IMPROVED PHYSICAL PERFORMANCE AS A THERAPEUTIC OBJECTIVE IN PATIENTS WITH ANGINA

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- 1 Improvement in physical performance, based on exercise tolerance, self-assessed work and physician-rated functional capacities, is proposed as a measure of efficacy of anti-anginal therapy in the rehabilitation of the cardiac patient.
- 2 Improved physical performance parallels changes in frequency of anginal attacks and a nitroglycerin requirements following β -blocker therapy.
- 3 Nadolol (a β -blocker), given once daily is as effective as propranolol, given four times daily as an anti-anginal agent.

Introduction

THE most prevalent health problem in the developed world is ischaemic heart disease. It is the most common cause of death in the US, with the current annual mortality rate greater than 675,000 patients. In addition, approximately 1.3 million patients have experienced a myocardial infarction, and even more suffer from congestive heart failure arising from primary heart disease (Hillis & Braunwald, 1977).

Thus, it is not surprising that a host of chemotherapeutic, and more recently surgical, approaches have been introduced to treat angina pectoris, although sublingual glyceryl trinitrate (nitroglycerin) remains the mainstay of current therapy for prompt relief of anginal attacks. The objective of the various modalities of treatment is to diminish myocardial oxygen consumption or to increase oxygen supply to the heart.

With the introduction of β -adrenoceptor blockers as anti-anginal agents (Dornhorst & Robinson, 1962; Black *et al.*, 1964), the rationale of effective therapy was directed to controlling myocardial oxygen consumption by reducing (1) heart rate, (2) arterial BP and (3) myocardial contractility. However, the latter action, that is, myocardial depression, can pose a serious problem in the production of adverse effects in predisposed patients (Aronow, 1976).

Pool (1976) has emphasized the importance of evaluating improvement of physical performance as a practical aspect of the response to β -blocker therapy in angina. Accordingly, the effectiveness of nadolol (a non-cardioselective β -adrenoceptor antagonist without intrinsic sympathomimetic

activities, developed by The Squibb Institute for Medical Research), as an anti-anginal drug was assessed, in comparison with propranolol, on the basis of its effect on physical performance along with the conventional measurements of weekly frequency of anginal attacks, nitroglycerin consumption and exercise tolerance.

Nadolol has been shown in animal studies to be strikingly less depressant on the myocardium than propranolol (Lee *et al.*, 1975). Furthermore, nadolol has a terminal plasma half-life in normal subjects of at least 17 hours (Dreyfuss *et al.*, 1977). However, clinical experience has shown that the plasma half-life can be as long as 24 h depending on dose. This suggests the feasibility of a once daily dosage regimen for nadolol. Whereas propranolol is metabolized extensively by the liver, during the first passage before reaching the general circulation (Walle & Gaffney, 1972; Shand, 1975), nadolol is excreted unaltered in the urine and faeces (Dreyfuss *et al.*, 1977) and is not affected in this way.

Methods

Following institutional review committee approval and informed patient consent, 31 investigators in 13 countries (9, Germany; 4, Sweden; 3 each, Brazil and the Philippines; 2 each, Austria, Egypt and England; and 1 each, Argentina, Belgium, Colombia, Mexico, New Zealand and Venezuela) enrolled 527 patients (426 males and 101 postmenopausal females) whose

ages ranged from 30-79 years. Patients were selected on the basis of frequent attacks of classical angina pectoris, characterized by substernal or left sternal pain occurring in attacks precipitated by effort, excitement, heavy meals or exposure to cold, and relieved by nitroglycerin. These attacks occurred at a weekly frequency of at least five times for the 3 months before the study. Except for nitroglycerin (used only to terminate an attack and not prophylactically), any anti-anginal medication was to be discontinued at least 4 weeks prior to entry into the study. Patients were excluded if they had aortic or mitral valvular heart disorder, sinus bradycardia, or greater than first degree heart block. Patients selected for the study were blindly assigned, in accordance with a table of random assignments maintained in a central location, to nadolol or to propranolol in a 3:2 ratio. Matching placebo, nadolol and propranolol tablets were manufactured. The tablets were placed in blister foil packs. Patients assigned to nadolol received nadolol as their initial daily dose followed by matching placebo for the remaining three doses. For patients assigned to propranolol, the active medication was divided into four equal daily doses. Before preparing the clinical supplies the propranolol tablets had been demonstrated to be bioequivalent to Inderal tablets of the same strength by carrying out bioavailability studies in human volunteers.

However, principally for failure to adhere to the protocol or for lack of adequate data while on treatment, 128 patients (24%) had to be excluded from any evaluation of the efficacy of treatment.

The study was divided into two periods: (1) an initial placebo period of 3-8 weeks to adapt the patient to the study conditions (including the exercise-stress test procedure), to establish baseline frequency of anginal episodes and requirements for nitroglycerin, and to determine the patient's baseline exercise tolerance and work capacity; (2) a 14-week period of active therapy during which dosage titration to an optimal daily maintenance dosage was accomplished.

Daily oral doses of nadolol and propranolol varied from 40-240 mg. Nadolol was given as a single daily dose in the morning whereas propranolol was administered in divided doses, four times daily. The endpoints of dose titration were: (1) at least a 50% reduction in the frequency of weekly anginal attacks; (2) at least a 50% decrease in weekly nitroglycerin consumption; (3) resting heart rate slowing to below 55 beats/min; or (4) a fall in standing systolic BP to less than 100 mmHg.

Evaluation of efficacy was based on the following parameters: (1) reduction in weekly frequency of anginal attacks; (2) decrease in weekly nitroglycerin consumption; (3) increased exercise tolerance; and (4) enhanced work capacity. The first two parameters

were followed by means of daily patient diaries, and were analyzed only if the baseline weekly frequency of attacks was five or more. Change in work capacity was based on the patient's self-assessment of ability to perform work. Maximum improvement was +3, maximum deterioration was -3, and a 0 scale rating constituted no change. In addition, change in functional capacity, as classified by the New York Heart Association (NYHA), was also determined after treatment with nadolol and propranolol. The NYHA classification is: (I) patients without limitation of physical activity; (II) patients with slight limitation of physical activity; (III) patients with marked limitation of physical activity; and (IV) patients with inability to carry on any physical activity without discomfort.

The exercise-stress test was carried out in all hospital centres on an electrically braked bicycle ergometer, generally according to the recommendations of Sanne (1973). The braking force is constant if the pedalling rate is maintained at about 60 rev/minute. Routinely the previously resting patient increased his work load at 3-min intervals by 30 W,

Table 1 Patient population*

	<i>Nadolol</i>	<i>Propranolol</i>
Geographical area:		
Brazil/Argentina	23	16
Central America	18	13
Egypt	41	28
England	16	10
Germany/Austria	82	58
New Zealand	12	8
Philippines	18	12
Scandinavia	27	16
Other	1	0
TOTALS	238	161
Age, average (range)	55.9 (30-79)	55.5 (32-75)
Sex	191 M/47 F	129 M/32 F
Body weight, average (range)	73.1 kg (38.7-110.5)	71.7 kg (41.0-110.0)
Hypertensive	37	34
Diabetic	14	15
Previous myocardial infarction (>6 months earlier)	71	59
Frequency of anginal attacks (weekly)	13.2	14.1
Exercise ergometry (time in seconds)	350	350

*Does not include 128 patients excluded from evaluation of drug efficacy.

up to a maximum of 120 or 150 W, that is, four or five stages. Further details of the exercise protocol are given in Appendix I. Testing was carried out at the same time of day for each patient. Nitroglycerin was prohibited for 1 h before the test. The test endpoints were: (a) a 2 mm change in the ST segment of the electrocardiogram; or (b) pain or fatigue, whichever occurred first.

All of the above parameters, whether subjective or objective in character, were assessed by a physician not aware of the particular β -blocker that the patient was receiving.

Results

The randomization procedure followed resulted in a comparability of the nadolol and propranolol treatment groups as judged by age, sex, body weight, frequency of anginal attacks and exercise ergometer measurements. However, coexistent hypertension or diabetes mellitus, and a history of myocardial infarction occurred more frequently in the propranolol group (Table 1).

There was no significant difference between the response to nadolol or propranolol based on frequency of anginal attacks (Tables 2 and 3). Among those patients experiencing at least five anginal attacks weekly during the placebo period, 63% of 175 patients receiving nadolol and 67% of 107 on propranolol had at least a 50% reduction in the frequency of their attacks. Conversely, only 17% and 19% of those treated with nadolol and propranolol, respectively, failed to experience at least a 25% reduction in the frequency of attacks. Not unexpectedly, the nitroglycerin consumption was similarly reduced in the two treatment groups.

There was no appreciable difference in the improvement in exercise ergometric performance between the two treatment groups. With nadolol there was a mean increase of 38% in exercise time compared with a 36% increase after treatment with propranolol. The mean increase in heart rate produced by exercise ergometry after nadolol was less than after propranolol. However, the ST segment and double product (that is, heart rate $\times$ systolic BP) changes induced by exercise were affected to the same extent by both β -blockers. On

Table 2 Mean change in frequency of anginal attacks

Anginal attacks per week	Number of patients	Nadolol			Number of patients	Propranolol		
		Baseline attacks	End treatment attacks	Change *		Baseline attacks	End treatment attacks	Change *
5-15.9	125	8.0	2.9	-61%	79	8.0	4.0	-46%
> 16	50	26.2	13.8	-45%	28	31.0	10.3	-57%
All patients	175	13.2	6.0	-59%	107	14.1	5.6	-52%

*The mean percentage change is derived by calculating the percentage change for each patient, and averaging these values.

Table 3 Response at optimal daily dose

Optimal daily dose (mg)	Number of patients	Nadolol		Cumulative response rate	Number of patients	Propranolol		Cumulative response rate
		Patients responding *				Patients responding *		
40	25	14		6%	17	7		4%
80	58	41		23%	26	14		13%
120	58	45		43%	28	20		25%
160	47	38		58%	53	41		51%
240	50	41		75%	37	29		69%
Totals	238	179			161	111		

*Response based on reduction of frequency of anginal attacks and/or increased ergometric exercise time.

completion of the double blind study patients were maintained on long-term treatment with nadolol up to 3 years. Thirty patients were placed on the bicycle ergometer 3 and 24 h post-dosing with nadolol to determine whether the improved performance was maintained throughout the 24-h period following the single daily dose. The results of this investigation demonstrated that the improved work performance was maintained throughout the 24-h period.

Among those patients who assessed their own ability to perform work, nadolol and propranolol produced similar improvement (Table 5).

Of 232 patients receiving nadolol for whom 'before' and 'after' NYHA classifications of functional capacity were available, 45% had their classification improved after therapy, 51% remained in the same classification and 4% deteriorated. The values for 160 patients receiving propranolol were 51%, 49% and 0%, respectively.

A summary of the absolute and comparative responses of the several parameters to approximately 3 months of nadolol or propranolol therapy is presented in Table 6.

Conclusions

Angina pectoris was first described as a clinical entity by Heberden in 1772 who reported: "There is a disorder of the breast . . . They who are afflicted with it, are seized, while they are walking with a painful and most disagreeable sensation in the breast, which seems as if it would extinguish life, if it were to increase or continue, but the moment they stand still, all this uneasiness vanishes . . ." (Friedberg, 1972). Approximately a century later chemotherapeutic measures were introduced by two English physicians. Lauder Brunton, in 1867, used amyl nitrite to relieve

Table 4 Mean change in exercise ergometry

<i>Parameter</i>	<i>Drug</i>	<i>Number of patients</i>	<i>Pretreatment</i>	<i>Mean values Post-treatment</i>	<i>Change †</i>
Exercise time (s)	NAD	224	350	412	+ 38%
	PROP	150	350	407	+ 36%
Heart rate (beats/min)	NAD	109	124	99	− 16%
	PROP	86	121	108	− 9%
ST segment Depression (mm)	NAD	107	1.5	1.1	*
	PROP	85	1.5	1.2	
Double product	NAD	109	22103	15402	− 23%
	PROP	85	21317	16045	− 18%

*Not evaluated

† The mean percentage change is derived by calculating the percentage change for each patient, and averaging these values.

NAD, Nadolol; PROP, propranolol.

Table 5 Change in work capacity

<i>Change after therapy</i>	<i>Nadolol (220 patients)</i>	<i>Propranolol (153 patients)</i>
	<i>Number of patients</i>	<i>Number of patients</i>
+ 3	10 (4.5%)	7 (4.6%)
+ 2	52 (23.6%)	34 (22.2%)
+ 1	96 (43.6%)	67 (43.8%)
0	51 (23.2%)	33 (21.6%)
− 1	11 (5.0%)	10 (6.5%)
− 2	0 (—)	2 (1.4%)
− 3	0 (—)	0 (—)

Table 6 Summary of results

<i>Criteria</i>	<i>Treatment</i>	<i>Number of patients evaluated</i>	<i>Mean change (%)</i>
Anginal attack frequency	Nadolol	175	− 59
	Propranolol	107	− 52
Nitroglycerin consumption	Nadolol	158	− 57
	Propranolol	102	− 52
Exercise tolerance (time)	Nadolol	224	+ 38
	Propranolol	150	+ 36
Self-assessed work capacity	Nadolol	213	+ 1.04
	Propranolol	152	+ 0.95

angina, and William Murrell (1879), introduced nitroglycerin solution to abort anginal attacks. However, it was a half century later, in 1928, before it became clear that angina pectoris developed as a result of inadequate oxygenation of the myocardium. Our present understanding of the pathophysiological basis of angina is that an imbalance occurs between regional myocardial oxygen perfusion and metabolic requirements of the heart. Therefore, angina is relieved either by increasing the supply of oxygen or diminishing the demand. Current medical and surgical therapeutic approaches to angina are directed to restoring the balance between myocardial supply and demand.

Since 1964, when propranolol was first proposed for the treatment of angina pectoris, there has been substantial support for the use of β -blockers as anti-anginal agents (Sharma *et al.*, 1971; Aronow, 1976; Conolly *et al.*, 1976; Prichard, 1976; Short, 1977). A number of β -adrenoceptor antagonists have been developed. Some are described as cardioselective, others not. Some have intrinsic sympathomimetic activity and/or local anaesthetic (quinidine-like) action. Most of the currently available β -blockers have a relatively short plasma half-life, ranging from approximately 2-5 h (Riess *et al.*, 1974; Ablad *et al.*,

1974). However, practolol (Bodem & Chidsey, 1973), once used extensively but no longer available for clinical use, and sotalol have plasma half-lives in the range of 10-16 hours. Johnsson & Regardh (1976) have reported that, although a β -blocker may have a relatively short plasma half-life, its pharmacological activity follows zero-order kinetics and this permits a twice daily dosage regimen. Nadolol, a new β -blocking agent, has the longest plasma half-life among the β -blockers currently available. Therefore, it seems reasonable to expect that nadolol will be effective on once daily dosage. A more convenient dosage schedule will encourage improved patient compliance, which is recognized as a problem in any long-term treatment programme (Zweifler & Esler, 1976; Podell & Gary, 1976).

In this multicentre study the efficacy of nadolol, given once daily, has been shown to be comparable to that of propranolol, administered four times daily, for the management of angina pectoris. In addition to the usual clinical evidence of efficacy, such as reduction in frequency of anginal attacks and decrease in consumption of nitroglycerin, there was also improvement in physical performance (as judged by exercise tolerance testing, self-assessed work capacity and physician-rated functional capacity).

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Appendix I

Bicycle ergometer

Exercise stress testing with the bicycle ergometer will follow the recommendations of Sanne (1973). A fixed limit representing physiologically undefined levels of submaximal loads is designated. The exercise test will be carried out using an electrically braked bicycle ergometer. The calibration will be checked every 6 months during the investigation. The braking force will be constant between 45-75 rev/minute. The pedalling rate will be checked by means of a speedometer and kept close to 60 rev/minute. The height of the handle will be fixed during the entire study. The height of the saddle will be adjusted individually to give nearly stretched knee joints in the most distant position and will be kept at the same height during repeated tests. The length of the crank should be constant at 17.5 cm.

The general procedure for the exercise test will start with the patient resting. The work load will be increased, stepwise to 30 W. A working time of 3 min at every stage will be used. The schedule of exercise is listed below:

Stage	Watts	Duration (min)
1	30	3
2	60	3
3	90	3
4	120	3
5	150	3

During the first test, the patient will not exceed 120 W; however, the load may be increased to 150 W on subsequent tests.

Patients were trained on the bicycle ergometer on several occasions during the pretreatment placebo period. On analyzing the results only the final reading at the end of the placebo period was assessed to determine the pretreatment values (Table 4). The post-treatment value was obtained from the final exercise stress test made at the end of the maintenance period on the optimal daily dose of nadolol or propranolol.