope and cardiotachometer respectively throughout each study. Electrocardiographic records were taken and sphygmomanometric measurements of the brachial arterial pressure were made at each minute throughout the study. The patients' indication of the onset of pain was separately documented. The electrocardiograph records were analysed by a third observer who was not present at the time of the study and who had no knowledge of the drug given or the time of onset of pain. The study was therefore a serial comparison, double-blind in design and single-blind in analysis, placebo controlled, randomized in order, with each patient serving as his own control.

TECHNIQUES, MEASUREMENTS, AND STATISTICAL METHODS

The electrocardiogram was recorded from adhesive-disc electrodes applied to each shoulder, lower rib-cage, and the V5 position, calibrated externally (1 mm = 0·1 mV), and recorded on an ultraviolet recorder (SE Laboratories model 3012) at a recording speed of 50 mm/sec. S-T segment depression was measured as the linear depression of the J point from the isoelectric line joining two consecutive P-R segments. The J point was indentified as the first detectable point of change after the nadir of the S wave (fig. 1). This point is least affected by the random artefacts that occur on the exercise electrocardiogram and it is also probably clear of changes due to atrial repolarization. T wave height was measured as the peak height from the isoelectric line. Measurements were averaged over five consecutive complexes in which the isoelectric line was completely stable. Heart rate was measured from the same electrocardiogram complexes. The systemic arterial pressure was measured by sphygmomanometer from the right brachial artery. Measurements were made at one-minute intervals and averaged during the final two minutes of each six-minute phase of the study.

The onset of pain in the control studies were consistently within 20 seconds in an average time of onset of 200 seconds on repeated exercise testing. The discriminatory limits of changes in exercise tolerance—that is, time of onset of pain—were, therefore, arbitrarily taken as $\pm 20\%$ of the time of onset of pain in the placebo study. The degree of improvement in exercise tolerance associated with the administration of each drug was calculated as the percentage decrease in duration of pain during exercise—that is, no pain after a drug represented 100% increase in exercise tolerance.

Probability of statistical significance of changes was calculated by Student's *t* test for paired data.

Results

The study was accomplished without untoward incident. There were no side effects of any of the drugs administered, and all patients tolerated all three drugs both intravenously and orally without complaint.

There was no statistically significant change in any variable between the sitting and standing postures either before or after exercise in any study. For the sake of tabular and diagrammatic clarity measurements during sitting are, therefore, omitted.

COMPARATIVE DEGREE OF CARDIAC BETA-RECEPTOR ANTAGONISM

There was a significant reduction in the resting standing heart rate in all patients after each of the three drugs by both routes of administration (tables II and III). The higher resting heart rates after intravenous oxprenolol ($P < 0·05$) and practolol ($P < 0·02$) as compared to propranolol may reflect the intrinsic sympathomimetic activity of these two drugs when administered in this form. The higher resting heart rate after oral practolol ($P < 0·001$) as compared to oral oxprenolol and propranolol possibly indicates a similar phenomenon. The higher resting heart rate after intravenous as compared to oral oxprenolol ($P < 0·05$) may indicate that its sympathomimetic activity is reduced when given orally.

The equal reduction in exercise tachycardia after each drug by both routes of administration implied a similar degree of blockade of the cardiac heart rate beta-receptors to the sympathetic effects of exercise.

COMPARISON OF INTRAVENOUS PREPARATIONS

Symptoms.—All patients experienced angina during the placebo study (table I). Of the 48 expected anginal attacks, nine did not occur and 21 attacks were delayed in onset by more than 20% of the placebo value after the intravenous injection of a beta-receptor antagonist. The separate results for each of the three drugs were similar—that is, nearly two-thirds of all anginal attacks were conspicuously improved by each of the three intravenously administered beta-receptor antagonists. The average percentage increase in exercise tolerance in patients who

TABLE I—*Effects of Beta-adrenoreceptor Antagonists Compared to Placebo Response on Onset of Pain in Serial Studies in Patients with Angina Pectoris*

Anginal Pain*	Intravenous (16)†			Oral (14)†		
	Propranolol	Oxprenolol	Practolol	Propranolol	Oxprenolol	Practolol
Abolished	3 (197)	2 (190)	4 (226)	6 (218)	3 (210)	6 (213)
Delayed	6 (167)	8 (190)	7 (159)	4 (169)	8 (193)	2 (188)
Unchanged	4 (186)	4 (233)	2 (263)	2 (210)	2 (225)	4 (250)
Aggravated	3 (275)	2 (255)	3 (205)	1 (173)	1 (120)	2 (173)

Numbers in parentheses relate to the average time in seconds of onset of pain in the placebo study for the associated group of patients.
*Changes in time on onset of pain were greater than or less than 20% of placebo time.
†For explanation of these differences in number of patients see text.

TABLE II—*Electrocardiographic and Circulatory Effects of Intravenous Propranolol, Oxprenolol, and Practolol Compared to Placebo in 16 Patients with Uncomplicated Angina Pectoris*

Variable	State	Placebo	Propranolol	Oxprenolol	Practolol
S-T segment, depression (mm)	Standing	0·2 ± 0·1	0·1 ± 0·1	0·1 ± 0·1	0·1 ± 0·1
	Walking	2·0 ± 0·1	1·0 ± 0·3*	1·0 ± 0·3*	0·8 ± 0·2*
Peak Height T wave (mm)	Standing	0·7 ± 0·2	0·1 ± 0·1*	0·2 ± 0·1*	0·1 ± 0·1*
	Walking	3·2 ± 0·4	5·1 ± 0·7*	4·3 ± 0·6†	4·3 ± 0·5†
	Standing	3·3 ± 0·4	3·4 ± 0·5	3·2 ± 0·4	3·5 ± 0·4
	Walking	2·8 ± 0·3	4·8 ± 0·6†	4·0 ± 0·6‡	4·1 ± 0·4‡
Heart rate per min	Standing	83 ± 2	64 ± 2*	67 ± 2*	68 ± 2*
	Walking	121 ± 4	98 ± 2*	100 ± 2*	98 ± 2*
	Standing	88 ± 3	64 ± 2*	69 ± 2*	70 ± 2*
Systolic blood pressure (mm Hg)	Standing	136 ± 3	131 ± 3	133 ± 3	130 ± 3
	Walking	194 ± 7	151 ± 6*	157 ± 6*	148 ± 4*
	Standing	141 ± 4	136 ± 5	138 ± 3	140 ± 3
Diastolic blood pressure (mm Hg)	Standing	93 ± 2	92 ± 2	93 ± 1	91 ± 2
	Walking	98 ± 2	94 ± 3	95 ± 3	93 ± 2
	Standing	93 ± 2	95 ± 3	95 ± 3	93 ± 2

Data expressed as mean ± standard error of mean.
*P < 0·001.
†P < 0·01.
‡P < 0·02.
Significance of differences relate to comparison with placebo value.

TABLE III—*Electrocardiographic and Circulatory Effects of Oral Propranolol, Oxprenolol, and Practolol, Compared to Placebo in 14 Patients with Uncomplicated Angina Pectoris*

Variable	State	Placebo	Propranolol	Oxprenolol	Practolol
S-T segment depression (mm)	Standing	0·2 ± 0·1	0·1 ± 0·1	0·1 ± 0·1	0·2 ± 0·1
	Walking	2·0 ± 0·3	0·7 ± 0·2*	0·8 ± 0·3*	0·7 ± 0·2*
Peak height T wave (mm)	Standing	0·6 ± 0·1	0·1 ± 0·1*	0·2 ± 0·1*	0·2 ± 0·1*
	Walking	3·7 ± 0·5	4·8 ± 0·6†	4·7 ± 0·7†	4·6 ± 0·6†
	Standing	3·3 ± 0·4	3·8 ± 0·5	3·3 ± 0·6	3·3 ± 0·5
	Walking	2·9 ± 0·3	4·7 ± 0·7‡	4·1 ± 0·5†	3·9 ± 0·4†
Heart rate per min	Standing	81 ± 2	64 ± 2*	63 ± 1*	68 ± 1*
	Walking	118 ± 3	95 ± 3*	95 ± 2*	95 ± 3*
	Standing	84 ± 3	65 ± 2*	66 ± 2*	71 ± 2*
Systolic blood pressure (mm Hg)	Standing	138 ± 3	130 ± 3*	132 ± 3‡	127 ± 3*
	Walking	191 ± 6	145 ± 3*	154 ± 6*	145 ± 4*
	Standing	140 ± 3	133 ± 3†	135 ± 2†	128 ± 3‡
Diastolic blood pressure (mm Hg)	Standing	93 ± 2	91 ± 2	93 ± 2	91 ± 2
	Walking	93 ± 3	93 ± 2	90 ± 2	89 ± 2
	Standing	92 ± 2	93 ± 2	93 ± 2	91 ± 2

Data expressed as mean ± standard error of mean.
*P < 0·001.
†P < 0·02.
‡P < 0·01.
Significance of differences relate to comparison with placebo value.

were improved was 61%, 67%, and 72% after intravenous propranolol, oxprenolol, and practolol respectively. In eight of the 48 exercise studies the intravenous administration of a beta-receptor antagonist was followed by a *reduction* in exercise tolerance greater than 20% of the placebo response; in three of these studies propranolol was the drug used, in two oxprenolol, and in three practolol. Between-drug comparison in the same patients showed close similarity in response. In patients in whom pain was ameliorated six responded to all the three drugs, five to two of the three drugs, and only two to a single drug. In two patients all three beta-receptor antagonists induced an onset of anginal pain earlier than 20% of the placebo response; in a further patient two of the three drugs induced an earlier onset of pain.

Electrocardiographic Changes.—The resting electrocardiogram was normal in all patients in the placebo study (table II, fig. 2). Each of the three drugs produced a statistically significant increase in the peak height of the T waves at rest without change in the isoelectric S-T segment.

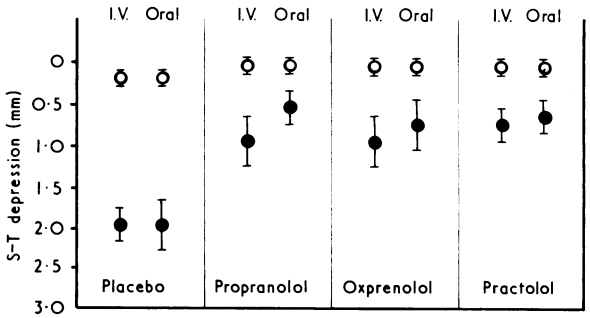

FIG. 2—Summary of changes in electrocardiographic S-T segment before and after beta-adrenoreceptor antagonists. Data plotted as mean ± standard error. O = Rest. ● = Exercise.

During exercise in the placebo study there was conspicuous depression of the S-T segment in all patients ($P < 0.001$). This was significantly diminished in 15 of the 16 patients after all three beta-receptor antagonists, irrespective of the effect on symptoms. The peak height of the T wave during exercise was unchanged after all three drugs.

Changes in Heart Rate and Blood Pressure.—There was a significant reduction in the heart rate both at rest and during treadmill exercise after each drug as compared to placebo (table II, figs. 3 and 4). The systemic arterial pressure of all patients was within the normal range at rest (a criteria of patient selection). There was no conspicuous change in the resting blood pressure, but during exercise there was a significant reduction in the average systolic pressure after all three drugs; the diastolic pressure was unchanged.

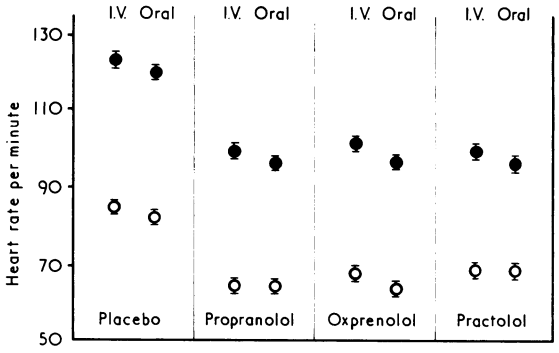

FIG. 3—Summary of changes in heart rate before and after beta-adrenoreceptor antagonists. Data plotted as mean ± standard error. O = Rest. ● = Exercise.

COMPARISON OF ORAL PREPARATIONS

Symptoms.—Although all patients had consistently experienced pain during the control training period and during the intravenous placebo study, two patients failed to develop angina during the oral placebo study (table I). As the study was based on comparison with placebo, these two patients were not included in the further analysis. Of 42 potential anginal attacks in the remaining 14 patients, 15 did not occur and 14 were delayed by more than 20% of the placebo value. The individual results for each of the three drugs were similar. Thus two-thirds of all anginal attacks were conspicuously ameliorated by a single oral dose of each of the three beta-receptor antagonists. The average percentage increase in exercise tolerance in patients who were improved was 66%, 83%, and 93% after oral propranolol, oxprenolol, and practolol respectively. In four of the

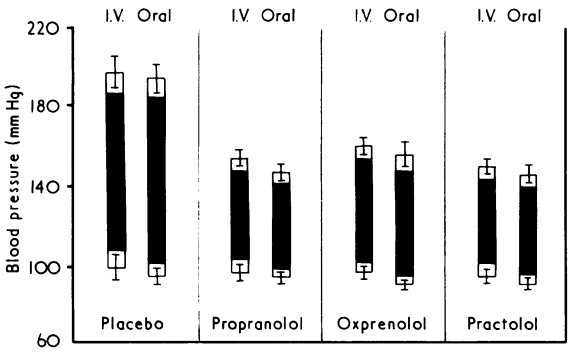

FIG. 4—Summary of changes in exercise blood pressure before and after beta-adrenoreceptor antagonists. Data plotted as mean ± standard error.

42 exercise studies administration of an oral beta-receptor antagonist was followed by a *reduction* in exercise tolerance greater than 20% of the placebo response. In one patient propranolol and practolol induced an earlier onset of pain and in another patient oxprenolol and practolol were responsible. Comparison of the effects of different drugs in the same patients showed only minor differences in response. In patients in whom pain was ameliorated seven responded to all the three drugs, three to two drugs, and only one to a single drug. In two patients two of the three drugs induced an earlier onset of pain.

Electrocardiographic Changes.—The resting electrocardiogram was normal in all patients in the placebo study (table III, fig. 2). Each of the three drugs produced a statistically significant increase in the peak height of the T wave at rest without change in the isoelectric S-T segment. During exercise in the placebo study there was conspicuous depression of the S-T segment ($P < 0.001$). This was significantly diminished in 13 of the 14 patients after all three beta-receptor antagonists, irrespective of the effect on symptoms. The peak height of the T wave during exercise was unchanged after all three drugs.

Changes in Heart Rate and Blood Pressure.—There was a conspicuous reduction in heart rate both at rest and during treadmill exercise after each drug as compared to placebo (table III, figs. 3 and 4). The systemic blood pressure of all patients was within the normal range at rest. The systolic blood pressure before, during, and after treadmill exercise was significantly reduced by all three drugs; the diastolic pressure was unchanged.

COMPARISON OF CHANGES AFTER INTRAVENOUS AND ORAL PREPARATIONS

There was a relatively close level of agreement between the changes in symptoms, changes in electrocardiogram, and changes in heart rate and blood pressure after the two modes of administration of all three drugs. Of the eight patients who improved after intravenous propranolol, seven improved after the oral preparation. Similar figures for oxprenolol were eight and six, and for practolol nine and six. Changes in the degree of electrocardiographic S-T depression and peak height of the T wave, changes in heart rate, and changes in systolic blood pressure were not statistically significantly different after the intravenous and oral administration of any of the three drugs, except that the heart rate was higher after intravenous as compared to oral oxprenolol.

CORRELATION BETWEEN CHANGES IN EXERCISE TOLERANCE, ELECTROCARDIOGRAM, HEART RATE, AND SYSTEMIC ARTERIAL PRESSURE

There was no meaningful correlation between the changes in exercise tolerance and changes in S-T segment depression. All but one patient showed conspicuous reduction in electrocardiographic S-T segment depression after all three drugs by both routes of administration. Thus there was a reduction in S-T depression in 84 of 90 studies, irrespective of changes in time of onset of pain. There was a reduction in the degree of S-T segment depression in patients in whom there was no change in symptoms or even in those in whom angina was worsened. Conversely, pain was relieved in the patient who showed no electrocardiographic improvement.

There was a close relation between the degree of S-T segment depression and heart rate ($r = 0.380$; $P < 0.001$) and between S-T segment depression and systolic blood pressure ($r = 0.256$; $P < 0.01$) when all studies were grouped together. In both instances values were normally distributed along the calculated regression line.

Discussion

This study was particularly concerned with testing the comparative effectiveness of single intravenous and oral doses of propranolol, oxprenolol, and practolol in patients with exercise-induced angina pectoris for the reasons outlined in the introduction. The results are clear-cut but to bring them into therapeutic perspective it is essential to emphasize the specific factors in the trial that may limit their more general clinical application.

Patients were carefully selected. Only relatively young male patients with exercise-induced stable angina and without other cardiac or metabolic disease were studied. Their heart size, electrocardiogram, and left ventricular function were normal at rest but exercise-induced angina was accompanied by reversible electrocardiographic and haemodynamic signs of acute myocardial ischaemia. Such a close selection of patients imposes considerable limitations on any attempt to apply the results of these studies to a broader clinical population. But the definition of such a patient cohort is essential in such a diverse clinical syndrome as angina pectoris if answers are to be obtained by such specific therapeutic questions as were posed in the present study.

The design of the trial may be criticized on the count that only the effects of a single dose of each drug were examined. Although such a test situation readily discloses the *immediate* effects of each drug, the results obviously cannot be directly used to predict the results of long-term multidose trials or uncontrolled clinical treatment. Neither does this study give any information of the comparative efficacy of these drugs during their long-term administration nor any indication of their optimum dosage in the individual patient.

The method of assessment used in these studies also had shortcomings in the wider clinical application of these results. Although treadmill walking provides a test situation similar to the exercise stress that normally precipitates angina, in these studies it was necessarily carried out under controlled environmental and physiological conditions, a situation quite unlike that obtaining in everyday life. However, such controlled laboratory conditions are essential if valid objective therapeutic comparisons are to be made.

The doses of drugs used in any comparative trial must be equated in terms of relevant common variable. With the beta-receptor antagonists three objective methods of dose equation may be used. Drug plasma concentrations have been advocated as a measure of describing the probable concentration of the antagonists of the beta-receptor site. But this is only applicable in any comparative drug evaluation if the concentration and beta-antagonistic activity of unchanged drug and *all its metabolites* are precisely known. Probably of more direct pharmacological relevance is the titration of each dose of beta-receptor antagonist against an agonist such as isoprenaline, or the less precise method of equating the dose of each drug in terms of the degree of heart rate suppression to a constant exercise load. Both methods were used in the present study. The doses of drugs used were equated in terms of their dose-response relation to isoprenaline-induced tachycardia; the final single doses used

were chosen on the basis that they produced a near-axmimum suppression of the heart rate during teadmill exercise (Taylor *et al.*, 1973).

These critical reservations naturally detract from the wider application of these findings to the general angina population in everyday life on long-term treatment with beta-receptor antagonists. But their specific validity is enhanced by a number of the design aspects of the trial. Rigid precautions were taken to eliminate patient and observer bias, reproducibility of symptoms was carefully defined in each patient, the method of assessment was carefully chosen to impart sufficient sensitivity to the test situation to allow adequate discrimination between individual changes in exercise tolerance, the study was placebo-controlled, double-blind in design with single-blind analysis, and the drugs under comparison were administered in random serial order to each patient.

The results clearly showed that two-thirds of expected anginal attacks were abolished or significantly shortened by all of the beta-receptor antagonists, and in the doses used each drug was equally efficacious in this respect. Despite some individual patient variation most patients who responded to one preparation also responded to the others. Electrocardiographic evidence of left ventricular myocardial ischaemia was conspicuously reduced irrespective of the changes in anginal pain; all three drugs were equally effective in this respect. Likewise, the reduction in exercise tachycardia and systolic blcod pressure was universal after all three drugs in both modes of administration, again irrespective of changes in exercise tolerance.

There was no meaningful relation between the changes in exercise tolerance or any of the objective circulatory or electrocardiographic variables measured. But there was a significant correlation between the circulatory and electrocardiographic changes both in the individual patient and in the grouped results.

These findings may be interpreted as indicating that in equal heart rate suppressive doses all three drugs are similarly effective in lessening the degree of myocardial ischaemia and improving exercise tolerance in most patients with exercise-induced angina pectoris. But it must also be emphasized that despite similar reductions in heart rate and blood pressure during exercise and equal improvement in electrocardiographic evidence of myocardial ischaemia, 15% of anginal attacks were worsened by these drugs. Despite the debate that has recently centred around the possible pathophysiological mechanisms involved (Robinson, 1971; Taylor, 1973) this therapeutic paradox remains one of the outstanding problems in the management of angina pectoris with these agents.

Although there are many reports of the effects of beta-receptor antagonists in angina pectoris, most fail to satisfy the criteria necessary to interpret their findings in the general clinical scene (Sharma and Taylor, 1973). In many studies the patients have been poorly defined or their selection has been such as to comprise a clinically heterogenous group. The design of the trial has rarely been adequate. The method of assessment has often depended on historical subjective criteria alone, and the sensitivity of discrimination of the changes under study has been frequently insufficient to support the quantitative conclusions reached. These criticisms apply with added emphasis to most comparative therapeutic trials reported, in which equipotency of drug dosage has also been largely ignored. But in those trials which satisfy many of the essential criteria of patient selection, trial design, and method of assessment comparison of two or more of these drugs either in intravenous or oral form has yielded similar results to the present study (Wilson *et al.*, 1969; Prichard *et al.*, 1970; Sharma *et al.*, 1971; Coltart, 1971). However, we know of no serial single-dose comparative evaluation of the symptomatic electrocardiographic and circulatory effects of these three drugs in equivalent dosage in intravenous and oral form, other than that of the present study.

In addition to the direct therapeutic results and conclusions, there are a number of additional observations that are of wider interest. Much discussion has centred around the possible therapeutic value of the various ancillary pharmacological properties of the beta-receptor antagonists. These properties include local anaesthetic or membrane stabilizing activity—possessed by propranolol and oxprenolol but not by practolol; intrinsic sympathomimetic activity—possessed by oxprenolol and practolol but not by propranolol; cardioselective activity—possessed by practolol but not by propranolol or oxprenolol; and ability to penetrate the blood-brain barrier and cause "central" effects—possessed by propranolol but not by practolol. The fact that in equipotent doses, at least as judged by the suppression of the heart rate response to exercise, these three drugs were equally efficient in improving exercise tolerance would suggest that these ancillary pharmacological properties are of little or no direct relevance in the relief of anginal pain. In addition, although these studies cannot supply a direct answer as to the specific importance of the unchanged drug or its metabolic breakdown products in the relief of angina, the fact that similar symptomatic, electrocardiographic, and circulatory effects results after their intravenous and oral administration in all instances affords some evidence that such breakdown products are probably of therapeutic relevance only in so far as they exert antagonism against endogenous sympathetic activity at the cardiac beta-receptor sites.

Finally, it is important to emphasize that these studies furnish no information of the dose-response relation to any of the three drugs and neither do they allow the identification of patients in whom symptoms may be improved or aggravated. But if it is accepted that the electrocardiographic changes do indeed represent lessening of myocardial ischaemia, and there is reasonable evidence for such an assumption (Kemp *et al.*, 1968; Braunwald *et al.*, 1969; Reid *et al.*, 1971), then the fact that these agents result in conspicuous electrocardiographic improvement in nearly all patients irrespective of their effect on symptoms suggests that these drugs may possibly afford some long-term benefit despite their less than ideal symptomatic performance in many anginal patients.

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