TABLE I.—Results of Exercise-tolerance Tests in 11 Patients with Angina Pectoris

Exercise Tolerance Improved				Exercise Tolerance No Change or Worse								
Case No.	Date	Pain On		Pain Off		Case No.	Date	Pain On		Pain Off		
		min.	sec.	min.	sec.			min.	sec.	min.	sec.	
Subjectively Improved												
1	25/3/58	6	0	—	40	4	8/11/57	2	20	—	40	
	24/6/58	8	20	—	45		24/3/58	3	0	—	40	
	2/2/59	10	0	—	40		6/6/58	2	40	—	25	
	18/8/59	12	5	—	35		17/11/58	2	20	—	20	
	16/6/60	11	10	—	30		21/5/59	3	0	—	30	
2	19/6/57	3	30	1	30	5	20/2/60	3	10	—	40	
	24/7/57	3	10	1	10		10/11/58	2	20	—	45	
	7/1/58	6	0	1	30			18/2/59	3	10	—	40
	21/9/58	9	30	1	10			6/7/59	2	40	—	30
	3/1/59	10	0	—	40			6/1/60	3	5	—	45
3	6/7/59	14	0	—	55	6		15/7/57	12	0	1	0
	2/2/60	9	45	—	50		7/11/57	5	0	1	30	
	17/11/58	7	0	—	25		24/3/58	5	25	1	20	
		2/5/59	10	15	—		30	10/11/58	6	15	1	0
		17/8/59	12	5	—		35	6/7/59	5	40	1	15
27/2/60		16	10	—	40	2/3/60	6	10	1	10		
								7	9/8/57	3	50	—
	11/12/57								2	50	—	55
	5/5/58								3	40	1	40
	10/9/58								3	20	—	20
	21/1/59								3	30	—	20
	8							11/5/59	3	20	—	30
								29/9/59	3	40	—	35
								24/2/60	2	50	—	15
								26/9/57	4	30	—	40
								7/1/58	5	10	—	50
								20/8/58	5	30	—	30
5/5/59	5	10	—	50								
17/2/60	4	55	—	40								
Subjectively No Change or Worse												
9	1/10/58	2	30	—	40	11	26/6/57	3	20	1	10	
	9/1/59	4	40	—	25		20/10/57	2	0	—	50	
	8/4/59	9	30	—	20		4/11/57	1	5	1	10	
	8/7/59	9	20	—	30							
	17/2/60	8	20	—	15							
10	6/6/58	4	20	—	45							
	10/9/58	4	10	—	40							
	19/1/59	6	20	—	35							
	6/7/59	9	35	—	50							
	17/2/60	8	55	—	35							

TABLE II.—Comparison of Subjective Assessment with Exercise-tolerance Test in a Group of 11 Patients with Angina Pectoris

Subjective Assessment	Exercise Tolerance Improved	Exercise Tolerance No Change or Worse	Total
Improved	3	5	8
No change or worse ..	2	1	3
Total	5	6	11

first importance in therapeutic trials in angina pectoris, where remarkable subjective improvement tends to occur when any treatment is begun. Evans and Hoyle (1933) found that 38% of a group of patients given a placebo reported improvement in their angina, and an uncontrolled trial of any drug is therefore valueless. If, however, a double-blind trial is undertaken, and there are a substantial number of patients in both the control and test groups reporting improvement when their condition is unchanged, this could obscure a significant difference between the placebo and the drug on trial. Assessment by an exercise-tolerance test would undoubtedly overcome some of these difficulties if care is taken to standardize the conditions of the test. In particular, it is important to ensure that the rate of walking, the time interval from the last meal, the amount of clothing worn, and the room temperature remain constant throughout, and the patient should always be allowed to rest for at least 15 minutes before the test is done (Wayne and Laplace, 1933; Wayne and Graybiel, 1934).

It has been held that to exercise a patient until he gets pain is an unjustifiable risk; but, as Wayne and Laplace (1933) point out, "he is asked to do no more while under close control than he is in the habit of doing several times a day without supervision."

Summary

The progress of 11 patients with angina pectoris was assessed subjectively and by a standardized exercise-tolerance test. There was agreement between the two methods in only four patients, and disagreement in the other seven.

The implications of this finding with regard to therapeutic trials in angina pectoris are discussed.

I am grateful to Sir George Pickering for advice and encouragement.

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CLINICAL EVALUATION OF PHENIPRAZINE IN ANGINA PECTORIS

BY

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The use in angina pectoris of drugs which inhibit monoamine oxidase is a problem of current therapeutic interest. Conflicting reports on the use of one such compound, iproniazid, have been obtained; considerable success was claimed by Cossio (1958), Master (1958), and Towers and Wood (1958); but little therapeutic effect was found by Dewar *et al.* (1959) and Snow and Anderson (1959). The use of iproniazid is, however, limited by its toxic effects. A preliminary report on a similar monoamine oxidase inhibitor, pheniprazine hydrochloride (beta-phenylisopropylhydrazine; "cavodil"), which apparently has no toxic effects, was very encouraging (Mackinnon *et al.*, 1960), but little objective evidence was presented to support the conclusions. In view of this it was decided to carry out a controlled study of the clinical value of pheniprazine as a long-acting coronary vasodilator in patients suffering from angina pectoris.

Patients and Methods

Twelve out-patients aged from 49 to 70, with well-authenticated and typical features of angina pectoris, were studied. The angina had been static for the previous 12 months. There were nine men and three women, and in all of them the presumptive aetiology was coronary artery disease; one woman aged 43 (Case 11) had familial hypercholesterolaemia. Four patients had electrocardiographic evidence of previous myocardial infarction. All patients were taking trinitrin freely for their anginal attacks.

A double-blind technique was employed. An initial control period of one month was allowed when no additional coronary vasodilators were taken apart from trinitrin. One month's supply of either pheniprazine or an identical placebo was provided, neither the patient nor the observer knowing which drug was given. Two tablets of 3 mg. each were administered twice daily.

The patient was also given a specific number of trinitrin tablets. All patients attended at monthly intervals, and at each visit the number of trinitrin tablets consumed in the previous month was checked by the observer, thus ensuring an objective assessment of the number of anginal attacks. In addition, exercise-tolerance tests were carried out at the beginning of the study and at monthly intervals. The test was a modification of the two-step technique: the patient stepped up and down two steps, each 1 ft. (30 cm.) high, being timed on each occasion until the patient was stopped by either angina or dyspnoea. A note was made of the number of circuits undertaken and the time taken. An electrocardiogram was recorded before starting the exercise and immediately afterwards, using limb lead II and lead V₆ simultaneously. Ischaemic changes were indicated by S-T depression of the type and timing described by Wood (1956). Only one patient (Case 6) was unable to undergo the exercise-tolerance tests.

Results

Table I indicates the weekly number of trinitrin tablets taken during the control period and while the patients were on pheniprazine and the placebo. In eight patients both pheniprazine and placebo produced a fall in trinitrin consumption; but in only two of these did the fall with pheniprazine appreciably exceed that produced by the placebo (Cases 3 and 11). The remaining patients showed no change in trinitrin requirements with pheniprazine. The mean weekly consumption of trinitrin over the whole series was less with pheniprazine than in the control period; but the difference was not statistically significant. The trinitrin requirements during administration of the placebo also did not differ significantly from either the control period or while the patients were on pheniprazine.

The results of the exercise-tolerance tests are shown in Table II. The mean number of circuits undertaken while on pheniprazine was significantly greater than in the control period ($P < 0.02$). An increase was also evident with placebo, but this was not significant, nor was there any significant difference between the performance with pheniprazine and that with the placebo. The rate of exercise did not vary significantly in the control period and during administration of pheniprazine and placebo. Table III shows that ischaemic changes were present after exercise in the electrocardiograms of eight patients while on pheniprazine—in three of these patients not showing ischaemic changes after exercise during the control period the S-T depression appeared after pheniprazine.

TABLE I.—Weekly Consumption of Trinitrin During Control Period and During Administration of Pheniprazine and Placebo

Case No.	Age	Sex	Duration of Angina	No. Trinitrin Tablets per Week		
				Control Period	Pheniprazine	Placebo
1	64	F	10 years	22	9	11
2	51	M	3 "	15	9	10
3	58	M	14 "	61	24	39
4	49	M	2 "	23	19	18
5	65	M	9 "	10	13	11
6	54	M	3 "	16	5	5
7	62	F	11 "	22	13	12
8	56	M	7 "	14	18	22
9	58	M	2 "	14	15	16
10	62	M	8 "	30	35	96
11	43	F	13 "	35	3	10
12	57	M	5 "	42	29	18
Mean				25.3	16.0	22.3
Standard error				4.3	2.8	7.2

TABLE II.—Results of Exercise-tolerance Tests

Case No.	Total No. of Circuits			Mean Time per Circuit (sec.)			Cause of Stopping		
	Control Period	Pheniprazine	Placebo	Cont.	Phen.	Pl.	Cont.	Phen.	Pl.
1	9	32	27	8.3	2.0	6.1	A	A	A
2	31	70	63	2.7	2.4	2.4	A	A	A
3	27	28	25	3.3	2.7	5.4	A	A	A
4	20	28	26	3.8	2.5	2.9	A	A	A
5	35	40	38	3.0	2.3	4.1	A	A	A
7	—	23	12	—	4.8	12.1	—	D	D
8	—	40	21	—	1.8	2.1	—	D	D
9	16	30	21	3.4	2.8	2.6	D	D	D
10	—	14	—	—	4.3	—	—	A	A
11	17	40	10	3.0	3.0	3.5	A	A	A
12	13	41	35	2.3	1.9	1.7	A	A	D
Mean	21.0	35.1	27.8	3.7	2.8	4.3			
S.E.	2.9	4.3	4.8	0.7	0.3	1.0			

A = Angina pectoris. D = Dyspnoea.

TABLE III.—Progress of Ischaemic Changes in the Electrocardiogram

Case No.	Presence of Ischaemic Changes		
	Control Period	Pheniprazine	Placebo
1	+	++	+
2	+	+	+
3	++	++	++
4	++	+	+
5	+	+	+
7	Not done	+	0
8	" "	++	+
9	+	++	+
10	Not done	++	Not done
11	+	++	" "
12	+	++	+

One patient (Case 1) expressed great satisfaction with pheniprazine and did show an improvement in the amount and rate of exercise; but the electrocardiographic changes of ischaemia became more pronounced, presumably because of the increased exertion (see Fig.). One other patient (Case 3) also experienced considerable subjective relief with pheniprazine, but no corresponding improvement was evident in exercise-tolerance tests.

Increase in ischaemic change during the exercise-tolerance test after administration of pheniprazine.

Only one patient had minor abdominal discomfort with pheniprazine. No consistent changes in pulse, blood-pressure, or weight occurred and no other side-effects were encountered with the drug.

Discussion

It has been stated that in the administration of any anti-anginal drug the therapeutic effect is directly related to the personality of the physician and his own belief in the curative powers of the drug, together with the suggestibility of the patient and the intensity of the patient's desire to be cured (Greiner *et al.*, 1950). This view is supported by Cole *et al.* (1958), who studied the effects of four coronary vasodilators in cases of angina pectoris and found a decrease in the frequency of chest pain in every patient regardless of whether an active drug or a placebo was being administered. The

importance of a double-blind technique in the investigation of an anti-anginal agent is therefore plain. More important still is the objective index of improvement provided by the electrocardiogram during a standard exercise-tolerance test.

Mackinnon *et al.* (1960) found considerable improvement with pheniprazine in 41% of 28 patients; but the improvement was assessed solely on subjective criteria—that is, on frequency of anginal attacks. In the present study there was a fall in trinitrin requirements with both pheniprazine and the placebo, in accordance with the findings of Cole *et al.* (1958); but there was no significant difference in the frequency of angina with administration of pheniprazine and placebo. The exercise-tolerance tests did show a significant increase in the amount of activity possible with pheniprazine, although the rate of performance did not alter. This apparent improvement was not, however, reflected in the electrocardiographic findings after exertion. In fact, the increased exertion produced an increase in the severity of ischaemic pattern in three patients. The primary action of pheniprazine is as an antidepressive agent, and it is possible that the resulting euphoria was responsible for the great improvement claimed by two patients, and may also have produced the increase in activity during the exercise-tolerance tests. However, the potential hazards of increasing exertion in patients with angina pectoris without a corresponding improvement in myocardial blood supply are obvious, and were well exemplified by the electrocardiographic changes in several patients during the course of the present study.

Summary

An objective study has been made of the clinical effect of a new monoamine oxidase inhibitor, pheniprazine hydrochloride (beta-phenylisopropylhydrazine; "cavodil"), in 12 patients with angina pectoris, using a double-blind technique.

No significant change in the frequency of anginal attacks followed the administration of the drug. Pheniprazine did, however, produce an increase in amount of exertion undertaken during exercise-tolerance tests; but the potential hazards of this in the absence of a corresponding increase in myocardial blood supply are pointed out.

It is concluded that pheniprazine is of no real value in treating angina pectoris and may, in fact, be contra-indicated.

My thanks are due to Dr. D. Verel for his helpful advice, and to the electrocardiographic technicians of the Sheffield Region Cardiovascular Centre for their willing co-operation in this study. I am also indebted to Bengel Laboratories Ltd. for the supply of cavodil.

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Preliminary Communications

Clinical Assessment of "Etrynit" for Angina Pectoris

For any drug to equal glyceryl trinitrate it must be shown to be as effective, as harmless, and as cheap: its effectiveness can be judged by the rapidity of onset and the duration of effect.

Glyceryl trinitrate is generally accepted as the drug of choice, both for the rapid relief of the pain of angina and to prevent it if taken just prior to exertion. Unfortunately, its evanescent action limits its usefulness and it is of no value if taken at prescribed intervals during the day. A new preparation, the trinitric acid ester of trimethylol propane ("etrynit"), has been studied in Scandinavia (Nordqvist, 1959) and found to be of clinical value, although no papers have yet been published. The drug is claimed to be as effective as glyceryl trinitrate in the treatment of acute attacks and to have a longer duration of action.

A controlled trial has therefore been carried out to compare etrynit with glyceryl trinitrate, and this paper is concerned only with the first claim—namely, the rapid relief of pain in the acute attack of angina.

METHOD

A double-blind controlled trial was organized, using apparently identical tablets containing glyceryl trinitrate 1/130 gr. (0.5 mg.) and etrynit 10 mg., and the results were assessed by the established technique of sequential analysis (Armitage, 1954; Snell and Armitage, 1957). Thirty-five ambulant patients were treated. They were attending a cardiac clinic and had angina of effort, diagnosed by reliable clinical stories, supported in 33 instances by electrocardiographic changes. No patients with mitral- or aortic-valve disease or anaemia were included. There were 20 men, aged 38 to 64, and 15 women, aged 42 to 70. The electrocardiogram was abnormal in all but two, the abnormalities being either those of old cardiac infarction (20) or "coronary insufficiency" (13). Five patients were receiving anti-coagulants, and these were continued. All were familiar with the use of sublingual glyceryl trinitrate to abort acute attacks of pain and all had had that drug for at least one month before starting the trial.

Each patient was given two boxes, identified only by numbers, and was asked to use no therapy other than the tablets in one box completely before starting the second box. The tablets were taken sublingually, in halves if this proved potent enough, and each box lasted about a week. One box contained glyceryl trinitrate and the other etrynit, and the boxes were filled in random order by the use of Fisher and Yates's (1957) statistical tables. When both boxes had been used the patient returned to the clinic and recorded the number of the box which contained the tablets he preferred, together with any side-effects or other comments. Although it was not strictly necessary statistically, the entire experiment was then repeated, so each patient received four boxes of tablets in all. The result of this second experiment confirmed the findings of the first.

RESULTS

A sequential analysis chart with boundaries equivalent to 5% significance was prepared, and as each result became available the pharmacist was able to translate