Br. J. Pharmac. (1982), **72**, 347–354

LIDOFLAZINE IN THE EARLY STAGES OF ACUTE MYOCARDIAL ISCHAEMIA

SUSAN J. COKER, O. FAGBEMI & J.R. PARRATT

University of Strathclyde, Department of Physiology and Pharmacology, Royal College, 204 George Street, Glasgow G1 1XW

1 Pretreatment of anaesthetized rats with intravenously administered lidoflazine (an antianginal agent) reduced the incidence and severity of ventricular arrhythmias which resulted from acute coronary artery ligation. Ventricular fibrillation was completely prevented by doses of 50 μg/kg and 2 mg/kg and no animal so treated died (contrast 50% incidence of fibrillation in the controls and 30% mortality).

2 In anaesthetized greyhound dogs, lidoflazine (2 mg/kg) administration resulted in transient reductions in systemic arterial pressure, LV $dP/dt\,max$ and cardiac output. Coronary sinus Po_2 was markedly increased, indicating pronounced coronary vasodilatation.

3 Lidoflazine pretreatment inhibited the increase in epicardial ST-segment elevation which resulted, in dogs, from short (3 min) occlusions of the left anterior descending coronary artery. This effect was especially marked at sites where, in control occlusions, ST-segment elevation was most pronounced.

4 Lidoflazine greatly reduced the number of ventricular ectopic beats which usually resulted from more prolonged (30 min) periods of acute coronary artery occlusion. There was no ventricular fibrillation in these dogs (contrast 25% incidence in the controls).

5 Lidoflazine did not modify the ventricular fibrillation which results from reperfusion of a previously ischaemic area of the left ventricular wall.

Introduction

Lidoflazine (1-[4,4-di-(4-fluorophenyl) butyl]-4-(2,6-dimethylanilino carbonyl) methylpiperazine) is a long-lasting and orally active coronary vasodilator drug which, when administered over several weeks, stimulates the development of collateral vessels. The experimental studies with this compound have been reviewed by Parratt (1969) and, more recently, by Vanhoutte & Van Nueten (1980). There has been renewed interest in lidoflazine because of the evidence that it protects cardiac muscle against the deleterious effects of ischaemia and subsequent reperfusion (Nayler, 1980; Flameng, Daenen, Xhonneux, Van de Water & Van Belle, 1980; Flameng, Daenen, Borgers, Thone, Xhonneux, Van de Water & Van Belle, 1981). The mechanism of this protection is unclear but lidoflazine interferes with the slow channel transport of Ca^{2+}, at least in smooth muscle, and it is possible that lidoflazine alleviates myocardial damage, at least in part, by preventing mitochondrial calcium overload (Flameng *et al.*, 1981).

Despite some evidence (de Geest, Kesteloot & Piessens, 1979) that prolonged treatment with lidoflazine is of some benefit in the long term management of patients following myocardial infarction, little is known about the effects of the drug on the early life-threatening ventricular arrhythmias which are a consequence of acute myocardial ischaemia. Schaper, Xhonneux, Jageneau & Janssen (1966) showed in dogs that prolonged oral treatment with the drug reduced the incidence of ventricular fibrillation following abrupt coronary artery occlusion whereas Carmeliet & Xhonneux (1971) found that lidoflazine was ineffective in reversing ventricular arrhythmias 24 h after coronary artery ligation. The aim of the present studies was three fold. Firstly to determine whether lidoflazine is effective against the *early* life-threatening arrhythmias that occur soon after coronary artery occlusion. Secondly, to determine if it reduces the incidence of arrhythmias following reperfusion and thirdly to examine, using epicardial mapping techniques, whether lidoflazine reduces the severity of myocardial ischaemic damage.

Methods

Studies in anaesthetized rats

The effect of lidoflazine on early arrhythmias resulting from myocardial ischaemia was evaluated using

0007-1188/82/060347-08 $01.00

the technique described by Clark, Foreman, Kane, McDonald & Parratt (1980). Male Sprague-Dawley rats, weighing 250–450 g were used for this study. Anaesthesia was induced with pentobarbitone sodium, 6 mg/100 g injected intraperitoneally, with small additional amounts administered intravenously as required.

Systemic arterial blood pressure was recorded from the left common carotid artery using either a capacitance transducer (Elema-Schönander, type EMT35), or a resistance transducer (Gould Statham P23 ID). A catheter was placed in a femoral vein for administration of drugs, and the trachea was cannulated to allow artificial ventilation. The electrocardiogram (ECG) was recorded using standard limb leads. Arterial blood pressure and the electrocardiogram were monitored continuously on an oscilloscope and recorded on a Mingograf 81 or 82 ink-jet recorder (Elema-Schönander, Stockholm). Rectal temperature was maintained at approximately 38°C. The chest was opened by left thoracotomy at the fifth intercostal space and the fifth and fourth ribs were sectioned approximately 2 mm from the left margin of the sternum. Immediately after opening the chest, the animals were ventilated with room air using a stroke volume of approximately 2 ml/100 g and a rate of 54 strokes/min. After opening the pericardium the heart was exteriorized by gentle pressure on the chest wall, and a 6/0 braided silk suture attached to a 10 mm micropoint reverse cutting needle (Mersilk W812, Ethicon) was placed under the left coronary artery as described by Clark *et al.* (1980). The heart was replaced in the chest cavity and any animal in which this procedure itself produced arrhythmias or a sustained fall in mean arterial blood pressure to less than 70 mmHg was discarded from the study at this point. After an equilibration period of 15 min the ligature was tied and the blood pressure and electrocardiogram recorded for at least 30 min. After this period there are very few ventricular arrhythmias until 1–2 h after ligation (Clark *et al.*, 1980). Only the early arrhythmias (up to 30 min post-ligation) were evaluated in this study. The number of ventricular ectopic beats was counted and recorded together with the incidence and duration (in seconds) of both ventricular tachycardia (VT) and ventricular fibrillation (VF) as described in detail by Clark *et al.*, 1980.

Lidoflazine, generously supplied by Janssen Pharmaceuticals Ltd., was dissolved in glacial acetic acid in a beaker placed on a boiling-water bath. The resultant solution was slowly diluted with hot water under constant stirring to give a stock solution of 4 mg/ml of lidoflazine in 1% acetic acid. This was diluted as required with 0.9% w/v NaCl solution (saline) and administered intravenously in doses of 5 and 50 μg/kg and 2 mg/kg 15 min before ligation of the coronary artery. Both solvent controls (1% acetic acid) and saline controls were used for comparison with the drug-treated groups.

Studies in anaesthetized greyhounds

Adult greyhound dogs of either sex and weighing between 20 and 32 kg were anaesthetized with sodium thiopentone (25 mg/kg administered intravenously followed by α-chloralose, 85 mg/kg i.v.). They were intubated and ventilated with oxygen. Ventilation was controlled with a Palmer respiratory pump, 25 strokes/min, the stroke volume of which was adjusted to give an arterial CO_2 tension of about 36–40 mmHg. Reflex respiratory movements were prevented by the intravenous administration of pancuronium (0.15–0.2 mg/kg). Catheters were placed under fluoroscopic control in the descending aorta, the lumen of the left ventricle and in the pulmonary artery, coronary sinus and descending vena cava for pressure measurements and blood sampling as previously described (Marshall, Parratt & Ledingham 1974; Marshall & Parratt 1979). Pressures were measured with resistance type transducers (Elcomatic 751A) and recorded on a Mingograf 82 ink-jet recorder (Siemens-Elema). Left ventricular (LV) pressure was differentiated (LV dP/dt) using a Siemens-Elema differentiating circuit and records of left ventricular pressure at high gain allowed accurate assessments to be made of left ventricular end-diastolic pressure (LVEDP). Cardiac output was measured by thermodilution and temperature measured from the mid-oesophagus using a direct recording (Ellab) thermocouple.

The heart was exposed through a left thoracotomy and the pericardium overlying the anterolateral aspect of the heart incised. The anterior descending branch of the left coronary artery at a point approximately halfway between the tip of the atrium and the apex of the heart was prepared for occlusion with limited dissection. A major branch of the main vein adjacent to the artery (the anterior coronary vein) was catheterized by the Seldinger technique with a 6 inch Longdwel teflon catheter (size 20G). This catheter was not tied in position. It will be referred to in the text as the coronary vein catheter and after coronary artery ligation has been shown to drain blood predominantly from the ischaemic area (Marshall *et al.*, 1974). Simultaneous blood samples were taken, without exposure to air, at regular intervals from this vein and from the coronary sinus, right atrium, pulmonary artery and descending aorta. Blood was analysed for O_2 and CO_2 tensions, for O_2 content and for pH as outlined by Ledingham, McBride, Parratt & Vance (1970).

For the studies involving epicardial ST-segment mapping a triangular sheet of rubber in which were embedded nine silver electrodes (impedance 600 to

1200Ω) was sutured to the anterior surface of the left ventricle so that at least six of the electrodes lay in areas supplied by the artery to be occluded (Marshall & Parratt, 1977; 1979). Care was taken to keep the epicardium moist with saline throughout the experiment. Aortic blood pressure, left ventricular pressure, left ventricular d*P*/d*t*, pulmonary artery pressure and epicardial electrocardiograms (ECGs) were recorded on a Mingograf ink-jet recorder (impedence > 1 megohm). After baseline haemodynamics, blood gases and epicardial ECGs had been obtained, the artery was occluded and epicardial ECGs at each of the nine sites (3 simultaneously) were recorded by means of a rapid switching circuit at 1, 2 and 3 min after occlusion and at a paper speed of 50 mm/s. Only short (i.e. 3 min) occlusions were used in this study because longer occlusions occasionally result in bursts of ventricular dysrhythmias and conduction defects (e.g. QRS widening), both of which mask shifts in the ST-segment. In each animal three control occlusions were performed and occlusions repeated 15, 45 and 75 min after the administration of lidoflazine (2 mg/kg i.v.). The control values in Table 3 are those for the third control occlusion. The results were analysed statistically using Student's *t* test for paired data.

Two hours after this first dose of lidoflazine a second dose of 2 mg/kg was again injected intravenously and the coronary artery occluded for 30 min. The number of ventricular ectopic beats which occurred during this period was counted (cf. Marshall & Parratt, 1979) and at the end of the 30 min occlusion period the ischaemic area was reperfused by releasing the occlusion. In control dogs this invariably led to the occurrence of serious ventricular arrhythmias and almost all these control animals fibrillated (Coker, Ledingham, Parratt & Zeitlin, 1982). In the same model therefore, the effect of lidoflazine was examined on these two different types of ventricular arrhythmia (Parratt, 1982) i.e. those that occur whilst ischaemia is present and those that occur immediately following reperfusion.

Results

Effects of lidoflazine on early arrhythmias resulting from acute myocardial ischaemia in rats

The results are summarized in Tables 1 and 2. There was no significant difference between the two control groups (saline versus drug solvent) with regard to the distribution of ventricular ectopic beats (VEBs; Table 1) or in the incidence and duration of either ventricular tachycardia (VT) or ventricular fibrillation (VF; Table 2). Lidoflazine in the lowest dose used (5 μg/kg) had no effect on these arrhythmias but with a dose of 50 μg/kg there was a moderate, statistically insignificant reduction in the total number of VEBs (Table 1) and in the duration of VT (Table 2). The most striking effect however, was the abolition of VF and the fact that none of the animals administered this dose of lidoflazine died (Table 2). A rather larger dose (2 mg/kg) of lidoflazine (equivalent to that used in the greyhound studies) also significantly reduced the duration of VT (Table 2); and ventricular ectopic activity, especially in the initial (0–20 min) postligation period (Table 1). The two largest doses of lidoflazine caused significant reduction in arterial pressure; 15 min after drug administration (i.e. at the same time the coronary artery was ligated) systemic arterial pressure was still decreased relative to the controls (Table 2). Only the 2 mg/kg dose of lidoflazine significantly reduced heart rate (by − 16%).

Haemodynamic effects of lidoflazine in anaesthetized greyhounds

A dose of 2 mg/kg was chosen; this was the same as that used in our previous studies which were concerned with examining the effects of different coronary vasodilator drugs on blood flow and metabolism in the acutely ischaemic myocardium (Marshall & Parratt, 1974). In the present study, where it was administered before coronary artery occlusion, lidoflazine administration resulted in pronounced but

Table 1 The effect of lidoflazine* on early post-infarction ventricular arrhythmias in anaesthetized rats

Group	*Time of onset of ventricular arrhythmias* (min)	*Ventricular ectopic beats after ligation* 0–5	6–10	11–15	16–20	21–25	26–30 min	*Total*
Control	5–7	9±3	284±71	389±65	292±54	94±13	14±4	1082±214
Solvent	6–7	—	293±67	367±72	274±42	83±21	18±3	1035±219
Lidoflazine 5 μg/kg	6–7	—	185±23	371±71	167±16	112±16	21±6	856±141
Lidoflazine 50 μg/kg	6–7	—	162±7	289±66	85±14	74±16	9±3	619±102
Lidoflazine 2 mg/kg	6–7	—	97±5*	142±20	64±15*	54±8	16±6	373±54*

Lidoflazine was given intravenously 15 min before coronary artery ligation. There were 10 animals in each group. *$P < 0.05$.

Table 2 The effect of lidoflazine on early post-infarction ventricular arrhythmias in anaesthetized rats

Group	Duration of Ventricular tachycardia (s)	Duration of Ventricular fibrillation (s)	Incidence of VF (%)	Mortality (%)	Blood pressure (mmHg)
Control	68.8 ± 12.6	28.4 ± 2.7	50	30	—
Solvent	64.3 ± 6.7	25.7 ± 4.2	40	30	123 ± 4/103 ± 4
Lidoflazine 5 μg/kg	62.7 ± 16.3	23.5 ± 3.6	40	10	—
Lidoflazine 50 μg/kg	42.4 ± 14.6	0*	0*	0*	97 ± 4/84 ± 5*
Lidoflazine 2 mg/kg	18.5 ± 5.1*	0*	0*	0*	85 ± 7*/69 ± 7*

Lidoflazine was given intravenously 15 min before coronary artery ligation. There were 10 animals in each group.
*$P < 0.05$. VF = ventricular fibrillation.

short-lasting (2–3 min) decreases in systemic arterial pressure and LV d*P*/d*t* (Figure 1). Control studies with the vehicle alone demonstrated similar, although less marked, haemodynamic effects. A reduction in LV d*P*/d*t* with such a pronounced reduction in afterload does not necessarily indicate a decrease in myocardial contractility. Certainly, by the time the coronary artery was occluded, there was again no significant difference between control and lidoflazine-treated animals although systemic blood

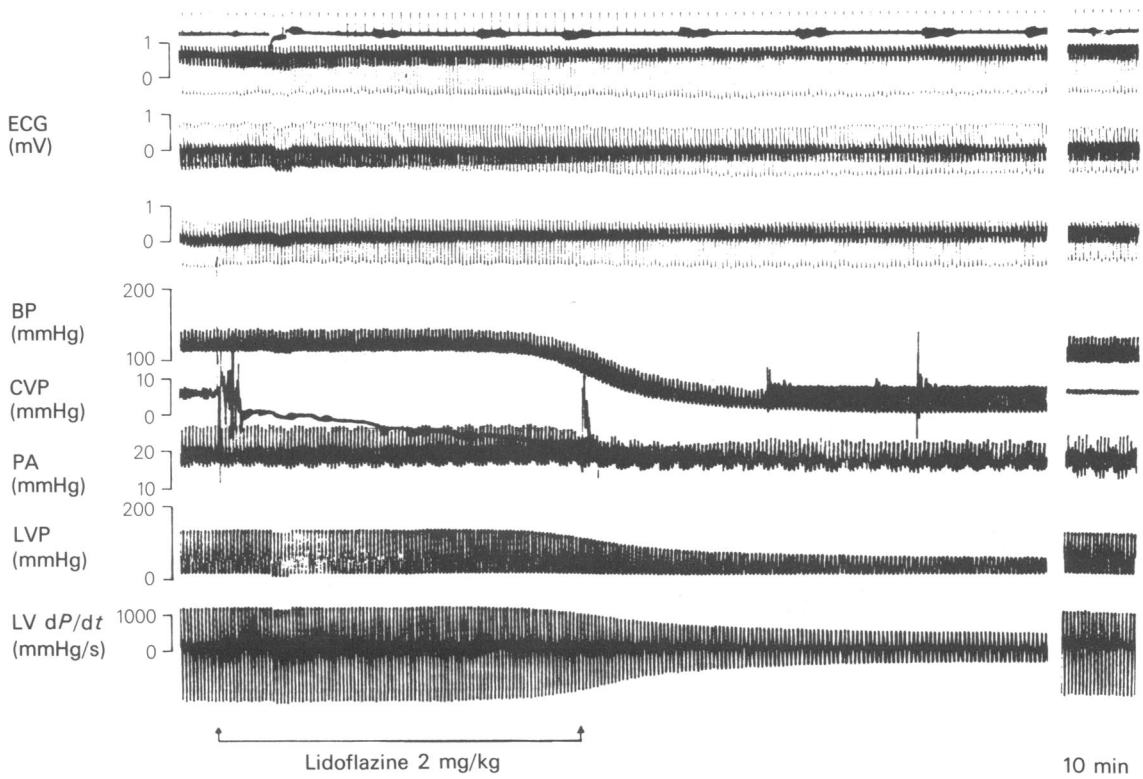

Figure 1 The effect of lidoflazine 2 mg/kg, injected slowly into the right atrium on, from above, epicardial recordings from these three different sites, systemic arterial pressure (BP), central venous pressure (CVP), pulmonary artery pressure (PA), left ventricular (LV) pressure and d*P*/d*t* in an anaesthetized dog. The time-marker at the top of the record is in seconds.

Table 3 Total ST-segment elevation (mV) recorded from nine epicardial electrodes, before and at various times after, acute 3 min coronary artery occlusions in anaesthetized greyhounds

Time after occlusion (min)	*Control*	*control (Vehicle)*	*Post-lidoflazine 15 min*	*45 min*	*75 min*
0	3.4±0.8	4.0±1.3	6.1±1.8	5.8±1.4	8.5±1.6
1	17.7±3.8	17.7±2.6	11.4±2.3	14.3±4.3	20.8±2.8
2	23.6±3.1	23.5±3.4	17.9±2.9	19.7±4.6	25.0±3.9
3	29.0±3.2	25.7±4.7	22.7±4.0	25.0±6.9	27.0±6.2

Values are means ± s.e.mean of 7 experiments.

pressure and heart rate tended to be lower than in the control (or lidoflazine-vehicle) animals, e.g. 136±17/97±13 (mean 110±13 mmHg) and 155 beats/min after lidoflazine and 155±16/116±10 (mean of 129±12 mmHg) and 169±16 beats/min in the controls. Pulmonary artery pressure (mean of 20±3 mmHg) and LVEDP (14±4 mmHg) were the same in the two groups as were LV $dP/dt\,max$ (1620±250 mmHg/s in the controls and 1260±210 mmHg/s after lidoflazine) and cardiac output (1.56±0.14 l/min in both the vehicle-treated controls and in the drug-treated group). These haemodynamic effects of lidoflazine are less than those obtained in the same model after the induction of acute myocardial ischaemia (Marshall & Parratt, 1974).

Effect of lidoflazine on arterial and coronary sinus blood gases and pH

Lidoflazine had no effect on systemic arterial blood gases and pH but, as one would expect from its pronounced coronary vasodilator activity, it greatly increased coronary sinus P_{O_2} (25±2 mmHg pre-lidoflazine and 41±5 and 32±4 mmHg 2 and 10 min respectively after lidoflazine) and oxygen content (8.4±1.1 ml/100 ml pre-drug and 14.2±2.2 and 12.6±2.2 ml/100 ml 2 and 10 min after lidoflazine administration). Coronary sinus P_{CO_2} was slightly, but not significantly, reduced by lidoflazine administration.

Effect of lidoflazine on ischaemia-induced epicardial ST-segment changes

The effect of lidoflazine (and the drug solvent) on *total* epicardial ST-segment elevation (sum of nine sites) following 1, 2 and 3 min periods of coronary artery occlusion in seven dogs is shown in Table 1. The solvent had no effect on local ST-segment elevation induced by ischaemia but in the lidoflazine-treated animals the increase was delayed, especially if one takes into consideration that the control ST-segment elevation prior to occlusion tended to increase over the time course of the experiment (e.g. 3.4±0.8 mV prior to the third control occlusion, Table 3 and 8.5±1.6 mV prior to the last post-lidoflazine occlusion). For example the changes in ST-segment elevation during the control occlusion were 14.3±3.1, 20.1±2.7 and 25.6±3.3 mV at 1, 2 and 3 min respectively. Fifteen minutes after lidoflazine these changes were reduced to 5.3±2.1 ($P<0.05$), 11.7±3.0 and 16.5±4.4 mV respectively ($P<0.01$). Forty-five minutes after administration the respective values on occlusion were 8.0±3.5 ($P<0.05$) at 1 min, 13.3±4.0 ($P<0.01$) at 2 min and 18.6±6.7 mV (not significant) at 3 min.

This effect is even more marked if one looks at individual leads rather than summing changes from all the nine epicardial electrodes (compare results obtained with another potential antianginal compound MG 8926; Marshall & Parratt, 1977). The most marked reduction in ST-segment elevation by lidoflazine occurs in those leads (1, 2 and 3; Table 4) where it was most pronounced before drug administration i.e. in areas where the severity of ischaemia was greatest.

Coronary artery occlusion resulted in marked changes in P_{CO_2} and in pH of local venous blood draining from the ischaemic region (e.g. P_{CO_2} increased from 57±4 to 63±5 mmHg, pH decreased

Table 4 ST-segment elevation (mV) from nine individual epicardial electrodes 3 min after acute coronary artery occlusion

Epicardial lead	*Control*	*15 min-post lidoflazine*
1	7.14±0.80	4.86±0.94*
2	5.86±0.74	4.29±0.68*
3	4.57±0.57	3.29±0.36*
4	3.43±0.43	2.71±0.61
5	2.57±0.39	2.29±0.71
6	2.14±0.40	2.00±0.44
7	1.71±0.29	1.57±0.30
8	1.14±0.14	1.57±0.53
9	0.60±0.40	0.40±0.40
Total	29. 0±3.2	22.7 ±4.0

Values are means ± s.e.means, $n = 7$. *$P<0.05$

from 7.32 ± 0.02 to 7.24 ± 0.05 units). Rather less pronounced changes occurred following coronary occlusion 15 min after lidoflazine administration (P_{CO_2} 56 ± 4 to 60 ± 3 mmHg; pH 7.25 ± 0.03 to 7.23 ± 0.04 units).

Effect of lidoflazine on arrhythmias resulting from 30 min coronary artery occlusion in greyhounds and on subsequent reperfusion

There were four lidoflazine-treated dogs in this study. Usually there are about 300–600 ventricular ectopic beats in the immediate 30 min post-ligation period (e.g. Marshall & Parratt, 1980; Marshall & Muir, 1981). In a control series of eight dogs corresponding to the lidoflazine-treated group the mean number of arrhythmias in the six survivors was 525 ± 152; the incidence of VF was 25%. Lidoflazine pretreatment markedly suppressed the incidence of VEB's (250, 0, 20 and 40 VEB's respectively in the four treated dogs, mainly 5–15 min after occlusion) and no animal fibrillated during the occlusion. However, all four dogs fibrillated when the occlusion was released.

Discussion

Two positively beneficial effects of lidoflazine are apparent from the present study. Firstly, there is clear evidence, from both the anaesthetized rat and greyhound studies, that lidoflazine reduces the incidence and severity of the early arrhythmias that result from acute myocardial ischaemia. Secondly, there is some evidence that pretreatment with the drug reduces, or delays, the severity of ischaemic myocardial electrocardiographic changes.

The demonstration of antiarrhythmic effect of lidoflazine (Tables 1 and 2) supports the early study of Schaper *et al.* (1966) in dogs. There is however a major difference between that study and the present one. Schaper *et al.* gave lidoflazine, in a daily oral dose of 20 mg/kg, for a period of 28 days and occluded the circumflex coronary artery 2 h after the last dose. The incidence of early (within 1 h) ventricular fibrillation was 16 out of 20 in the controls but only 2 out of 10 in the lidoflazine-treated group. This striking result was not discussed by the authors but one explanation, suggested by Carmeliet & Xhonneux (1971), is that prolonged treatment with this coronary vasodilator drug could have stimulated the development of the coronary collateral circulation. Indeed, Schaper himself (1971) provides evidence for such an accelerated growth of coronary collateral vessels following prolonged oral treatment with the drug. This, as Meesmann (1982) has clearly demonstrated, would reduce the incidence and severity of ventricular arrhythmias resulting from subsequent coronary artery ligation.

The present studies demonstrate, both in the rat and the greyhound, that acute pretreatment with lidoflazine reduces the severity of these arrhythmias. Indeed, ventricular fibrillation was not observed in dogs pretreated with 2 mg/kg of lidoflazine or in rats given either 50 μg/kg or 2 mg/kg of the drug. Coronary vasodilatation certainly results from administration of this dose of lidoflazine in the dog (Marshall & Parratt, 1974) and the evidence for this effect in the present study was the marked and sustained increase in coronary sinus P_{O_2} (e.g. from 25 ± 2 to 41 ± 5 mmHg). The question as to whether such coronary vasodilatation *per se* would reduce the severity of early post-infarction arrhythmias is as yet unanswered. Some calcium antagonists are antiarrhythmic in this situation (e.g. nifedipine, niludipine and nisoldipine, Fagbemi & Parratt, 1981(a) and (b); bepridil, Marshall & Muir, 1981); other coronary vasodilators, such as prostacyclin (Coker & Parratt, 1981) are also effective whereas dipyridamole and carbochromen are not (Fagbemi & Parratt, unpublished). An alternative explanation is that the antiarrhythmic effect of lidoflazine results from an effect on cellular calcium transport; certainly many 'calcium antagonists' do have antiarrhythmic activity, especially early in ischaemia (Parratt, 1982). Inhibition of the fast inward Na^+ current also cannot be excluded as a mechanism of protection (Carmeliet & Xhonneux, 1971). A possible clinical consequence of these findings is that lidoflazine should reduce the severity of post-infarction arrhythmias. Unfortunately there is as yet no clear evidence that this is so, at least in secondary prevention trials (de Geest *et al.*, 1979).

Although there is convincing evidence that pretreatment with lidoflazine reduces the incidence and severity of ventricular arrhythmias which occur whilst a coronary artery occlusion is present, the drug clearly does not prevent the very serious arrhythmias, almost certainly of great clinical importance, that occur when an ischaemic area is subsequently reperfused with blood. Thus, in the present study, all four lidoflazine-treated dogs reperfused after a 30 min occlusion period fibrillated; similar results were obtained in the chronic lidoflazine study of Schaper *et al.* (1966). These reperfusion arrhythmias have a different electrophysiological basis and a different sensitivity to drugs from 'ischaemic arrhythmias'.

Acute pretreatment with lidoflazine also reduced the development of epicardial ST-segment changes in those sites where it was most pronounced. Such electrocardiographic changes have been used as an index of myocardial ischaemic damage (for references see Marshall & Parratt, 1977; 1980; Parratt, Marshall & Ledingham, 1980) and probably reflect accumulation of extracellular K^+ (Marshall & Par-

ratt, 1980). A reduction in the egress of K^+ from ischaemic cells by lidoflazine could explain both the antiarrhythmic effect described above and the delay in epicardial ST-segment changes following short coronary artery occlusions. Whether this means that lidoflazine would reduce the severity of ultimate myocardial ischaemic damage cannot, of course, be adduced from these studies.

We should like to thank Professor I McA. Ledingham for the continued use of facilities at the Western Infirmary and we are indebted to Ian Douglas, Dick Thomson, Alan Fleming, Lynne Brady and Margaret Macdonald for excellent technical assistance, and to Howard Smith for constructing and maintaining the epicardial ECG equipment. The work was supported by grants from the Scottish Hospital Endowments Research Trust.

References

CARMELIET, E. & XHONNEUX, R. (1971). Influence of lidoflazine on cardiac transmembrane potentials and experimental arrhythmias. *Naunyn-Schmiedebergs Arch. Pharmak.*, **268,** 210–228.

CLARK, C., FOREMAN, M.I., KANE, K.A., McDONALD, F.M. & PARRATT, J.R. (1980). Coronary artery ligation in anaesthetised rats as a method of the production of experimental dysrhythmias and for the determination of infarct size. *J. Pharmac. Methods*, **3,** 357–368.

COKER, SUSAN J., LEDINGHAM, I. McA., PARRATT, J.R. & ZEITLIN, I.J. (1982). Ventricular fibrillation resulting from reperfusion of the acutely ischaemic canine myocardium is prevented by the thromboxane synthetase inhibitor UK–37,248. *Scot. Med. J.*, (in press).

COKER, SUSAN J. & PARRATT, J.R. (1981). The effects of prostaglandins E_2, F_2 , prostacyclin, flubiprofen and aspirin on arrhythmias resulting from coronary artery ligation in anaesthetised rats. *Br. J. Pharmac.*, **74,** 155–159.

DE GEEST, H., KESTELOOT, H. & PIESSENS, J. (1979). Secondary prevention of ischaemic heart disease: a long-term controlled lidoflazine study. *Acta Cardiol.*, suppl. **24,** 1–116.

FAGBEMI, O. & PARRATT, J.R. (1981a). Calcium antagonists prevent early post-infarction ventricular fibrillation. *Eur. J. Pharmac.*, **75,** 179–185.

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

FLAMENG, W., DAENEN, W., BORGERS, M., THONE, F., XHONNEUX, R., VAN DE WATER, A. & VAN BELLE, H. (1981). Cardioprotective effects of lidoflazine during one hour normothermic global ischaemia. *Circulation*, **64,** 796–807.

FLAMENG, W., DAENEN, W., XHONNEUX, R., VAN DE WATER, A., THONE, F. & BORGERS, M. (1980). Lidoflazine protection against normothermic myocardial ischaemia in the dog. In *Myocardial Protection and Exercise Tolerance: the Role of Lidoflazine, a new Anti-Anginal Agent. Royal Society of Medicine Series 29*, pp.89–94. ed. Towse, G. London: Academic Press.

LEDINGHAM, I. McA., McBRIDE, T.I., PARRATT, J.R. & VANCE, J.P. (1970). The effect of hypercapnia on myocardial blood flow and metabolism. *J. Physiol.*, **210,** 87–105.

MARSHALL, R.J. & MUIR, A.W. (1981). The beneficial actions of bepridil in acute myocardial infarction in anaesthetised dogs. *Br. J. Pharmac.*, **73,** 471–479.

MARSHALL, R.J. & PARRATT, J.R. (1974). Drug-induced changes in blood flow in the acutely ischaemic canine myocardium; relation to subendocardial driving pressure. *Clin. exp. Pharm. Physiol.*, **1,** 99–112.

MARSHALL, R.J. & PARRATT, J.R. (1977). The haemodynamic and metabolic effects of MG 8926, a prospective antidysrhythmic and anti-anginal agent. *Br. J. Pharmac.*, **59,** 311–322.

MARSHALL, R.J. & PARRATT, J.R. (1979). The effects of disopyramide phosphate on early post-coronary artery ligation dysrhythmias and on epicardial ST-segment elevation in anaesthetized dogs. *Br. J. Pharmac.*, **66,** 241–250.

MARSHALL, R.J. & PARRATT, J.R. (1980). The early consequences of myocardial ischaemia and their modification. *J. Physiol., Paris*, **76,** 699–715.

MARSHALL, R.J., PARRATT, J.R. & LEDINGHAM, I. McA. (1974). Changes in blood flow and oxygen consumption in normal and ischaemic regions of the myocardium following acute coronary artery ligation. *Cardiovasc. Res.*, **8,** 204–215.

MEESMANN, W. (1982). Early arrhythmias and primary ventricular fibrillation after acute myocardial ischaemia in relation to pre-existing coronary collaterals. In *Early Arrhythmias Resulting from Myocardial Ischaemia; Mechanisms and Prevention by Drugs*. ed. Parratt, J.R. London: Macmillan (in press).

NAYLER, W.G. (1980). The protective effect of lidoflazine on ischaemic and reperfused heart muscle. In *Myocardial Protection and Exercise Tolerance: the Role of Lidoflazine, a new Anti-Anginal Agent. Royal Society of Medicine Series 29*, pp.79–87, ed. Towse, G. London: Academic Press.

PARRATT, J.R. (1969). Pharmacological aspects of the coronary circulation. In *Progress in Medicinal Chemistry*, Vol 6, pp.11–66. ed. Ellis, G.P. & West, G.B. London: Butterworths.

PARRATT, J.R. (1982). Inhibition of the slow calcium current and early ventricular arrhythmias. In *Early Arrhythmias Resulting from Myocardial Ischaemia; Mechanisms and Prevention by Drugs*. ed. Parratt, J.R. London: Macmillan (in press).

PARRATT, J.R., MARSHALL, R.J. & LEDINGHAM, I. McA. (1980). Interventions for improving blood flow, oxygen availability and the balance between oxygen supply and demand in the acutely ischaemic myocardium. *J. Physiol., Paris*, **76,** 791–803.

SCHAPER, W. (1971). *The Collateral Circulation of the Heart*. Amsterdam: North Holland.

SCHAPER, W.K.A., XHONNEUX, R., JAGENEAU, A.H.M. & JANSSEN, P.A.J. (1966). The cardiovascular pharmacology of lidoflazine, a long-acting coronary vasodilator. *J. Pharmac.*, **152,** 265–274.

VANHOUTTE, P.M. & VAN NUETEN, J.M. (1980). The pharmacology of lidoflazine. In *Myocardial Protection and Exercise Tolerance: the Role of Lidoflazine, a new Anti-Anginal Agent. Royal Society of Medicine Series 29.* pp.61–77. ed. Towse, G. London: Academic Press.

(*Received February 8, 1982.*
Revised February 22, 1982.)