Clinical Evaluation of Verapamil in Angina Pectoris

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Summary: A controlled double-blind study of verapamil in 16 anginal patients used two dose levels—40 mg. t.d.s. and 120 mg. t.d.s.—and was compared with propranolol 100 mg. t.d.s. At the higher dosage verapamil produced a significant improvement in frequency of angina, trinitrin consumption, and exercise tolerance, and had a favourable and significant effect on the amount and duration of ischaemic S–T depression occurring in the electrocardiogram during exercise. In the lower dose verapamil produced significant subjective improvement but no objective benefit in the electrocardiogram. No significant differences were found between the favourable results with the higher dosage of verapamil and propranolol.

The action of verapamil is not fully understood, but its favourable effects in angina may be due to a direct action on the myocardium, possibly with accompanying coronary vasodilatation.

Introduction

The advent of beta-receptor blocking agents in the management of angina pectoris has been a major advance in a field where previously the profusion of long-acting coronary vasodilators used was a testimony to their ineffectiveness. Pronethalol was the first successful drug in the treatment of angina (Dornhorst and Robinson, 1962; Alleyne *et al.*, 1963), and was soon superseded by propranolol, which has a therapeutic potency tenfold that of pronethalol and is free of the untoward side-effects of that compound (Black *et al.*, 1964). More recently a newer compound has been produced, verapamil (Cordilox, iproveratril, Isoptin), which on the basis of experimental work by Hass (1964) was introduced as a new beta-receptor blocking agent, and it was claimed that, unlike propranolol, verapamil does not induce either coronary artery vasoconstriction or bronchoconstriction (Haas, 1964). These experimental results have, however, been challenged (Fitzgerald and Barrett, 1967; Wilkinson, 1967; Grant *et al.*, 1968), and in the present state of knowledge it cannot be convincingly maintained that verapamil is indeed a beta-receptor blocking agent.

However, some preliminary clinical studies of the use of verapamil in angina have shown its efficacy (Hoffmann, 1964; Fischer, 1965; Hofbauer, 1966) but these have been uncontrolled and assessment has been largely subjective, though another study by Wette *et al.* (1966) has shown improvement in the ischaemic patterns in the electrocardiogram after long-term treatment with verapamil. Provided verapamil has no deleterious effects on the heart or other organs then the exact mechanism of action in angina, whether this involves beta-receptor blockade or direct depression of myocardial contractility, is of less importance than whether the drug is an effective agent in angina pectoris. It was with these considerations in mind that it was decided to undertake a controlled double-blind evaluation of verapamil in the treatment of angina, basing the assessment mainly on the objective criteria provided by exercise tolerance tests, and at the same time a comparison was made in the same patients between verapamil and propranolol, already widely used in the treatment of angina.

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Patients and Methods

Sixteen outpatients aged from 40 to 66 years with typical attacks of angina were studied. None of them was suffering from or had previously had cardiac failure. Myocardial infarction had occurred in three patients previously, though in all three at least a year had elapsed since the event. There were 13 men and 3 women with angina of 9 to 96 months' duration, and in all of them the anginal attacks had settled down to a stable pattern. Trinitrin was taken freely for the attacks, weekly consumption ranging from 6 to 197 tablets. All patients showed S–T depression in the electrocardiogram on exercise so that an objective index of myocardial ischaemia was obtainable. The preparations studied were verapamil 40 mg. t.d.s., verapamil 120 mg. t.d.s., propranolol 100 mg. t.d.s., and a placebo. A double-blind technique was employed.

All patients attended the clinic monthly and the study began with a control period of one month, when the only drug taken for angina was trinitrin. During the next four months of the trial the patients were given individual monthly supplies of identical tablets in random order comprising verapamil 40 mg., verapamil 120 mg., propranolol 100 mg., or a placebo, the tablets to be taken three times daily. Neither the patient nor the observer knew which drug had been given. In addition each patient was supplied with a specific number of trinitrin tablets at each visit to be used freely for their anginal attacks; they were also given a record card and were asked to fill it in each day, stating only the number of attacks they had had that day. At each monthly visit this card was collected and a new one issued and the remaining trinitrin tablets were counted, giving a more objective assessment of the number of attacks. To eliminate any errors from a carry-over effect of the previous month's therapy only the last two weeks of the four-week period was used in obtaining the incidence of anginal attacks and the number of trinitrin tablets consumed. Any side-effects during the previous month were also noted.

Exercise tolerance tests were carried out at the beginning of the study and at subsequent monthly visits. The test used was a modification of Master's two-step test and has been described in detail previously (Sandler, 1961). In addition to conventional electrocardiography recording chest lead V5 before and after exercise, the patient was monitored continuously during exercise by radiocardiography, which is more sensitive in revealing ischaemic change and also safer by ensuring that ischaemic change can be detected immediately, especially if unaccompanied by angina, allowing the exercise to be terminated immediately (Sandler, 1967). Depression of the S–T segment of plane or sagging contour lasting at least 0.08 sec. in either the radiocardiogram or V5, was accepted as indicating myocardial ischaemia (Lloyd-Thomas, 1961; Master and Rosenfeld, 1961; Bellet *et al.*, 1962); junctional depression was accepted as significant only when the QX/QT ratio exceeded 50% (Master and Rosenfeld, 1961). The indices of assessment which

were recorded during the exercise test were the number of circuits accomplished by the patient and the exercise time before angina and/or ischaemic change developed in the electrocardiogram, the duration of angina, the degree and duration of S–T depression either in the radiocardiogram or in lead V5, and the heart rate before and during exercise. In addition the resting blood pressure was measured in the lying and standing positions before each exercise test was begun, to determine whether any of the preparations taken during the previous month had exerted a hypotensive effect.

The nature and purpose of the investigation was made clear to all the patients.

Results

Table I shows the weekly incidence of angina recorded by the patient and the number of trinitrin tablets used during the control period and with each of the four preparations studied. In this and the subsequent tables, in addition to calculating mean values for the whole group, the differences in individual patients resulting from the various preparations compared with the control period have been analysed statistically, so that variation between different subjects could be eliminated and any changes produced by the drugs could become more apparent. The significance of differences (P values) are shown in all the tables. Compared with the control period there was a significant reduction in the actual number of anginal attacks and a significant change in the incidence of attacks recorded by the patients after treatment with propranolol and high and low doses of verapamil, though there were no significant differences between the three preparations themselves. When trinitrin consumption is considered (Table I) there is seen to be a significant reduction after the use of verapamil 120 mg. t.d.s. and propranolol, and in addition the mean change in weekly trinitrin is significantly less with verapamil 40 mg. t.d.s. as well as with 120 mg. t.d.s. but not with propranolol.

TABLE I.—*Weekly Incidence of Angina Recorded by Patient and Number of Trinitrin Tablets Used (Mean Values for 16 Patients)*

	Control Period	Placebo	Propranolol (100 mg. t.d.s.)	Verapamil (40 mg. t.d.s.)	Verapamil (120 mg. t.d.s.)
Recorded attacks:					
Mean ± S.E.	9·7 ± 2·4	6·5 ± 1·9	4·3 ± 1·8*	4·4 ± 1·0*	4·0 ± 1·0*
P		> 0·15	< 0·05	< 0·005	< 0·0005
Mean change		− 3·4	− 5·4*	− 3·0	− 5·7*
P		> 0·2	< 0·03	> 0·1	< 0·005
Trinitrin used:					
Mean ± S.E.	17·4 ± 3·1	11·2 ± 3·0	9·0 ± 2·9*	11·0 ± 2·8	6·9 ± 2·2*
P		> 0·05	< 0·05	> 0·05	< 0·005
Mean change		− 3·1*	− 6·6	− 10·5*	− 8·1*
P		< 0·03	> 0·3	< 0·05	< 0·05

S.E. = Standard error. * Significant change (P < 0·05).

TABLE II.—*Exercise Tolerance Tests: Number of Circuits, Incidence and Duration of Angina in the 16 Patients (Mean Values)*

	Control Period	Placebo	Propranolol (100 mg. t.d.s.)	Verapamil (40 mg. t.d.s.)	Verapamil (120 mg. t.d.s.)
Circuits accomplished:					
Mean ± S.E.	39·4 ± 5·8	48·3 ± 8·1	60·6 ± 8·3*	54·4 ± 8·6	66·4 ± 8·5*
P		> 0·1	< 0·05	> 0·05	< 0·01
Mean change		+ 8·9	+ 21·1*	+ 17·2*	+ 26·9*
P		> 0·05	< 0·02	< 0·01	< 0·0005
Angina:					
No. of patients	15	12	10	12	9
Time to angina (sec.):					
Mean ± S.E.	265·6 ± 43·5	233·6 ± 36·7	303·5 ± 38·9	285·8 ± 44·8	289·4 ± 39·2
P		> 0·2	> 0·2	> 0·3	> 0·3
Mean change		+ 5·1	+ 147·2*	+ 60·1*	+ 169·3*
P		> 0·4	< 0·01	< 0·05	< 0·005
Duration of angina:					
Mean ± S.E.	139·2 ± 21·8	130 ± 30·0	108·9 ± 29·1	107 ± 17·4	121 ± 28·6
P		> 0·4	> 0·2	> 0·1	> 0·3
Mean change		− 16	− 35	− 26*	− 48
P		> 0·2	> 0·1	< 0·05	> 0·05

* Significant change (P < 0·05).

Table II shows the results of the exercise tolerance tests. Verapamil 120 mg. t.d.s. and propranolol produced a significant increase in the mean number of circuits accomplished, and the mean increase in the number of circuits was also significant with both preparations as well as with verapamil 40 mg. t.d.s. The placebo had no significant effect. The number of patients developing angina during exercise was reduced with all four preparations, the lowest incidence occurring with verapamil 120 mg. t.d.s. Although there were no significant differences with any preparation in the mean exercise time before angina developed, the mean increase in the exercise time was significant with verapamil 40 mg. and 120 mg. t.d.s. and with propranolol, but no significant differences were evident between the three drugs themselves. The only significant finding in relation to the duration of angina induced by exercise was in the mean reduction of duration which followed the use of verapamil 40 mg. t.d.s.—no significant changes were produced by propranolol, verapamil 120 mg. t.d.s., or the placebo.

The electrocardiographic changes during the exercise tests are recorded in Table III, which shows the degree and duration of ischaemic S–T depression in both the radiocardiogram and lead V5. In the radiocardiogram both verapamil 120 mg. t.d.s. and propranolol produced a favourable and significant mean change in the amount of S–T depression developing during exercise, but only propranolol significantly altered the duration of the S–T depression on the radiocardiogram. It is of interest that there was a significant change in the duration of S–T depression following use of the placebo. In conventional lead V5 both verapamil 120 mg. t.d.s. and propranolol were associated with a favourable and significant effect on the mean change in duration of S–T depression after termination of exercise, and this finding was highly significant with verapamil (P<0.0005).

Table IV shows the changes in heart rate during exercise with the four preparations. Compared with the control period the heart rate before exercise was significantly lower after

TABLE III.—*Electrocardiographic Changes During Exercise Tests in the 16 Patients*

	Radiocardiogram		Lead V5	
	Amount of S–T Depression (mm.)	Duration of S–T Depression (seconds)	Amount of S–T Depression (mm.)	Duration of S–T Depression (seconds)
Control				
Mean ± S.E.	1·04 ± 0·11	327·5 ± 103·4	0·5 ± 0·12	300 ± 93·5
Placebo:				
Mean ± S.E.	0·96 ± 0·14	270 ± 25·9	0·55 ± 0·05	290 ± 35
P	> 0·3	> 0·2	> 0·3	> 0·4
Mean change	− 0·07	− 60*	− 0·12	− 52
P	> 0·2	< 0·05	> 0·4	> 0·2
Propranolol 100 mg. t.d.s.:				
Mean ± S.E.	0·83 ± 0·17	270 ± 23·2	0·75 ± 0·11	270 ± 15·5
P	> 0·1	> 0·2	> 0·05	> 0·3
Mean change	− 0·43*	− 167·5*	− 0·16	− 123·7*
P	< 0·01	< 0·002	> 0·05	< 0·002
Verapamil 40 mg. t.d.s.:				
Mean ± S.E.	1·08 ± 0·16	276 ± 10·8	0·54 ± 0·04	295·1 ± 17·8
P	> 0·4	> 0·3	> 0·3	> 0·3
Mean change	+ 0·06	− 73·1	− 0·06	− 46·9
P	> 0·02	> 0·3	> 0·2	> 0·1
Verapamil 120 mg. t.d.s.:				
Mean ± S.E.	0·89 ± 0·16	377·1 ± 75·7	0·6 ± 0·07	354 ± 130·6
P	> 0·2	> 0·3	> 0·2	> 0·35
Mean change	0·25*	− 80	− 0·06	− 375*
P	P = 0·05	> 0·05	> 0·2	< 0·0005

* Significant change (P < 0·05).

TABLE IV.—*Changes in Heart Rate During Exercise in the 16 Patients*

	Control Period	Placebo	Propranolol (100 mg. t.d.s.)	Verapamil (40 mg. t.d.s.)	Verapamil (120 mg. t.d.s.)
Before exercise:					
Mean ± S.E.	83·1 ± 6·3	81·8 ± 5·6	65·6 ± 3·4	77·0 ± 5·3	77·6 ± 3·6
After exercise:					
Mean ± S.E.	120·5 ± 6·3	118·3 ± 6·4	93·8 ± 5·6	113·0 ± 5·6	110·7 ± 5·6

propranolol administration only ($P<0.01$), and a similar result was found after exercise ($P<0.01$). None of the other preparations significantly slowed the heart rate either before or after exercise.

TABLE V.—*Blood Pressure Changes in the 16 Patients After Administration of Placebo, Propranolol, and Verapamil (Mean Values)*

	Control Period	Placebo	Propranolol (100 mg. t.d.s.)	Verapamil (40 mg. t.d.s.)	Verapamil (120 mg. t.d.s.)
Systolic pressure (mm. Hg)					
Lying: Actual pressure	150·4	156·9	146·7	148·0	146·7
Lying: Change in pressure		+5·2	−3·6	−2·4	−3·6
Standing: Actual pressure	150·1	153·4	145·4	142·7	141·9
Standing: Change in pressure		+1·7	−4·7	−7·4	−8·2
Diastolic pressure (mm. Hg):					
Lying: Actual pressure	90·2	89·3	85·1	89·4	84·9
Lying: Change in pressure		−0·9	−5·9	−0·8	−4·3
Standing: Actual pressure	95·7	91·9	88·9	92·0	87·0
Standing: Change in pressure		−3·9	−6·8*	−3·1	−8·7*

* Significant change ($P < 0.05$).

Table V shows the changes in the systolic and diastolic blood pressures recorded in the standing and lying positions after administration of the various preparations. None of the drugs produced any significant differences in the mean systolic or diastolic pressures, standing or lying, compared with the control period. However, when the more sensitive index of mean change in pressures is considered both verapamil 120 mg. t.d.s. and propranolol produced a significant fall in the standing diastolic pressure ($P<0.002$ with verapamil, $P<0.01$ with propranolol).

Side-effects were minimal; two patients had nausea with verapamil 120 mg. t.d.s. and two had transient dizziness with verapamil—one with 40 mg. t.d.s. and one with 120 mg. t.d.s. There was no evidence that verapamil embarrassed cardiac function in any way, either in high or in low dose. There was no clinical evidence of bronchospasm with verapamil in any patient, although this applied also to the use of propranolol in this group of patients.

Discussion

The value of sympathetic beta-receptor blocking agents in the treatment of angina has already been well established (Gillam and Pritchard, 1965; Birkett and Chamberlain, 1966; Grant *et al.*, 1966). The present study confirms objectively the improvement in myocardial ischaemia occurring during exercise in anginal patients taking propranolol 300 mg. orally daily. However, as a result of the intensive beta-adrenergic blockade produced by propranolol unwelcome side-effects may occur such as bronchoconstriction and deterioration in existing heart failure, and sometimes coronary artery vasoconstriction may develop (Wolfson *et al.*, 1966). Verapamil was introduced as a new mild beta-blocking agent which had a direct vasodilating action on the coronary circulation (Melville *et al.*, 1964; Luebs *et al.*, 1966) and which did not produce any bronchoconstriction.

Experimental evidence showed that verapamil can antagonize the effects of isoprenaline in isolated heart preparations and in anaesthetized animals (Haas, 1964; Schmid and Hanna, 1967), but it has been pointed out that, unlike with the use of propranolol, this occurs only with doses high enough to produce myocardial depression (Melville *et al.*, 1964; Melville and Benfey, 1965; Shanks, 1967). Furthermore, it has been shown that the abolition of exercise tachycardia, which is an important effect of a true beta-blocker, does not occur when verapamil was given to healthy volunteers (Fitzgerald and Barrett, 1967), but Bateman (1967) pointed out that reduction of exercise tachycardia has been shown in anginal patients (Atterhög and Porjé, 1966). In the present study, however, verapamil did not slow the heart rate during exercise, though propranolol clearly did produce this effect.

The coronary vasodilator action of verapamil has been shown experimentally (Schlepper and Witzleb, 1962; Haas, 1964; Schmahl and Betz, 1964) and has been confirmed in normal human subjects (Knoch *et al.*, 1963; Luebs *et al.*, 1966), but Mignault (1966) was unable to find any angiocardiographic evidence of coronary vasodilatation in anginal subjects after intravenous verapamil. There have been several favourable reports on the use of verapamil in angina pectoris, but they have been largely uncontrolled and subjectively assessed, results being based on improvement on incidence of angina (Hoffmann, 1964; Fischer, 1965; Hofbauer, 1966; Mignault, 1966). The suggestibility of anginal patients with any new preparation has been well established (Greiner *et al.*, 1950) and the favourable response to placebos clearly shown (Cole *et al.*, 1968), so that the necessity for a double-blind trial becomes apparent. Neumann and Luisada (1966) did find significant improvement in the incidence of angina with verapamil in a double-blind trial in 30 geriatric patients, but assessment was again wholly subjective and therefore of limited value in view of the lack of direct relationship between the development and severity of angina and the degree of actual coronary insufficiency (Russek *et al.*, 1955).

The present study shows clearly that verapamil in a dose of 120 mg. three times daily significantly reduces the incidence of angina and the weekly consumption of trinitrin and also leads to a significant increase in the amount of exercise possible before the development of angina. On a more objective basis, however, the use of verapamil 120 mg. t.d.s. is associated with significantly less S–T depression in the radiocardiogram during exercise and also leads to a significant reduction in the duration of such depression recorded in lead V5 after exercise has finished. Verapamil in the smaller dose of 40 mg. three times daily also resulted in a significant improvement in the incidence of angina and trinitrin consumption, and significantly increased exercise tolerance with a significant shortening of duration of subsequent angina. There was, however, no corresponding improvement in the more objective findings in the amount and duration of S–T depression during exercise with verapamil 40 mg. t.d.s. Propranolol 100 mg. three times daily was found to be as effective as verapamil 120 mg. three times daily in improving the incidence of angina, trinitrin consumption, amount and duration of exercise before the development of angina, and the degree and duration of ischaemic S–T depression. No significant differences were evident between the beneficial effects of the two drugs. It is of interest also that verapamil 120 mg. t.d.s. was associated with a significant fall in standing diastolic pressure in the present study, which suggests a reduction in peripheral vascular resistance possibly by direct action on the peripheral arteriolar wall in the same way that the coronary vasodilatation may occur.

A hypotensive action of verapamil has also been shown experimentally by Ross and Jorgensen (1967), who attributed this effect to systemic and splanchnic vasodilatation occurring in anaesthetized cats. Propranolol administration also resulted in a fall in standing diastolic pressure, but here the mode of action is not clear, since direct arteriolar vasodilatation has not been found as a result of propranolol treatment, and it is considered more likely that the hypotensive action of this drug is probably due either to blockade of pressor stimuli mediated through the cardiac sympathetic nerves (Prichard and Gillam, 1964) or to a chronic reduction in cardiac output (Frohlich *et al.*, 1968). The mode of action of propranolol in angina probably involves several different mechanisms (Frieden, 1967), including prevention by beta-receptor blockade of the myocardial oxygen-wasting effects of catecholamines liberated by exertion or emotion, suppression of myocardial contractility by a quinidine-like action, topical anaesthesia, and reduction of cardiac work by the hypotensive action of the drug. In the absence of satisfactory evidence that therapeutic dose levels of verapamil produce beta-receptor blockade and the lack of consistent evidence that the drug produces coronary vasodilatation

in anginal subjects, its undoubtedly beneficial effects in angina are probably attributable to a direct suppression of myocardial contractility by the quinidine-like effect of the drug shown by Melville *et al.* (1964).

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Preliminary Communications

Rubidomycin in Acute Leukaemia in Adults

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Summary: In a preliminary study rubidomycin was found capable of inducing remission in adults with acute leukaemia, the remission rate in acute myeloblastic leukaemia comparing favourably with that achieved with previous forms of therapy. Marrow aplasia and cardiotoxicity occurred in a number of patients. Supportive measures during the former and early recognition by frequent electrocardiography can do much to mitigate these toxic effects.

INTRODUCTION

Rubidomycin is the first antibiotic to show therapeutic effect in acute leukaemia in man. It was discovered in France and shortly afterwards independently in Italy, where it was called daunomycin. It has been shown to be effective when used in acute leukaemia in children and adults (Bernard *et al.*, 1967) or when given in combination with other chemotherapeutic agents in acute lymphoblastic leukaemia (Mathé *et al.*, 1967). The incidence of remission in patients with myeloblastic leukaemia has been higher than that recorded for any other form of therapy (Dreyfus *et al.*, 1968). This study has been concerned mainly with the use of rubidomycin in the particularly intractable group of adult acute myeloblastic leukaemia. It has also been used to treat a few patients with acute lymphoblastic leukaemia who have relapsed after conventional therapy.

PATIENTS TREATED AND METHOD OF ADMINISTRATION

Twenty-two adults with leukaemia have been treated with rubidomycin between November 1966 and June 1968. Sixteen adults between the ages of 17 and 81 with acute myeloblastic leukaemia received treatment. Eight of these had had some form of chemotherapy but were not in remission, while the other eight had received only blood transfusions or antibiotics. The three patients with acute lymphoblastic leukaemia had all had at least four chemotherapeutic agents. One of them had not achieved remission, while the other two had had two and four remissions respectively.

Rubidomycin hydrochloride is supplied as a microcrystalline orange-red powder readily soluble in water. About 2 ml. of sterile normal saline is required to dissolve the contents of one ampoule. The total volume injected is some 15 to 20 ml. It was administered by injection into the tubing of a fast-flowing intravenous saline infusion. Great care was taken to avoid extravasation of the material, which was intensely painful even in small amounts and might cause necrosis. The rate of infusion was increased after the injection to prevent stasis.

Two schedules of administration were employed during the study. The first was to give 2 mg./kg. body weight daily to a maximum of 10 mg./kg. unless signs of toxicity supervened. About half the patients were treated in this way. The second method[1] was to give an initial dose of 2 mg./kg./day, then

[1] This administration is based on the protocol of the Groupe Européen de Chimiothérapie Anticancéreuse, with whom we are undertaking a co-operative trial.