Comparison of two adrenergic beta-receptor blocking agents, alprenolol and propranolol, in treatment of angina pectoris

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Twenty-six patients with typical angina pectoris were treated with alternating four-week courses of alprenolol 400 mg daily, propranolol 160 mg daily, and placebo for 12 months (standard dose regimen). Subsequently, 17 of the patients took part in a 6-month dose-response study in which the dose was increased by one and a half and two times the standard dose. All patients were given digitalis throughout except for 8 in the dose response study.

Statistically significant increases in the total work performed on a bicycle ergometer were found with both active compounds when compared with placebo, the increases being around 10 per cent on standard dose, and between 35 and 47 per cent in the dose response study. No obvious influence of digoxin on exercise tolerance was found.

Patients with previous myocardial infarction responded better at standard dose levels, and also sustained an improved exercise tolerance on placebo, when compared with those who had not had an infarct.

Both compounds reduced the heart rate and blood pressure at rest and after exercise. Triple product values (product of heart rate, systolic pressure, and QT time) were decreased on both drugs in comparison with placebo, both at rest and at the end of effort, by 15 to 20 per cent. At the higher dose levels, the 'normalization' times of the systolic blood pressure after work were slower with propranolol than with alprenolol.

Aspects of the clinical trial investigation in angina pectoris patients are discussed, including the problems of digitalization during long-term treatment with beta-blockers.

There was no difference in the cardiac depressant effects between the two drugs. With the exception of 4 patients, side effects were slight.

Adrenergic beta-receptor blocking compounds have been used for some time in the treatment of angina pectoris. The available beta-blockers differ in certain ways, and there has been much discussion as to how this might influence their effectiveness. It has, for instance, been suggested that a beta-blocker having some intrinsic beta-receptor stimulating effect, such as alprenolol, might be less prone to cause cardiac failure than a drug without such an effect, such as propranolol. However, the suggestion has also been made that the latter type of beta-blocker could be more efficacious owing to a higher degree of inhibition of chronotrophic stimuli. Furthermore, studies of prophylactic treatment with beta-blockers in angina have usually been of a short-term charac-

ter. The purpose of the present study was to make a long-term comparison of these two beta-blockers in order to elucidate these points.

Obtaining a patient population for the evaluation of newly introduced beta-receptor blocking agents in the treatment of angina pectoris is complicated by previously established and satisfactory therapy with analogous compounds in many patients.

Accurate assessment of the response of angina to treatment is also made difficult by the effects of the normal fluctuation of the disease, often related to climatic and emotional changes.

It is also becoming increasingly difficult in hospital practice to find patients with 'steady state' angina suffering from one to two attacks a day or more, such patients being considered most suitable for these types of study. Proper readjustment of the patient's daily routine, together with the free use of

prophylactic glyceryl trinitrate, is usually responsible for this reduced frequency of attacks.

In view of these problems, it proved necessary to draw on patients from four departments of cardiology in London. This report presents the results of such a study in patients treated with alternating monthly courses of alprenolol, propranolol, and placebo for a period of at least 12 months at the usual dose level recommended in current clinical practice. In view of the long-term nature of the study, it was decided that all patients would receive digoxin 0·25 mg daily. At the end of this period of treatment, a dose response study was performed at two additional therapeutic levels of each compound, including the omission of digoxin in certain selected patients.

The dose levels chosen for the two beta-blockers have been found to be equipotent with regard to inhibition of isoprenaline-induced and exercise-induced tachycardia in man (Åblad *et al.*, 1967; Kaltenbach *et al.*, 1971).

Patients and methods

Patients with angina were very critically selected and at whichever of the four cardiac departments they attended, were seen and examined by the same physician (D.J.H.), except when she was away on annual holidays when another of us (M.B.C.) maintained the continuity. Patients were chosen whose anginal symptoms had been in an unchanged state for a minimum of 3 months, and who were complaining of a minimum of 5 attacks a week.

Factors in selection included the ability of the patient to leave employment for regular hospital attendance, emotional stability, and competence as a good witness. Patients suffering from asthma or other respiratory disease, anaemia, aortic stenosis, or intermittent claudication were excluded.

Of the 26 patients, 10 continued with previous treatment (diuretics, anticoagulants, tranquillizers) during the study. Glyceryl trinitrate was taken freely for the anginal attacks, and in some cases prophylactically as well if this had been their previous practice, in which case separate recordings on diary cards were made by the patient.

A simple record card was completed by the patient and returned to the hospital at each visit, showing the number of prophylactic and therapeutic glyceryl trinitrate tablets taken each day, the number of daily anginal attacks, and any possible precipitating factors such as sudden weather change or emotional crises.

The degree of angina in each patient was assessed according to one of six grades:

1) Angina on strenuous effort only.
2) Angina on walking at normal speeds for over half a mile.
3) Angina on walking at normal speeds for less than half a mile.

4) Angina on slow walking for a short distance.
5) Angina on slight effort and occasionally at rest.
6) Frequent angina at rest.

At each visit, conditions were standardized as far as possible in terms of appointment time, intake of tablet to examination time (usually 1 to 2 hours), time of previous light meal, and a 30-minute rest period before examination.

Using a mechanically braked Monark bicycle ergometer (Varberg, Sweden), exercise tests were carried out at every visit using a standard procedure of 4 minutes at each load of 300, 600, and 900 kpm/min until the onset of anginal pain. During the course of the study, it was noted that in some patients, a slower increment stepwise seemed more desirable (i.e. 300, 450, 600 kpm/min) as cessation of exercise took place immediately after an increase in load. A basic metronome speed of 100 a minute was used.

Total work performed during the exercise test was calculated by multiplying load by time, i.e. 300 kpm/min for 4 minutes = 1200 kpm.

It was stressed to each patient that the pain end-point should be no more than that experienced under otherwise 'normal' conditions, e.g. walking up an incline, which would force them to stop.

In some cases, dyspnoea rather than pain determined the end-point during exercise, but the same criteria as above still held. In such cases, the dyspnoea end-point had been evident from the start of the study.

At each exercise test, a note was made on the specially designed clinical record sheet of the exact reason for discontinuing exercise, the time of onset of pain, and the exact duration of pain. Heart rate and blood pressure recordings were taken at rest, at the end of each step of exercise, and at 2, 4, and 6-minute intervals during the post-exercise phase.

Electrocardiograms were recorded from all leads before and after exercise, and a left praecordial recording was made during the last 15 seconds of each phase of exercise, and during the post-exercise period. To facilitate a better quality recording, the reference electrode to the left leg was sited on the forehead, and the right leg to the right arm.

Recordings of the room temperature, external temperature, and the patient's weight were made at each visit. Care was also taken to ensure that the time interval between tablet intake and the start of the exercise test remained at about 1 hour.

Electrocardiographic abnormalities during the exercise test were assessed on the change in the QT ratio based on Bazett's formula (Bazett, 1920), it being accepted that digitalis precluded significant interpretation of the ST segment depression. Thus, measurements of the QT ratio were recorded at rest, on stopping exercise, and at 2, 4, and 6-minute intervals after stopping exercise, the latter recordings being made while the patient was still sitting on the bicycle.

At every visit, a blood sample was taken for the estimation of the serum level of alprenolol, carried out by gas-liquid chromatography (Ervik, 1969). Periodic screening investigations including haemoglobin, white cell count,

blood urea, and liver function tests were carried out during the study.

Two separate studies were undertaken during this trial, the initial standard dose study, followed by the dose response study.

Standard dose study

There was an initial run-in period of 8 weeks during which all patients received placebo tablets one q.i.d., and a full medical assessment including exercise tolerance every 2 weeks. In a few cases previously on propranolol, a deterioration of the anginal state occurred, thus necessitating their exclusion from this study, and therefore excluding patients in whom benefit would have been most evident.

Subsequently, patients received 4 weeks of alternating treatment in a double-blind random crossover manner of alprenolol 100 mg q.i.d., propranolol 40 mg q.i.d., i.e. the standard dose regimen, and placebo tablet one q.i.d., the tablets being identical in shape, colour, size, and taste. To avoid the onset of side effects, it was recommended that every 4-week course should start at a dose of half a tablet q.i.d. for the first 7 days, followed by one tablet q.i.d. for the remaining 21 days.

Patients were advised that an evaluation was being carried out on 3 different drugs that had been used in the treatment of angina pectoris. All gave their consent.

In the statistical evaluation, Student's t test for paired differences has been used, two-tailed, unless otherwise stated.

Dose response study

a) At the end of 12 months double-blind study using the standard dose regimen, all patients entered a dose response study where their exercise tolerance was assessed after three-week alternating courses of alprenolol and propranolol therapy at higher dose levels. The doses used were alprenolol 600 mg daily and propranolol 240 mg daily, then alprenolol 800 mg daily and propranolol 320 mg daily (i.e. one and a half and twice the standard dose regimen). Once again, the study was double-blind in a random crossover manner, and patients remained on digoxin.

b) After these four courses of treatment, those patients who reported subjective improvement and had increased exercise tolerance then continued with the optimal effective dose of the beta blockers *without* digoxin therapy. However, of the 16 patients under study at this stage, only 8 satisfied the criteria for digoxin withdrawal based on the presence of a normal heart size on the chest x-ray, no evidence of pulmonary venous congestion, no previous history of a myocardial infarction or heart failure, and that pain and not dyspnoea was the endpoint of the exercise tolerance test.

These dose response studies took place on all patients during the period October 1970 to May 1971.

Results

Although a total of 43 patients entered the study during the first 12 months starting September 1969,

only 26 (20 men and 6 women) completed at least one 3-month period of treatment (Table 1). Results of 73 treatment periods are assessed in Tables 2, 3, and 4. Eight patients defaulted for non-medical reasons during the run-in period, and a further 8 patients were withdrawn from the study when their clinical condition began to deteriorate during the first few days on placebo therapy, and it was considered essential for them to be on continued beta-blocker therapy. One further patient fell out due to side effects (headache) from digoxin administered during the run-in period.

Exercise tolerance during run-in and placebo periods

When looking at the total work in the four control tests and the subsequent placebo tests, it was apparent that, on average, the second, third, and fourth tests (on placebo) were about 20 per cent improved on the first test, but exercise tolerance then fell though still remained 8 per cent higher in the subsequent placebo tests.

As we had a significant number of patients who could be stratified into those with pain as the endpoint during exercise, and those with dyspnoea, and also into two groups depending on whether or not there was a previous history of myocardial infarction, it was felt that the results of exercise tolerance of these groups on placebo should be assessed. There was no significant difference between the pain and the dyspnoea groups. Patients with a previous myocardial infarction (MI +) seemed to sustain an improved exercise tolerance with placebo averages around 20 per cent higher than the first exercise test, in contrast to those with no previous history (MI −) who, after the initial run-in improvement (as seen in the group as a whole), steadily decreased. This is also apparent in the Fig. where the total work has been averaged (with correction for missing values) for each quarter of the year. Initially, the results follow a similar trend until the end of the first 12 months, when the exercise tolerance of the MI − group continues to decrease, against the steady state of the MI + patients.

Standard dose study

Total work Analysis of each separate 3-month block showed no significant difference in total work for any drug compared to placebo. However, when the 3-month blocks were averaged for each patient, and the calculated mean values averaged, there was a statistically significant difference of 11·4 per cent increase of total work on alprenolol (P < 0·01) and 9·3 per cent increase with propranolol (P < 0·05) (Table 2). In those patients who were changed from

TABLE I *Data for 26 patients included in study*

| Case No.	Sex	Age (yr)	Grade of angina	Duration of angina (mth)	Other therapy	Myocardial infarction
1	M	57	3	7		+
2	M	52	4	10	D	+
3	M	51	4	5		+
4	M	56	2	3		−
5	M	45	3	9		−
6	M	59	2	24	D, A	+
7	F	65	3	36	A	+
8	M	65	4	30		+
9	F	61	2	12	A	+
10	M	53	3	12	A	+
11	M	67	3	12		−
12	M	61	2	12		−
13	M	60	3	18	D	+
14	M	49	4	24		−
15	M	54	4	48		−
16	M	59	3	24	A	+
17	M	33	1	60		+
18	F	67	2	8		−
19	F	58	4	36	S	+
20	M	44	2	60	A	+
21	M	62	3	56		+
22	F	62	4	18		−
23	M	69	3	48	S	−
24	M	46	3	5	D	+
25	M	54	3	3		−
26	F	49	2	24		−
Means 20M	6F	56·1		23·2		15+ 11−
Range		±1·7		3 to 60		

D, diuretic; A, anticoagulant; S, sedative.
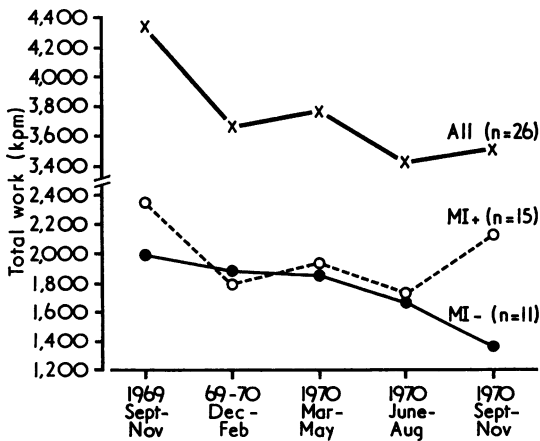
FIG. *Total work at 'run-in' and placebo tests over 15 months (weighted means) for all patients, and divided into those with previous myocardial infarction (MI+) and those without (MI−).*

the 300, 600, 900 kpm/min protocol to the 300, 450, 600 protocol of exercise test during the study, there was no statistically significant difference between the total work performed with either protocol. In a few cases, it was not possible to make comparisons using the same protocol in a 3-month block. In the majority of such cases, the possible difference was so small as to be considered insignificant, as the total work was low (in fact identical up to 1200 kpm) on both protocols. There were a few cases, however, where the difference in exercise protocol might have influenced the results significantly. In those cases, adjustments have been made, and always to the disadvantage of the beta-blockers.

When looking at the best average responses in total work, irrespective of the drug, it was seen that the patients were well divided into two groups. One group had a median value of 27 per cent (range from +16 to +81%, in 15 patients), while the other group of 11 patients had a median value of 0 per cent (range of −23 to +10%). As the mean placebo results varied little with time, once the first run-in tests were done, we have considered the first group as 'responders' and the second group as the 'non-

TABLE 2   *Total work (kpm) performed by all patients on standard dose regimen: values are means of all completed 3-month periods of treatment (* Responders)*

Case No.	Alprenolol 400 mg daily	% change from placebo	Propranolol 160 mg daily	% change from placebo	Placebo
1	3400	81*	2325	24*	1875
2	1667	14	1933	32*	1467
3	975	18*	1050	27*	825
4	2900	−9	3008	−2	3067
5	1200	−43	1650	−23	2125
6	3000	17*	2950	15*	2563
7	1500	0	1200	−25	1500
8	2100	35*	1500	−3	1550
9	1269	4	1594	31*	1219
10	1050	27*	875	6	825
11	1975	10	1725	−4	1800
12	3388	35*	3131	22*	2570
13	3500	8	3767	17*	3233
14	3500	0	3800	9	3500
15	991	18*	1350	60*	842
16	1956	18*	1913	15*	1663
17	3594	35*	3600	35*	2663
18	925	21*	916	20*	766
19	733	2	733	2	716
20	4600	−9	5043	0	5062
21	2525	0	2350	−6	2513
22	1550	−7	1303	−22	1666
23	1517	1	1583	5	1500
24	2119	9	2275	18*	1938
25	925	16*	675	−16	800
26	825	−4	900	5	856
Mean	2065	11·4	2044	9·3	1889
SEM	215	4·3	221	3·9	205
P values by Wilcoxon matched-pairs signed ranks text	<0·05	<0·01	<0·05	<0·05	
Number of responders	11			12	
Mean increase of responders	28%			26%	

responders'. Thus 57 per cent of the 26 patients responded with at least a 26 per cent increase in exercise tolerance on the standard dose.

Stratification of patients into MI+ and MI− patients showed that MI+ patients increased their exercise tolerance by an average of 12·5 per cent (propranolol) to 17·3 per cent (alprenolol), compared with 4·9 per cent (propranolol) to 3·5 per cent (alprenolol) for the MI− patients. These figures are significantly different for the two groups (P < 0·05). Of the 15 responders, 11 were MI+ and 4 MI−, whereas of the non-responders, 4 were MI+ and 7 MI− (P = 0·10 for difference in distribution by Fischer test).

Attack rate and glyceryl trinitrate consumption   Twenty-two patients recorded attacks and/or glyceryl trinitrate consumption therapeutically, and the mean values for both active compounds and

placebo were calculated with no statistically significant differences in either variable being noted on the average (Table 3). During the run-in period, though 18 of the 26 patients had more than 5 attacks and/or consumed more than 5 glyceryl trinitrate a week during the first 4 weeks, these decreased about 40 per cent towards the end of the run-in period (Table 4). In view of this, only half of the patients had sufficient numbers of attacks or tablets consumed to make an individual assessment meaningful. We have chosen the limit of 2·5 attacks and/or tablets consumed per week as the limit for assessability. It was then found that 14 of the 26 patients were assessable with regard to these two variables. There was no difference between the two active drugs; in some patients, alprenolol was more effective, in others propranolol was more so, and in about one-third they were equally effective. Nine of the 14 assessable patients had a decrease of 20 per cent or more in either the

TABLE 3 *Weekly attack rate and glyceryl trinitrate consumption on standard dose regimen: values are means of all completed 5-month periods of treatment*

Case No.	Alprenolol		Propranolol		Placebo	
	Attack rate	Glyc. trin. consumpt.	Attack rate	Glyc. trin. consumpt.	Attack rate	Glyc. trin. consumpt.
1	4	1·3	2·9	1·4	2·8	2·4
2	4·8	4	6	4·2	8·4	6·1
3	2·7	2	2·3	1·8	3·2	2
5	3·9	1·6	7·3	1·6	5·9	0·5
6	0·9	0·8	0·9	0·9	1·6	1·5
7	3·3	4	7	7	6·3	7
9	1·1	1·2	1·4	1·5	1·3	1·1
10	9	19·8	7·8	17	5·3	11·5
11	1	1·5	0·3	0·3	0	0
12	0·4	0·4	0·6	0·8	1·1	1·1
13	5	15·8	6·7	13·7	6·8	20·6
14	0	0	1·5	1·5	2	2
15	20·8	20·8	11·9	11·9	19·1	19·1
16	12·1	12·1	8·7	9·3	9·8	10·8
18	0·2	2·7	0·1	2·5	0·4	0·3
19	7·1	0·2	5·3	0·1	5·3	1·1
21	0·8	0·4	1	0·2	0·7	0·7
22	1·8	0·8	1	1	1·2	0·8
23	10·3	2·9	9·4	1·4	12·2	12·2
24	6·4	10·2	6·3	9·4	7·7	3·2
25	2·3	2·3	0·5	1·6	3	2·5
26	2·2	2	2·5	0·8	2·5	2·5
Means	4·60	4·80	4·15	4·15	4·85	4·95

The differences are statistically not significant

Four patients (Cases 4, 8, 17, and 20) recorded no attacks or glyceryl trinitrate consumption after the run-in period, and have been excluded from this Table.

attack rate or the glyceryl trinitrate consumption or both on one of the beta blockers.

In order to analyse the seasonal variation of the glyceryl trinitrate consumption, we have taken all the figures for 16 patients who consumed at least 2·5 tablets per week during at least one month of the study. Figures from alprenolol and propranolol periods were included as there was no significant difference from placebo. The seasonal variation is very slight after the initial decrease. Low values for December 1969 and January 1970 may be due to the

TABLE 4 *Gylceryl trinitrate consumption per week for the first 8 weeks, i.e. during the run-in period with placebo**

Week	1-2	3-4	5-6	7-8
Mean	9·3	8·1	5·4	5·5
SEM	2·4	2·1	1·4	1·4

* Of the 26 patients, only 22 took glyceryl trinitrate for the attacks. For the other four patients, the number of attacks has been included in the calculations.

fact that not all patients had entered the trial at that time. Later on there seems to be a slight decrease in the summer months, and an increase again toward the autumn.

Heart rate and blood pressure Calculations of the mean values showed that both active compounds produced a reduction in the resting heart rate, the rate recorded on completion of a standardized work load (i.e. 1200 kpm), and the rate on cessation of exercise; the effect of propranolol was more conspicuous. Systolic pressure at rest and on completion of 1200 kpm was also reduced by both compounds, there being no statistically significant difference between alprenolol and propranolol (Table 5).

QT ratio Measurements of the QT ratio at the point of maximum exercise, when ischaemic changes in the heart would be most marked, showed a significant reduction with both compounds, when compared with placebo values (Table 6). At standard dose levels, the differences between placebo-alprenolol readings at rest, end of exercise, and at 2 minutes

326   *Hetherington, Comerford, Nyberg, and Besterman*

TABLE 5   *Comparison of heart rates and systolic blood pressure measurements on standard and high dose schedules*

		Rest	SEM	At 1200 kpm	SEM	End of exercise	SEM	Post-exercise 2 min	6 min
Heart rate									
Standard dose	Placebo	78	1·47	108	2·29	121	5·21	94	83
	Alprenolol	67	1·07	95	2·0	103	3·22	78	72
	Propranolol	59	1·08	89	1·52	95	2·86	69	63
High dose	Placebo	75	1·92	106	3·36	116	9·12	90	79
	Alprenolol	65	1·14	89	1·75	95	2·0	71	69
	Propranolol	53	1·11	81	1·81	88	2·08	60	58
Systolic blood pressure									
Standard dose	Placebo	134	2·55	155	2·95			152	135
	Alprenolol	130	2·0	147	2·95			146	129
	Propranolol	128	2·24	146	2·81			143	128
High dose	Placebo	135	3·06	150	2·63			149	134
	Alprenolol	123	2·83	142	3·30			143	122
	Propranolol	122	2·52	139	3·49			145	128

All heart rates on each dose level are significantly different from each other (p < 0·01 or less). Blood pressure levels on each drug are significantly different from those on placebo (p < 0·025 or less), but not between drugs.

and 6 minutes after exercise were all statistically significant. Differences between the two compounds only occurred at rest, with propranolol having a lower reading.

TABLE 6   *Comparison of QT ratio measurements*

	Rest	End of exercise	2' post-exercise	6' post-exercise
Standard dose study				
Placebo	0·982	1·065	1·005	0·990
Alprenolol	0·938	1·027	0·968	0·951
Propranolol	0·924	1·022	0·967	0·944

Differences between placebo–alprenolol, and placebo–propranolol are all statistically significant (P < 0·001)
Differences between alprenolol–propranolol are only significant at rest (P < 0·05)

	Rest	End of exercise	2' post-exercise	6' post-exercise
Dose response study				
Placebo	0·979	1·069	1·010	0·982
Alprenolol	0·973	1·037	0·986	0·967
Propranolol	0·948	1·044	0·974	0·963

Differences between placebo–alprenolol are statistically significant at end of exercise (P < 0·001) and at 6' post-exercise (P < 0·05)
Differences between placebo–propranolol are statistically significant at rest, end of exercise and 2' post-exercise (P < 0·02) and at 6' post-exercise (P < 0·05)
Differences between alprenolol–propranolol only significant at rest (P < 0·02)

Triple product   The triple product (TP) of heart rate, systolic blood pressure, and left ventricular ejection time is well correlated with myocardial oxygen consumption (Goldstein and Epstein, 1972). We have calculated a triple product of heart rate, systolic blood pressure, and QT time for all treatment periods, based on the means of the heart rate, systolic blood pressure, and QT ratio for each individual treatment period.[1] The values were all decreased on both drugs in comparison with placebo at rest, and at the end of exercise by 17 to 27 per cent (Table 7).

[1] With Bazett's formula for the QT ratio, the equation can be written $TP = 3 \cdot 1 \times \sqrt{HR} \times BP \times QT$ ratio.

TABLE 7   *Calculations of means of triple product of heart rate, systolic blood pressure, and QT ratio*

	Rest	End of exercise	% reduction on comparison with placebo
Standard dose only			
Placebo	1155	1829	—
Alprenolol	1000	1529	17
Propranolol	909	1445	21
Dose response study			
Placebo	1151	1733	—
Alprenolol	967	1323	25
Propranolol	846	1254	27

Dose response study

By October 1970 when the dose response study started, only 18 of the 26 patients remained in the trial due to 4 withdrawals (2 myocardial infarctions, 1 death, 1 patient with side effects), 1 defaulter, and 3 others who had completed insufficient treatment periods on the standard dose regimen. On increasing the dose, one patient complained of drowsiness, and was withdrawn from this part of the study, though continued with the original standard dose regimen. Results of the remaining 17 patients are presented in Tables 8 to 10.

Total work There was a striking increase of between 35 and 47 per cent in exercise tolerance with an increased dose, which was statistically significant for both drugs. However, no significant difference was found between one and a half and two times the standard dose regimen (Table 8). The total work values have been shown for the first four 3-week periods (i.e. two periods on one and a half and two periods on two times the standard dose regimen), and for comparison all mean values for alprenolol and propranolol at standard dose, as well as placebo mean values.

There was no significant difference between the group who continued digoxin, and those who did not, nor between the two drugs (Tables 9 and 10). The apparent decrease on propranolol without digoxin was largely due to one patient (Case 24). It should also be noted in Table 10 that owing to side effects at the highest dose level, the results on three of the patients (Cases 12, 13, and 17) were those for one and a half times the standard dose level. Case 23 was excluded from these calculations as he was unable to maintain higher dose levels due to the onset of hypotension and lassitude, and he returned to the standard dose regimen.

Stratification of the patients into MI+ and MI− did not show any difference between these groups with regard to increase of the total work on increased dose.

Attack rate and glyceryl trinitrate consumption Results were assessable in 5 patients only, using previously mentioned criteria. The attack rate and/or tablet consumption differed by more than 20 per cent in 3 patients, all of whom had lower figures on propranolol.

Heart rate and blood pressure Both active compounds decreased these variables more than at

TABLE 8 *Dose response study – total work performed (expressed in kpm) in initial four 3-week periods. For comparison, means of all placebo and active treatment periods from standard dose trial, for 17 patients, have been included*

Case No.	Placebo	Alprenolol 400 mg daily	%	Propranolol 160 mg daily	%	Alprenolol 600 mg daily	%	Propranolol 240 mg daily	%	Alprenolol 800 mg daily	%	Propranolol 320 mg daily	%
5	2125	1200	−44	1600	−25	1200	−44	1950	−8	1700	−20	2050	−4
6	2563	3000	17	2950	15	3900	52	4200	64	3450	34	4200	64
9	1219	1269	4	1594	30	1200	−2	1800	48	1760	44	2325	92
11	1800	1975	9	1725	−5	2250	25	2210	23	2250	25	2250	25
12	2570	3388	31	3131	21	4800	37	3450	34				
13	3233	3500	8	3767	16	4700	45	3000	−7	3800	18	3800	18
15	842	991	17	1350	60	1200	43	1650	96	1425	69	1200	43
16	1663	1956	17	1913	15	2100	26	2145	29	2550	53	2100	26
17	2663	3594	34	3600	35	5400	103	4200	58	3900	46	3700	39
18	766	925	20	916	19	1200	57	1200	57	1170	53	1200	57
19	716	733	2	733	2	900	26	1050	47	1050	47	960	34
20	5062	4600	−9	5043	−1	5100	±0	5400	7	5600	11	4700	−7
21	2513	2525	±0	2550	1	2500	−1	3000	19	3550	41	3700	47
23	1500	1517	1	1583	5	1800	20	1650	10				
24	1938	2119	9	2275	17	4250	119	3000	55	2950	52	5400	179
25	800	925	15	675	−16	1525	91	1125	41	1200	50	1500	88
26	856	825	−4	900	5	1050	23	1050	23	750	−12	930	9
Means	1931	2061	7·5	2123	11·4	2651*	39·4	2475*	35·1	2474*	35·5	2667*	47·3
SEM	274	287	4·3	296	4·8	398	10·3	310	6·6	355 n=15	6·5	378 n=15	12·0

All drug means are significantly different from placebo with P < 0·01 or less.
* Significantly different from corresponding standard dose with P < 0·02 or less.
There is no significant difference between the effects of one and a half times and twice the standard dose on either drug.

TABLE 9   *Calculations of total work performed (expressed in kpm) on twice the standard dose regimen (alprenolol 800 mg daily, propranolol 320 mg daily) for six 3-week periods: digitalis therapy withdrawn in last 4 periods*

Case No.	Placebo	With digitalis		Without digitalis			
		Alprenolol	Propranolol	Alprenolol	Propranolol	Alprenolol	Propranolol
5	2125	1700	2050	1500	1650	1500	1650
11	1800	2250	2250	2400	2250	3300	2325
16	1663	2250	2100	2100	2325	2200	2100
18	766	1170	1200	1600	1600	1500	1500
20	5062	5600	4700	5400	5250	5700	5400
21	2513	3550	3700	3400	3500	3150	2700
24	1938	2950	5400	3000	2775	3300	2650
25	800	1200	1500	1425	1000	1100	1500
Means	2083	2621	2863	2603	2544	2719	2478
SEM	477	517	547	473	472	528	451
Percentage increase		26	38	26	22	30	19

All drug means are significantly different from the placebo value with $P < 0.05$ or less.
There is no significant difference between alprenolol and propranolol with or without digoxin.

standard dose levels except for heart rate at rest on alprenolol (Table 5). It should be noted that at the end of exercise, high doses of alprenolol depressed the heart rate to about the same level as the standard dose of propranolol.

The rate of return to normal of the systolic blood pressure after work was different for the two beta-blockers. On alprenolol, the pre-exercise level was reached 6 minutes after exercise, whereas at that time on propranolol, systolic blood pressure was still significantly higher than before work ($P < 0.02$).

QT ratio This was slightly higher at the end of exercise for both beta-blockers when comparing the values on standard dose, but still significantly lower than on placebo. The rate of return to normal of the QT ratio after exercise was quicker on alprenolol where the value two minutes after exercise was almost the same as the resting value, whereas with propranolol the value at 6 minutes was still higher ($P < 0.05$).

Triple product This was decreased to about the same level as was found on the standard dose due

TABLE 10   *Dose response study – calculations of total work performed on twice standard dose regimen (alprenolol 800 mg daily, propranolol 320 mg daily) for six 3-week periods: digoxin therapy continued throughout*

Case No.	Placebo	Alprenolol	Propranolol	Alprenolol	Propranolol	Alprenolol	Propranolol
6	2563	3450	4200	4150	4150	4200	4300
9	1219	1760	2325	1450	1950	1600	1500
13	3233	4700	3000	2100	3900	3450	4500
15	842	1425	1200	1200	1350	1450	1425
17	2663	5400	4200	4400	3600	4100	4500
19	716	1050	960	1300	1125	975	1225
26	856	750	930	1125	975	950	1050
12	2570	5100	3800	7200	7200	4500	4950
Means	1833	2954	2577	2866	3031	2653	2931
SEM	361	683	504	775	751	547	622
Percentage increase		61	40	56	65	44	60

All drug means are significantly different from the placebo value with $P < 0.05$ or less.
There is no significant difference between alprenolol and propranolol with or without digoxin.

to the further decrease in heart rate and blood pressure being offset by the higher QT value compared with the standard dose results.

Serum levels of alprenolol

Variable levels were noted during the studies with a range in 46 samples of from 3 to 471 ng/ml (mean 6·2) during the 400 mg daily dose regimen, in 19 samples of from 8 to 308 ng/ml (mean 7·8) at 600 mg daily, and in 32 samples of from 6 to 497 ng/ml (mean 11·8) at 800 mg alprenolol daily. One patient (Case 21) had exceptionally high serum levels on 400 mg daily (220 to 479 ng/ml in 4 samples).

Drop-outs, complications, and side effects

During the entire 20 months of this study, only 4 patients complained of marked side effects, or suffered severe complications, necessitating their withdrawal from the trial (Table 11). One female patient complained of swollen and painful hands and feet, with fever, during one of the alprenolol and one of the propranolol treatment periods. The symptoms subsided 48 to 72 hours after stopping the drug. These episodes occurred during the 7th and 12th months of the study, and the patient had also complained of headaches during two of the placebo periods. Two patients were withdrawn

when they suffered a further myocardial infarction (one during alprenolol and one during propranolol treatment). One death occurred in a male patient during the 12th month of treatment while on alprenolol; this as well as one death in the run-in period were considered to be due to the normal course of the disease.

The side effects and complications in the standard dose study are given in Table 12. The overall incidence was 1 per 12 treatment periods for alprenolol, 1 per 13·7 treatment periods for propranolol, and 1 per 6 treatment periods for placebo. The side effects that did not cause withdrawal from the study were varied, transient, and in no case interfered with the patient's normal daily progress, nor necessitated any changes in therapy. Fifteen of the patients did not complain of any side effects at all.

Of the 17 patients in the dose response study, 2 had to reduce the dose immediately from twice to one and a half the standard dose on account of either dyspnoea or blurred vision (Cases 12 and 17). Two other patients (Cases 13 and 23) were unable to sustain the higher dosage and had to reduce after a 12-week period from twice to one and a half, and from one and a half to standard dose respectively, due to the onset of normotensive dizziness, or lassitude associated with hypotension.

Laboratory investigations and patient's weight

The analysis of the screening investigations showed no pathological variation during the course of the study. Average weights remained about the same on all three treatments.

TABLE 11 *Summary of side effects, drop-outs, and complications*

Number of patients entering the study (September 1969 to September 1970)	43
Defaulted for non-medical reasons	8
Withdrawn due to deterioration in run-in (placebo) period	7
Withdrawn due to sudden death	1
Withdrawn due to headaches on digoxin in run-in period	1
Remaining patients to complete at least one 3-month period of treatment in standard dose trial	26
Defaulted for non-medical reasons (after at least one 3-month period on standard treatment)	1
Withdrawn due to myocardial infarction	2
Withdrawn due to sudden death	1
Withdrawn due to swollen joints (see text)	1
Not completed standard dose programme by October 1970	3
Remaining patients for dose-response study (October 1970)	18
Withdrawn in first period due to drowsiness	1
Patients with side effects in dose-response study after at least two treatment periods, necessitating reduction of dose to one and a half times standard dose or standard dose	4

TABLE 12 *Side effects and complications reported in standard dose study*

	Alprenolol	Propranolol	Placebo
Myocardial infarction	1	1	
Sudden death	1		1*
Swollen joints	1	1	
Indigestion	1	1	5
Nausea			1
Dry mouth	2		
Blurred vision		2	
Headache			4
Insomnia			1
Dizziness		1	4
Lassitude	1		2
Palpitations			1
No. of side effects	7	6	19
No. of treatment periods	84	82	113

* During the run-in period.

Discussion

The present study confirms the efficacy of the adrenergic beta-receptor blocking drugs in the treatment of angina pectoris. Previous studies with alprenolol have shown an increased exercise tolerance of between 20 and 60 per cent after an oral 100 mg dose (Adolfsson, Areskog, and Rasmuson, 1971; Sealey *et al.*, 1970, 1971; Dagenais, Pitt, and Ross, 1971; Sowton and Smithen, 1971: Fritz-Hansen, Rasmussen, and Nyberg, 1973; Keyriläinen, Nyberg, and Uusitalo, 1973). Similar findings were reported with propranolol after a 40 mg dose orally (Gianelly *et al.*, 1967; Battock, Alvarez, and Chidsey, 1969).

The lower figure of around a 10 per cent increase in this study may be due to the long-term treatment period (average of 17 months per patient) set against the background of the normal course of the disease. A further explanation may be found in the varying methodology of different investigators. Total work performed may vary depending on whether a single load, or stepwise increases are used. Redwood *et al.* (1971) suggested that it was better to start below the critical load, and increase it after a few minutes. However, the time on each load should not be too long as this might result in changes caused by prolonged exercise after 10 to 15 minutes (Ekelund, 1967).

Accepting a 15 per cent increase in exercise tolerance over placebo values as an indication of response, there were 11 alprenolol and 12 propranolol 'responders'. The mean increases in exercise tolerance in these two treatment groups were 28 and 26 per cent, respectively. Those of the responders who continued with the dose response study (9 patients) showed a further increase of at least as much as that reached on the standard dose on either or both drugs in practically all cases. Of the 7 non-responders who continued with the dose response study, 6 also showed a significant increase in exercise tolerance. This confirms that the optimum dose is quite often higher than the one chosen from the start of the study as the standard dose.

The improvement in exercise tolerance of between 35 and 47 per cent in the dose response study confirmed the finding of Sandler (1971) and other investigators (J. Hoy and E. Sowton, 1970, unpublished data) that the effects of increasing the dose of one beta-blocker are unlikely to follow the same patterns as increasing the dose of another. However, in our findings, the differences in the results of the groups at one and a half and twice the standard dose levels were not statistically significant. Sealey *et al.* (1970) showed an average increase in total work of 32 per cent after alprenolol 100 mg but only a 25 per cent increase after 200 mg. In some of his patients, the obvious decrease in exercise tolerance on the higher dose was probably due to a fall in blood pressure towards the end of exercise, resulting in a fall in the coronary perfusion pressure, or a lowered perfusion pressure in the legs, whereas in others (3 out of 10), exercise tolerance increased clearly without a concomitant obvious reduction in blood pressure, as in the present trial.

The results during the run-in period of an 'overshoot' of about 20 per cent in the second to the fourth tests supported both Sealey's findings (1970) of the necessity for repeated tests to eliminate the 'rapport' period response, and also the recommendation of Redwood *et al.* (1971) that several test periods should be employed to enable patients to become accustomed to the bicycle exercise technique.

In the exercise tests, we have chosen as the end point the onset of that degree of pain which would, under normal circumstances, force that patient to discontinue his activity. It has been stressed that deliberate exercise to this point could be considered dangerous and non-ethical. We are of the opinion that if a patient exerts himself to that degree of pain in his home, it is safe for him to repeat this under hospital conditions with continuous monitoring, and where resuscitation facilities are to hand if required. Furthermore, it is very difficult to decide the exact onset of vague discomfort during exercise preceding actual pain. Though slightly more than half of the patients studied complained of pain at the end point during exercise, 7 complained of acute dyspnoea throughout the trial. There was no significant difference in total work increase between patients with pain at the end point and those with dyspnoea. It was felt that this breathlessness was due to acute left ventricular failure, and that the rapid disappearance of symptoms after stopping exercise was accompanied by a rapid return to normal of left ventricular function (Sharma and Taylor, 1970).

Other workers (Taylor, 1971) have recommended digitalis before beta-blockade for patients with angina associated with congestive cardiac failure, because of the combined effectiveness. However, in the group of 8 patients in the dose response study where digitalis was withdrawn, the apparent decrease in exercise tolerance on the highest dose of propranolol was due largely to one patient, and was not statistically significant. Though Smith, Bousvaros, and McGregor (1966) in a double-blind study on 15 anginal subjects failed to show any obvious influence of digitalis on exercise tolerance in angina pectoris patients, it could well be only beneficial to those patients with some degree of cardiomegaly. In the absence of heart failure, Parker *et al.* (1969)

were unable to find any evidence of significant clinical or haemodynamic benefit from digitalis in exertional angina. Their findings were in contrast to those of Malmborg (1965) who reported that digitalis therapy was of value in approximately 50 per cent of patients with coronary artery disease, even when clinical signs of congestive failure were lacking. In this latter study, patients were exercised in the supine position, which in terms of haemodynamic consequences is probably quite different from exercise in the sitting position.

Our findings in the attack rate and the glyceryl trinitrate consumption confirm the impressions of other authors (Sharma *et al.*, 1971; Sowton and Smithen, 1971) that such measurements for the quantitative assessment of anginal therapy are useless. The only possible exception may be those patients who experience many attacks of angina every day (Riseman, 1966).

Pentecost, George, and Nagle (1971) have pointed out a major pitfall in the assessment of therapy in prescribing a fixed dose for all patients. They suggested an initial run-in period of at least 6 weeks, followed by a dose response study based on the subjective comments of the patients themselves in regard to an improvement in their angina. We do not accept that this subjective assessment is valid in those patients in whom the attack rate and/or glyceryl trinitrate consumption may be low and thus of little value in helping the patient to determine his own status. Furthermore, improvement in exercise with increasing doses may not be accurately noted by the patient. A comparison of the objective measurement of exercise tolerance gives a more reliable guide to the therapeutic effect. We agree with Sandler (1971) that an exercise tolerance test with electrocardiographic control is the simplest method of studying antianginal drugs in patients with relatively infrequent attacks.

The mechanism of action of adrenergic beta-blockers in angina has been well shown. The triple product at the end of exercise was decreased in the present study by both compounds at equipotent doses to about the same degree, in comparison with placebo. However, if the imbalance between oxygen demand and supply at the point of angina is assumed to be the same, one would expect the same triple product after beta-blockade at cessation of work. The fact that it was lower after beta-blockade, which Robinson (1967) also found using the simple product of heart rate and blood pressure, indicated that the oxygen sparing effect of the reduced external load on the heart was offset by another effect of the beta-blockers which tended to increase oxygen consumption. One such factor may be the heart size. The importance of the relation of heart size to myo-cardial oxygen consumption was confirmed by the results of Dagenais *et al.* (1971) who found that under the influence of nitrates, there was an increase in exercise tolerance without a decrease in the heart rate – blood pressure product at the point of angina. Nitrates are known to decrease heart size.

Contrary to widespread belief, there was no difference in the average resting heart rates on placebo of the exercise responders and non-responders. The beta-blocking effects of both alprenolol and propranolol were seen in the significant reduction of heart rate when compared with placebo values, both at rest, at 1200 kpm, and at the end of exercise. Though the absolute values were lower with propranolol, it should be noted that the heart rate increase from rest to the end of exercise was reduced to the same degree (16%) by both drugs on standard doses, and more by alprenolol (27%) than by propranolol (15%) at higher dose levels due to the resting heart rate not being further depressed by the higher dose of alprenolol (Table 10). This bears out the absence of intrinsic beta-stimulating effect of propranolol in contrast to alprenolol, and is not due to incomplete blockade (Åblad *et al.*, 1971).

In the electrocardiographic evaluation of angina, measurement of the ST segment depression has usually been used as an index of myocardial ischaemia. However, digitalis is known to give false positive results (Kawai and Hultgren, 1964) and, therefore, the QT ratio was estimated instead. It is accepted that healthy subjects react to exercise with a shortening of the QT ratio with or without digoxin, while patients with ischaemic heart disease develop a lengthening of the QT ratio with exercise (Frankl, Deitz, and Soloff, 1968). Decrease of the QT ratio can be interpreted as evidence of lessened myocardial ischaemia, possibly due to an improved balance between oxygen delivery and demand by the heart. Though it is accepted that levels of 1·08 or more indicate ischaemic heart disease (Master and Rosenfeld, 1961), the absolute value may be less important than the actual increase during exercise (Frankl *et al.*, 1968). In this study, the QT ratio increased as expected, but only to approximately 1·07 on placebo. On both active compounds, it was significantly lower, both at standard dose and high dose levels (Table 5). On this basis, it appears that there was less ischaemic change during exercise with alprenolol and propranolol than with placebo. Furthermore, the normalization time was more rapid with alprenolol than propranolol. It was interesting to note that the same difference of normalization occurred in the systolic blood pressure after effort on the higher doses.

In repeated serum alprenolol level estimations, an increase in the mean levels occurred as the daily dose

was raised, but there was considerable individual variation which supports similar findings of other authors (Sowton and Smithen, 1971). There was no correlation between the therapeutic effect and serum levels in individual cases, and it appeared impossible to predict with reasonable accuracy the individual degree of beta-blockade for a set serum level.

This trial has shown that both compounds are equally effective (at doses with equal beta-receptor inhibitory effect) in increasing exercise tolerance at all three dose levels, with about 60 per cent of the patients responding noticeably on the standard dose levels, increasing to about 90 per cent when the dose is increased by one and a half or twice. With increasing dosage, a larger increase in exercise capacity was also found in those patients who had responded favourably at standard dose levels. Though further side effects occurred at higher dose levels in some cases, they affected only the minority, and all patients were able to continue treatment with one step down in the dose, maintaining improved exercise tolerance.

An unexpected finding was that patients with a previous myocardial infarction respond better at standard dose levels than those who have not had an infarction.

Neither drug turned out to be more cardiodepressant than the other, but possible differences might have been masked by digitalization. Though alprenolol, in equipotent dosages, caused less decrease of the heart rate during work than propranolol, it was not less efficacious.

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