PAPERS AND ORIGINALS

Double-blind Evaluation of Verapamil, Propranolol, and Isosorbide Dinitrate against a Placebo in the Treatment of Angina Pectoris

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Summary

In the treatment of angina pectoris a double-blind evaluation of verapamil (Cordilox) at two dose levels—namely, 80 mg thrice daily and 120 mg thrice daily—propranolol (Inderal) 100 mg thrice daily, and isosorbide dinitrate (Vascardin) 20 mg thrice daily has been made against a placebo. The assessment was based on relief from daily attacks of angina on effort and the response to a whole-body exercise test. We can find no statistically significant difference between the effects of verapamil (120 mg three times a day) and propranolol (100 mg three times a day) in the treatment of angina of effort. Both of these preparations are more effective than a placebo both in the reduction of daily attacks ($P < 0.01$) and in the prolongation of exercise test ($P < 0.05$). Isosorbide dinitrate (20 mg three times a day) appears to be no more effective than a placebo in the treatment of angina on effort, but 14 out of 32 patients experienced headache of such severity that even when the dose was reduced to 10 mg thrice daily this drug therapy had to be withdrawn. Both propranolol (100 mg three times a day) and verapamil (120 mg three times a day) had a significant lowering effect on the diastolic blood pressure as measured with the patient standing ($P < 0.01$).

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Introduction

The value of beta-adrenergic blocking agents in the management of angina on effort is well established (Alleyne *et al.*, 1963; Hamer *et al.*, 1964; Keelan, 1965). However, not all patients with ischaemic heart disease benefit from beta-blockade because of the negatively inotropic effect of this type of therapy, and the search for other drugs in the treatment of angina pectoris has continued.

Verapamil, a derivative of papaverine, was discovered in 1963 and first used in the treatment of angina because of its coronary arterial dilator properties in experimental animals. Its exact mode of action is not known, but it can abolish the tachycardia induced by both isoprenaline and atropine (Oram *et al.*, 1971). Certainly verapamil does not act solely as a beta-blocker (Ross and Jorgensen, 1967), nor does it have a quinidine-like action (Singh and Vaughan-Williams, 1972). It has been suggested that as a calcium-ion antagonist it interferes with electro-mechanical coupling (Fleckenstein *et al.*, 1968). However, our experience suggests that in man an important action of verapamil is to augment the effect of vagal tone on the specialized conducting tissue of the heart (Livesley and Oram, 1972). This action must be by direct effect, since Ross and Jorgensen (1967) showed that verapamil can produce bradycardia in cats even after vagotomy.

Verapamil has been used in the treatment of myocardial ischaemia (Phear, 1968; Sandler *et al.*, 1968), and it was the conflicting results of these reports which stimulated us to begin our comparative trial.

Isosorbide dinitrate is a popular antianginal agent, which probably acts by its vasodilator properties (Case *et al.*, 1964; Goldstein *et al.*, 1971) in a manner similar to trinitrin.

Present Trial

PATIENT SELECTION

In 1969 all patients with chest pain attending the outpatient clinic of the cardiac department, King's College Hospital, were screened for entry to the drug trial. From our experience we

agree with Banks and Shugoll (1967) that there is at least a 25% overdiagnosis of angina pectoris on clinical grounds alone. Patients were excluded if angina was associated with one or more of the following conditions: anaemia, valvar heart disease, congestive heart failure, a history of paroxysmal nocturnal dyspnoea or bronchial asthma, myocardial infarction in the previous three months, a diastolic blood pressure over 100 mm Hg on the first attendance, diabetes mellitus, thyrotoxicosis, hypothyroidism, hypokalaemia, or current therapy with digoxin or diuretics. Of the remaining patients all had experienced angina on effort which had been stable for three months and had an E.C.G. which was abnormal at rest (W.H.O., 1959) or became abnormal during the exercise test. In addition the patients required at least five trinitrin tablets each fortnight for the relief of exercise-induced anginal symptoms when these tablets were not used prophylactically.

Out of 42 patients selected and approached for entry to the trial 9 were withdrawn for various reasons. A further patient attended for the third and final control exercise test at the end of the trial complaining of persistent chest pain and was found by serial E.C.G.s and serum enzyme studies to have had a recent acute myocardial infarction.

Of the final 32 patients investigated 25 were men aged 36·0-69·2 years (mean 52·2 years) and 7 were women aged 47·5-61·3 years (mean 54·4 years).

DRUGS AND DOSAGE

After having taken only trinitrin for two weeks the patients were given a placebo in addition for two weeks (treatment period A). They were subsequently allocated to one of five monthly periods of therapy (period B, C, D, E, or F) in groups of five patients. Cases 1-5 began therapy in the rotation of periods B, C, D, E, and F, cases 6-10 began therapy in rotation of periods C, D, E, F and B, and so on. The drug and dosage used for each period is given below. The different drug preparations were in an identical sugar-coated tablet form. The patient's completion of each course of drugs was checked by a tablet count. Neither serum nor urine drug levels were estimated during the trial.

Treatment Periods.—Period A, placebo for two weeks; period B, verapamil 120 mg three times a day for four weeks; period C, verapamil 80 mg three times a day for four weeks; period D, propranolol 100 mg three times a day for four weeks; period E, isosorbide dinitrate 20 mg three times a day for four weeks; period F, placebo for four weeks; period G, no therapy other than trinitrin. The placebo consisted of lactose, maize starch, magnesium stearate, and sodium lauryl sulphate.

Trinitrin tablets were provided in bottles of 100 and the patients were directed not to take them prophylactically. The residual trial and trinitrin tablets were checked at each fortnightly attendance and a fresh bottle containing 100 trinitrin tablets was provided. No other drugs were prescribed except for occasional patients taking anticoagulant therapy.

METHODS AND DESIGN

The patients attended a special outpatient clinic on the same day of the week. The observations were made by one of us (B.L.) and the patients were encouraged to lead an active daily life. The duration of the trial was 19 months.

At the onset of the two-week run-in period details of the case history, physical examination, and previous drug therapy were noted for each patient. At the end of this period, when the physician knew that placebo had been administered, a specific inquiry was made for side effects to encourage patients to report any incidents which occurred later in the trial. The only notable side effect was a severe headache experienced by some patients when taking period E tablets (isosorbide dinitrate 20 mg three times daily). This symptom persisted even when the dose was reduced to 10 mg three times a day, and 14 patients were unable to tolerate even this dose and continued with the next treatment period.

During each fortnight the patients recorded on a special card the number of attacks of angina and the trinitrin consumption. At each attendance residual trinitrin tablets were checked from the bottle against the patient's stated consumption. After the initial placebo run-in period the trial drugs were administered in a "double-blind" manner for monthly periods. Only enough trial tablets were provided for each monthly period, to be taken daily at 8 a.m., 2 p.m., and 8 p.m. To prevent any "carry-over" effect from one period to the next the attack rate and trinitrin consumption for the last two weeks of the month only were accepted for evaluation. The patient performed the exercise tolerance test only at the end of the month to reduce any error due to excessive exercise training.

On each fortnightly attendance the following additional observations were made. The blood pressure was taken with the patient standing and the fifth-point diastolic pressure was recorded, the weight was recorded, a standard 12-lead E.C.G. was taken, and the exercise test was performed as described below.

EXERCISE TEST

E.C.G. radiotelemetry was performed using the radiocardiograph transmitter and receiver developed by Medical and Industrial Equipment Ltd., London. This technique has been used previously (Holter, 1957; Bellet *et al.*, 1962; Bellet and Muller, 1965; Magel *et al.*, 1969). The advantages of monitoring the E.C.G. during exercise are well recognized (Rosenfeld *et al.*, 1964; Master, 1968).

A bipolar chest lead was recorded. The indifferent electrode was placed just below the suprasternal notch and the other electrode was placed in the V5 position. These sites were chosen following the work of Wood *et al.* (1950) and also because of their reproducibility in any particular patient. The electrodes were of the lightweight disposable type produced by Dracard Ltd. (Hubner, 1969), and their socket, which connected with the transmitter, was fixed to the chest wall with Scotch tape to prevent the distortion which would otherwise have occurred on the record due to the patient's movement. The transmitter was carried in a belted pouch at the level of the patient's waist, and this allowed the patient to be completely mobile. The E.C.G. trace was displayed on an oscilloscope and recorded simultaneously on a Siemen's Cardiostat recorder. Although the patient was allowed to rest by sitting on a high chair the body trunk was erect at all times. No change was seen on the E.C.G. of any patient as the body position was changed from sitting to standing (Friesinger *et al.*, 1965). The time constant of the E.C.G. recorder was not prolonged when the telemetry apparatus was linked to the recorder (Gold, 1967).

The exercise consisted of a simplified version of the large muscle mass exercise of Kaltenbach (1968). For this modified procedure the patient stood holding a bar which was fixed to the wall above a step. The height of the step was adjusted so that when one foot was placed on the step the other remained on the floor with the patient's hip flexed to 90°. At a signal the patient pulled himself up and placed both feet on the step and then stepped down again putting both feet on to the floor. The cycle was repeated continuously in time with a metronome, each click of the metronome being the time for one foot movement. A rate of 92 steps a minute had been selected by previous trial. When the patient was poised with both feet on the step and his body at maximal height he breasted the wall bars and his head just tipped an adjustable board situated above. The patient exercised until he wished to stop because of symptoms or until, in the highly motivated patient, the rhythm of the exercise became irregular.

The intention of this exercise was to produce a significant and sustained tachycardia. This stress test commonly produced heart rates in the range 180-200/min in 30 normal controls studied previously.

The patient's bipolar chest lead was monitored throughout the procedure. E.C.G. records were obtained initially at rest and then at 30-second intervals during the exercise. The peak exercise E.C.G. record was obtained during the termination of the exercise. Further records were collected in the recovery period as changes were noted to occur on the oscilloscope monitor. In addition records were obtained after two and five minutes' rest. During this trial, although several patients had E.C.G. evidence of previous extensive myocardial infarction, not one suffered more than his usual anginal symptoms as a result of the maximum tolerance exercise test.

The E.C.G. recorder used was a battery-driven model, and to allow accurate calculation of the patient's heart rate the paper speed was checked by introducing a 50 c.p.s. mains artefact on to the record. The heart rates were expressed as the mean of three consecutive R-R intervals measured in millimetres and were recorded during rest, at peak exercise, and after two and five minutes' rest.

Results

The results of the second fortnight of each treatment period are given in table I. The work done during the exercise was estimated as the product of the exercise time in seconds and the body weight in kilogrammes (kg/sec). In order to have adequate control observations throughout the six months of the trial the mean of the results of three control periods were obtained. The first control period occurred at the end of the initial two-week run-in on placebo (period A). The second control period was distributed as a monthly drug period (period F) in the trial. The third control period (period G) was obtained at the end of the trial one month after the patient had been taking trinitrin alone for the relief of his symptoms. The figures for the control period given in table I are the mean of the results obtained from the three control periods A, F, and G. The mean blood pressure records of these periods have been corrected to the nearest 5 mm Hg.

The results during the second fortnight of each treatment period are given in detail (table I) and have been compared using the Wilcoxon signed rank test, as summarized in table II. There was no statistically significant difference between propranolol (100 mg three times a day), which is well established in the treatment of angina pectoris, and verapamil (120 mg three times daily). In the light of the data we have provided we must regard the efficacy of these two treatments as similar. If the 14 patients who experienced headache are disregarded isosorbide dinitrate (20 mg three times a day) is no more effective than a placebo in the treatment of angina pectoris.

In addition we have shown that both propranolol (100 mg

TABLE I—*Results during Second Fortnight of Each Treatment Period*

Case No.	Mean Control				Verapamil 120 mg Thrice Daily				Verapamil 80 mg Thrice Daily				Propranolol 100 mg Thrice Daily				Isosorbide 20 mg Thrice Daily			
	Trinitrin Consumption	No. of Attacks	B.P.	Work Done (kg/sec)	Trinitrin Consumption	No. of Attacks	B.P.	Work Done (kg/sec)	Trinitrin Consumption	No. of Attacks	B.P.	Work Done (kg/sec)	Trinitrin Consumption	No. of Attacks	B.P.	Work Done (kg/sec)	Trinitrin Consumption	No. of Attacks	B.P.	Work Done (kg/sec)
1	6	6	140/85	6,777	7	5	150/85	6,525	2	2	150/90	7,475	1	1	130/80	6,943				
2	0	17	140/95	18,592	0	2	120/70	37,440	0	5	155/90	20,436					0	17	140/95	21,141
3	36	36	175/110	7,792	18	16	170/100	7,998	14	14	150/105	9,244	14	12	160/120	9,000	10	10	185/110	7,812
4	0	2	150/95	12,686	0	0	130/85	16,782	0	0	145/80	18,078	0	0	150/80	12,023				
5	2	2	130/70	14,074	2	2	140/75	13,709	0	0	135/75	17,052	0	0	125/70	15,050	8	8	130/75	16,416
6	5	12	130/90	9,326	2	2	120/80	13,152	0	1	120/95	1,496	1	1	125/95	15,412	3	12	130/105	9,925
7	4	13	160/110	20,722	0	2	140/90	46,020	0	1	150/105	19,090	0	5	130/90	24,225	4	11	140/95	19,494
9	3	1	110/80	9,280	0	0	130/80	9,240	0	0	115/70	9,430	0	0	110/75	9,711				
10	45	45	160/80	8,819	12	12	130/65	12,459	15	11	130/80	13,824	10	8	160/70	11,531				
12	18	17	140/85	5,320	0	0	150/85	6,090	0	0	160/90	4,340	2	2	140/80	5,616				
13	28	15	100/70	7,291	25	25	110/70	8,707	28	28	110/75	7,475	15	15	120/75	7,740				
14	0	3	130/90	12,811	0	0	120/80	8,610	0	0	125/85	9,000	0	0	120/75	8,167				
16	40	40	140/85	6,369	38	38	130/65	7,755	25	25	140/75	8,832	1	1	130/80	8,254				
17	104	104	120/80	7,294	45	45	110/65	12,246	59	59	120/70	9,569	41	41	115/70	8,426	80	80	115/75	7,038
19	17	15	125/85	15,253	4	4	150/85	16,748	2	2	130/90	15,022	0	0	130/95	16,962				
20	12	12	140/85	4,449	2	2	120/80	5,246	4	4	140/75	5,220	7	7	160/85	4,165	3	3	140/85	4,334
22	16	8	160/100	8,366	14	7	170/95	7,630	10	5	190/105	7,700	8	4	165/105	7,923	10	6	170/80	6,480
24	9	7	150/85	9,393	0	0	160/80	8,967	0	0	140/80	6,375					0	0	135/80	9,490
27	2	2	135/100	17,405	0	0	130/90	18,810	0	0	120/80	22,100	2	2	125/90	21,195				
28	2	3	145/90	11,663					2	3	140/80	10,687	2	2	120/75	12,022				
29	72	72	160/105	7,135	27	27	140/105	12,566	58	58	160/120	11,165	33	33	140/95	13,454	71	70	160/105	78,125
30	10	9	190/100	7,597	4	2	200/90	9,075	7	7	240/115	7,527	1	1	170/105	8,251				
31	52	51	110/80	3,372	64	64	130/80	2,023	61	61	110/75	2,751	75	75	110/70	3,153	58	57	130/85	2,983
32	30	48	110/80	10,680	2	8	100/60	6,778	29	47	120/85	7,551	8	12	105/70	10,922	19	26	110/75	9,997
33	3	3	120/85	17,978	0	0	110/80	22,394	0	0	120/80	25,162	0	0	120/85	15,407	1	1	120/85	16,124
34	0	0	140/95	14,556	0	0	130/90	26,040	0	0	130/85	30,780	0	0	130/85	28,813	0	0	160/90	18,040
36	9	0	140/80	8,089	0	0	140/70	6,403	0	0	140/70	9,057	0	0	160/70	8,963	0	0	160/80	6,720
37	20	21	130/80	10,751	46	46	105/75	8,262	28	28	100/70	10,307	21	21	120/75	13,285	11	11	105/80	12,312
38	7	7	145/95	13,345	0	0	150/95	17,427	6	6	160/90	8,617	0	0	120/80	13,928	0	0	130/85	16,625
39	100	100	130/80	7,720	52	52	120/75	5,716	92	92	160/85	5,122	14	28	130/85	5,352				
40	31	24	130/85	10,201	13	13		17,690	26	24	135/80	14,883	13	13	120/90	12,705	39	22	120/80	13,115
42	4	4	130/100	9,866	2	2	150/115	10,380	2	2	130/90	8,961	1	1	125/80	14,509				

TABLE II—*Summary of Comparative Effects of Various Treatments during Second Fortnight. Results expressed as Significance of P Values*

	Verapamil 120 mg Thrice Daily *v.* Placebo	Verapamil 80 mg Thrice Daily *v.* Placebo	Propranolol 100 mg Thrice Daily *v.* Placebo	Isosorbide Dinitrate 20 mg Thrice Daily *v.* Propanolol	Verapamil 120 mg Thrice Daily *v.* Propranolol 100 mg Thrice Daily	Verapamil 80 mg Thrice Daily *v.* Propranolol 100 mg Thrice Daily
Reduction in trinitrin consumption	< 0·05	< 0·01	< 0·01	N.S.	N.S.	N.S.
Reduction in number of attacks	< 0·01	N.S.	< 0·01	N.S.	N.S.	< 0·05
B.P. Systolic fall	N.S.	N.S.	< 0·05	N.S.	N.S.	< 0·05
B.P. Diastolic fall	< 0·01	< 0·05	< 0·01	N.S.	N.S.	N.S.
Prolongation of exercise time	< 0·05	N.S.	< 0·05	N.S.	N.S.	N.S.
Increase in work done	< 0·05	N.S.	< 0·05	N.S.	N.S.	N.S.
Increase in R-R interval (fall in heart rate):						
At rest	< 0·01	N.S.	< 0·01	N.S.	< 0·01	< 0·01
At peak exercise	< 0·01	N.S.	< 0·01	N.S.	< 0·01	< 0·01
At 2 min recovery	< 0·01	N.S.	< 0·01	N.S.	< 0·01	< 0·01
At 5 min recovery	< 0·01	N.S.	< 0·01	N.S.	< 0·01	< 0·01

N. S. = Not significant

three times a day) and verapamil (120 mg three times daily) had a significant lowering effect ($P < 0.01$) on the diastolic blood pressure, as measured with the patient standing erect.

Discussion

Evans and Hoyle (1933) reported a 38% improvement in a group of patients given only placebo treatment for angina pectoris. Even if a double-blind trial is undertaken a substantial number of patients may report improvement in both the trial and test periods when their conditions are unchanged (Mitchell, 1961). It is therefore important to have not only an effective controlled trial of drugs considered for the treatment of angina but also a test period of adequate duration.

In order to evaluate treatment it is important that the patient himself records the frequency of attacks and his trinitrin consumption during his daily activities, as therapy is being given to improve the quality of his daily life, which only he can assess.

Comparative assessment using an exercise tolerance test is an important adjunct to the investigation of the drug treatment of angina provided the conditions of the test are standardized. As a result of the conclusions of Wayne and Laplace (1933) the exercise test was arranged to occur under relatively constant conditions of recording time in the day, postcibal state, adequate pre-exercise rest, amount of clothing worn, and performance of the exercise at room temperature. The best exercise stress test is one involving whole-body muscle mass, and this can be easily and conveniently monitored by radiotelemetric E.C.G. control (Holter, 1957). The exercise can be continued until the patient wishes to stop. The appearance of ischaemic S-T segment depression before the development of pain is not an indication for stopping the test, since he is doing "no more under close control than he is in the habit of doing several times a day without observation" (Wayne and Laplace, 1933).

Depression of the S-T segment greater than 0·5 mm when measured 80 msec after the peak of the R wave was accepted as abnormal. However, it has never been proved that the depression of the S-T segment can be used to allow a linear quantitative assessment of the severity of myocardial ischaemia, although this has been assumed previously (Gianelly *et al.*, 1969). Indeed, during this trial 22 of the 32 patients did not develop abnormal S-T segment depression at the peak exercise stage in all of the three controlled exercise tests they performed. This absence of reproducibility encouraged us to ignore this finding in the evaluation of the trial.

Aerobic myocardial metabolism is dependent on the existence of a myocardial oxygen supply which is at least equal to if not in excess of its requirements. It is well recognized that as the heart rate rises the myocardial oxygen requirement also rises (Lange Andersen *et al.*, 1970). This relation is almost linear, and as the heart rate rises there is an increase in coronary blood flow (Forrester *et al.*, 1971). Advanced atherosclerosis involving the major coronary arteries will cause obstruction to coronary flow. Accordingly under these conditions the increase in volume of coronary flow required to provide for the increasing oxygen requirements of a heart beating more rapidly in response to exercise will not be able to occur. At a critical level of heart rate, and therefore at a critical level of body exercise, myocardial hypoxia will occur. This was confirmed by Balcon *et al.* (1969) in their observations on the critical tension time index required to precipitate angina in individual patients. Our results indicate that both propranolol (100 mg three times a day) and verapamil (120 mg three times daily) significantly reduce the heart rate at rest and throughout the exercise test, and this action together with their hypotensive effects may account for the value of these preparations in the treatment of exercise-induced angina pectoris.

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