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Propranolol in the Prophylactic Treatment of Angina Pectoris

H. F. MIZGALA, M.D., F.R.C.P.[C], A. S. KHAN, M.D., F.R.C.P.[C]
and R. O. DAVIES, M.D., Ph.D., *Montreal*

ANGINA pectoris is thought to result from an imbalance between myocardial oxygen demand and available supply. While occlusive coronary artery disease is believed to be the single most important anatomical factor implicated in the etiology of this disease, other factors may also be involved and play a significant role in its course and severity.[1] Sympathetic overactivity has been implicated as having a deleterious effect in patients with this disease.[2, 3] Indeed, animal experiments have demonstrated that following excessive myocardial sympathetic stimulation, myocardial oxygen consumption may increase in excess of what is necessary for the generation of the required cardiac output.[2] In such circumstances, oxygen demand may even surpass what is afforded by the concomitant increase in coronary blood flow, leading to ischemia of the myocardium. Thus, parenteral infusions of isoproterenol can consistently produce ischemic myocardial necrosis in rats.[4] It is conceivable that in some patients with coronary artery disease, the oxygen wasting of excessive sympathetic tone may be an important factor in provoking attacks of angina at lower levels of physical activity.

For the most part, the medical and surgical therapy of ischemic heart disease has been directed to the increase of myocardial blood supply, in the hope of alleviating anginal symptoms. Early efforts directed at reducing myocardial oxygen requirements by decreasing cardiac sympathetic tone consisted of surgical sympathectomy. Although results were promising, evaluation was difficult because of the associated interruption of cardiac sensory pathways.[5] The recent introduction of specific beta-adrenergic receptor blocking agents has permitted selective blockade of the cardiac sympathetic response, providing a new approach to the treatment of angina pectoris.

Controlled clinical studies have indicated that propranolol, when administered orally in adequate doses, reduces the frequency and severity of chest pains and increases exercise tolerance in a significant proportion of patients with angina pectoris.[6-12]

The usual practice in administering propranolol to patients with angina is to commence treatment at 40 or 80 mg. per day, given in divided doses, and to increase the dose stepwise until benefit is observed or until signs of intolerance are evident. In some controlled trials the effects of one dose of propranolol were compared with those of an identical number of placebo tablets, the dose having been selected after a run-in period with gradually increasing doses of propranolol[6, 12] In other trials, all patients received the same dose of propranolol.[7-11]

Hebb, Godwin and Gunton[14] studied the effects of increasing doses of propranolol (40, 80, 160 mg. per day) in each of a group of 25 patients, and observed that the reduction in anginal attacks and consumption of nitroglycerin tablets was greater at higher doses. Gillam and Prichard[13] reported that reduction of propranolol dosage to one-half of that administered, by substitution with placebo tablets using a double-blind technique, produced less benefit than that noted before interruption of regular therapy. In the present study, the effects of propranolol 160 mg. per day and later 320 mg. per day were compared to the response during administration of placebo, and observations included both subjective and objective parameters. All patients received both doses as well as placebo tablets in a trial using a controlled experimental design.

METHODS

Patient Selection

The study was carried out in the cardiac clinic of The Montreal General Hospital. Eighteen patients (Table I) were selected on the basis of the following criteria: typical history of angina pectoris; relative stability of symptoms for at least six months and daily anginal episode(s); electrocardiographic evidence of remote myocardial infarction or post-exercise electrocardiographic changes consistent with ischemic heart disease. Patients with clinical or radiological evidence of overt cardiac decompensation, valvular heart disease, hypertension or myocardial infarction occurring within one year of the start of the trial were excluded. All patients had regularly attended the cardiac clinic for at least one year before the start of the study; they had been seen regularly by one of the authors (H.F.M.), and were considered to be reliable witnesses. Seven of the 18 subjects had taken part in a similar study in the past. There were 17 men and one woman. The average age was 59 years, with a range of 37 to 71. Three patients had normal electrocardiograms at rest, with a clearly positive response to exercise. In 11 patients the electrocardiograms showed evi-

From the Division of Cardiology, Department of Medicine, The Montreal General Hospital, Montreal, Quebec.

Reprint requests to: Dr. H. F. Mizgala, Division of Cardiology, The Montreal General Hospital, Montreal 25, Quebec.

TABLE I.—CLINICAL DATA AND AVERAGE DAILY NITROGLYCERIN CONSUMPTION DURING OBSERVATION PERIODS

Clinical data					*Trial periods*[x]							
No.	*Age*	*Sex*	*Electrocardiograms*	*Other drugs*	P_1	1_A	1_B	P_2	2_A	2_B	P_3	*Anginal status*
1	52	M	ST-T changes	None	4.4	5.2	5.1	5.3	3.0*	1.8†	5.3	Stable
2	69	M	Anteroseptal M.I. ST-T changes	None	1.5	2.0	2.0	2.0	0.7*	0.5†	2.1	Stable
3	68	M	Inferior wall M.I.	Phenobarbital, Tuinal at bedtime	4.2	1.4*	1.1†	5.3	3.2	3.8	4.0	Stable
4	69	M	Inferior wall M.I. ST-T changes	None	1.6	1.0*	0.9†	3.9	7.1	6.2	6.7	More severe
5	67	M	Inferior wall M.I.	None	2.0	1.1*	1.0†	2.2	1.4	2.0	2.2	Stable
6	55	M	ST-T changes	None	35.5	15.6*	5.6†	14.9	22.8	23.1	12.5†	More severe
7	62	M	Ant. septal M.I. ST-T changes	None								
8	52	F	Ant. M.I. ST-T changes	Digoxin, Hydrochlorothiazide	16.9	16.2	22.1	18.1	5.5*	6.8†	37.9	More severe
9	66	M	L.B.B.B.	None	2.2	0*	0†	4.1	3.9	6.3	6.1	More severe
10	37	M	Inf. wall M.I.	Phenobarbital three times a day	2.0	0.6*	0.4†	1.8	2.2	2.6	2.3	Stable
11	60	M	Abn. L.A.D. + 2-step test	None	2.0	5.3	2.5	3.0	0.6*	0.8†	2.4	Stable
12	48	M	Inf. & post. M.I.	None								
13	71	M	Normal tracing + 2-step test	Hydrochlorothiazide	1.7	1.6*	1.7†	1.0	2.0	1.0	1.0	Less severe
14	58	M	Ant. septal M.I.	Tuinal at bedtime	0.4	0.2*	0.2†	0.8	0.8	1.1	1.8	More severe
15	60	M	ST-T changes	Phenobarbital at bedtime	2.8	1.8*	1.9†	3.7	4.2	2.8	3.8	Stable
16	56	M	ST-T changes	Digoxin, Hydrochlorothiazide	2.1	2.8*	3.0†	3.0	2.3	2.4	2.9	More severe
17	65	M	ST-T changes	None	28.9	14.1	11.8	20.2	9.0*	0†	25.7	Stable
18	64	M	L.B.B.B.	None								

[x] P_1, P_2, P_3 — single-blind interval placebo periods.
[x] 1_A, 1_B, 2_A, 2_B — double-blind trial periods of placebo or propranolol.
* Propranolol 160 mg./day.
† Propranolol 320 mg./day.

dence of remote myocardial infarction, while left bundle branch block was noted in two others. Two patients had ST-T abnormalities suggesting ischemia.

Long-acting nitrates were discontinued at least eight weeks before the start of the study, but no other change was made in treatment. Five patients received nitroglycerin only. Seven patients continued maintenance digoxin and hydrochlorothiazide; one patient received warfarin because of a history of intermittent cerebrovascular insufficiency; one received chlordiazepoxide 10 mg. three times a day; and four others continued taking small doses of phenobarbital, 30 mg., two to four times a day.

Design and Procedures of Study

The study was double-blind, with cross-over of propranolol with placebo. Propranolol was administered at two dose levels of 160 mg. and 320 mg. per day, in four equally divided doses, during two consecutive three-week observation periods (Fig. 1). Full dosage of propranolol or placebo was achieved only on the fifth day of each observation period. During the double-blind placebo period, subjects took an identical number of tablets of similar colour, appearance and taste. Interval single-blind observation periods of two weeks each, labelled P1, P2 and P3, were introduced at the beginning of the study, before the cross-over, and at the end of the study, in order to reassess each subject's anginal status independent of therapy during the study. A code identifying the sequence of propranolol and cross-over placebo administration for each patient was sealed and kept by the hospital pharmacist until the completion of the study. Patients were instructed to swallow the tablets with water and to use sublingual nitroglycerin 0.6 mg. as previously, for the relief of anginal attacks. All subjects were given specially prepared diary cards, and were asked to keep a record of all anginal pains and nitroglycerin tablets consumed during each 24-hour period. Average daily nitroglycerin consumption was calculated for each patient, omitting the first five days of each observation period. Patients were seen at the end of each observation period and were questioned directly regarding the frequency and severity of chest pains and change in exercise tolerance. Each patient was questioned in a non-specific fashion and was also asked a series of previously prepared questions pertaining to possible adverse effects. The subjects were examined for the presence of congestive heart failure, and standing and reclining pulse rates and blood pressures were recorded.

Six of the 18 patients were subjected to semi-quantitated exercise tolerance tests at the end of each period of observation. Patients walked on a

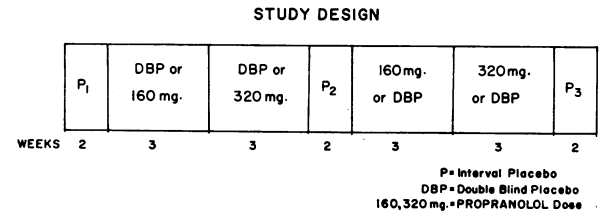

Fig. 1.—Design of double-blind crossover study.

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treadmill at a 5% upgrade. Walking was begun at 1 m.p.h. with increments of 0.5 m.p.h. every two minutes. Exercise was stopped at the onset of chest pain, and patients were asked to sit quietly on a chair until the anginal symptoms subsided. Total work was quantitated using McAlpin's formula and expressed as exercise units (EU), consisting of the sums of the various walking speeds multiplied by the duration of walking at each speed.[15] Thus,

1 m.p.h. x 2 min = 2 EU
1.5 m.p.h. x 2 min = 3 EU
2.0 m.p.h. x 2 min = 4 EU

for a total of 9 EU.

All exercise tests were performed at room temperature, at least three hours after the last meal and with radiotelemetric, audiovisual monitoring.* A bipolar chest lead was employed and 15-second tracings were recorded before each test, at the end of each two-minute period of walking, and at one-minute intervals after the walking was stopped, until the tracings returned to pre-exercise patterns. All tests were completed without incident.

RESULTS

Sixteen of the original 18 patients completed the study. Two (Nos. 12 and 18) dropped out after the first placebo period because of the inconvenience of frequent clinic visits. One patient (No. 7) admitted at the end of the study that he had not taken the medication regularly and had not kept an accurate record of his anginal attacks. Data from this patient were, therefore, omitted from the final results. Table I lists the pertinent clinical data of all subjects taking part in the study, as well as their average daily nitroglycerin consumption during the entire trial. Comparison of daily nitroglycerin consumption during periods P1, P2 and P3 in each patient provided a measure of the relative stability of the disease in this group of patients. During the entire period of study, anginal symptoms were stable in eight of the subjects, slightly increased in severity in six and appeared to be less severe in the remaining subject. Average nitroglycerin consumption for the whole group during the entire study was 5.6 tablets per day, ranging from 1.2 to 16 tablets, and confirmed the clinical severity of the condition in the patients studied. In one patient (No. 6), anginal symptoms became very severe after the end of the second propranolol period when the patient was receiving placebo therapy. The trial was discontinued in this patient and propranolol reinstituted.

Fig. 2 depicts the patients' subjective responses while receiving low and high doses of propranolol. The frequency of anginal attacks was considered decreased by 14 of the 15 subjects

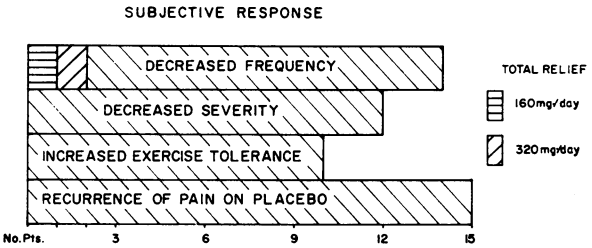

Fig. 2.—Subjective responses of patients at both doses of propranolol.

during propranolol compared to the response reported during double-blind placebo. One patient experienced total relief of symptoms at the 160 mg. daily dose (No. 9), and in another (No. 17) this occurred at the higher dose level. Twelve patients thought their anginal attacks were less severe and 10 noted an increase in exercise tolerance. No patient complained of more severe symptoms while taking propranolol. All 15 subjects reported that their symptoms became worse after crossing over from propranolol to a placebo.

Actual average daily nitroglycerin consumption during the entire study is listed in Table I. In all except two patients (Nos. 13 and 15) an obvious decrease in daily nitroglycerin consumption occurred during propranolol administration, relative to that observed during double-blind placebo periods. These data, expressed as percentage differences in average daily nitroglycerin consumption, are depicted in Fig. 3a.

At the dose level of 160 mg. per day, one patient (No. 9) experienced total relief of symptoms. In 12 others decreases of 31 to 83% in daily nitroglycerin consumption were noted, while in two patients (Nos. 13 and 16) slight increases of 10 and 18% were recorded. The mean percentage decrease in nitroglycerin consumption for the whole group, excluding the patient who experienced relief of symptoms, was 48% and was statistically significant ($P \leq 0.01$).

Administration of the higher dose of propranolol (Fig. 3b) resulted in additional benefit to some patients. The mean percentage decrease in average daily nitroglycerin consumption at the higher dose level relative to the 160 mg. dose was 12%. While not statistically significant for the whole group ($P > 0.05$), one additional patient (No. 17) obtained complete relief of anginal symptoms and further obvious improvement occurred in five others. In four patients little further improvement was noted, and at this higher dose one patient (No. 9) remained symptom-free. Nitroglycerin consumption increased in two patients (Nos. 8 and 11) by 22 and 40% respectively, while two other patients (Nos. 13 and 16) remained without benefit.

*Park's Electronics, Model No. R.B.-27.

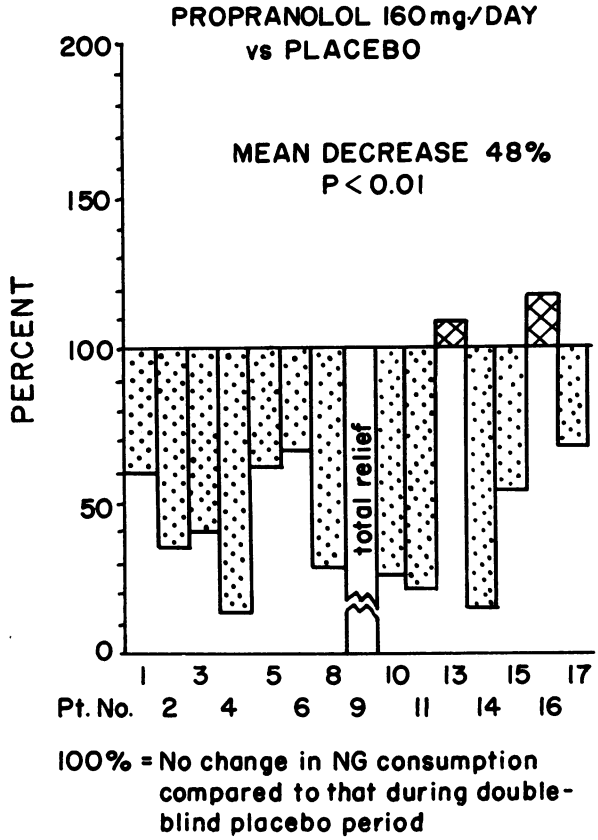

Fig. 3a.—Percentage decrease in average daily nitroglycerin consumption during administration of propranolol, 160 mg./day.

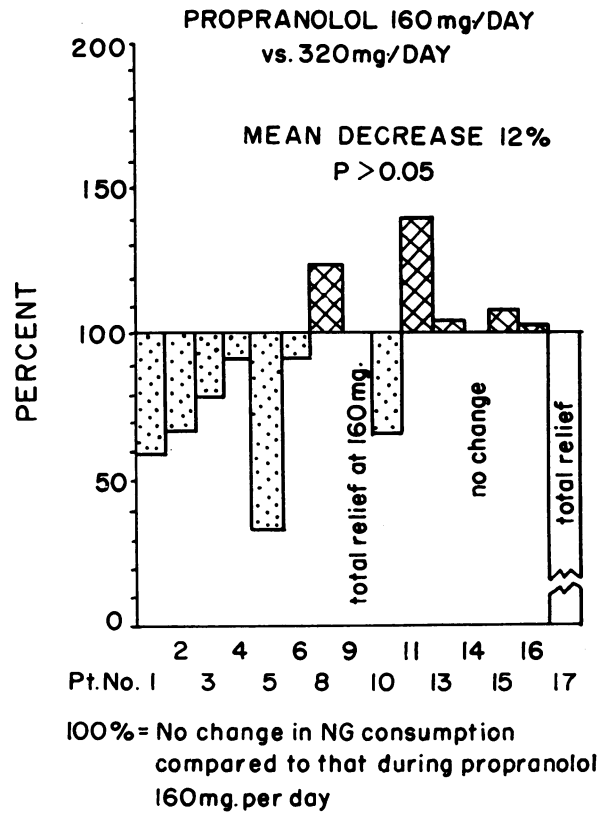

Fig. 3b.—Decrease in average daily nitroglycerin consumption during administration of propranolol, 320 mg./day relative to 160 mg./day.

Results of the quantitated exercise tolerance tests carried out in six of the subjects after each observation period expressed as exercise units (EU) are listed in Table II. At the lower dose of propranolol, three of the six subjects (Nos. 1, 2 and 6) achieved higher levels of performance than after administration of single- or double-blind placebo. In two subjects (Nos. 5 and 10) exercise tolerance increased relative to the adjacent placebo period only. At the higher dose level five patients increased their exercise tolerance to levels exceeding their performance after placebo or low-dose propranolol periods. Propranolol at both doses did not increase the exercise tolerance of patient No. 13. It is worth noting that in this patient, average daily nitroglycerin consumption did not decrease during administration of propranolol.

TABLE II.—EXERCISE TOLERANCE IN SIX SUBJECTS AFTER EACH OBSERVATION PERIOD, EXPRESSED AS EXERCISE UNITS* (EU)

Patient number	*Trial Periods*[x]						
	P1	*1A*	*1B*	*P2*	*2A*	*2B*	*P3*
1	7	7	—	8.5	10†	13‡	7
2	10	8.6	13.4	13.4	20†	22‡	11.5
5	3	4.6†	16.2‡	8	8	8	9.5
6	3	7†	12.7‡	3.8	4	—	—
10	9	17†	31.4‡	17	22	20	17
13	3.5	6.5†	9.8‡	6	11.5	11.0	10

[x] P_1, P_2, P_3—single-blind interval placebo periods.
[x] 1_{A-B}, 2_{A-B}—double-blind trial periods of placebo or propranolol.
* Exercise units—see text.
† Propranolol 160 mg./day.
‡ Propranolol 320 mg./day.

Percentage change in quantitated exercise tolerance is shown in Fig. 4. At the 160 mg. daily dose of propranolol, three patients (Nos. 1, 2 and 6) increased their exercise tolerance by 45, 80 and 78% respectively. The average increase for the whole group was 18%. At the higher dose level, however, exercise tolerance increased by 48 to 150% in five of the six subjects tested. The three subjects whose exercise tolerance increased at the lower level increased it further at the higher dose. Two of the three subjects whose exercise tolerance appeared to decrease at the 160 mg. level (Nos. 5 and 10) improved their tolerance by 100 and 44% respectively on the higher dose.

Because of the small number of patients subjected to quantitative exercise tolerance tests, no valid conclusions could be reached regarding

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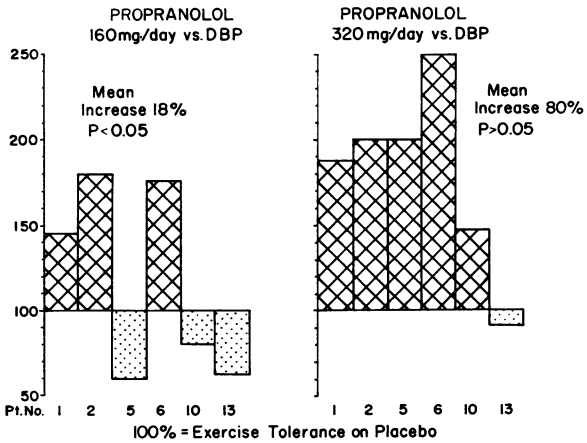

Fig. 4.—Percentage increase in quantitated exercise tolerance at both doses of propranolol relative to double-blind placebo.

the electrocardiographic changes that occurred during the study. Slower heart rates were noted at rest and during exercise. No atrioventricular or intraventricular conduction disturbances were observed. In one patient, frequent atrial extrasystoles occurring during exercise while on placebo were consistently abolished at both doses of propranolol.

All patients developed significant slowing of the pulse rate during propranolol administration. Average pulse rates for the whole group during double-blind placebo administration was 85.5 per minute; 64.1 per minute during administration of 160 mg. propranolol; and 67.1 per minute during administration of the higher dose. Propranolol produced no change in blood pressure recorded in the standing or reclining positions, except a small but statistically significant decrease (5 mm. Hg) in the standing diastolic pressure at doses of 320 mg. per day.

ADVERSE REACTIONS

Adverse reactions occurring during administration of placebo and propranolol are recorded in Table III. These were generally mild and well tolerated, and did not cause any of the patients to withdraw from the study. Loose bowel movements, mild abdominal cramps, anorexia and congestive heart failure were reported only while the subjects received propranolol. Nausea, lightheadedness, dizziness and fatigue were reported during both propranolol and placebo periods. Loose bowel movements were reported by five patients; in three they occurred at both dose levels, and in two at the higher dose only. Bowel movements in these patients were no more frequent than usual, but stools were somewhat looser and more watery. Abdominal cramps were reported by two subjects at the higher dose only, but

TABLE III.—ADVERSE EFFECTS ENCOUNTERED DURING THE ENTIRE STUDY

		Propranolol			
Effect	*Total number*	*160 mg.*	*320 mg.*	*160 and 320 mg.*	*Placebo*
Loose bowels....	5		2	3	
Abdominal cramps.....	2		2		
Anorexia.....	2	1	1		
Nausea.....	2			1	1
Congestive heart failure.....	1	1			
Lightheadedness.	5		2	1	2
Dizziness.....	3		1	1	1
Drowsiness.....	3		1	1	1
Fatigue.....	7	3		2	2
Skin rash.....	1				1

these were mild and not troublesome. Two patients noted decreased appetite; in one this occurred at the 160 mg. level while in the other it was noted at the higher dose level only. Nausea occurred during administration of propranolol in one patient and during placebo in another. Lightheadedness, dizziness, drowsiness and fatigue occurred with approximately equal frequency during placebo and propranolol administration. One patient developed a generalized maculopapular skin rash during a placebo period. This was diagnosed and treated as an "id" reaction to tinea pedis.

None of the patients developed bronchospasm during propranolol administration.

In one subject, No. 17, overt congestive heart failure occurred at the lower dose of propranolol. At the end of this period of observation the patient complained of shortness of breath on exertion, orthopnea and ankle edema. On examination the neck veins were full at 30° elevation, rales were heard at both lung bases and a trace of pretibial edema was noted. These signs and symptoms had been absent at the preceding visit. Seven days after the administration of digitalis and hydrochlorothiazide, all signs of congestive failure disappeared and the patient re-entered the study under careful observation. The trial was completed and heart failure did not recur. It is worth noting that at the higher dose level anginal symptoms were completely relieved, only to return when the patient was given placebo during the last interval placebo period.

DISCUSSION

It is extremely difficult to assess accurately the beneficial effects of any form of treatment in angina pectoris. Although various surgical procedures have been devised to increase myocardial blood flow, and newer coronary vasodilators have been introduced and studied, their

beneficial effects remain the subject of continuing debate and bitter controversy. Confusion in assessing anti-anginal agents arises for several reasons. Angina pectoris is a symptom-complex the manifestations of which are largely subjective and difficult to evaluate. The natural course of this disease is not only extremely variable *per se,* but can be influenced by a variety of uncontrollable environmental factors occurring during the course of a clinical trial. Changing weather conditions, variations in daily activities and the various emotional and physical stresses of everyday life can influence the frequency of anginal attacks. These factors can introduce apparent inconsistencies between subjective and objective results. Thus a patient may report feeling better and capable of more effort with a drug while his daily nitroglycerin consumption remains stable or even increases. For these reasons we have chosen to examine several criteria. Frequency and severity of anginal attacks as reported by the patients were considered a measure of subjective improvement. Average daily nitroglycerin consumption and quantitated exercise tolerance tests were used as imperfect but adequate objective criteria.

To evaluate more accurately the effect of propranolol in patients with angina pectoris, we chose subjects whose symptoms appeared stable during preceding observation, and in whom daily anginal attacks were frequent enough that beneficial effects could be more easily appreciated. The stability of the disease in each patient during the entire trial could also be evaluated by observing the frequency of anginal attacks during the single-blind interval placebo periods adjacent to each observation period.

It has been suggested that the bradycardia and dramatic response in some patients receiving propranolol destroys the value of a double-blind study. This is a valid objection which may have partially influenced our evaluation of the subjective response to the drug. In order to minimize this factor, our patients were questioned regarding symptoms, beneficial effects and adverse reactions before being examined. Moreover, very few of our subjects were aware of slowing of the pulse during administration of the active drug, and it is unlikely that this would have distorted the recording of their daily nitroglycerin consumption.

The subjective response to propranolol was very favourable. Two patients were completely relieved of symptoms. It is quite possible that this would have occurred in a greater proportion of patients had we chosen subjects with less severe disease. It is interesting to note that all 15 patients noticed an increase in their symptoms immediately after the discontinuation of propranolol, confirmed by the increase in daily nitroglycerin consumption in all but two (Nos. 13 and 16). In one patient (No. 6) the symptoms became so severe when propranolol was discontinued that the trial was stopped and the active drug reinstituted. It appears that in the majority of our subjects propranolol decreased the frequency and severity of anginal symptoms and increased exercise tolerance.

Objective confirmation of these beneficial effects can be seen by comparing the average daily nitroglycerin consumption during administration of propranolol and placebo. Even at the lower dose level a statistically significant reduction in daily nitroglycerin consumption was noted. In seven patients further reduction occurred at the higher dose level, and another patient was completely relieved of symptoms. This further benefit was appreciable in six of these subjects, suggesting that dosage is variable and must be individualized. While significant benefits have been reported in patients receiving as little as 60 mg. per day,[16] better and more consistent results are obtained with daily doses of 250 to 400 mg.[6] In two subjects, anginal attacks seemed to increase at the higher dose. In patient No. 8 the disease was unstable and daily nitroglycerin consumption was increased during the trial. In patient No. 11 daily nitroglycerin consumption was so low during administration of the smaller dose that a slight change was reflected as a marked percentage increase.

The increased exercise tolerance reported by 10 of our 15 patients while taking propranolol is supported by the results of the exercise studies performed in six of the subjects. At the lower dose the increase in quantitative exercise tolerance was not significant for the group as a whole, but in three of the six subjects exercise tolerance was nevertheless remarkably improved. Exercise tolerance increased significantly in five of the six subjects at the higher dose. It is worth noting that in two patients (Nos. 5 and 10) exercise tolerance improved at the higher dose only. Parallel decreases in average daily nitroglycerin consumption were also noted for these patients at this dosage. Subject No. 13, whose daily nitroglycerin consumption was not changed by propranolol, also failed to increase his exercise tolerance at both doses.

Repetitive exercise can lead to increased work tolerance in patients with angina pectoris.[14, 15] While this effect of training cannot entirely be disregarded and may have contributed to the increased performance of these subjects, it cannot be considered as the sole explanation.

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Changes of this magnitude are unlikely after such a short period of training. Furthermore, in four of the six subjects tested, propranolol was given during the first half of the study, and exercise tolerance reverted to near control levels during the latter part of the trial when placebo was being administered. Results of the exercise tests were evaluated by comparing exercise tolerance during propranolol administration with average exercise tolerance during the two double-blind periods. Table II makes it quite clear that these results would have been more impressive and the factor of training minimized, had we compared exercise tolerance during propranolol to exercise tolerance during the adjacent placebo periods.

None of the patients reported a worsening of symptoms during propranolol administration, but two of our subjects (Nos. 13 and 16) did not seem to benefit from the drug. Although it is possible to speculate that higher doses might have been effective, and essentially this trial has reaffirmed that the beneficial response to propranolol is dose-related in the majority of patients, it is more likely that these patients were "non-responders" to propranolol. While most patients with angina pectoris seem to benefit from propranolol, a small but significant proportion fail to receive any benefit. Poor and variable intestinal absorption of propranolol does not seem to be a factor since these patients develop the bradycardia characteristic of beta-adrenergic blockade. In addition, response may fail to occur in spite of parenteral administration. This lack of response in some patients remains obscure and unexplained, and unless a therapeutic trial is attempted, there is no way to predict which patient suffering from angina will benefit. Tolerance to propranolol has not been reported thus far.

Patients tolerated propranolol very well and adverse reactions – loose bowel movements, abdominal cramps, anorexia and nausea—were mild. These reactions may be due to the autonomic imbalance resulting from selective sympathetic blockade. Mild diarrhea is known to occur after administration of other sympathetic blockers and is a frequent side effect of guanethidine. Postural hypotension was not a problem. Lightheadedness, dizziness and drowsiness were reported by some subjects, but this occurred almost as frequently with placebo as with propranolol. Overt congestive heart failure was seen in only one of our subjects and was the most serious adverse effect noted. This occurred in spite of the fact that we selected patients very carefully to avoid this complication, choosing only those without evidence of cardiac decompensation. This confirms other reports[17, 18] that propranolol may precipitate heart failure in subjects with borderline compensation. This adverse effect is a predictable pharmacological property of beta-adrenergic blocking agents, which should not be given to patients with overt congestive heart failure. Subclinical failure is difficult to recognize, and since the positive inotropic effect of digitalis is not reversed by propranolol, we now give digitalis in full doses and diuretics when necessary to patients considered for propranolol therapy. Cardiac decompensation has not been a problem in any of the patients subsequently given this drug. It is worth noting that the one patient referred to who developed cardiac decompensation continued the trial after treatment with digitalis and diuretics, and with the higher dose his anginal symptoms were completely relieved.

Propranolol has a marked negative chronotropic effect and depresses myocardial conducting tissue.[19] For these reasons its use should be avoided in patients with pre-existing bradycardia or a significant degree of atrioventricular block.

Theoretically, beta-adrenergic blockade can induce or aggravate bronchospasm.[20, 21] Although this was not encountered in our study, it did occur in one patient during a subsequent trial. Bronchospasm, wheezing and dyspnea developed after one week of treatment and responded in four days to treatment with bronchodilators. This patient had a history of "asthma" 15 years previously, but had been asymptomatic since.

The mechanisms whereby propranolol exerts its beneficial effect in patients with angina pectoris have not been fully elucidated. Evidence thus far suggests that it may be the net result of a number of hemodynamic effects. Although all our patients developed significant bradycardia while receiving propranolol, there was no correlation between beneficial effect and the degree of reduction in heart rate. This was also observed by Hebb, Godwin and Gunton.[14]

The effects of sympathetic stimulation or of catecholamines on the performance of the myocardium are mediated by beta-adrenergic mechanisms. Isoproterenol administration or exercise results in an increased heart rate, an increased strength and velocity of myocardial contraction, decreased ventricular end-diastolic volume and pressure, and an increased cardiac output. As a result, cardiac work and myocardial oxygen consumption are increased. Beta-adrenergic blocking agents inhibit the effect of catecholamines on the myocardium. This inhibition is believed to be the result of a simple competitive antagonism at the receptor site, and it can

be overcome by sufficiently high concentration of the sympathetic activator.

Administration of propranolol is followed by several important hemodynamic changes, resulting in either an increase or a decrease in myocardial oxygen requirements. The bradycardia, the drop in mean aortic pressure, decrease in strength and velocity of myocardial contraction and the decrease in cardiac output all result in decreased cardiac work and oxygen consumption. On the other hand, the prolonged systolic ejection period at rest and with exercise and the increased ventricular dimensions during exercise favour increased cardiac work and myocardial oxygen requirement. The net effect is a reduction in myocardial oxygen consumption of the order of 25%.[22] This oxygen-sparing effect can most easily be explained by propranolol's beta-adrenergic blocking properties rather than by non-specific myocardial depression.[23] Since angina pectoris occurs because of a disproportion between myocardial oxygen supply and demand, propranolol may, in part, exert its beneficial effect by diminishing or preventing the increased myocardial oxygen requirements which take place during the sympathetic stimulation resulting from exertion or emotional stress.

Theoretically, propranolol should be a net coronary vasoconstrictor. This effect has been demonstrated in human and animal observations.[22, 24] Some evidence, however, suggests that in subjects with coronary artery disease, propranolol may suppress coronary vasoconstriction during anginal attacks, improving oxygen supply to the affected areas. This was observed by Wolfson *et al.*[22] during an anginal attack in a patient undergoing cardiac catheterization. This is further supported by Mendez and Kabela,[25] who showed that beta-adrenergic blockade suppresses the initial coronary vasoconstriction which takes place after the injection of catecholamines, and by unpublished observations of McGregor.[26] It appears therefore that propranolol may cause both vasoconstriction and vasodilation. It is tempting to speculate that in this manner it could effect a redistribution of coronary blood flow, favouring the ischemic areas.

In some patients anginal attacks are directly related to transient arrhythmias. Propranolol's antiarrhythmic properties may play a role in relieving angina in such subjects.

While propranolol is an effective agent in the prophylactic management of angina pectoris and offers a new pharmacological approach, early results of Wolfson, Amsterdam and Gorlin[27] suggest a beneficial influence on prognosis.

Summary Propranolol in doses of 160 mg. and 320 mg. per day was administered to 15 patients with severe angina pectoris in a double-blind crossover trial. The majority reported a decrease in the severity and frequency of anginal attacks as well as an increase in exercise tolerance.

At the 160 mg. daily dose, one patient was completely relieved of symptoms, and average daily nitroglycerin consumption decreased by an average of 48% for the group. Three of six patients subjected to quantitated treadmill exercise tests increased their exercise tolerance significantly.

At the 320 mg. daily dose, one additional patient was completely relieved of anginal symptoms; nitroglycerin consumption was further decreased in five patients and exercise tolerance increased in five of the six patients exercised.

Propranolol did not aggravate anginal symptoms in any of the patients, but two failed to show objective improvement. There is no way to predict which patients will respond, short of a therapeutic trial. Adverse effects were mild and well tolerated. Propranolol may precipitate congestive heart failure in some patients. It should be given only to patients receiving digitalis. It is contraindicated in patients with a history of asthma, of pre-existing sinus bradycardia and of significant degrees of heart block. The mechanism of action appears to be complex. Although it is most probably related to a myocardial oxygen-sparing effect, propranolol may occasionally act by virtue of its antiarrhythmic properties and may also influence beneficially coronary blood flow.

Résumé Nous avons étudié 15 malades souffrant d'une forme stable et sévère d'angine de poitrine. Nous leur avons administré du propranolol en quatre doses séparée totalisant 160 et 320 mg par jour. Il s'agissait d'une étude à double insu, par permutation. Les périodes d'observation ont été de trois semaines chacune, tant pour chaque niveau posologique que pour le placébo. Un placébo connu a été administré pendant deux semaines au début de l'étude, pendant une semaine avant la permutation et à la fin de l'étude. Les résultats de ce traitement ont été évalués d'après le nombre de comprimés de nitroglycèrine consommés chaque jour. A six des malades, on a fait faire des exercices donnés sur tapis roulant et on a pris des ECG d'effort. A la posologie de 160 mg, la consommation de nitroglycérine a diminué de 31 à 83% (moyenne de 48%) chez 12 des 15 sujets. Une amélioration plus considérable a été notée chez huit malades avec la dose forte. Deux malades n'ont pas été améliorés, à aucune des doses. Chez cinq des six sujets soumis aux exercices, la tolérance à l'effort a été augmentée de 48 à 150%. Les réactions secondaires ont été minimales. Le propranolol diminue efficacement la fréquence et la sévérité des douleurs angineuses et augmente la tolérance à l'effort. Chez certains malades, les doses sont plus efficaces.

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SPECIAL ARTICLE

Farm Accidents in Saskatchewan

A. F. HUSTON, M.D., M.R.C.P.* and CHRISTIAN SMITH,†
Regina, Sask.

HIGHLY mechanized farming is the basis of economic life on the Canadian prairies, particularly in Saskatchewan. In spite of some diversification in recent years, dependence on farming is likely to persist and the health, safety and working conditions of farmers and their families are legitimate and important subjects for physicians to study. Although Canada is one of the world's leading agricultural producers, except for an editorial in this Journal on "Tractor Accidents"[1] the specific subject of farm accidents has received relatively little attention in the country's medical journals.

The general problem of accidental death and injury has been the subject of several communications in recent years. An approach to the problem of accidents has been discussed[2] with some brief comments on farm accidents, and editorial comments have appeared on the responsibility of public health workers in the face of the problem.[3] A policy statement on accident prevention has been made by the Canadian Public Health Association,[4] re-emphasizing that accidents form one of Canada's leading public health problems and that this country has one of the world's highest recorded accident fatality rates. In this statement much of the emphasis is on traffic and home accidents, but it is recorded that over 200 deaths in Canada in 1964 were due to farm accidents. In 1961 the challenge of accident prevention in public health was expressed and it was suggested that the training public health workers receive in the fundamentals of disease prevention can readily be applied to accident prevention as well.[5] Traffic accidents as an epidemiological problem have been studied[6] and their neurosurgical aspects described.[7] The problem of home accident prevention has been discussed,[8] while accidents in childhood,[9] to Indians,[10] and the general problem of accident proneness[11] have all received attention. It therefore appears timely to comment on the problem of accidents on the farm as seen in a province whose main activity is agriculture.

Much information about farm accidents is available in Saskatchewan and elsewhere in reports and monographs. A survey of farm accidents based on Ontario experience has been published,[12] while quite extensive information is made available in Saskatchewan in reports to the Saskatchewan Department of Public Health.[13-15] There has been more extensive reporting in other countries, and particular reference to the major problem of tractor accidents

*Medical Rehabilitation Consultant, Medical Rehabilitation and Chronic Care, The South Saskatchewan Hospital Centre, Regina.
†Former Director of Health Education, Saskatchewan Department of Public Health, Regina; now of Lumsden, Sask.

Reprint requests to: Dr. A. F. Huston, 2856 Rae Street, Regina, Saskatchewan.