as an adjuvant to ganglion and adrenergic blocking drugs in the treatment of premalignant and malignant hypertension.

Summary and Conclusions

A co-operative clinical trial in general practice carried out by three practitioners in Glasgow is reported.

The drug concerned was a new hypotensive agent, methoserpidine ("decaserpyl"), a synthetic isomer of reserpine.

The effect of the drug was investigated mainly in 43 patients with essential (benign) hypertension. A definite hypotensive action was demonstrated in approximately two-thirds of the patients and was judged sufficient to be certainly beneficial clinically in one-third.

Almost all the patients obtained symptomatic improvement. The drug was found to be virtually free from side-effects and tranquillizing action.

Dosage of the drug should usually be 30 mg. daily initially, it being subsequently increased or decreased, if required, within the range of 10–60 mg. daily.

The findings broadly confirm the results reported in other investigations of this drug. Our experience indicates that methoserpidine is a useful drug for the management of mild and moderate cases of essential hypertension in general practice.

We would like to express our appreciation to Roussel Laboratories Limited for making available supplies of decaserpyl, and to Dr. J. J. Segall and Mr. W. Kirk for their assistance.

REFERENCES

- Brun, F., and Rondelet, J. (1959). *Lyon méd.*, **202**, 843.
 Fife, R., Maclaurin, J. C., and Wright, J. H. (1960). *Brit. med. J.*, **2**, 1848.
 Gros, H., Peterfalvi, M., and Jequier, R. (1959). *Algérie Méd.*, **63**, 297.
 La Barre, J. (1960). *Thérapie*, **15**, 663.
 Mériel, P., Galinier, F., Suc, J. M., Putois, J., and Bounhoure, J. P. (1959). *Sém. méd. prof. méd.-soc.*, **35**, 747.
 Mir, B. J., and Lewis, J. J. (1960). *J. Pharm. Pharmacol.*, **12**, 677.
 Peacock, J. H. (1960). *Lancet*, **2**, 65.
 Read, F. H. (1961). *Med. J. Aust.*, **1**, 245.
 Tricot, R., Colonna, D., and Alderete, B. (1960). *Presse méd.*, **68**, 905.
 Velluz, L. (1959). *Ann. pharm. franç.*, **17**, 15.
 — et al. (1958a). *Bull. Soc. chim. Fr.*, No. 5, 673.
 — Peterfalvi, M., and Jequier, R. (1958b). *C.R. Acad. Sci. (Paris)*, **247**, 1905.

CLINICAL EVALUATION OF PROPATYLNITRATE IN ANGINA PECTORIS

BY

GERALD SANDLER,* M.D., M.R.C.P.

From the Sheffield Region Cardiovascular Centre and the City General Hospital, Sheffield

Although many preparations have been investigated for use as long-acting coronary vasodilators in angina pectoris few have survived a controlled unbiased study. Many claims of success have been based on a subjective assessment by the patient of improvement in his anginal attacks. Apart from the frequent spontaneous fluctuations in this symptom in the natural course of ischaemic heart disease, there is ample evidence that improvement will occur in any patient with angina with any new preparation irrespective of its active or inert properties (Greiner *et al.*, 1950). The necessity for a controlled double-blind trial is therefore apparent. In addition, however, an objective assessment of the anti-anginal activity must be made which relies as little as possible on the patient's own interpretation of his progress, and this is best accomplished by some form of exercise-tolerance test.

With these considerations in mind it was decided to carry out a clinical evaluation of a new coronary vasodilator, propatyl nitrate ("gina"), which is chemically related to both glyceryl trinitrate and erythrol tetranitrate. Preliminary experimental observations have indicated its effectiveness in producing coronary vasodilatation in animals, and clinically it has been found to give both rapid relief of pain in an acute attack of angina pectoris and a prophylactic sustained action (Nordqvist and Varnauskas, 1960). For the present study an exercise-tolerance test has been devised which is more physiological than the Master two-step test (Master and Oppenheimer, 1929).

Patients and Methods

Thirteen out-patients aged 43 to 70 with well-authenticated and typical features of angina pectoris were studied (Table I). The angina had been static for the previous 12 months. There were nine men

and four women, and in all of them the presumptive cause was coronary artery disease; one woman aged 43 (Case 12) had familial hypercholesterolaemia. Four patients had electrocardiographic evidence of previous myocardial infarction. All the patients were taking glyceryl trinitrate freely for their anginal attacks.

TABLE I.—Age-and-Sex Distribution of Patients Studied

Case No.	Age in Years	Sex	Duration of Angina
1	50	M	7 years
2	58	M	13 "
3	60	F	8 "
4	61	M	3 "
5	51	M	3 "
6	70	M	2 "
7	58	M	5 "
8	60	F	5 "
9	52	F	3 "
10	65	M	9 "
11	58	M	2 "
12	43	F	7 "
13	54	M	2 "

A double-blind technique was employed. Both the immediate and prolonged action of propatyl nitrate were studied. In investigating the immediate action in relieving anginal attacks a comparison was made with glyceryl trinitrate tablets in treating attacks occurring both during normal activity and after exercise-tolerance tests. The sustained effect of the drug in reducing the frequency of anginal attacks was compared with that of pentaerythritol tetranitrate (PETN; "mycardol").

An initial control period of one month was allowed when no additional coronary vasodilators were taken apart from glyceryl trinitrate. In the next three months of the study, individual monthly supplies of tablets of identical appearance containing propatyl nitrate, an inert placebo, and PETN were provided in random order, neither the patient nor the observer being aware of which drug was given. The dosage of propatyl nitrate was 10 mg. sublingually four times daily. The patients

*Now at the Royal Infirmary, Leicester.

were also supplied with a specific number of glyceryl trinitrate tablets. All patients attended monthly, and at each visit the number of glyceryl trinitrate tablets consumed in the previous month was checked by the observer, thus ensuring an objective assessment of the number of anginal attacks. In the subsequent two months of the study the patients were given, again in random order, a month's supply of either propatyl nitrate or glyceryl trinitrate, both of identical appearance, and were asked to take one tablet sublingually whenever an anginal attack occurred. They were advised to take these tablets as freely as desired, and no other coronary vasodilator was allowed. A note was made of the monthly consumption as before, and, in addition, of the approximate speed of relief of angina as stated by the patient.

Exercise-tolerance tests were carried out at the beginning of the study and at monthly intervals. The test was a modification of the Master two-step technique, the patient stepping up and down two steps each 1 ft. (30 cm.) high. The patient was allowed to exercise at his own speed until he was stopped either by the onset of angina, occurring in most patients, or, in a few cases, by dyspnoea. The total number of circuits accomplished was recorded, as was the time taken. An electrocardiogram was obtained before starting the exercise, immediately afterwards, and at intervals of a minute until all electrocardiographic signs of ischaemia had disappeared. This time was noted. Leads II and V5 were used and recorded simultaneously. When angina occurred after the exercise a glyceryl trinitrate tablet was given and a note made of the time required for the pain to go. ST depression of the type and timing described by Wood (1956) was regarded as significant of ischaemia. The nature and the purpose of the tests were explained to all the patients.

The weight, resting pulse, and resting blood-pressure were also recorded in all patients at each monthly visit.

The final phase of the study was designed to assess the rapidity of relief of angina with propatyl nitrate. A series of exercise-tolerance tests were carried out at fortnightly intervals in six patients who were on no additional coronary vasodilators apart from glyceryl trinitrate. Identical tablets of propatyl nitrate, glyceryl trinitrate, and placebo were given in random order to relieve the angina induced by the exercise-tolerance test, and the time required for the pain to disappear was noted in each case.

Only one patient (Case 13) in the series was unable to undertake exercise-tolerance tests during the course of the study.

Results

Table II indicates the weekly consumption of glyceryl trinitrate tablets during the control period and while the patients were on propatyl nitrate, PETN, and placebo. In six patients there was a fall in glyceryl trinitrate requirements with propatyl nitrate, but this

TABLE II.—Weekly Frequency of Angina in the Different Periods of the Study

Case No.	Weekly Consumption of G.T. Tablets				Weekly Consumption of Other Tablets	
	Control Period	PPN q.d.s.	Placebo	PETN	PPN Alone*	Disguised G.T. Alone
1	22	22	15	14	6	15
2	7	10	7	—	8	8
3	15	14	10	7	11	6
4	61	42	38	37	10	33
5	23	10	10	19	25	28
6	10	10	11	7	10	8
7	16	13	5	15	16	15
8	25	48	48	32	25	25
9	14	21	16	15	19	28
10	14	15	18	21	27	23
11	27	19	18	42	18	17
12	62	63	58	61	68	56
13	10	7	10	3	10	10
Mean	23.5	22.6	20.3	22.8	19.5	20.9
S.E.	±4.4	±4.8	±4.7	±4.7	±4.5	±3.8

PPN=Propatyl nitrate. G.T.=Glyceryl trinitrate. * Only in anginal attacks.

occurred also in seven patients on PETN and in seven on the placebo. The mean weekly consumption of glyceryl trinitrate did not differ significantly between each other. Table II also shows the weekly requirements of propatyl nitrate and glyceryl trinitrate when these drugs were used alone, and although there was a reduction in frequency of angina with propatyl nitrate this was not a significant fall, and was evident also with use of the disguised glyceryl trinitrate tablets.

The results of the exercise-tolerance tests are shown in Table III. The total amount of exercise increased, but not significantly with PETN, propatyl nitrate used prophylactically, and the placebo. There was no significant difference apparent between the three preparations. When propatyl nitrate was used alone there was a significant increase in the total amount of exercise ($P<0.05$), and this occurred with the disguised glyceryl trinitrate also ($P<0.05$), but there was no difference between the two drugs themselves. The mean rate of performance of exercise also increased significantly both with propatyl nitrate used alone and with the disguised glyceryl trinitrate ($P<0.05$).

When propatyl nitrate was given prophylactically with standard glyceryl trinitrate for the acute attacks of angina, the difference in rate of performance was no longer significant. Nor was there a significant change with PETN.

TABLE III.—Results of Exercise-tolerance Tests

Case No.	Total No. Circuits						Mean Time/Circuit (Seconds)					
	Control	PPN q.d.s.	Placebo	PETN	PPN* Alone	Disguised G.T. Alone	Control	PPN q.d.s.	Placebo	PETN	PPN* Alone	Disguised G.T. Alone
1	9	15	17	—	38	48	5.6	4.5	5.6	—	3.2	—
2	—	41	50	—	40	—	—	2.5	2.5	—	2.3	—
3	31	38	63	69	80	—	2.7	2.5	2.4	2.6	2.4	—
4	27	26	25	—	20	28	3.3	5.2	5.4	—	3.0	2.6
5	16	37	32	22	23	29	4.0	2.2	2.3	2.8	2.2	2.7
6	35	40	38	40	41	50	3.0	2.0	4.0	2.3	2.2	2.1
7	25	23	15	18	23	23	3.0	2.0	3.0	6.8	4.4	4.1
8	21	35	—	46	45	44	2.1	2.0	—	2.1	2.2	3.6
9	21	35	25	30	35	40	2.6	2.4	1.7	2.3	2.6	2.2
10	40	40	35	13	43	40	2.9	1.9	1.7	2.3	1.8	1.5
11	21	21	—	21	20	17	3.8	3.7	—	6.0	3.5	3.2
12	17	15	10	40	15	30	3.0	3.0	3.5	2.5	2.7	2.8
Mean ± S.E.	24.2 ± 2.4	30.5 ± 2.9	31.0 ± 5.1	33.2 ± 5.9	35.2 ± 5.1	34.9 ± 3.5	3.4 ± 0.2	3.1 ± 0.3	3.3 ± 0.4	3.3 ± 1.0	2.8 ± 0.1	2.7 ± 0.2

* Only in anginal attacks.

Table IV shows that ischaemic changes followed exercise in all 12 patients in the control period. In five the ischaemic changes became more pronounced after a prophylactic course of propatyl nitrate; only one patient (Case 9) showed an improvement with propatyl nitrate, and in her case improvement occurred with PETN also.

TABLE IV.—*Severity of Ischaemic Changes on the Electrocardiogram During Exercise Tolerance Tests*

Case No.	Control Period	PPN q.d.s.	Placebo	PETN	PPN* Alone	Disguised G.T. Alone
1	+	++	+	N.D.	+	N.D.
2	+	++	+	N.D.	+	+
3	+	+	+	+	+	N.D.
4	++	++	+	N.D.	++	++
5	+	++	++	+	++	++
6	+	+	+	+	+	+
7	+	+	+	+	+	+
8	+	++	N.D.	+	++	++
9	++	+	+	+	++	++
10	+	++	+	+	++	++
11	+	++	N.D.	++	++	++
12	+	+	+	+	+	+

N.D. = Test not done. * Only in anginal attacks.

The mean time taken for the electrocardiographic changes of ischaemia to revert to normal was shortest when propatyl nitrate was used alone and also after a course of PETN, but the time did not differ significantly from the control period (Table V). Similar findings were evident when the time taken for relief of anginal pain was considered, but again this was not a statistically significant finding.

In the final study of rapidity of relief of angina induced by exercise-tolerance tests, propatyl nitrate produced a more rapid effect than glyceryl trinitrate, although the difference in the mean time taken for relief was just not significant (Table VI). Comparison of propatyl nitrate and placebo, however, showed a significantly faster relief of angina with the former ($P < 0.05$); although glyceryl trinitrate produced more rapid relief than the placebo the difference was small and not a significant one.

There were no changes in weight, pulse, or blood-pressure attributable to propatyl nitrate in any patient during the course of the study, and no consistent toxic effects or side-effects were encountered. In fact, several patients experiencing unpleasant side-effects with glyceryl trinitrate had no similar reactions when propatyl nitrate was used to abort any anginal attack.

Discussion

It has been stated that in the administration of any anti-anginal agent the therapeutic effect is directly related to the personality of the physician and his own

TABLE VI.—*Speed of Relief of Angina Induced by Exercise-tolerance Tests with PPN, Placebo, and Disguised Glyceryl Trinitrate Tablets*

Case No.	PPN (Seconds)	Placebo (Seconds)	Disguised G.T. (Seconds)
1	55 90 120	135	85 105
3	10	50	160
5	50 60 35 45	100	72 60
	75 125 150	195 155	57
11	60	110	130 135
12	30	155 120 40	218
Mean $\pm$ S.E.	71.8 $\pm$ 10.8	117.8 $\pm$ 16.5	113.6 $\pm$ 20.6

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, Kaye, and Griffiths (1958), who studied the effects of four coronary vasodilators in patients with angina pectoris, and found a decrease in the frequency of chest pain regardless of whether an active drug or placebo was being administered. The importance of a double-blind technique is therefore plain. More important still is an objective index of improvement provided by an exercise-tolerance test.

The Master two-step test has been criticized as being unphysiological and also for not taking into account differences in habits of exertion, in physical capacity, and in training of patients; in addition, the amount of exercise carried out by the patient within the prescribed time may be insufficient to produce electrocardiographic changes of ischaemia. Fife, Howitt, and Stevenson (1958) claim that this test often produces inconclusive results. The exercise-tolerance test employed in the present study has the advantage of a more physiological performance of exertion at the patient's own rate and within the limits of his own capacity. Results are more conclusive as electrocardiographic evidence of ischaemia developed in all 12 patients exercised during the control period. The patient stops at the onset of angina, and although it is claimed that exercise-tolerance tests are not without risk in patients with angina (Grossman and Grossman, 1955) this risk is very slight. Objections have been raised against exercise-tolerance tests in anginal patients, owing to this slight potential hazard, but one is, after all, only carrying out, under close medical supervision,

TABLE V.—*Duration of Electrocardiographic Changes and Angina after Exercise-tolerance Tests*

Case No.	Time for E.C.G. Changes to Revert to Normal (Minutes)						Time for Disappearance of Angina (Minutes)					
	Control	PPN q.d.s.	Placebo	PETN	PPN* Alone	Disguised G.T. Alone	Control	PPN q.d.s.	Placebo	PETN	PPN* Alone	Disguised G.T. Alone
1	9.0	8.0	8.0	—	5.0	—	4.0	2.3	1.7	—	2.0	—
2	—	7.0	1.00	—	6.0	8.0	—	4.0	4.0	—	2.5	2.5
3	9.0	9.0	—	4.0	5.0	—	0.8	1.8	D	1.8	0.1	—
4	6.0	7.0	6.0	—	6.0	5.0	5.0	5.8	5.0	—	5.0	5.0
5	4.0	5.0	6.0	4.0	4.0	4.0	0.8	1.0	0.5	0.8	1.0	0.5
6	3.0	4.0	4.0	4.0	4.0	4.0	2.0	2.0	2.5	2.5	2.1	2.0
7	4.0	2.0	4.0	1.0	1.0	1.0	2.0	2.0	2.0	1.0	1.0	1.0
8	4.0	6.0	—	7.0	4.0	6.0	5.0	D	—	D	D	D
9	7.0	6.0	6.0	5.0	—	7.0	0.7	D	D	D	D	D
10	5.0	4.0	4.0	4.0	4.0	5.0	D	D	1.3	1.8	D	D
11	3.0	5.0	—	5.0	4.0	5.0	D	2.3	—	2.0	1.8	5.0
12	2.0	2.0	1.0	1.0	1.0	3.0	D	1.5	2.5	3.3	1.7	3.0
Mean $\pm$ S.E.	5.1 $\pm$ 0.7	5.4 $\pm$ 0.6	5.4 $\pm$ 0.9	3.9 $\pm$ 0.4	4.0 $\pm$ 0.6	4.8 $\pm$ 0.6	2.5 $\pm$ 0.9	2.5 $\pm$ 0.5	2.4 $\pm$ 0.5	1.9 $\pm$ 0.3	1.9 $\pm$ 0.5	2.7 $\pm$ 0.7

* Only in anginal attacks. D = Dyspnoea.

exercise which the patient is in the habit of undertaking daily without any supervision whatsoever.

In over 200 personally supervised tests of the type described in this study, no ill effects were noted.

In the present study there was a fall in the mean weekly glyceryl trinitrate requirements with propatyl-nitrate, PETN, and placebo, in accordance with the findings of Cole *et al.* (1958). The differences in the frequency of angina, however, between propatyl-nitrate or PETN on the one hand and the placebo on the other were not significant. Similarly there was no significant increase in the total amount of exercise performed in the exercise-tolerance test with either propatyl-nitrate or PETN. When propatyl-nitrate was used alone the rate of performance of exercise did increase significantly, but this apparent improvement was not reflected in the electrocardiogram. In fact, in four of the eight patients showing an increase in rate of performance with propatyl-nitrate the ischaemic changes became more marked, suggesting that the acceleration of exertion occurred without a corresponding improvement in myocardial blood supply.

A course of propatyl-nitrate reduced the duration of subjective and objective evidence of myocardial ischaemia induced by exercise. In addition propatyl-nitrate gave more rapid relief than glyceryl trinitrate when used in treating an acute anginal attack produced by an exercise-tolerance test. These results conflicted with the subjective assessment of the patients, most of whom claimed that propatyl-nitrate was slower in relieving an anginal attack than glyceryl trinitrate. This illustrates the difficulty in assessing the value of drugs used in relieving angina and the unreliability of the patient's own evaluation or interpretation of his progress.

Nordqvist and Varnauskas (1960) found propatyl-nitrate to be of value both in relieving acute attacks of angina and in prophylaxis in angina pectoris. The present study does not wholly support these findings, as there was no conclusive evidence of its efficacy as a long-acting coronary vasodilator. The investigation does, however, indicate the possible value of propatyl-nitrate in the acute attack of angina pectoris. It may be of particular value in those patients experiencing unpleasant side-effects with glyceryl trinitrate, and also in those chronic severe anginal patients no longer experiencing relief with glyceryl trinitrate.

The failure of PETN either to alter significantly the frequency of anginal attacks or to improve performance in exercise-tolerance tests is of interest, and supports similar results reported by Dewar, Horler, and Newell (1959).

Summary

The clinical effect of propatyl-nitrate, a new coronary vasodilator, has been studied in 13 patients with angina pectoris. A double-blind technique was employed, and the use of the drug was investigated both for immediate relief of acute angina and for its more sustained action. To ensure an objective assessment an exercise-tolerance test has been devised which allows the patient to exercise at his own speed and within the limits of his own capacity.

There was no significant change in either the frequency of anginal attacks or the total amount of exercise undertaken while the drug was in use.

When propatyl-nitrate was taken freely, however, there was a significant increase in the rate of performance of exercise but no corresponding improvement in the electrocardiographic changes of ischaemia. Pentaerythritol tetranitrate (PETN), which was included in the double-blind study, also failed to influence significantly either the frequency of anginal attacks or the exercise-tolerance tests.

Propatyl-nitrate was more rapid than glyceryl trinitrate in relieving acute attacks of angina induced by exercise-tolerance tests.

It is concluded that propatyl-nitrate may be of value in treating acute attacks of angina. Its use is suggested in patients experiencing unpleasant side-effects with glyceryl trinitrate and in those who have become resistant to that drug. No evidence has been found to support its use as a long-acting coronary vasodilator.

The importance of a controlled double-blind study and objective criteria of improvement in the assessment of an anti-anginal drug is pointed out.

I am indebted to Dr. D. Verel for his encouragement and helpful advice; to the electrocardiographic technicians of the Sheffield Region Cardiovascular Centre for their willing co-operation in this study; and to Dr. K. Boheimer, of Bayer Products, for the supply of "gina" tablets.

REFERENCES

- Cole, S. L., Kaye, H., and Griffiths, G. C. (1958). *J. Amer. med. Ass.*, **168**, 275.
 Dewar, H. A., Horler, A. R., and Newell, D. J. (1959). *Brit. Heart J.*, **21**, 315.
 Fife, R., Howitt, G., and Stevenson, J. (1958). *Scot. med. J.*, **3**, 15.
 Greiner, T., Gold, H., Cattell, M., Travell, J., Bakst, H., Rinzier, S. H., Benjamin, Z. H., Warshaw, L. J., Bobb, A. L., Kwit, N. T., Model, W., Rothendler, H. H., Messeloff, C. R., and Kramer, M. L. (1950). *Amer. J. Med.*, **9**, 143.
 Grossman, L. A., and Grossman, M. (1955). *J. Amer. med. Ass.*, **158**, 179.
 Master, A. M., and Oppenheimer, E. T. (1929). *Amer. J. med. Sci.*, **177**, 223.
 Nordqvist, P., and Varnauskas, E. (1960). *Svenska Läk.-Tidn.*, **57**, 2173.
 Wood, P. H. (1956). *Diseases of the Heart and Circulation*, 2nd ed. Eyre and Spottiswoode, London.

"Should infectious disease continue to be taught? Surely it might be argued that this is one aspect of medicine of which it can truly be said that improvements in sanitation and hygienic living, the application of the preventive effects of immunizing procedures and the discovery of specific forms of chemotherapy—such advances have eradicated from the community the major part of man's communal diseases and causes of death. And yet, even as one makes that boast one is reminded that there are large areas of the world where infectious diseases of one kind or another still constitute the main menace; and we must remember that the graduate may practise in any part of the world. But, even in our own country, it is still the laymen's jibe that the commonest infection of all, the "common cold," still marches through the community undeterred by the advances of modern medicine, and this should remind us all that virus infections remain very largely uncontrolled. There is indeed a necessity for the student to be made aware of the fact that when, as a doctor, his telephone rings, on a quarter to one-third of the occasions it will be a bacterium or virus which has occasioned its ringing." (*Annual Report on the Work of the Infectious Diseases Hospitals, 1960*, submitted to the Western Regional Hospital Board by Professor T. Anderson.)