Br. J. Pharmac. (1983), **79**, 037–043

Comparison of two calcium antagonists, verapamil and fendiline, in an experimental model of myocardial ischaemia mimicking classical angina on effort

Vera Csik, L. Szekeres & Eva Udvary

Department of Pharmacology, University Medical School of Szeged, H-6701 Szeged, Dom ter 12, Hungary

1 The effects of verapamil (0.15 /kg) and fendiline (3 mg/kg) were studied in anaesthetized, thoracotomised dogs with a critical constriction of the left anterior descending coronary artery, paced in excess of the initial rate by 60–70 beats/min. Epicardial ST-segment elevation and changes in lactate uptake were used to assess the severity of myocardial ischaemia.

2 Both drugs prevented the ST-segment elevation and the reduced lactate uptake that resulted from atrial pacing.

3 The anti-ischaemic effect of fendiline is mainly due to its negative chronotropic action, whereas that of verapamil is due in part to bradycardia and in part to the reduced preload and afterload. In addition, both agents increase coronary flow to the ischaemic area and thus improve the myocardial oxygen supply/oxygen requirement ratio.

Introduction

We have recently described a technique for the assessment of potential anti-ischaemic activity and have suggested that it would be a useful method for the evaluation of potential anti-anginal agents (Szekeres, Csik & Udvary, 1976). The effects of nitroglycerine have been examined in this preparation (Szekeres & Udvary, 1983) and the purpose of the present study is to describe the effects in this model, of two drugs (verapamil and fendiline) that act mainly by inhibiting the transmembrane influx of Ca^{2+}. These calcium antagonists reduce oxidative metabolism in cardiac muscle (Fleckenstein, Döring, Janke & Byoh, 1975) and have been used in the treatment of angina pectoris (Ferlinz & Turbow, 1980; Subramanian, Lahiri, Paramasivan & Raftery, 1980; Carlens, 1981) especially where, in addition, antihypertensive or antiarrhythmic effects are also desired (Kaltenbach, 1977; Pedersen, 1981).

Methods

Experiments were carried out on mongrel dogs of either sex and weighing between 12 and 16 kg. They were anaesthetized with pentobarbitone sodium (35 mg/kg, by intravenous injection). They were then prepared as described in the papers by Szekeres, Csik & Udvary (1976) and by Szekeres & Udvary (1983). In brief, flow in the circumflex branch of the left coronary artery and in the ascending aorta was measured using Nycotron electromagnetic flow probes and pressure from catheters in the lumen of the left ventricle and in the femoral artery with Statham P623 transducers. The maximum rate of the pressure rise within the left ventricle (LV dP/dt_{max}) was used as an index of myocardial contractility.

Another catheter was introduced through the left jugular vein and coronary sinus into the great cardiac vein, and blood was withdrawn at a constant rate through the cuvette of a KIPP CC-Oxymeter. Oxygen saturation changes were registered by a recording galvanometer (KIPP Micrograph BD 5) and blood returned to the animal via the brachial vein. At intervals blood samples from the femoral artery were withdrawn for analysis of the arterial oxygen saturation. Oxygen content of the blood was calculated from these data using a conversion factor of 1.39 ml of oxygen per haemoglobin (measured spectrophotometrically as cyanhaemoglobin).

Three silver epicardial electrodes embedded in a band of rubber were sutured to the surface of the left anterior ventricular wall and epicardial ECG recordings were taken before, and at various times after, drug treatment. Heart rate was computed from these recordings.

Peripheral and coronary vascular resistances, *left*

ventricular minute work, oxygen consumption and myocardial oxygen extraction were calculated as described by Szekeres *et al.*, (1976). Following a 25–30 min stabilization period, infusions of either verapamil or fendiline were started.

Investigations in an experimental model for myocardial ischaemia

This model has been previously described by us in detail (Szekeres *et al.*, 1976). The left anterior descending coronary artery was autoperfused from the femoral artery and coronary flow reduced by a screw clamp until a critical degree of stenosis was achieved as demonstrated by the failure of a 20 s total coronary occlusion of this artery to evoke a hyperaemic response. Epicardial electrograms were recorded from the myocardial segment supplied by the constricted coronary artery; there was little evidence of ischaemia except when the animals were paced 60–70 beats/min in excess of the control heart rate.

Oxygen consumption and lactate uptake of the segment supplied by the constricted segment were determined from arterial and local coronary venous differences.

Blood flow in the left anterior descending (LAD) and left circumflex (LCS) coronary arteries was recorded simultaneously with Nycotron electromagnetic flowmeters and myocardial oxygen extraction (ml O_2/100 ml blood) was calculated from:

$$\frac{\text{Arterial-coronary venous } O_2 \text{ content}}{\text{Arterial } O_2 \text{ content}}$$

To calculate the myocardial oxygen supply/oxygen requirement index in the area supplied by the LAD, oxygen consumption during pacing, but in the absence of coronary constriction, was taken as the baseline oxygen requirement and oxygen consumption during pacing in the presence of coronary constriction was taken as the actual oxygen requirement. Theoretically in the absence of coronary constriction this index should be equal to 1.0; after restricting the flow it decreases.

Drugs

The following were used: verapamil HCl (Isoptin, Iproveratril) and fendiline HCl (Sensit), kindly supplied by Knoll AG, Ludwigshafen and Thiemann GmbH, Lünen/Westf. respectively, and were dissolved in 0.9% w/v NaCl solution. The doses used are in terms of the hydrochloride. Statistical analysis was made by means of the Student's *t* test, the criterion for significance being $P < 0.05$.

Results

Haemodynamic effects of verapamil and fendiline in normal dogs

Verapamil (bolus of 0.15 mg/kg followed by a continuous infusion of 0.015 mg kg^{-1} min^{-1} for 10 min) significantly reduced blood pressure, heart rate, LV dP/dt_{max}, coronary and peripheral vascular resistances, external cardiac work and myocardial oxygen consumption (MVO_2), whereas LCA blood flow and myocardial oxygen extraction were markedly increased (Table 1).

Fendiline (bolus of 3 mg/kg followed by an infusion of 0.2 mg kg^{-1} min^{-1} for 15 min) also elicited a prominent coronary vasodilator effect (from 72 ± 17 to 103 ± 18 ml 100 g^{-1} min^{-1}) but had less marked effects on blood pressure (100 ± 4 to 89 ± 7 mmHg), heart rate (163 ± 17 to 148 ± 16 beats/min) and LV dP/dt_{max} (4341 ± 1220 to 3961 ± 1039 mm Hg s^{-1}). External cardiac work did not change, but there were decreases in cardiac output (−12%), peripheral vascular resistance (−7%), coronary vascular resistance (−29%) and in MVO_2 (from 10.5 ± 1.9 to 9.5 ± 1.9 ml 100^{-1} min^{-1}). Myocardial oxygen exraction increased significantly ($P < 0.001$) by 47%.

Haemodynamic effects of verapamil and fendiline in the ischaemic model

The results for verapamil are shown in Table 2.

The effects of atrial pacing were not different from those reported previously (Szekeres *et al.*, 1976). Verapamil reduced heart rate and dP/dt_{max} and both drugs slightly diminished blood pressure. Verapamil also had a significant protective effect against pacing-induced LVEDP elevation, and increased coronary blood flow in the constricted coronary artery. The protective effects of fendiline were less marked; there was no change in the pacing-induced increase in LVEDP but the reduction in flow induced by pacing in the stenosed artery (from 61 ± 6 to 52 ± 6 ml 100 g min^{-1}) was prevented by fendiline (flow in the stenosed artery after pacing 61 ± 7 ml 100 g^{-1} min^{-1}).

Effect of calcium antagonists on epicardial and metabolic changes in dogs with a critically constricted coronary artery

The protective action of verapamil on pacing-induced epicardial ST-segment changes in the area supplied by the stenosed coronary artery (LAD) is shown in Figure 1 and the data are summarized in Figures 2 and 3. There is a marked protective effect against pacing-induced ST-segment elevation,

Table 1 Haemodynamic effects of verapamil (0.15 mg/kg followed by a continuous infusion of 0.015 mg/kg/min for 10 min) in anaesthetized dogs

	Control	*Value at time of maximal change*	*% change*	*Time of maximal change* (min)	*Duration of effect* (min)
Blood pressure (mmHg)	95±6	77±5***	−19	10	33
Heart rate (beats/min)	169±8	153±9*	−10	14	14
LV dP/dt_{max} (mmHg/s)	4016±571	2470±456*	−38	15	35
Cardiac output (ml/min)	1557±200	1571±267	+1	10	30
External cardiac work (kgm/min)	1.8±0.3	1.5±0.2**	−16	9	33
Coronary blood flow ($ml\,100g^{-1}\,min^{-1}$)	89±9	113±13**	+27	10	25
Coronary resistance (arbitary units)	1.1±0.1	0.8±0.1**	−28	10	30
Myocardial O_2 consumption ($ml\,100g^{-1}\,min^{-1}$)	16.2±3.0	13.5±2.2*	−17	8	17
Myocardial O_2 extraction	1.3±0.1	1.9±0.1***	+46	11	31

Values are mean ± s.e. of at least 5 experiments.
* Significantly different from control at $P<0.05$; ** $P<0.01$; *** $P<0.001$.

against the diminished lactate uptake in the ischaemic area and an improvement in the myocardial O_2 supply/O_2 requirement ratio. The duration of this drug-induced reduction in consequence of ischaemia was about 80 min for verapamil and about 30 min for fendiline.

Since verapamil itself induced bradycardia, pacing started from a lower initial heart rate. The importance of this negative chronotropic effect of verapamil can only be estimated by readjusting the pacing rate to give the same frequency as that seen in the paced heart before verapamil treatment. Even when such a readjustment was made however, a definite protective effect was still present, although it was rather less marked (i.e. the increase in ST-elevation at the higher pacing rate was now only

Table 2 The influence of verapamil on pacing-induced changes in dogs with a critically stenosed coronary artery

	Control			*During pacing*		
	Untreated	*Treated*	*% change*	*Untreated*	*Treated*	*% change*
Blood pressure (mmHg)	91±4	83±4**	−9	82±5	78±3	−5
Heart rate (beats/min)	186±8	168±5***	−10	242±9	228±5	−6
LV dP/dt_{max}	6383±683	5591±645**	−12	10147±951	9487±696	−5
LVEDP (mmHg)	5.1±1.1	5.4±1.2	−5	8.7±1	6.8±1.5**	−22
Coronary flow in circumflex branch (ml/100 g/min)	82±7	99±9*	+19	104±12	100±10	−4
Coronary flow in stenosed LAD (ml/100 g/min)	65±5	68±4	+5	52±8	65±5*	+25

Values are mean ± s.e. of 10 experiments.
* Significantly different from control at $P<0.05$; ** $P<0.01$; *** $P<0.001$.

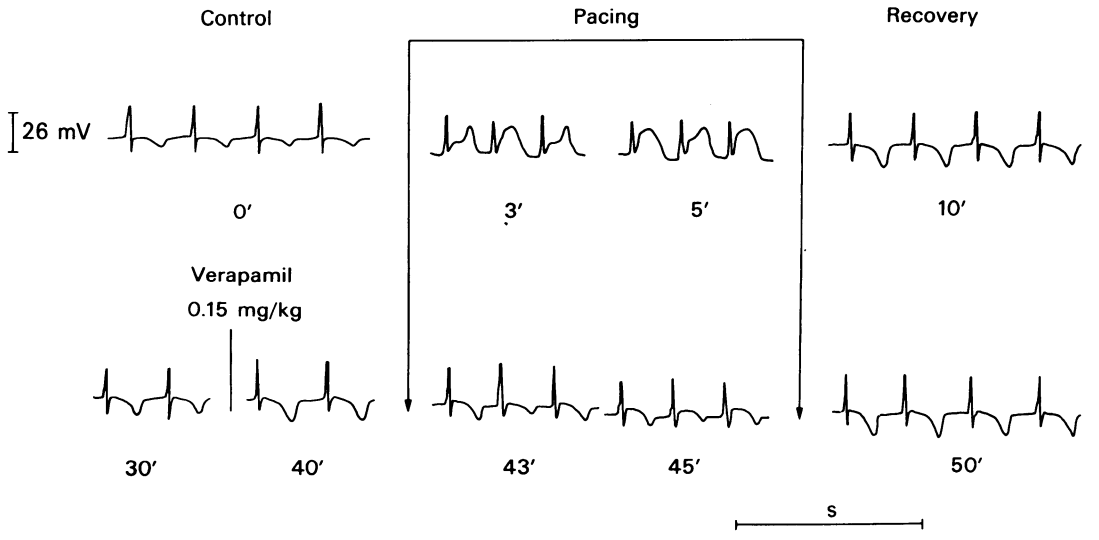

Figure 1 The effect of verapamil (0.15 mg/kg) on the epicardial ECG of the anaesthetized dog with critical constriction of the left anterior descending coronary artery (LAD) and subsequent pacing. Upper panel, no treatment; lower panel, verapamil treatment.

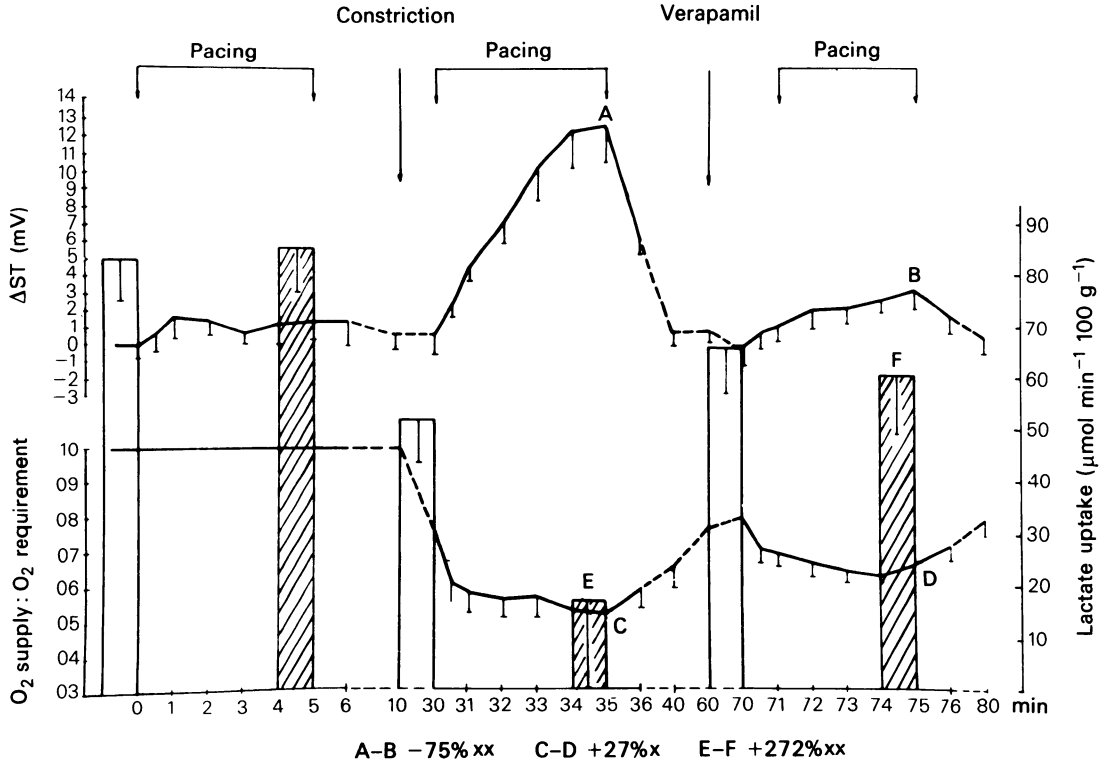

Figure 2 The effect of verapamil (0.15 mg/kg) on epicardial ST-segment elevation (upper continuous line), myocardial lactate uptake (columns) and the oxygen supply/demand ratio (lower continuous line) in anaesthetized dogs with critical coronary artery constriction ($n = 12$).

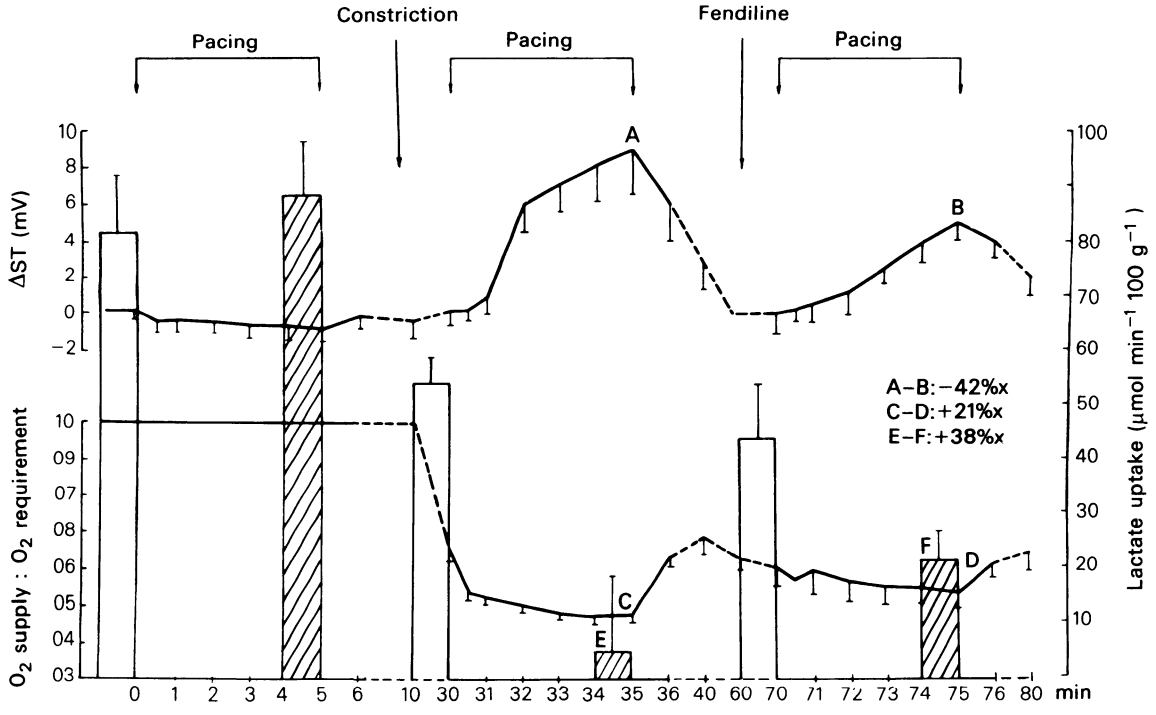

Figure 3 The effect of fendiline (3 mg/kg) on epicardial ST-elevation, myocardial lactate uptake and the oxygen supply/demand ratio in anaesthetized dogs with critical coronary artery constriction. Symbols as in Figure 2. ($n = 8$).

9.0 mV instead of 14.0 mV). The myocardial lactate production observed during the control pacing period was completely prevented by the drug. These data are summarized in Table 3 and show that verapamil has a significant protective action against ST-segment elevation and myocardial lactate production in the case of a higher pacing rate as well.

Discussion

The present studies in a canine model of ischaemia which mimics, in certain aspects at least, the alterations in myocardial oxygen demand and supply in classical angina pectoris, demonstrate that both verapamil and fendiline prevent the ischaemia-induced

Table 3 The influence of verapamil on epicardial ST-segment changes and on lactate uptake in dogs with a critically stenosed coronary artery and with heart rate held constant

	Pacing rate 220± 4 beats/min		
	Control	*Verapamil*	*% change*
Change in ST-segment elevation (mV)	+12.6±1.2	+ 3.1±0.8**	−75
Change in lactate production (−) or uptake (+) (μmol min^{-1} 100 g^{-1})	−63.8±7.8	+17.2±9.0*	+127

Values are mean ± s.e. of 5 experiments.
* Significantly different from control at $P<0.05$; ** $P<0.01$.

ST-segment elevation and reduction of lactate uptake induced by pacing. There are a number of possible mechanisms for this protective action of the calcium-antagonists. For example, Berdeaux, Coutte, Guidicelli & Boissier (1976) suggested that bradycardia plays a major role in the anti-ischaemic effect of verapamil. In dogs, they found that verapamil (0.05 mg kg^{-1} for 10 min) decreased heart rate and blood pressure and increased epicardial and endocardial flow in both the normal and ischaemic regions of the myocardium. In the ischaemic region the endocardial/epicardial flow ratio increased, and this was accompanied by a less pronounced ST-segment elevation during coronary occlusion. In contrast, when the hearts were paced, neither blood flow in the ischaemic region nor ST-segment elevation were modified by verapamil and the endocardial/epicardial ratio decreased. The authors concluded therefore that the main factor responsible for the beneficial effect of verapamil is the reduction of heart rate. Our data only partially support this conclusion. We have found that, despite eliminating the heart rate lowering effect of verapamil, the drug was still able to prevent pacing-induced ischaemic changes (lactate production, epicardial ST-elevation). However, with fendiline a protective effect was found only if the heart rate was allowed to decrease; after readjusting the pacing rate to the pre-drug value the protective effect disappeared.

Opinions concerning the importance of the negative inotropic action of these drugs vary. Strauer (1974) suggested for example that calcium-antagonists would not be appropriate for treatment of an acute anginal attack. Atterhög & Ekelund (1975) studied the haemodynamic effects of intravenous verapamil in healthy middle-aged men, both at rest and during exercise, and found that in clinical doses the negative inotropic effect of verapamil was rather moderate, probably because this is limited by the reflex activation of the sympathetic system resulting from systemic hypotension.

A significant reduction in left ventricular end-diastolic pressure (LVEDP) during exercise has also been suggested as contributing to the beneficial effect of verapamil in angina (Carlens, 1981). In our experimental model we came to a similar conclusion regarding the anti-ischaemic effect of this drug. Although LVEDP was not affected by verapamil in the absence of pacing, it significantly reduced filling pressure in the frequency-loaded, flow-restricted heart. In addition, we found a significant decrease in the blood pressure. These data demonstrate that both preload and afterload are reduced by the drug in this ischaemic model.

A third important action of the calcium channel blockers is the reduced Ca^{2+}-dependent vascular smooth muscle tone in the coronary and systemic circulations. This leads to coronary vasodilatation (which may improve the relation of myocardial oxygen supply to myocardial oxygen consumption) and to a decrease in systemic vascular resistance (leading to a diminution in cardiac work). The myocardial oxygen demand:supply ratio is thus greatly improved. In the present experiments, both drugs increased normal coronary blood flow, increased myocardial oxygen extraction and reduced myocardial oxygen consumption. It is not surprising therefore that they also restored to normal the pacing-induced reduction in coronary flow and improved the myocardial oxygen supply/oxygen demand ratio. Similar results were also obtained in dogs after complete coronary occlusion (Da Luz, De Barros, Leite, Pileggi & Decourt, 1980). Verapamil, administered intravenously 30 min before coronary occlusion, significantly reduced ST-segment elevation as compared with occlusion alone. Heart rate and end-diastolic pressure were also reduced but systolic pressure remained essentially unchanged. There was a significant increase in retrograde coronary flow and a decrease in regional coronary resistance. However, our results showing a reduction in myocardial oxygen consumption and maintained myocardial lactate uptake indicate that not only an improved oxygen supply but also reduced myocardial oxygen demand is responsible for the improvement of the supply/demand ratio.

Ferlinz & Turbow(1980) come to similar conclusions in patients with coronary artery disease. Verapamil was given to twelve such patients at rest and during stress with atrial pacing. Angina occurred in all patients with atrial pacing before verapamil but after verapamil the threshold to pain was increased in six patients and no pain at all was experienced by the remaining six. Before administration of verapamil lactate extraction decreased during atrial pacing, and nine of the twelve patients exhibited electrocardiographic ST-segment depression. After lactate extraction normalized during atrial pacing, the ST-segment in the electrocardiogram reverted to baseline in all but one patient. These findings indicate that verapamil decreases left ventricular myocardial metabolic demand and concomitantly increases the anginal threshold.

The available results do not preclude the possibility that a direct metabolic action of these drugs also contributes to the anti-ischaemic effect of verapamil, as has been demonstrated for β-adrenoceptor blocking drugs (Szekeres, Csik & Udvary, 1978).

We are grateful to Professor J.R. Parratt (Glasgow) for his valuable suggestions as well as for critical comments on the manuscript. We also wish to thank Irene Krassói and Mrs Éva Mészáros for their technical assistance.

References

ATTERHÖG, J.-H. & EKELUND, L.-G. (1975). Haemodynamic effects of intravenous verapamil at rest and during exercise in subjectively healthy middle-aged men. *Eur. J. clin. Pharmac.*, **8,** 317–322.

BERDEAUX, A., COUTTE, R., GUIDICELLI, J.-F. & BOISSIER, J.-R. (1976). Effects of verapamil on regional myocardial blood flow and ST segment. Role of the induced bradycardia. *Eur. J. Pharmac.*, **39,** 287–294.

CARLENS, P. (1981). Effect of intravenous verapamil on exercise tolerance and left ventricular function in patients with severe exertional angina pectoris. *J. cardiovasc. Pharmac.*, **3,** 1–10.

FERLINZ, J. & TURBOW, F.M.E. (1980). Antianginal and myocardial metabolic properties of verapamil in coronary artery disease. *Amer. J. Cardiol.*, **46,** 1019–1026.

FLECKENSTEIN, A., DÖRING, H.-J., JANKE, J. & BYON, Y.K. (1975). Basic actions of ions and drugs on myocardial high energy phosphate. In *Handbook of Experimental Pharmacology*, Vol. XXVI. pp. 345–405. Berlin: Springer.

KALTENBACH, M. (1977). Medikamentöse Therapie der koronaren Herzkrankheit. *Arzneim.-Forsch.*, **27,** 703–707.

DA LUZ, P.L., DE BARROS, L.F.M., LEITE, J.J., PILEGGI, F. & DECOURT, L.V. (1980). Effect of verapamil on regional coronary and myocardial perfusion during acute coronary occlusion. *Amer. J. Cardiol.*, **45,** 269–275.

PEDERSEN, O.L. (1981). Calcium blockade as a therapeutic principle in arterial hypertension. *Acta pharmac. tox.*, **49,** 1–31.

STRAUER, B.E. (1974). Inotropic effects of nifedipine: a new coronary dilating agent. *Int. J. clin. Pharmac.*, **9,** 101–107.

SUBRAMANIAN, B.V., LAHIRI, A., PARAMASIVAN, R., & RAFTERY, E.B. (1980). Verapamil in chronic stable angina. A controlled study with computerised multistage treadmill exercise. *Lancet*, **ii,** 841–844.

SZEKERES, L. CSIK, V. & UDVARY, E. (1976). The effect of nitroglycerin and dipyridamole on cardiac metabolism and dynamics in a new experimental model of angina pectoris. *J. Pharmac. exp. Ther.*, **196,** 15–28.

SZEKERES, L., CSIK, V. & UDVARY, E. (1978). The effect of beta-adrenoceptor blocking drugs on free fatty acid and glucose utilization of the isolated canine heart with normal and restricted flow in the presence and absence of noradrenaline. *Acta biol. med. germ.*, **37,** 817–820.

SZEKERES, L. & UDVARY, E. (1983). Haemodynamic factors influencing myocardial ischaemia in a canine model of coronary artery stenosis: the effects of nitroglycerine. *Br. J. Pharmac.*, (in press).