Effect of nifedipine on exercise tolerance in angina pectoris

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SUMMARY Nifedipine is a new antianginal drug, the calcium-antagonistic inhibitory action on excitation-contraction coupling apparently being so pronounced that, in therapeutic dosage, all other pharmacological properties are negligible. Its effect on exercise tolerance in angina was assessed by an exercise study involving 14 patients: single-stage exercise tests were chosen and the advantages of this are given. Our results suggest that the onset of action occurs after about 20 minutes, reaches a peak of activity at approximately one-half to two hours, and some effect may still be present at three hours. There was a significant improvement in exercise times with a mean rise of 50 per cent over placebo.

In recent years various antianginal drugs have been introduced which inhibit the flow of calcium ions across the membrane of the myocardial cell. Earlier examples were verapamil and prenylamine. Nifedipine is the latest and most potent of this class.¹ It restricts calcium ion influx across the cell membrane during excitation so that contraction of both cardiac and vascular smooth muscle is affected.^{1,2} Laboratory studies have confirmed that it reduces the tone of vascular smooth muscle, including that of the coronary arteries, and has a negative inotropic effect on the isolated myocardium.³ In man a drop in peripheral vascular resistance occurs but in therapeutic dose no negative inotropic effect results. In normal resting subjects coronary blood flow, as measured by Xenon 133 uptake, shows an overall increase of 30 to 40 per cent and in patients with coronary arterial disease from 0 to 30 per cent.⁴ In resting subjects with normal coronary arteries this is associated with a rise in coronary sinus oxygen saturation,⁵ showing that the increase in flow is not simply a physiological response to increased myocardial oxygen demand. Ekelund and Atterhog⁶ exercised 10 patients with angina pectoris on a bicycle ergometer and showed significant improvement in exercise tolerance with nifedipine as compared with placebo. Our report is an exercise study using a treadmill and its aims were to establish whether or not nifedipine was an active antianginal agent and to ascertain the duration and intensity of action of the drug.

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Subjects and methods

Eighteen patients were investigated, of whom 14 completed the trial. Details of the investigation to which the patient was to be submitted were explained to each patient and his or her signed informed consent was obtained. Ten were men and four were women. The age range was 43 to 71 years (mean 57). The duration of anginal symptoms was five months to eight years (mean three years two months). All had electrocardiograms consistent with the presence of myocardial ischaemia, either at rest or on exercise. All were in a stable phase with no myocardial infarction within the previous 12 months. Early in our screening of volunteers, we found a poor correlation between daily frequency of attacks and ease of provoking angina in the laboratory. The suitability of patients was therefore decided on exercise performance rather than upon symptoms. During the test week the only other medication permitted was sublingual glyceryl trinitrate which was omitted before the daily tests. No patient had electrocardiographic evidence of left bundle-branch block or left ventricular hypertrophy, and none was receiving digitalis. Patients were also excluded with valvar heart disease and with a history of heart failure. The exercise apparatus was a motor-driven treadmill, adjustable for speed and slope (PK Morgan Limited, Chatham). It had an emergency stop button for the patient and a safety harness triggering an automatic cut-out. Factors which might influence exercise tolerance were controlled: the patients were asked not to smoke on those days on which they would be exercised; the first exercise of each day was at

approximately the same time, namely one and one-half to two hours after the previous meal which was similar in content on each day; the treadmill and laboratory furniture were kept in the same position; the investigators were the same each day; the laboratory was kept at the same temperature and no person unknown to the patient was allowed to enter the room during the tests.

Each patient was investigated for five consecutive days and on each day was exercised from rest to the onset of angina. Exercise was terminated as soon as angina had begun. The time from rest to the onset of angina was recorded. The radiotelemetric electrocardiograph was carefully monitored throughout the procedure, the recording electrode being in the V5 position and the indifferent electrode was below the manubrium sterni. Exercising was repeated from three to six times each day with intervening rest periods of never less than 20 minutes.

The first three days were spent in familiarising the patient with the treadmill and determining the most suitable speed and slope which would repeatedly induce angina between 80 and 120 seconds from rest. On day one each patient began with a multistage test in which walking was started at 2 km/h and increased stepwise by 2 km/h at three minute intervals until angina pectoris was induced. Subsequent tests were single-stage pro-

cedures in which the patient was exercised at the speed of that three minute period during which angina pectoris was induced. Further adjustments in speed and slope were then made until the symptom was regularly induced within the desired 80 and 120 seconds. On days four and five each exercise was carried out at this predetermined load.

Treatment on day four was single-blind. After the first exercise each patient was given a placebo capsule which was identical in appearance and peppermint taste to nifedipine but was told that it could be either. He was asked to bite the capsule and keep the fluid in the mouth as long as possible to aid buccal absorption. Exercising was then repeated as on previous days, up to another six times at the same speed and slope. The times taken from resting to the onset of angina were recorded.

Treatment on day five was double-blind. Procedures on day five were exactly similar to day four except that some patients (group A) had 10 mg nifedipine and others (group B) had a placebo. Patients were allocated in a random fashion into one or other group. The data were assessed by analysis of variance.

Results

Of the 14 patients who completed the study, 13 showed an obvious tendency to an increased exercise

Table 1 Details of exercise tests of 14 patients with angina pectoris

Case no.	Slope (°)	Speed (kph)	Capsule given (h)	Exercise	Day 4						
					1	2	3	4	5	6	7
1*	12	4	D4 14.28	Starting time (h)	14.20	14.47	15.09	15.30	15.59	16.25	—
			D5 14.28	Duration (s)	80	98	83	87	79	75	—
2*	6	3	D4 14.25	Starting time (h)	14.16	14.40	15.05	15.31	16.00	16.22	16.45
			D5 14.28	Duration (s)	80	90	92	56	40	70	95
3	10	5	D4 10.25	Starting time (h)	10.14	10.55	11.28	12.00	12.30	—	—
			D5 10.28	Duration (s)	100	85	95	90	100	—	—
4*	7	5	D4 10.50	Starting time (h)	10.47	11.15	11.45	12.27	13.00	—	—
			D5 10.43	Duration (s)	85	85	95	115	135	—	—
5	7	5	D4 11.03	Starting time (h)	11.01	11.20	11.58	12.45	—	—	—
			D5 11.06	Duration (s)	70	100	100	90	—	—	—
6*	10	5	D4 10.23	Starting time (h)	10.13	10.44	11.10	11.37	12.09	—	—
			D5 10.09	Duration (s)	105	110	113	111	100	—	—
7	12	5	D4 10.28	Starting time (h)	10.15	10.48	11.26	11.48	12.24	—	—
			D5 10.18	Duration (s)	90	105	90	95	85	—	—
8	8	2	D4 10.52	Starting time (h)	10.40	11.15	11.43	12.16	12.46	—	—
			D5 10.47	Duration (s)	62	66	63	73	65	—	—
9*	12	6	D4 10.40	Starting time (h)	10.25	11.02	11.45	12.07	12.40	—	—
			D5 10.45	Duration (s)	77	75	80	87	80	—	—
10	8/9	2	D4 10.47	Starting time (h)	10.36	11.15	11.43	12.10	12.35	—	—
			D5 10.37	Duration (s)	85	75	82	84	95	—	—
11	8	4	D4 10.30	Starting time (h)	10.27	11.05	11.35	12.05	12.26	—	—
			D5 10.49	Duration (s)	67	62	60	75	67	—	—
12*	10	6	D4 14.29	Starting time (h)	14.21	15.05	15.28	15.53	—	—	—
			D5 14.52	Duration (s)	118	120	125	126	—	—	—
13*	12	5	D4 10.37	Starting time (h)	10.18	10.50	11.20	11.50	12.18	—	—
			D5 10.23	Duration (s)	130	148	142	135	145	—	—
14	10	4	D4 15.10	Starting time (h)	14.52	15.32	15.59	16.38	—	—	—
			D5 14.51	Duration (s)	80	80	84	72	—	—	—

D4, day 4; D5, day 5.

* Nifedipine on day 5.

Endpoint: onset of angina pectoris.

tolerance during the training days, and exercise loads necessarily were increased to keep the time from resting to the onset of angina pectoris within the required limits. This was not possible in two patients without uncomfortable speeds and slopes and longer times were permitted. In six patients the improvement in exercise tolerance with training was such that the workloads had to be increased on day three. Thus a test of less than five days would have been inadequate.

Table 1 gives the details of the exercise tests in 14 patients with angina pectoris. The time in hours refers to the 24 hour clock and the duration of each exercise test is recorded in seconds. It will be noted that every effort was made to make the exercise tests on day 5 comparable with those on day 4.

Seven patients received the placebo on day four and nifedipine on day five (group A). The other seven had placebo both days (group B). Table 2 shows the longest times walked by each patient after each capsule (max time) compared with the precapsule times (base time). In group A patients, on day four (placebo), the improvements ranged from 7 to 59 per cent, with a mean of 20 per cent (Table 2). On day five (nifedipine) the improvements ranged from 17 to 186 per cent, with a mean of 70 per cent. The extremes of the ranges are from the same two patients. The difference

between the improvements is statistically significant; $SE \pm 21.79$, $t = 2.27$, $p < 0.05$ (5% value of t with 12° freedom is 2.18). The changes in performance in group B patients (placebo on both days) ranged from a 0 to 43 per cent improvement on day four (mean 15%) and from a 6 per cent decrease to an increase of 75 per cent on day five (mean 19%): the difference between these improvements is insignificant; $t = 0.35$. In group A patients (nifedipine) the mean improvement of day five over day four was 50 per cent (range 10 to 127%) and in group B (placebo) 4 per cent (range -18 to +32%). This difference is significant: $SE \pm 16.4$, $t = 2.77$, $p < 0.05$.

In group A patients, except for one (case 13) the difference between nifedipine and placebo response was apparent with the first exercise after treatment (Table 3). Mean improvements were 7.5 per cent with placebo and 32.9 per cent with nifedipine. Intervals between treatment and the first exercise thereafter were very variable over the group (10 to 36 minutes) but relatively constant for each patient. The corresponding improvements for group B were 5.8 per cent (day four) and 7.7 per cent (day five).

In group A the time interval between giving nifedipine and the longest exercise time before the onset of pain (maximum time) varied from 29 to 140 minutes with a mean of 74 minutes (Table 4). The best times after placebo in the same patients were obtained between 15 and 141 minutes with an almost identical mean of 75.7 minutes. Thus, though there was an improved performance with nifedipine, the timing of the peak, on average, did not differ from that obtained with placebo.

It had been our intention that on day five exercises should be continued until performance figures had fallen from the peak or maximum values to near base values; thereby we would have had an estimate of duration of action. Unfortunately, none of our patients taking nifedipine was able to exercise for more than twice after their peak values because of fatigue and only one of them, our poorest responder (case 12), had performance figures approaching base times. The last exercises were performed between 83 and 184 minutes after treatment (Table 4).

In this acute study there were no significant side effects. One group A patient felt flushed and had mild headache both days but was worse on placebo. Another had headache on placebo but not on nifedipine. A third patient had dryness of the mouth on nifedipine.

Discussion

Tests involving reproducible exercise are frequently

Day 5						
1	2	3	4	5	6	7
14.18	14.46	15.07	15.29	15.56	16.18	—
77	110	115	100	110	95	—
14.18	14.40	15.05	15.25	15.58	16.20	16.42
70	100	120	122	103	115	45
10.15	10.53	11.26	11.50	12.20	—	—
102	128	130	110	105	—	—
10.35	11.16	11.51	12.25	13.00	13.32	—
105	140	195	225	300	240	—
10.53	11.33	12.06	12.41	13.14	—	—
100	175	150	95	100	—	—
9.58	10.35	11.06	11.38	12.01	12.37	13.00
112	185	190	190	170	165	175
10.05	10.47	11.15	11.38	12.02	12.28	—
100	85	105	107	100	90	—
10.37	11.08	11.41	12.09	12.37	—	—
52	52	58	56	65	—	—
10.28	11.05	11.38	12.07	12.48	—	—
76	90	97	105	94	—	—
10.27	10.57	11.22	11.45	12.10	—	—
105	80	100	102	95	—	—
10.46	11.10	11.35	11.58	12.25	—	—
68	63	58	64	58	—	—
14.42	15.19	15.46	16.13	—	—	—
133	155	155	135	—	—	—
10.02	10.33	11.08	11.38	12.07	—	—
133	148	205	166	170	—	—
14.38	15.06	15.35	16.11	—	—	—
88	88	70	95	—	—	—

Table 2 Exercise times of 14 patients with angina pectoris

Group A							Group B						
Case no.	Day 4 (placebo)			Day 5 (nifedipine 10 mg)			Case no.	Day 4 (placebo)			Day 5 (placebo)		
	Base time (s)	Max time (s)	Improvement (%)	Base time (s)	Max time (s)	Improvement (%)		Base time (s)	Max time (s)	Improvement (%)	Base time (s)	Max time (s)	Improvement (%)
1	80	98	23	77	115	49	3	100	100	0	102	130	27
2	80	95	19	70	122	74	5	70	100	43	100	175	75
4	85	135	59	105	300	186	7	90	105	17	100	107	7
6	105	113	8	112	190	70	8	62	73	18	52	65	25
9	77	87	13	76	105	38	10	85	95	12	105	102	-3
12	118	126	7	133	155	17	11	67	75	12	68	64	-6
13	130	148	14	133	205	54	14	80	84	5	88	95	7
Mean			20			70	Mean			15			19

used in order to assess the efficacy of antianginal drugs. Birkett and Chamberlain⁷ believe exercise studies to be of greater value than carefully designed prolonged double-blind trials. In long-lasting trials consumption of glyceryl trinitrate may inadequately reflect changes in effort tolerance, particularly in patients who limit its use because of side effects.⁸ The frequency of attacks may not decrease with increased effort tolerance if this leads to greater activity, as shown in this study. A drug which increases effort tolerance should be of value to patients with angina pectoris even when, because of increased activity, neither the number of attacks nor the amount of glyceryl trinitrate consumed are reduced. An exercise study of the present design also involves each patient for a shorter time than a prolonged trial, so that he is off possibly more efficacious treatment for a shorter period and is, therefore, at less risk.

Single stage tests⁷⁻⁹ may be more meaningful than multistage tests¹⁰ in quantifying changes in exercise performance, as they take account of haemodynamic responses induced by exercise. It has been shown that the triple product of heart rate $\times$ ejection $\times$ systolic aortic root pressure is proportional to

myocardial oxygen consumption¹¹⁻¹² and achieves a constant level for each patient at the onset of angina unless excessive workloads are used.¹³ When a patient is exercised at a constant workload from rest, the rate of increase in triple product is maximal at the onset lessening as exercise continues and reaches a plateau with steady state in about four minutes.¹³ The graphical recording of this response approximates to an inverted exponential curve (Fig. 1 and 2). Thus, if the level of triple product at which angina occurs is achieved early at a particular workload, any improvement caused by treatment may, on re-exercising at the same workload, lead to only a short delay in the onset of symptoms (Fig. 1, A¹ and A²; and Fig. 2, A). Conversely, if the anginal threshold is reached at a time approaching the steady state the same therapeutic intervention would cause a much longer delay in the onset of pain and indeed, at that particular workload, might prevent its occurrence entirely (Fig. 1, B¹ and B²; and Fig. 2, B). It is thus misleading to regard the difference between the time of onset of angina pectoris before and after a therapeutic intervention as a linear measure of improvement. Indeed it will be seen that any such difference is of greater

Table 3 Percentage improvement of first exercise time after taking capsule compared with pre-capsule exercise time (base time) and interval between taking capsule to exercise

Group A					Group B				
Case no.	Day 4 placebo		Day 5 nifedipine 10 mg		Case no.	Day 4 placebo		Day 5 placebo	
	%	Min	%	Min		%	Min	%	Min
1	22.5	19	42.9	18	3	-15	30	25.5	25
2	12.5	15	42.9	12	5	42.8	17	75.0	22
4	0	25	33.0	33	7	16.6	20	-15.0	29
6	4.76	21	65.2	26	8	6.45	23	0	21
9	-2.6	22	18.4	20	10	-2.6	22	-24.0	20
12	1.7	36	16.5	27	11	-7.5	35	-7.35	21
13	13.8	13	11.3	10	14	0	22	0	15
Mean	7.5		32.9			5.8		7.7	

Table 4 Time interval between taking capsule and longest exercise time to demonstrate improvement; group A took placebo and nifedipine and group B took only placebo

Group A			Group B		
Case no.	Times of max time after taking capsule		Case no.	Times of max time after taking capsule	
	Day 4 placebo (min)	Day 5 nifedipine 10 mg (min)		Day 4 placebo (min)	Day 5 placebo (min)
1	20	40	3	126	60
2	141	59	5	20	30
4	135	140	7	21	81
6	48	60	8	85	51
9	85	83	10	109	69
12	86	29	11	96	70
13	15	107	14	50	81
Mean	75.7	74		72.4	63.1

significance if the time of onset of angina before the therapeutic intervention is of short duration. For example, an improvement of 20 seconds occurring when the time to angina is 80 seconds from the onset of exercise is of greater significance for suggesting improvement than a similar 20 second delay occurring when the time from resting to angina pectoris before the therapeutic intervention is 180 seconds.

From examination of the curves in Fig. 1 and 2, it will be seen that the ratio of the time to angina pectoris after therapeutic intervention to that before that intervention is almost constant for a particular patient at different workloads. The difference, maximum time minus base time, lessens with higher loads, but the ratio of the two remains fairly constant. This method makes feasible the comparison of improvements of different patients with different times to angina pectoris before a therapeutic intervention. It can only apply if the

Fig. 1 This applies to an antianginal drug which lowers peripheral vascular resistance and therefore triple product (TP) response to exercise, without altering TP at anginal onset. A^1 and B^1 are TP response of same patient before treatment to different work loads. A^2 and B^2 are the corresponding responses after the same treatment. ($a^2/a^1 = b^2/b^1$) but $a^2 - a^1$ is less than $b^2 - b^1$.

Fig. 2 This applies to a drug which increases coronary arterial flow and therefore TP at anginal onset, leaving peripheral vascular resistance unaltered. ($a^2/a^1 = b^2/b^1$) more closely than $a^2 - a^1 = b^2 - b^1$.

workload is constant and the same for both test drugs and placebo.

The drawback of the method is that it requires that the times to the onset of angina under constant conditions should be reproducible within fairly fine limits. Otherwise, natural fluctuation plus therapeutic effect may lead to steady state being reached before anginal onset. Moreover, the natural fluctuation and improvement previously mentioned are such that the patient has to be exercised several times before a work level is achieved which will precipitate angina pectoris every time between 80 and 120 seconds. In most of our patients this was achieved on exercise testing after two days, but in six of them a third day was required to achieve this reproducibility. In most patients the variation was over 50 per cent on the first day and it was not until day three that the results were reproducible with a 10 to 15 per cent range.

The placebo response of between 15 and 20 per cent in our patients is high for an acute study¹³⁻¹⁵

but may reflect the sensitivity of the method. Natural fluctuation in exercise tolerance and the tendency of it to improve after the first exercise could account for this. The close reproducibility of placebo response, however, increases the significance of the 50 per cent difference between nifedipine and placebo. This compares very favourably with similar studies carried out on beta-blockers.⁷⁻⁹

Subjective improvement, as shown by increased effort tolerance, was accompanied by a corresponding delay in the appearance of ischaemic ST segment depression or T wave changes in the effort electrocardiogram, indicating that nifedipine acts very causing a reduction in myocardial hypoxia for a given degree of exercise, rather than by suppressing anginal pain.

We were unable to give an accurate indication of the duration of action of nifedipine in the treatment of angina pectoris. As mentioned, we had planned that on day five exercises should be continued until the performance figures had fallen from the maximum values to near baseline values. None of our patients receiving nifedipine was able to exercise for more than two periods after their peak values because of fatigue, and only one of them, our poorest responder (case 12), had performance figures approaching base times. The last exercises were performed between 83 and 184 minutes after treatment (Table 4). Our results suggest, however, that the onset of action of nifedipine occurs after about 20 minutes, reaches a peak of activity at approximately one-half to two hours, and some effect may still be noted at three hours. This compares with a time of onset between five and 10 minutes for sublingual glyceryl trinitrate or isosorbide dinitrate, with a duration of action of approximately 90 minutes and 120 minutes, respectively.¹⁶

It is of interest that though there was an improved performance with nifedipine, the timing of the peak, on average, did not differ from that obtained with placebo. Table 1 shows the development of this peak for both nifedipine and placebo-treated patients. It suggests that the observation is at least in part the result of the warm-up phenomenon. It will be noted, however, that the peak, as well as being higher, is maintained in those patients receiving nifedipine whereas it falls away in those receiving placebo. Maintenance of the improvement, therefore, appears to be associated with the active therapeutic intervention.

Our findings suggest that nifedipine is an active antianginal agent and that its action is more prolonged than glyceryl trinitrate or isosorbide dinitrate. The evidence justifies its further clinical evaluation as an antianginal agent.

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