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The effect of felodipine on ventricular fibrillation after coronary artery ligation in the anaesthetized pig

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A 10 min ligation of the left anterior descending coronary artery in anaesthetized pigs resulted in ventricular fibrillation (VF) in 70% of control and propranolol-treated animals. Felodipine (10 nmol kg^{-1}) not only reduced ventricular ectopic activity by 90%, but also completely abolished VF. When a second occlusion was applied after 20 min of reperfusion, felodipine was less effective against VF, possibly due to decreasing felodipine concentrations or only a transient increase in VF threshold.

Introduction Evidence has been presented that the calcium antagonist nifedipine is effective against early ventricular arrhythmias after experimental coronary artery occlusion and reperfusion (Fagbemi & Parratt, 1982; Verdouw, Wolffenbuttel & Ten Cate, 1983), although other investigators have not always confirmed these findings (Sheehan & Epstein, 1982). Felodipine (Astra Pharmaceutical, AB Haessle, Mölndal, Sweden), 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3-ethoxycarbonyl-5-methoxycarbonylpyridine, is a new antihypertensive drug with a structure similar to that of nifedipine, but which probably exerts its vasodilator effects by interacting with calmodulin rather than by inhibiting transmembrane Ca^{2+} influx (Boström, Ljung, Mårdh, Forsen & Thulin, 1981). The present study was undertaken to investigate the antiarrhythmic efficacy of felodipine during coronary artery occlusion and reperfusion. Results are compared with those of an untreated group and with those of a group of animals treated with the β-adrenoceptor blocking agent, propranolol.

Methods Twenty-three young Yorkshire pigs (25–35 kg) were kept under anaesthesia with a continuous infusion of pentobarbitone sodium (8–10 mg $kg^{-1} h^{-1}$) after premedication with azaperone and metomidate (both compounds from Janssen Pharmaceutica, Beerse, Belgium). Rate and tidal volume of the respirator were set to maintain normal acid-base balance and oxygenation. Arterial blood pressure, measured with an 8F Millar catheter, and peripheral ECG leads were monitored continuously. An electromagnetic flow probe was placed around the ascending aorta after a midsternal thoracotomy. Seven animals served as controls, while the other animals received either felodipine (10 nmol kg^{-1}; $n = 9$) dissolved in 10% polyethylene glycol 400, or propranolol (0.5 mg kg^{-1}; $n = 7$) 30 min before acute occlusion of the LAD. The animals treated with felodipine did not receive any further medication, but in the other animals the bolus of propranolol was followed by a continuous infusion of 0.5 mg $kg^{-1} h^{-1}$. In pigs this dose regimen reduces the response to 2.0 μg kg^{-1} isoprenaline to less than 10%.

The experimental procedure consisted of three periods of 10 min left anterior descending (LAD) coronary artery occlusion, each followed by 20 min of reperfusion. Arterial plasma concentrations of felodipine (unchanged substance) were measured in samples drawn before each occlusion and at the time of ventricular fibrillation (VF). The Fisher exact test was employed to determine the statistical significance of the differences in the incidence of ventricular fibrillation between the various groups. The paired and unpaired Student's *t* tests (two tailed) were used to determine the significance of differences in cardiac performance, ventricular arrhythmias, and plasma levels.

Results Heart rate, mean arterial blood pressure, and cardiac output were similar for all three groups before treatment, but at the moment of occlusion the felodipine group had the lowest blood pressure, whereas the propranolol group had the lowest heart rate and cardiac output (Table 1). Five of the seven untreated animals died of ventricular fibrillation between 1 and 6 min after coronary artery ligation (Table 1). Both animals that survived the first occlusion, encountered VF during the second. Pretreatment with propranolol was ineffective in reducing the incidence of arrhythmias and the occurrence of ventricular fibrillation. On the other hand, pretreatment with felodipine not only reduced ventricular ectopic activity during the first 5 min but also completely abolished VF during the entire first occlusion. After 5 min, ventricular ectopic activity increased in the felodipine group but comparison with the other

Table 1 Haemodynamics before and ventricular arrhythmias during repeated 10 min occlusions of the left anterior descending coronary artery (LAD) in anaesthetized pigs

	Control ($n=7$)	*Propranolol* ($n=7$)	*Felodipine* ($n=9$)
Before occlusion			
Heart rate (Hz)	92 ±5*	83 ±6	89 ±5
Mean arterial pressure (kPa)	10.3 ±0.5	10.3 ±0.5	9.1 ±0.4[1]
Cardiac output (l. min^{-1})	2.46 ±0.20	1.96 ±0.15[2]	2.53 ±0.28
Occlusion 1			
PVCs (min^{-1})	7.3 ±1.8	5.7 ±2.3	0.4 ±0.2[1]
VF	5	5	0[3]
Occlusion 2			
PVCs (min^{-1})	—	—	0.4 ±0.2
VF	2	1**	5
Occlusion 3			
PVCs (min^{-1})	—	—	0.05 ±0.05***
VF	—	—	1
Survival after 3 occlusions	0	0	3

PVCs = ventricular arrhythmias (ventricular fibrillation VF, excluded) were only compared during the first 5 min of occlusion because of the high mortality due to VF in the control and propranolol groups during the first minutes.
[1] $P<0.05$ vs control and propranolol.
[2] $P<0.05$ vs control and felodipine.
[3] $P<0.005$ vs control and propranolol.
* All values as mean ± s.e.mean.
** One animal died in failure during reperfusion.
*** $n=4$.

groups could not be carried out because of the high early mortality in these groups. During the second occlusion, felodipine was less effective against ventricular fibrillation, despite a similar low number of ventricular arrhythmias as during the first occlusion. Plasma concentrations of felodipine were lower at the start of the second than of the first occlusion (2.18 ± 0.23 vs 2.93 ± 0.18 nmol l^{-1}; $n=6$, $P<0.05$), but it was not different in the animals which underwent VF from those which did not.

Reperfusion arrhythmias were observed in only one of the felodipine-treated animals ($>6\ min^{-1}$) during a total of 2 min but were absent in the eight other animals during all reperfusion periods.

Discussion The ultimate use of antiarrhythmic drugs depends to a large extent on their efficacy in preventing ventricular fibrillation. Acute LAD coronary artery occlusion in anaesthetized pigs leads to VF within minutes after the flow has been interrupted. The major reasons for this high incidence are the large area of the myocardium affected by the occlusion (40–45%) and the absence of a collateral circulation in the domestic pig. In this study, pretreatment with propranolol was not effective against ventricular fibrillation. Felodipine, on the other hand, not only reduced the incidence of ventricular ectopic activity, but also prevented VF during the first occlusion of 10 min. This finding is even more impressive when one considers that arterial blood pressure was the lowest in the felodipine group. Because of the short duration of the occlusion we cannot be certain that we are not dealing with just a delay in the onset of ventricular fibrillation. The finding that during the second occlusion VF occurred in 5 out of 9 animals seems to confirm this. For nifedipine it is known that the increase in fibrillation threshold in the rat isolated heart after coronary artery ligation is only transient (Thandroyen, 1982), but we must also take into account that plasma concentrations of felodipine were lower at the start of the second than of the first occlusion. Reperfusion arrhythmias were rare in the felodipine-treated animals but a comparison with the two other groups was not possible because of the high mortality in these groups before the first reperfusion. However, a higher incidence of reperfusion arrhythmias was observed in untreated animals of the same species after less severe ischaemia (Verdouw *et al.*, 1983). In conclusion, it appears that felodipine, in addition to a strong hypotensive action, possesses distinct antiarrhythmic properties.

References

BOSTRÖM, S.L., LJUNG, B., MÅRDH, S., FORSEN, S. & THULIN, E. (1981). Interaction of the antihypertensive drug felodipine with calmodulin. *Nature*, **292,** 777–778.

FAGBEMI, O. & PARRATT, J.R. (1981). Suppression by orally-administered nifedipine, nisoldipine and niludipine of early, life-threatening ventricular arrhythmias resulting from acute myocardial ischaemia. *Br. J. Pharmac.*, **74,** 12–14.

SHEEHAN, F.H. & EPSTEIN, S.E. (1982). Effects of calcium channel blocking agents on reperfusion arrhythmias. *Am. Heart J.*, **102,** 973–977.

THANDROYEN, F.T. (1982). Protective action of calcium channel antagonist agents against ventricular fibrillation in the isolated perfused rat heart. *J. mol. cell. Cardiol.*, **14,** 21–32.

VERDOUW, P.D., WOLFFENBUTTEL, B.H.R. & TEN CATE, F.J. (1983). Nifedipine with and without propranolol in the treatment of myocardial ischemia: effect on ventricular arrhythmias and recovery of regional wall function. *Eur. Heart J.*, Suppl. B (in press).

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