Coronary haemodynamic effects of short term intravenous administration of gallopamil in patients with stable exertional angina

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SUMMARY The effects of short term intravenous administration of gallopamil on coronary haemodynamic variables were studied in 10 patients with stable exertional angina and angiographically confirmed coronary artery disease that affected the proximal portion of the left anterior descending artery. Blood flow in the great cardiac vein was measured by a thermodilution technique, both at rest and during ischaemia induced by atrial pacing, before and after intravenous administration of gallopamil (0.02 mg/kg as a bolus dose given over three minutes, followed by an infusion of 0.0005 mg/kg/min). Gallopamil significantly prolonged the mean (SD) duration of pacing that was tolerated (11 (2.6) *vs* 14.8 (2.4)) min, significantly increased the mean (SD) peak heart rate attained during pacing (142 (15) *vs* 158 (11) beats/min), and reduced mean (SD) arterial pressure (133 (17) *vs* 116 (17) mm Hg). There were no changes in mean (SD) blood flow in the great cardiac vein (134.1 (57) *vs* 112.9 (38) ml/min, mean (SD) anterior regional coronary resistance (1.18 (0.6) *vs* 1.15 (0.5) mm Hg/ml/min), and mean (SD) anterior regional myocardial oxygen consumption (16.6 (6) *vs* 13.7 (4) ml/min).

These data confirm that gallopamil is an effective antianginal agent and suggest that a reduction of myocardial oxygen demand is the predominant mechanism by which the drug exerts its beneficial effects.

The antianginal efficacy of calcium channel blocking agents such as verapamil,¹⁻³ nifedipine,⁴⁻⁶ and diltiazem⁷⁻⁹ is well established. The mechanism of the effect depends on the affinity of the agent for its receptor sites and the cause of ischaemia, and is achieved by a reduction in myocardial oxygen consumption by an improvement in oxygen supply or both.

New calcium channel blocking agents are being developed to improve the efficacy and safety of antianginal action. One of these new calcium antagonists, gallopamil, a verapamil analogue, improved

exercise tolerance in patients with stable exertional angina.¹⁰⁻¹² There is evidence that gallopamil exerts its antianginal effect by improving the ratio of myocardial oxygen supply to oxygen demand. But the mechanism of this action has not been elucidated.

We studied 10 patients with stable exertional angina and angiographically confirmed disease of the proximal portion of the left anterior descending coronary artery. Thermodilution measurements of blood flow in the great cardiac vein—that is the venous efflux from the territory supplied by the left anterior descending artery¹³—were taken at rest and during myocardial ischaemia induced by rapid atrial pacing both before and after the short term intravenous administration of gallopamil. The effects of the drug on pacing tolerance were then related to

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coronary haemodynamic changes in the anterior region of the heart in which perfusion was jeopardised.

Patients and methods

PATIENTS

We studied 10 patients (nine men and one woman, mean age 54 years) with stable exertional angina. They all had a positive exercise test, defined as the development of typical chest pain associated with ST segment depression of >1 mm in the precordial leads. Patients with angina at rest or transient ST segment elevation during pain were excluded. No patient had a history of previous anterior myocardial infarction or showed abnormal Q waves in the precordial leads. The results of physical examination were normal. Left ventricular angiography and coronary arteriography showed significant coronary disease (stenoses of the luminal diameter $>50\%$) of the proximal portion of the left anterior descending artery in all 10 patients.

We studied patients within two weeks of coronary arteriography, without premedication, and at least three days after β blockers had been progressively tapered and withdrawn. Withdrawal phenomena, such as accelerated angina or other acute coronary events, were not seen. Nifedipine and nitrates were discontinued for at least 12 hours. No patient was taking verapamil or diltiazem. We obtained the informed consent of all patients before the study.

METHODS

The study was performed late in the morning in supine fasting patients. A triple thermistor thermodilution catheter with pacing electrodes was introduced under local anaesthesia into an antecubital vein and advanced to the great cardiac vein. The

position of the catheter was checked frequently by fluoroscopy during the procedure. Once the catheter was in position flow in the great cardiac vein while the patient was at rest was determined by a continuous infusion of a physiological saline solution (56 ml/min for 30 seconds). Arterial blood pressure was recorded continuously by means of a Teflon cannula in a brachial artery. Blood samples for the measurement of haemoglobin oxygen saturation were obtained from an artery and the great cardiac vein of nine patients. The heart rate was then increased by coronary sinus pacing, which increased by 10 beats per minute until the patient experienced chest pain or ST segment depression >2 mm developed in the anterior leads. Each pacing rate was maintained for two minutes. When the end point was reached, blood flow in the great cardiac vein was measured for 30 seconds in all patients and samples of arterial and great cardiac vein blood were again obtained in nine patients. A 12 lead electrocardiogram was recorded before and at the end of pacing, and leads V4, V5, and V6 were monitored throughout the test. After 40 minutes a bolus dose of gallopamil (0.02 mg/kg) was given intravenously over three minutes and this was followed by a continuous infusion of 0.0005 mg/kg/min. Ten minutes later baseline data were collected and atrial pacing was started again. When the patient experienced chest pain, when ST segment depression (>2 mm) developed, or when a heart rate of 170 beats per minute was reached, the coronary haemodynamic measurements were repeated. Venous blood samples for measuring gallopamil concentrations were also obtained at that time. An intravenous bolus dose (0.5 mg) of atropine was given to two patients in whom failure to capture occurred after gallopamil. No complications were observed during the pacing procedure.

Table 1 Clinical, haemodynamic, and angiographic data in 10 patients with stable exertional angina

Case No	Sex	Age	LVEDP (mm Hg)	EF (%)	Stenosis of		
					LAD	Cfx	RCA
1	M	58	23	68	90%	—	—
2	M	60	13	59	75%	—	—
3	M	60	16	74	75%	90%	—
4	M	50	24	69	100%	—	99%
5	M	59	16	56	99%	90%	75%
6	M	49	7	84	99%	—	—
7	F	55	19	79	100%	75%	—
8	M	52	12	82	75%	—	—
9	M	51	14	70	75%	75%	100%
10	M	50	12	78	75%	99%	99%
Mean (SD)		54 (4)	16 (5)	72 (9)			

LVEDP, left ventricular end diastolic pressure; EF, ejection fraction; LAD, left anterior descending coronary artery; Cfx, circumflex; RCA, right coronary artery.

Table 2 Resting values of haemodynamic variables in 10 patients with stable exertional angina

Case No	Heart rate (beats/min)		MAP (mm Hg)		Double product (bpm × mm Hg × 10 ⁻²)		GCVF (ml/min)		ARCR (mm Hg/ml/min)		MVO ₂ (ml/min)	
	Control	GP	Control	GP	Control	GP	Control	GP	Control	GP	Control	GP
1	71	75	129	121	139.2	137.2	58.8	63.4	2.19	1.9	5.3	5.3
2	108	102	141	131	209.5	191.8	104.3	104.3	1.35	1.25	13.1	12.9
3	73	85	120	102	124.8	120.7	93.5	89.8	1.28	1.13	9.7	9.7
4	58	65	110	102	93.4	92.9	43.2	36.9	2.54	2.76	6.9	5.8
5	82	76	134	117	150.9	130	91.3	62.3	1.47	1.88	12.6	8
6	60	63	104	104	100.2	92	52.8	58	1.97	1.79	6.9	6.7
7	113	103	129	96	206.8	141.1	52.8	30	2.44	3.2	6.8	3.4
8	72	72	108	125	113.8	116.6	82.4	128.7	1.31	0.97	10	15.5
9	70	66	100	96	114.1	101.6	45.6	50.3	2.19	1.91	—	—
10	67	71	100	92	91.8	94.4	56.9	43.9	1.76	2.1	6.8	4.9
Mean	77	78	117	109	134.4	121.8	68.2	66.8	1.85	1.89	8.7	8
(SD)	(19)	(14)	(15)	(14)	(43.2)	(30.7)	(22)	(31)	(0.5)	(0.7)	(3)	(4)

MAP, mean arterial pressure; GCVF, great cardiac vein flow; ARCR, anterior regional coronary resistance; MVO₂, myocardial oxygen consumption; GP, gallopamil.

There were no significant differences between control and gallopamil values.

CALCULATIONS AND STATISTICAL ANALYSIS

Great cardiac vein flow was calculated by thermol-dilution method by the formula:

$$\text{GCVF (ml/min)} = V_i \times \left(\frac{T_b - T_i}{T_b - T_m} - 1 \right) \times 1.08$$

where GCVF = great cardiac vein flow, V_i is the indicator rate of injection (56 ml/min), T_b is blood temperature, T_i is the temperature of injectate, and T_m is the temperature of the mixture of great cardiac vein blood and injectate; 1.08 is a constant related to the indicator.

Mean arterial pressure was measured by electronic filtration of the pressure curve and anterior regional coronary resistance was calculated as

$$\text{ARCR (mm Hg/ml/min)} = \frac{\text{MAP}}{\text{GCVF}}$$

where ARCR = anterior regional coronary resistance, MAP = mean arterial pressure, GCVF = great cardiac vein flow.

Anterior regional myocardial oxygen consumption was derived as (arterial oxygen content minus great cardiac vein oxygen content) × great cardiac vein flow. Heart rate was calculated from the electrocardiogram. Plasma gallopamil concentrations were measured by high performance liquid chromatography.

Statistical analysis was performed by Student's paired *t* test. All data are expressed as mean (SD).

Results

HAEMODYNAMIC AND ANGIOGRAPHIC FINDINGS

Four patients had disease of the proximal left ante-

Table 3 Peak pacing values of haemodynamic variables in 10 patients with stable exertional angina

Case No	Heart rate (beats/min)		MAP (mm Hg)		Double product (bpm × mm Hg × 10 ⁻²)		GCVF (ml/min)		ARCR (mm Hg/ml/min)		MVO ₂ (ml/min)	
	Control	GP	Control	GP	Control	GP	Control	GP	Control	GP	Control	GP
1	130	140	165	137	297.7	268.8	125.8	125.8	1.31	1.08	10.7	10.7
2	150	160	143	133	291	288	146.3	141.1	0.97	0.94	17	16.3
3	150	160	118	110	238.5	235.2	149.1	135.8	0.79	0.81	16.6	16.6
4	120	150	137	110	216	220.5	59.8	45.2	2.29	2.43	9.3	6
5	150	160	137	125	274.5	267.2	186.6	102.6	0.73	1.22	22.8	13
6	140	170	133	96	256.2	227.8	171.9	138.4	0.77	0.69	20.1	17
7	160	170	125	92	273.6	227.8	63.8	80.7	1.96	1.14	7.4	10.7
8	160	160	146	142	307.2	280	236	176.3	0.62	0.81	26.9	20.7
9	120	140	108	108	200.4	221.2	73.5	84.6	1.47	1.28	—	—
10	140	160	117	108	221.2	233.6	128.6	98.6	0.91	1.1	14	10.7
Mean	142	158	133	116	257.6	247	134.1	112.9	1.18	1.15	16.1	13.3
(SD)	(15)*	(11)*	(17)†	(17)†	(37.1)	(26)	(57)	(38)	(0.6)	(0.5)	(6)	(4)

**p* < 0.001; †*p* < 0.005.

See footnote to table 2 for abbreviations.

Fig 1 Effects of gallopamil on heart rate, mean arterial pressure (MAP), and double product in 10 patients with stable exertional angina. Resting and peak pacing values are shown. No difference was observed at rest whereas heart rate increased and mean arterial pressure decreased at peak pacing after gallopamil had been given. As a result the double product remained unchanged; however, pacing was tolerated for longer after gallopamil.

rior descending artery only, three had double vessel, and three had triple vessel disease (table 1). The mean ejection fraction was 0.72 (0.09) and the mean left ventricular end diastolic pressure was 16 (5) mm Hg.

HAEMODYNAMIC AND METABOLIC EFFECTS OF GALLOPAMIL AT REST (TABLE 2)

The heart rate was unchanged after administration of the drug (77 (19) vs 78 (14) beats/min, $p = \text{NS}$). Mean arterial pressure fell in all but one patient (case no 8); however, the difference did not reach statistical significance (117 (15) vs 109 (14) mm Hg). As a consequence the double product decreased slightly and not significantly (134 (42) vs 122 (31) beats/min $\times$ mm Hg $\times 10^{-2}$), as did anterior regional myocardial oxygen consumption (8.7 (3) vs 8.0 (4) ml/min, $p = \text{NS}$). No significant change was found in blood flow in the great cardiac vein (68.2 (22) vs 66.8 (31) ml/min) or anterior regional coronary resistance (1.85 (0.5) vs 1.89 (0.7) mm Hg/ml/min).

HAEMODYNAMIC AND METABOLIC EFFECTS OF GALLOPAMIL AT PEAK PACING (TABLE 3)

The end points of the coronary sinus pacing were angina in seven patients and ST segment depression of >2 mm without pain in the remaining three. After gallopamil only four patients complained of angina, five patients showed asymptomatic ST segment depression of >2 mm, and in one (case 6) pacing was stopped after the maximal pacing rate had been maintained for two minutes. In all but one patient (case 8) end points were reached at higher pacing rate after gallopamil (control 142 (15), gallopamil 158 (11) beats/min, $p < 0.001$). As a result gallopamil increased mean pacing time from 11.0 (2.6) to 14.8 (2.4) minutes ($p < 0.001$) while maximal ST segment depression decreased from 1.9 (0.5) to 1.6 (0.7) mm ($p = \text{NS}$).

As mean arterial pressure decreased from 133 (17) to 116 (17) mm Hg ($p < 0.005$) the peak pacing double product was slightly but not significantly reduced (fig 1). There was no significant change in great cardiac vein flow or in anterior regional coronary resistance (fig 2). Anterior regional myocardial oxygen consumption was also unchanged after gallopamil (from 16.1 (6) to 13.7 (4) ml/min, $p = \text{NS}$).

The mean plasma concentration of gallopamil at peak pacing was 41.4 (13.8) ng/ml.

Discussion

Gallopamil is a new calcium antagonist with the structure of a phenylalkylamine derivative, like vera-

Fig 2 Effects of gallopamil on great cardiac vein flow (GCVF) and anterior regional coronary resistance (ARCR) at rest and at peak pacing. No significant change was seen between resting values or peak pacing values.

pamil. It has the same electrophysiological properties as verapamil, but is three to five times as potent on a weight for weight basis.¹⁴ Oral gallopamil was as effective or more effective than propranolol in improving the exercise tolerance of patients with stable exertional angina after short term¹¹ and after long term administration.¹⁰ Moreover, the drug is well tolerated; few adverse effects were reported after long term oral treatment.¹⁰

The mechanism by which this drug exerts its beneficial effects has yet to be established. After long term oral administration Khurmi *et al* found that the rate-pressure product at peak exercise was higher than after placebo.¹⁰ Because the degree of ST segment depression was unchanged these workers suggested that the greater exercise capacity induced by gallopamil was the result of improved myocardial oxygen supply. By contrast, Rettig and Sen found that the double product did not increase at the end of exercise, either after short term or after long term oral administration.¹² Similarly, Scrutinio *et al* reported that the rate-pressure product was not modified at maximal workload¹¹; this suggests that the drug may improve exercise capacity by reducing oxygen demand.

In our study short term intravenous administration of gallopamil improved pacing tolerance, confirming the antianginal activity of the drug. Because all patients had a proximal lesion of the left anterior descending artery we measured blood flow in the great cardiac vein, which is a reliable index of blood flow through that artery,^{13 15 16} to assess haemodynamic changes in the area of the myocardium in which perfusion was jeopardised. Gallopamil did not increase blood flow in the great cardiac vein either at rest or at peak atrial pacing. Thus the beneficial effect of the drug does not seem to be related to increased perfusion of ischaemic regions. Moreover, myocardial oxygen consumption in the anterior region was similar at the peaks of the two pacing periods despite the higher heart rate that was achieved after gallopamil infusion. This suggests that the mechanism of action of the drug was a reduction in myocardial metabolic demand. Because most of our patients had multivessel disease, however, we cannot exclude the possibility that gallopamil increased blood flow to the non-anterior, yet potentially ischaemic myocardium and that such increase contributed to the improved performance induced by the drug. This possibility, however, seems remote, because the double product, a reflection of the maximal rate at which the obstructed coronary arteries deliver oxygen, was unchanged at peak pacing after gallopamil.

In conclusion, our data confirm that gallopamil is an effective antianginal drug that may well prove to

be a useful addition to current treatment of angina pectoris. A reduction of myocardial oxygen consumption seems to be the predominant mechanism by which the drug exerts its beneficial effects.

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