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Acute haemodynamic effects of felodipine during beta blockade in patients with coronary artery disease

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SUMMARY The acute effects of felodipine on left ventricular function and haemodynamics were studied in 11 patients with coronary artery disease. To block reflex sympathetic activation due to peripheral vasodilatation and to avoid effects secondary to changes in heart rate all patients received a standard regimen of beta adrenoceptor blockade and all measurements were made during sinus rhythm and right atrial pacing. At 30 minutes after an oral dose (0·075 mg/kg in solution) felodipine plasma concentration were 16·4 (3·5) nmol/l. A significant fall in systemic vascular resistance (30%) and increase in cardiac index (30%) occurred, whereas pulmonary vascular resistance was unchanged. Felodipine increased left ventricular ejection fraction and mean velocity of circumferential fibre shortening but had no effect on derivates of left ventricular pressure (dP/dt or dP/dt P^{-1}) during sinus rhythm or pacing. Thus at the dosage used felodipine was a potent dilator of systemic arterioles but had no direct effect on left ventricular function.

Felodipine is a new dihydropyridine compound, which has been claimed (in vitro) to be a potent vasodilator with less cardiodepressive effect than other calcium antagonists.[1] Its mechanism of action in relaxing vascular smooth muscle is unclear, although it has been suggested that it inhibits the activation, by calcium ions, of intracellular calmodulin[2] and only at high concentration does it act as a slow calcium channel blocker. A non-invasive study[3] of young healthy men confirmed its action as a vasodilator in man; there are, however, no direct measurements available of its effect on left ventricular function. In this study therefore we measured the systemic and left ventricular haemodynamic effects of felodipine in patients undergoing cardiac catheterisation for investigation of chest pain. We and others[4,5] have previously shown that control of heart rate and blockade of reflex sympathetic activation is essential to avoid masking direct negative inotropic actions of peripheral vasodilators.[6–8] For this reason measurements were carried out at rest and during atrial pacing in patients receiving beta blocking agents.

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Patients and methods

Eleven men aged 34–62 (mean 49·6) years were entered into the study. All patients had classical angina pectoris and positive exercise tests (Bruce protocol) and were about to undergo cardiac catheterisation. Coronary arteriography at the end of each study showed that all had coronary artery disease (four single vessel disease, six two vessel disease, and one left main stem disease). Seven of the 11 had had a previous myocardial infarct (more than three months before the study), but none had congestive heart failure, cardiac conduction abnormalities, valvular heart disease, or biochemical evidence of hepatic or renal disease. Medical treatment at entry to the study consisted of a beta adrenoreceptor blocker in nine patients, long acting oral nitrate in eight, calcium antagonists in four, and other vasodilators in two. Nitrates, vasodilators, and beta adrenoceptor blockers were discontinued for at least 24 hours before the study, and to standardise beta adrenoreceptor blocking treatment all patients received atenolol 100 mg six hourly for the same period.

The patients were studied after an overnight fast and premedication with diazepam (10 mg) orally. Heart rate was measured from electrocardiograms (mean of six beats). A Swan-Ganz thermodilution catheter was positioned in the pulmonary artery for

pressure recording, blood sampling, and estimation of cardiac output (mean of three readings). A bipolar pacing electrode was positioned in the right atrium. Arterial pressure was recorded from the sidearm of a sheath positioned in the femoral artery. A pressure tip catheter (Millar Instruments) was passed via the sheath to the left ventricle for high fidelity recordings; derivatives of left ventricular pressure (dP/dt and dP/dt P^{-1}) were obtained using analogue circuitry (Siemens). Stroke volume, ejection fraction,[9] and mean velocity of circumferential fibre shortening[10] were derived from left ventricular angiograms.

Control haemodynamic measurements were taken during sinus rhythm and during right atrial pacing at 100 beats/min, and a baseline left ventricular angiogram was then performed (40 ml Hexabrix at 12 ml/s) during pacing. Repeat measurements including left ventriculography were obtained 30 minutes after felodipine 0·075 mg/kg had been given orally. Blood samples for the estimation of plasma felodipine concentrations were taken during the baseline recordings, at 10, 20, and 30 minutes after the oral dose, and after the second left ventricular angiogram. To assess the haemodynamic effects of the contrast material used separate studies were carried out in a further seven patients who underwent the initial left ventricular angiogram but received no drug, after which haemodynamic measurements were made in the usual way. Results are expressed as mean (SE) and were analysed using Student's *t* test, a probability value of 0·05 being taken to indicate statistical significance.

Results

HAEMODYNAMIC EFFECTS OF CONTRAST INJECTION

The haemodynamic changes in seven patients after left ventriculography using 45 ml of Hexabrix (May and Baker) who received no felodipine were minor. Heart rate was increased by 6% and 5% at 10 and 20 minutes respectively, mean pulmonary pressure was increased by 10% at 20 minutes, and left ventricular dP/dt P^{-1} was increased by 5% at 20 minutes ($p < 0·05$ in each case). No significant changes were observed at 30 minutes.

PLASMA CONCENTRATIONS

The Figure shows the plasma concentrations of felodipine. After an oral dose of 0·075 mg/kg, plasma concentrations reached 16·4 (3·5) nmol/l at 30 minutes and fell to 12·4 (2·3) nmol/l after the second angiogram.

HEART RATE AND CARDIAC OUTPUT

During sinus rhythm, felodipine significantly increased heart rate from 55 (3) beats/min to 64 (3) beats/min and cardiac index from 2·3 (0·1) l/min per m^2 to 3·0 (0·1) l/min per m^2 ($p < 0·01$ in each case). Felodipine increased cardiac index from 2·6 (0·2) l/min per m^2 to 3·4 (0·2) l/min per m^2 ($p < 0·01$) during right atrial pacing. Although cardiac index was significantly increased by right atrial pacing before treatment the percentage increase produced by felodipine was identical in both conditions.

BLOOD PRESSURES

Felodipine produced small but significant reductions in arterial pressure during sinus rhythm and during atrial pacing. The extent of the change was more pronounced during atrial pacing than during sinus rhythm—that is, mean arterial pressure was reduced by 9·6% during atrial pacing compared with 6·6% during sinus rhythm (Tables 1 and 2). Felodipine increased pulmonary pressure during sinus rhythm and during pacing, the effect being more pronounced during sinus rhythm—that is, mean pulmonary pressure was increased by 30% compared with 18% during pacing (Tables 1 and 2). Neither pulmonary nor systemic pressure was significantly altered by pacing alone. Felodipine produced a small increase in left ventricular end diastolic pressure during sinus rhythm and during atrial pacing, but in neither instance was it statistically significant.

PULMONARY AND SYSTEMIC VASCULAR RESISTANCE

Felodipine appreciably reduced systemic vascular resistance but had less effect on pulmonary vascular

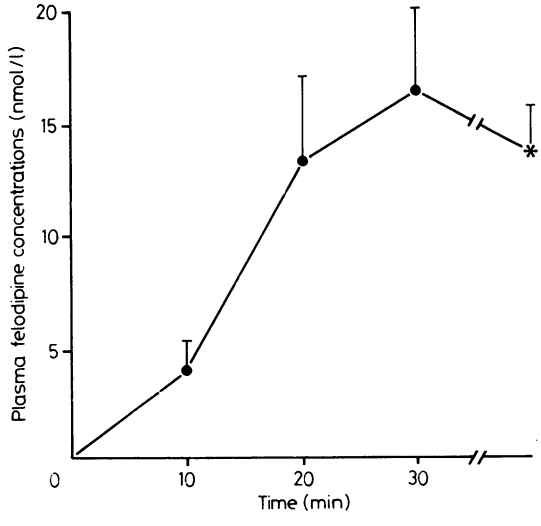

Figure *Plasma concentrations of felodipine after oral administration of 0·075 mg/kg. *After second left ventricular angiogram. Values are mean (SE).*

Table 1 *Effect of felodipine on haemodynamic indices during sinus rhythm. Values are mean (SE)*

	Control	*Felodipine*	*% Change*	*p value*
Heart rate (beats/min)	55 (3)	64 (3)	+16·4	0·001
Femoral artery pressure (mm Hg):				
Systolic	133 (6)	127 (7)	−4·5	NS
Diastolic	63 (3)	58 (4)	−7·9	0·05
Mean	91 (4)	85 (6)	−6·6	NS
Pulmonary artery pressure (mm Hg):				
Systolic	20·2 (1·6)	24·4 (1·7)	+20·8	0·005
Diastolic	4·9 (1·0)	6·5 (0·9)	+32·6	NS
Mean	11·1 (1·4)	14·5 (1·5)	+30·3	0·01
Left ventricular end diastolic pressure (mm Hg)	6·1 (1·3)	7·7 (1·3)	+26·9	NS
Cardiac index (l/min/m^2)	2·3 (0·1)	3·0 (0·1)	+29·6	0·001
Vascular resistance (dyn s cm^{-5}):				
Systemic	1603 (72)	1165 (78)	−27·3	0·001
Pulmonary	199·6 (28)	197 (20)	−1·3	NS
Peak dP/dt (mm Hg/s)	1410 (139)	1445 (138)	+2·5	NS
Peak dP/dt P^{-1} (s^{-1})	28·0 (3·1)	27·9 (3·0)	−0·6	NS

resistance. Thus systemic vascular resistance was reduced by 30% during pacing ($p < 0·01$) and by 27·3% during sinus rhythm ($p < 0·01$) (Tables 1 and 2). In contrast, pulmonary vascular resistance was reduced by 11% during pacing and by 1·3% during sinus rhythm, and neither was statistically significant.

INDICES OF LEFT VENTRICULAR FUNCTION

Increasing heart rate by atrial pacing produced a significant increase in left ventricular dP/dt and dP/dt P^{-1} before (18% and 22% respectively) and after (13% and 21% respectively) the administration of felodipine. Felodipine had no effect on these isovolumic indices of left ventricular function during sinus rhythm or during atrial pacing. In contrast ejection fraction, stroke volume, and mean velocity of circumferential fibre shortening were substantially increased (13%, 8%, and 19% respectively) at 30 minutes, although these changes did not reach statistical significance.

Discussion

The results confirm that felodipine is a potent dilator of systemic arterioles producing a significant reduction in systemic vascular resistance and a significant increase in cardiac index in a dose which had no effect on left ventricular peak dP/dt or peak dP/dt P^{-1}. Haemodynamic effects of the initial injection of contrast material can be excluded since no significant effects were detectable 30 minutes later. The dosage of felodipine used appears to have little effect on pulmonary arterioles, there being no significant change in pulmonary vascular resistance. During sinus rhythm felodipine produced a small but significant increase in heart rate despite concurrent beta adrenoreceptor blockade. There is no evidence that felodipine has a direct positive chronotropic action on the heart. The dose of atenolol used was high, and the low initial heart rates suggest that indeed substantial beta adrenoreceptor blockade was present. The small

Table 2 *Effect of felodipine on haemodynamic indices during right atrial pacing (100 beats/min). Values are mean (SE)*

	Control	*Felodipine*	*% change*	*p value*
Femoral artery pressure (mm Hg):				
Systolic	135 (8)	125 (9)	−6·8	0·05
Diastolic	78 (4)	66 (4)	−14·8	0·001
Mean	95 (5)	89 (6)	−9·6	0·001
Pulmonary artery pressure (mm Hg):				
Systolic	19·8 (2·3)	22·3 (1·8)	+12·4	NS
Diastolic	6·9 (1·0)	7·6 (1·1)	+9·3	NS
Mean	12·4 (1·9)	14·6 (1·9)	+17·7	NS
Left ventricular end diastolic pressure (mmHg)	5·6 (1·6)	7·1 (1·2)	+27·7	NS
Cardiac index (l/min/m^2)	2·6 (0·2)	3·4 (0·2)	+29·6	0·001
Vascular resistance (dyn s cm^{-5}):				
Systemic	1537 (88)	1075 (88)	−30	0·001
Pulmonary	198 (33)	176 (24)	−11·1	NS
Stroke volume (ml)	72·8 (7·0)	82·1 (10·8)	+12·8	NS
Ejection fraction	0·49 (0·04)	0·53 (0·05)	+8·2	NS
Velocity of circumferential fibre shortening (circ/s)	1·0 (0·07)	1·19 (0·11)	+19	NS
Peak dP/dt (mm Hg/s)	1660 (158)	1630 (141)	−1·8	NS
Peak dP/dt P^{-1} (s^{-1})	34·2 (3·0)	33·8 (2·7)	−1·3	NS

increase in heart rate may therefore have possibly been due to a reduction in parasympathetic stimulation. Felodipine reduced arterial pressure; however, this was greater during atrial pacing than during sinus rhythm suggesting that the increase in heart rate induced by felodipine tended to offset its hypotensive action. The reduction in diastolic arterial pressure was greater than that for systolic pressure, reflecting the primary action of the drug—that is, arteriolar dilatation. Pulmonary artery pressure was increased by felodipine, this effect being more pronounced during sinus rhythm. This is likely to be due to the increase in cardiac output in the absence of any change in pulmonary vascular resistance. These peripheral haemodynamic changes are similar to previous findings of a non-invasive study[3] and to the haemodynamic effects of nifedipine.[4 5]

The increase in left ventricular dP/dt and dP/dt P^{-1} observed with increasing heart rate confirms their value as useful indices of inotropic state in the present study. The absence of any change in response to felodipine indicates that at the dose used the drug does not depress myocardial function. Previous studies with nifedipine, in which heart rate and reflex sympathetic activity were not controlled, have shown increases in left ventricular dP/dt and dP/dt P^{-1} [6-8] despite evidence to the contrary in vitro.[11] This discrepancy can be explained by secondary increases in heart rate and sympathetic activation in vivo, so that when heart rate and sympathetic activation were controlled dP/dt and dP/dt P^{-1} were reduced.[4 5] The increase in stroke volume, ejection fraction, and mean velocity circumferential fibre shortening in the present study can be explained by the reduction in systemic arteriolar resistance.

These studies confirm that felodipine is a potent dilator of systemic arterioles with relatively little effect on the pulmonary circulation or systemic veins. The dose used in the present study produced a pronounced fall in systemic vascular resistance with no detectable effect on myocardial performance. This suggests that the drug is highly selective for smooth muscle and that it is likely to be a useful vasodilator for the treatment of cardiac failure or hypertension associated with myocardial damage.

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