Double-blind comparison of verapamil and practolol in the treatment of angina pectoris

B. FAGHER
M.D.

S. PERSSON
M.D.

S. E. SVENSSON
M.D.

Departments of Cardiology and Clinical Physiology, Lasarettet, Lund, Sweden

Summary

In thirteen patients with coronary insufficiency and angina pectoris the therapeutic effects of verapamil, 80 mg three times/day and practolol, 100 mg three times/day, were compared and tested against placebo in a double-blind cross-over fashion. Verapamil proved to be the most efficient drug as regards attack frequency and glyceryl trinitrate consumption as well as physical working capacity, bringing about a statistically significant increase of the exercise tolerance as compared to placebo after a treatment period of four weeks. Verapamil is a good alternative to β -blockers in the prophylactic treatment of angina. Possible modes of action of verapamil in angina pectoris are discussed. The study had to be interrupted because of the reports of side effects of practolol, explaining the small number of patients.

Introduction

The value of β -receptor blockade in the treatment of angina pectoris has been amply documented (for references, see Prichard, 1974). However, non-selective β -blocking agents are hazardous in patients with co-existing airway-obstructing disease, and the disadvantages of these drugs as well as of those with cardioselective action in latent cardiac decompensation are well known. Furthermore, serious side effects during long term treatment with different β -blockers have been reported (Greenblatt and Koch-Weser, 1974; Wright, 1975). The need for alternatives in the long term management of coronary artery disease is therefore indisputable.

Verapamil, originally introduced as a coronary vasodilator (Haas and Härtfelder, 1962), has been tested as an antianginal agent in several studies. Favourable results were reported by Atterhög and Porjé (1966), Sandler, Clayton and Thornicroft (1968), Livesley *et al.* (1973) and Andreasen *et al.* (1975), but not by Phear (1968). Verapamil in adequate doses was found comparable to propranolol by

Sandler *et al.* (1968) and by Livesley *et al.* (1973).

In the present study, verapamil was compared to the cardio-selective β -blocker practolol as regards the efficacy in improving the patients' well-being, in reducing the frequency of anginal attacks and the consumption of glyceryl trinitrate tablets and in increasing the capacity for physical exercise in patients with coronary insufficiency and angina pectoris.

Materials and methods

Patients

Initially, the study was planned to comprise twenty patients. During the course of the study, reports of adverse side effects from practolol were published (Felix, Ive and Dahl, 1974; Wright, 1975) and, on the recommendation of the Swedish Medical Board, the trial was interrupted. Thirteen patients, one female, aged 64 and twelve male patients, aged 43–71 (mean 57 years), completed the study. All patients had a previous history of stable angina pectoris for at least 1 year. Eight patients had a history of myocardial infarction 1 year or more previously. In five patients coronary heart disease had been verified by coronary angiography. All patients were on β -receptor blocker therapy at the start of the trial: tolamolol (eight), propranolol (two), alprenolol (two) and practolol (one). All these drugs were given in dosages considered optimal by the physician responsible. Blood pressure was within normal limits in all patients. None had present or past evidence of cardiac failure. The average roentgenological heart volume was 448 ml/m², with a range of 280–600 ml/m². No signs of obstructive lung disease were present. All had been out-patients of the Department of Cardiology, usually for many years and had previously been investigated with standardized exercise tests, some of them on several occasions.

Design of the study

All the patients underwent conventional physical

Correspondence: Dr S. Persson, Department of Cardiology, Lasarettet, Lund, S-221 85 Lund, Sweden.

FIG. 1. Number of attacks of angina pectoris per week and glyceryl trinitrate consumption per week during control period and double-blind trial. Mean $\pm$ s.e.m. are given. * $P < 0.05$; † $P < 0.01$.

examination, as well as a graded exercise test on a bicycle ergometer while on ordinary therapy. The purpose of the study was explained to the patients. They were told that three different compounds would be given but not informed about the expected different effects on objective indices such as pulse rate.

After an initial control period of 2 weeks, during which the patients received placebo, there were three periods each of 4 weeks during which placebo, verapamil, 80 mg three times/day, or practolol, 100 mg three times/day, in identical capsules, were given in a double-blind cross-over fashion. At the end of each period routine clinical examination and a bicycle ergometer test were carried out. The patients were asked to record any attacks of angina, and the number of glyceryl trinitrate tablets (0.5 mg) used, on a data sheet issued at the start of each period.

Bicycle ergometer test

Exercise tests were performed with the patient sitting on an electrically-braked bicycle ergometer (Siemens-Elema AB). The work load was increased stepwise after 6 min exercise at each load. The loads were usually 30, 50, 70, 100, 120 and 150 W and, from the findings at the first exercise test, the initial load was individually adjusted so that each patient would be able to complete at least three levels of work load before interruption. The physical working capacity was defined as the highest work intensity which the patient could perform for 6 min plus the increment to the next load multiplied by the work time on that load divided by 6 min (Granath, 1965). A 12-lead ECG was recorded before and intermittently during a 10-min period after the work test. During the work test a 6-lead precordial ECG was recorded every 2 min or more often if required. Systolic and diastolic blood pressures (auscultatory method) were deter-

mined before and after exercise. During work only the systolic blood pressure was determined every 2 min.

The effort test was interrupted if the patient experienced increasing chest pain, breathlessness or exhaustion. All male patients underwent five exercise tests. The female patient was excluded from exercise tests because she experienced angina at a work level of only 10 W.

Student's *t*-test for paired values was used for statistical analysis.

Results

The average number of anginal attacks and consumption of glyceryl trinitrate tablets are shown in Fig. 1. During verapamil treatment the frequency of anginal attacks was significantly reduced in comparison with the control period ($P < 0.01$) and was lower than during the placebo period. This latter difference was, however, not significant. Practolol did not appear to differ from placebo in this respect. The consumption of glyceryl trinitrate closely paralleled the frequency of anginal attacks.

As regards subjective well-being, of thirteen patients, seven preferred verapamil and two practolol; two found verapamil and practolol equally valuable and better than placebo and two considered verapamil equal to placebo and both superior to practolol (Table 1).

TABLE 1. Subjective well-being in relation to control period during placebo, verapamil and practolol treatment

	Placebo	Verapamil	Practolol
Much better	1	9	1
Better	8	2	8
Unchanged	4	2	2
Worse	—	—	2

TABLE 2. Capacity for physical exercise, expressed in watts, in twelve patients at the start of the trial (exercise test 1), during the control period and during treatment with placebo, verapamil and practolol. Mean $\pm$ s.e.m. given

Exercise test 1	84.2 $\pm$ 7.71
Control	82.8 $\pm$ 8.57
Placebo	89.8 $\pm$ 8.71*
Verapamil	99.9 $\pm$ 7.30*
Practolol	93.2 $\pm$ 7.38

* $P < 0.05$.

The results of the determination of the physical working capacity are shown in Table 2. The preliminary exercise test, although not strictly belonging to the study, is also included in this table for comparison. After verapamil treatment exercise tolerance was significantly better than after the placebo and the control periods. Practolol was slightly better than placebo in this respect without, however, a statistically significant difference. There was only a small difference between the first exercise test, when all patients had conventional β -receptor blockers, and the second exercise test (control), when all therapy had been withdrawn. The heart rate and blood pressure at rest before the exercise tests are shown in Table 3. Neither practolol nor verapamil seemed to

influence resting heart rate in comparison with the placebo and control periods. Systolic and diastolic blood pressures were significantly reduced on verapamil as compared to the placebo period. Practolol significantly reduced heart rate, systolic blood pressure and rate-pressure product as compared to placebo both at the maximal load tolerated and at the highest comparable load (Table 4). Verapamil slightly reduced heart rate and blood pressure during exercise but the differences were not statistically significant. The rate-pressure product at the end of the exercise was similar during verapamil and placebo treatment as well as after the control period and significantly higher than during β -receptor blockade.

Discussion

The beneficial effect of verapamil in angina pectoris that has been demonstrated supports previous experience (Sandler *et al.*, 1968; Livesley *et al.*, 1973; Andreassen *et al.*, 1975); these workers also reported subjective improvement (as reflected in a lower attack frequency and a reduced glyceryl trinitrate consumption) as well as an objective increase of exercise tolerance when using doses similar to those in the present study.

In previous studies practolol has been shown to

TABLE 3. Heart rate (beats/min) and blood pressure (mmHg) at rest before the different exercise test. Mean $\pm$ s.e.m. given

	Heart rate	Systolic blood pressure	Diastolic blood pressure
Exercise test 1	54 $\pm$ 2.0	139 $\pm$ 4.94	83 $\pm$ 2.25
Control	66 $\pm$ 3.3	142 $\pm$ 5.74	88 $\pm$ 3.12
Placebo	67 $\pm$ 3.3	142 $\pm$ 5.72*	86 $\pm$ 1.93†
Verapamil	64 $\pm$ 3.1	128 $\pm$ 2.86*	77 $\pm$ 2.17†
Practolol	62 $\pm$ 2.9	135 $\pm$ 4.62	82 $\pm$ 1.67†

* $P < 0.05$; † $P < 0.01$.

TABLE 4. Heart rate (beats/min), systolic blood pressure and rate pressure product (mmHg/min per 100) at the final observations before break (a) and at the highest comparable load (b) during conventional β -receptor blockade (exercise test 1) and during the trial. Mean $\pm$ s.e.m. given

	Heart rate	Systolic blood pressure	Rate pressure product
(a)			
Exercise test 1	98 $\pm$ 4.65	166 $\pm$ 6.32	164 $\pm$ 11.9
Control	121 $\pm$ 7.22	191 $\pm$ 8.11	234 $\pm$ 21.4
Placebo	123 $\pm$ 7.39†	187 $\pm$ 8.75†	244 $\pm$ 23.0†
Verapamil	121 $\pm$ 6.35	180 $\pm$ 7.59	220 $\pm$ 17.0*
Practolol	103 $\pm$ 5.23†	168 $\pm$ 7.74†	175 $\pm$ 14.4†
(b)			
Exercise test 1	86 $\pm$ 3.61	161 $\pm$ 5.98	137 $\pm$ 7.62
Control	106 $\pm$ 5.43	177 $\pm$ 7.97	189 $\pm$ 14.9
Placebo	102 $\pm$ 6.70†	169 $\pm$ 7.82†	176 $\pm$ 19.2†
Verapamil	97 $\pm$ 6.73	164 $\pm$ 8.31	162 $\pm$ 17.6
Practolol	89 $\pm$ 5.28†	158 $\pm$ 6.15†	141 $\pm$ 12.0†

* $P < 0.05$; † $P < 0.01$.

reduce the frequency of attacks (George, Nagle and Pentecost, 1970; Nestel, 1972) and to increase exercise tolerance (Sandler and Clayton, 1970; Balcon, 1971; Westerlund, 1971). The poor response in these respects in the present study is hard to explain, but might be due to coincidence in this rather small group of patients, the number having been limited by the unforeseen interruption of the trial due to the reports of serious side effects of practolol (Felix *et al.*, 1974; Wright, 1975). The β -receptor blocking effect of practolol as reflected in heart rate and blood pressure during exercise was evident in the present study and similar to previous β -blocking therapy (exercise test 1).

The comparatively high frequency of attacks and the high glyceryl trinitrate consumption during the control period might at least partly be explained as a rebound phenomenon after the abrupt withdrawal of the preceding β -blocking therapy (Miller *et al.*, 1975). Thus, the reduction of subjective symptoms during the treatment periods as compared to the control period might be hard to evaluate. However, the objective exercise tolerance was not significantly poorer after the control period than 2 weeks previously when the patients were still on their previous β -blocker. Physical working capacity is therefore a good way to compare the benefits of the different treatments in this study; in this respect verapamil also turned out to be the most effective drug, being significantly better than placebo as well as the preceding β -receptor blocking therapy.

The mode of action of verapamil in angina pectoris is not satisfactorily explained. Although introduced as a coronary vasodilator (Haas and Härtfelder, 1962) it is unlikely that this mechanism would operate in ischaemic tissue producing metabolites with strong vasodilator properties. Intravenous verapamil has also been reported as causing an insignificant fall in coronary blood flow in patients with coronary atherosclerosis (Luebs *et al.*, 1966). The drug has been shown to be a calcium-ion antagonist interfering with the inward flux of calcium ions across the cardiac cell membrane, thereby inhibiting the calcium-dependent transformation of phosphate-bound energy to mechanical work (Fleckenstein *et al.*, 1967; Nayler and Krikler, 1974). This mechanism should reduce myocardial oxygen consumption and might thus explain the action of verapamil in ischaemic heart disease. This suggests a negative inotropic effect, which has been demonstrated experimentally (Nayler and Szeto, 1972; Sing and Vaughan Williams, 1972), although not in humans in normal doses, whether at rest (Rydén and Saetre, 1971) or during exercise (Atterhög and Ekelund, 1974).

The rate-pressure product (Robinson, 1967) on maximal load tolerated was significantly lowered by

practolol. When evaluating left ventricular work and myocardial oxygen demand it seems reasonable also to take the ejection period into consideration, extending the above product to heart rate $\times$ blood pressure $\times$ ejection period (pressure-time/min: Shinebourne, Fleming and Hamer, 1968). Practolol significantly prolongs ejection time at rest (Gibson and Sowton, 1968) as well as during exercise, as can be deduced from the figures of Shinebourne *et al.* (1968). This is probably due to the negative inotropic properties of the drug. Since in the present study verapamil did not significantly change the rate-pressure product as compared to placebo it probably did not influence the ejection period either, which may indicate the absence of a cardio-depressive action on maximal load tolerated.

Reduction of myocardial oxygen consumption as a consequence of the calcium-ion antagonism may thus not fully explain the beneficial effect of verapamil in angina pectoris. Livesley *et al.* (1973) attributed the anti-anginal effect of the drug mainly to its vagomimetic action causing a decrease in heart rate and blood pressure. This suggestion is supported by the results of Atterhög and Porjé (1966) and those in the present study showing a reduction, (albeit not statistically significant) in heart rate and blood pressure of verapamil as compared to placebo on comparable work loads.

Thulesius, Lim and Gjörös (1974), using plethysmography, showed a marked local vasodilatation in the forearm after intra-arterial as well as intravenous infusion of verapamil in low doses. Their results on isolated preparations from arteries and veins implied that this effect was mainly on the arteries. It still remains to be shown, however, if verapamil may act *in vivo* upon human capacitance vessels and/or the greater arteries, thereby simulating the peripheral action of glyceryl trinitrate (e.g. Müller and Rörvik, 1958; Christensson, Karlefors and Westling, 1965).

The mode of action of verapamil in angina pectoris is thus still uncertain. However, the mechanisms seem to be different from those of β -receptor blocking drugs. The beneficial effects on subjective symptoms and well-being as well as on physical working capacity, in the present study even better than the cardioselective β -blocker practolol, makes it a good alternative to the β -blocking agents in the long term management of patients with coronary insufficiency and angina pectoris.

References

- ANDREASEN, F., BOYE, E., CHRISTOFFERSEN, E., DALSGAARD, P., HENNEBERG, E., KALLENBACH, A., LADEFOGED, S., LILLQUIST, K., MIKKELSEN, E., NORDERØ, E., OLSEN, J., PEDERSEN, J.K., PEDERSEN, V., BRUUN PETERSEN, G., SCHROLL, J., SCHULTZ, H. & SEIDELIN, J. (1975) Assessment of verapamil in the treatment of angina pectoris. *European Journal of Cardiology*, **2**, 443.

- ATTERHÖG, J.-H. & EKELEND, L.-G. (1974) The effect of verapamil on haemodynamics in healthy subjects at rest and during exercise. In: *Symposium on Arrhythmias. Isoptin* (Ed. by J.-H. Atterhög, A. Haakana and B. Norling), p. 51. Editio Cantor, Aulendorf.
- ATTERHÖG, J.-H. & PORJÉ, G. (1966) Isoptin vid angina pectoris. *Läkartidningen*, **63**, 2071.
- BALCON, R. (1971) Assessment of drugs in angina pectoris. *Postgraduate Medical Journal*, **47** (Suppl.), 53.
- CHRISTENSSON, B., KARLEFORS, T. & WESTLING, H. (1965) Haemodynamic effects of nitroglycerin in patients with coronary heart disease. *British Heart Journal*, **27**, 511.
- FELIX, R.H., IVE, F.A. & DAHL, M.G.C. (1974) Cutaneous and ocular reactions to practolol. *British Medical Journal*, **4**, 321.
- FLECKENSTEIN, A., KAMMERMEIER, H., DÖRING, H.J. & FREUND, H.J. (1967) Zum Wirkungsmechanismus neuartiger Koronardilatoren mit gleichzeitig Sauerstoffensparenden Myokard-Effekten, Prenylamin und Iproveratril. *Zeitschrift für Kreislaufforschung*, **56**, 839.
- GEORGE, C.F., NAGLE, R.E. & PENTECOSTE, B.L. (1970) Practolol in treatment of angina pectoris. *British Medical Journal*, **2**, 402.
- GIBSON, D. & SOWTON, E. (1968) Effects of I.C.I. 50172 in man during erect exercise. *British Medical Journal*, **1**, 213.
- GRANATH, A. (1965) Mitral valvulotomy. A clinical and haemodynamic pre- and postoperative study. *Acta medica scandinavica*, **178** (Suppl.), 433.
- GREENBLATT, D.J. & KOCH-WESER, J. (1974) Adverse reactions to β -adrenergic receptor blocking drugs: a report from the Boston Collaborative Drug Surveillance Program. *Drugs*, **7**, 118.
- HAAS, H. & HÄRTFELDER, G. (1962) α -Isopropyl- α [(N-methyl-N-homoveratryl)- γ -amino-propyl]-3,4-dimethoxyphenyl-acetonitril, eine Substanz mit coronargefässerweiternden Eigenschaften. *Arzneimittel-Forschung*, **12**, 549.
- LIVESLEY, B., CATLEY, P.F., CAMPBELL, R.C. & ORAM, S. (1973) Double blind evaluation of verapamil, propranolol, and isosorbide dinitrate against placebo in the treatment of angina pectoris. *British Medical Journal*, **1**, 375.
- LUEBS, E.-D., COHEN, A., ZALESKI, E.J. & BING, R.J. (1966) Effect of nitroglycerin, intensin, isoptin and papaverine on coronary blood flow in man. *American Journal of Cardiology*, **17**, 535.
- MILLER, R.R., OLSON, H.G., AMSTERDAM, E.A. & MASON, D.T. (1975) Propranolol-withdrawal rebound phenomenon. Exacerbation of coronary events after abrupt cessation of antianginal therapy. *New England Journal of Medicine*, **293**, 416.
- MÜLLER, O. & RÖRVIK, K. (1958) Haemodynamic consequences of coronary heart disease with observations during anginal pain and on the effect of nitroglycerin. *British Heart Journal*, **20**, 302.
- NESTEL, P.J. (1972) Practolol in the treatment of ischemic heart pain. Results of a controlled trial. *Medical Journal of Australia*, **1**, 1033.
- NAYLER, W.G. & KRIKLER, D. (1974) Verapamil and the myocardium. *Postgraduate Medical Journal*, **50**, 441.
- NAYLER, W.G. & SZETO, J. (1972) Effect of verapamil on contractility, oxygen utilization and calcium exchangeability in mammalian heart muscle. *Cardiovascular Research*, **6**, 120.
- PHEAR, D.N. (1968) Verapamil in angina: a double-blind trial. *British Medical Journal*, **2**, 740.
- PRICHARD, B.N.C. (1974) β -Adrenergic receptor blocking drugs in angina pectoris. *Drugs*, **7**, 55.
- ROBINSON, B.F. (1967) Relation of heart rate and systolic blood pressure to the onset of pain in angina pectoris. *Circulation*, **35**, 1073.
- RYDÉN, L. & SAETRE, H. (1971) The haemodynamic effect of verapamil. *European Journal of Clinical Pharmacology*, **3**, 153.
- SANDLER, G. & CLAYTON, G.A. (1970) Clinical evaluation of practolol, a new cardioselective beta-blocking agent in angina pectoris. *British Medical Journal*, **2**, 399.
- SANDLER, G., CLAYTON, G.A. & THORNICROFT, S.G. (1968) Clinical evaluation of verapamil in angina pectoris. *British Medical Journal*, **3**, 224.
- SHINEBOURNE, E., FLEMING, J. & HAMER, J. (1968) Haemodynamic responses to exercise in hypertension: place of the sympathetic nervous system evaluated by a new selective cardiac β -adrenergic blocking agent ICI 50172. *Cardiovascular Research*, **4**, 379.
- SINGH, B.N. & VAUGHAN WILLIAMS, E.M. (1972) A fourth class of anti-dysrhythmic action? Effect of verapamil on ouabain toxicity, on atrial and ventricular intracellular potentials, and on other features of cardiac function. *Cardiovascular Research*, **6**, 109.
- THULESIUS, O., LIM, B.H. & GJÖRES, J.E. (1974) Peripheral vascular actions of verapamil in man. In: *Symposium on Arrhythmias. Isoptin* (Ed. by J.-H. Atterhög, A. Haakana and B. Norling), p. 73. Editio Cantor, Aulendorf.
- WESTERLUND, A. (1971) Long-term assessment of practolol in angina. *Postgraduate Medical Journal*, **47** (Suppl.), 64.
- WRIGHT, P. (1975) Untoward effects associated with practolol administration: oculomucocutaneous syndrome. *British Medical Journal*, **1**, 595.