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THE HAEMODYNAMIC AND METABOLIC EFFECTS OF MG 8926, A PROSPECTIVE ANTIDYSRHYTHMIC AND ANTIANGINAL AGENT

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1 The antidysrhythmic, haemodynamic and metabolic effects of a new prospective antianginal and antidysrhythmic agent, N-(3,3-diphenylpropyl)-α-methyl-β-cyclohexylethylamine hydrochloride (MG 8926), have been compared with the chemically related substance, prenylamine, in anaesthetized greyhounds and guinea-pigs.

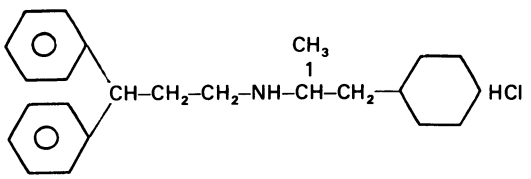
2 When given intravenously 20 min beforehand, both MG 8926 and prenylamine (5 mg/kg) significantly suppressed the early dysrhythmias induced by coronary artery ligation in anaesthetized greyhounds. At a dose of 1 mg/kg, MG 8926 also protected anaesthetized guinea-pigs from dysrhythmias induced by ouabain infusions.

3 In dogs pretreated with MG 8926, metabolic changes indicative of myocardial ischaemia (increased P_{CO_2} and potassium efflux, decreased oxygen content and pH) were less marked than those occurring in control animals.

4 Evidence was obtained that MG 8926, when given either before or after coronary occlusion, was capable of decreasing the severity of myocardial ischaemia as assessed by ST-segment changes in epicardial electrocardiograms.

Introduction

MG 8926 is a recently synthesized secondary amine structurally related to the antianginal drug prenylamine. It increases coronary flow in the isolated guinea-pig heart and partially inhibits pitressin-induced ST-segment changes in anaesthetized rats (M. Carissimi, personal communication 1975). In preliminary experiments we found that it also elevated coronary blood flow in the anaesthetized greyhound and reduced the incidence of cardiac dysrhythmias which result from acute ligation of the anterior descending branch of the left coronary artery in this experimental model. This paper describes the detailed haemodynamic effects of this compound and, where appropriate, these effects are compared with those of prenylamine.



N-(3,3-diphenylpropyl)-α-methyl-β-cyclohexylethylamine hydrochloride (MG 8926).

Methods

Anaesthetized greyhounds

Experiments were carried out on 27 greyhounds of either sex weighing between 23 and 31 kg. Anaesthesia was induced by intravenous administration of sodium thiopentone (20 mg/kg). After endotracheal intubation, respiration was applied from a positive-pressure ventilation pump (25 strokes/min), with 100% O_2 containing 0.5–1.0% trichlorethylene. The tidal volume of the pump was adjusted to maintain an arterial P_{CO_2} of 35–40 mmHg (1 mmHg = 1.33 mbar). Reflex movements were prevented by the intermittent intramuscular administration of suxamethonium chloride (100 mg).

In six of the dogs, myocardial nutritive blood flow was measured without thoracotomy by the radioactive xenon clearance method (Ledingham, McBride, Parratt & Vance, 1970; Marshall & Parratt, 1976). In order to measure myocardial O_2 availability and consumption, a catheter was positioned under fluoroscopic control in the coronary sinus and blood samples were taken, without exposure to air, from this catheter and, simultaneously, from a catheter in the descending aorta. The blood was analysed for P_{O_2}, P_{CO_2} and pH as previously described (Marshall, Parratt & Ledingham, 1974).

In another group of 12 dogs, catheters were placed, under fluoroscopic control, in the descending aorta (via the right femoral artery), the right atrium (via the right saphenous vein), the pulmonary artery and the coronary sinus (both via the left external jugular vein). A catheter-tip transducer (Millar Instruments, Inc., Houston, Texas) was inserted into the lumen of the left ventricle (via the left carotid artery in the neck) for the measurement of left ventricular pressure and also dP/dt (using an Elema-Schönander differentiating circuit). The frequency response of this transducer system is flat to 200 Hz. 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 either by dye-dilution, indocyanine green (2.5 mg) being injected as a bolus into the right atrium and blood withdrawn at a constant rate through a Waters densitometer, or by thermo-dilution, as described by Douglas, McDonald, Milligan, Mellon & Ledingham (1975). All cardiac output determinations were made in duplicate. There is a good correlation between cardiac output measurements made by these two methods (Douglas *et al.*, 1975).

In the remaining dogs, the heart was exposed through a left thoracotomy and the pericardium overlying the anterolateral aspect of the heart was incised. Blood flow in the circumflex branch of the left coronary artery was measured with a Nycotron 372 electromagnetic flow meter using a calibrated probe of 1.5–2.5 mm diameter. The anterior descending branch of the left coronary artery (LAD), at a point distal to the septal artery branch, was prepared for ligation with minimum dissection. A major branch of the main vein adjacent to the artery (the anterior coronary vein) was catheterized using the Seldinger technique with a 10 cm Longdwel teflon catheter (size 20G). This local coronary vein catheter was not tied in position and was manipulated until its tip lay well into the region of the myocardium which was to be made ischaemic. It has been shown that such a coronary vein catheter, after coronary artery ligation, drains blood predominantly from the ischaemic region (Fisher, Heimbach, Ledingham, Marshall & Parratt, 1973; Marshall *et al.*, 1974).

Blood samples were taken, without exposure to air, at regular intervals and were analysed for O_2 and CO_2 tensions, O_2 content and pH, as outlined by Ledingham *et al.* (1970), except that the value used for haemoglobin oxygen-binding capacity was 1.39. Blood samples from the aorta, coronary sinus and coronary vein were taken immediately before and 30 min after coronary artery ligation and were analysed for lactate (Hohorst enzymatic method using a Boehringer test combination) and for plasma potassium by standard flame photometry.

After a 20–25 min stabilization period, the ligature on the coronary artery was tied in one stage and the number of ventricular ectopic beats counted during each 5 min period for a total period of 30 min; no blood samples were taken during this time since manipulation of the coronary venous catheter sometimes itself induced arrhythmias. No arrhythmias occurred in any of the animals after 30 minutes. The arrhythmia counts obtained in these groups of dogs were compared with those previously obtained in untreated animals (Marshall & Parratt, 1974).

After the crucial 30 min period immediately after ligation, seven silver epicardial electrodes embedded in a band of rubber were sutured to the surface of the anterior left ventricular wall, so that at least four electrodes were situated in the obviously ischaemic zone. Frequent epicardial ECG recordings were taken before and at various times after drug infusion. A Portex nylon catheter (o.d. 1.34 mm) was then inserted into the peripheral stump of the ligated artery and was used for the measurement of peripheral coronary pressure (that is back pressure from the ischaemic zone measured with a capacitance transducer) and peripheral coronary blood flow (retrograde flow from this region).

At the end of each experiment, a bolus of diffusible dye was injected at a pressure of 50 mmHg into the peripheral stump of the ligated coronary artery. Fibrillation was immediately induced with potassium chloride and the dyed muscle quickly excised and weighed. The mass of this dyed ischaemic area of muscle was expressed as a percentage of the free ventricular wall.

Systemic arterial pressure (pulsatile and mean by electronic integration), mean right atrial pressure, pulmonary artery pressure, left ventricular pressure and dP/dt, LVEDP, left circumflex coronary blood flow and the electrocardiogram (standard limb lead II) were recorded on an Elema-Schönander ink-jet writing recorder (Mingograph 81). Myocardial O_2 extraction was calculated as outlined by Marshall & Parratt (1973) and cardiac work, peripheral vascular resistance, and whole body O_2 consumption as described by Ledingham, Parratt, Smith & Vance (1971).

In four additional dogs, the effects of prophylactically administered MG 8926 on ischaemia-induced epicardial ST-segment changes were investigated. These dogs were subjected to thoracotomy and a nylon snare placed around the LAD. Nine silver electrodes embedded in a triangular sheet of rubber were sutured on to the anterior surface of the left ventricle; epicardial electrocardiograms could be recorded simultaneously from any three sites through a rapid switching circuit. After control tracings from each site had been obtained the LAD was occluded and epicardial ECGs recorded from each site after 1, 2 and 3 min of occlusion. The snare was then released and the artery reoccluded after a rest period of at least

20 minutes. After two or three control occlusions the procedure was repeated 10 and 30 min after the administration of MG 8926 (5 mg/kg). Short 3 min occlusions were used in this series of animals, since releasing the occlusion after more than 3 min caused marked ventricular tachycardia and ventricular fibrillation.

All results were statistically analysed using Student's *t* test for paired or unpaired data. MG 8926 (as the hydrochloride) and prenylamine (as the lactate) were dissolved in warm distilled water and infused slowly into a femoral vein. All doses in the text refer to the salts.

Anaesthetized guinea-pigs

The preparation used was essentially that described by Dohadwalla, Freedberg & Vaughan Williams (1969). Female guinea-pigs weighing between 300–400 g were anaesthetized with urethane (1.6 g/kg, i.p.). Artificial respiration was applied using a Palmer small-animal pump with a stroke volume of 2–3 ml; the rate was 25 per minute. Rectal temperature was monitored with an Ellab thermocouple and the electrocardiogram (limb lead I or II) continuously monitored on an oscilloscope. Ouabain was infused into a jugular vein at a rate of 8 μg/min for 30 s every 2 minutes. At the end of every 2 min period the electrocardiogram was recorded for 10 s on a Mingograph 81 ink-jet writing recorder. The amounts of ouabain required to produce (a) unequal R-R intervals, (b) ventricular extrasystoles, (c) sustained ventricular tachycardia, (d) ventricular fibrillation and (e) cardiac arrest were noted. Five minutes before starting the ouabain infusion, animals were given intravenous 0.9% w/v NaCl solution (saline), MG 8926 or prenylamine. All injection volumes were less than 1 ml and control (saline) experiments were conducted every day to minimize any seasonal variations in the animals' responses.

Isolated electrically-driven atrial muscle of guinea-pig

Guinea-pigs weighing between 200–310 g were killed by stunning and exsanguination and the left atrium quickly excised and placed in a 10 ml organ bath containing Krebs–Henseleit solution (g/l: NaCl 6.9, KCl 0.35, $NaHCO_3$ 2.1, KH_2PO_4 0.16, $MgSO_4$ 0.29, $CaCl_2$ 0.56, glucose 2.0) bubbled with carbogen. The left atrial preparations were stimulated via a platinum electrode with supra-threshold (3–6 V) square wave pulses, of 5 ms duration and at 2 Hz. Contractions were measured by attaching the free end of the atria by means of a cotton thread to a strain gauge transducer (Ether UF1) and were recorded on a Devices M2 recorder.

To measure the effective refractory period of left atria, the stimulation was steadily increased until the atria could no longer follow each stimulus. This maximum driving frequency (MDF) is inversely related to effective refractory period (Ellis, 1956). In this investigation, control runs (usually two) were carried out at 30 min intervals until consistent MDFs were obtained. The test drug was then added to the organ bath and the procedure repeated either 10 or 20 min later (see Results section). Changes in maximal driving frequency (and thus reciprocal changes in effective refractory period) were expressed as percentages of the control value.

Results

Haemodynamic effects of intravenously administered MG 8926 in the closed chest greyhound

In order to ascertain the active dose-range of MG 8926, the haemodynamic effects of intravenous doses of 0.5, 2.5 and 5.0 mg/kg were investigated. The results are summarized in Table 1 and show that MG 8926 first caused discernible haemodynamic changes in intravenous doses of about 2.5 mg/kg. In this dose-range, MG 8926 reduced systemic blood pressure within 2–5 s of injection by 15–60 mmHg without significantly changing heart rate. External cardiac work and cardiac output were significantly elevated and, since heart rate remained constant, the increase in cardiac output could be attributed to an increase in stroke volume. Myocardial nutritional blood flow (as assessed by xenon clearance) was consistently elevated by MG 8926 (2.5 and 5.0 mg/kg) and, since systemic blood pressure was reduced, this indicates a reduction in coronary vascular resistance of between 30–55%. Since coronary sinus P_{O_2} rose (and therefore myocardial O_2 extraction fell) there was no change in myocardial O_2 consumption, and thus the ratio of available O_2 to consumed O_2 was increased by MG 8926 (from 2.7 ± 0.6 to 4.0 ± 0.6; $P < 0.05$). All these haemodynamic effects of MG 8926 were relatively transient and all parameters returned to control values within 10–15 min of injection.

A comparison of the haemodynamic effects of intravenously administered MG 8926 and prenylamine lactate (5 mg/kg) in the open chest anaesthetized greyhound

After the intravenous injection of MG 8926 (5 mg/kg; 6 dogs) there occurred an immediate transient decrease in blood pressure (mean decrease in diastolic pressure of 44 ± 7 mmHg). Neither heart rate (mean change + 8 ± 14 beats/min) nor left ventricular dP/dt *max* (mean change + 80 ± 140 mmHg/s) was affected by the drug. In the two experiments in which they were measured, cardiac output and myocardial blood flow were considerably but transiently increased (by

21% and by 68% respectively) and there was a marked reduction in myocardial O_2 extraction (from 41 ± 6 to 21 ± 5%; $P < 0.05$) 3 min after injection. The haemodynamic effects of MG 8926 in the open chest animal were, like those in the closed chest, transient so that 10 min after drug administration there were no significant changes in blood pressure (185 ± 12 mmHg systolic and 128 ± 6 mmHg diastolic before the drug and 187 ± 12 and 133 ± 6 mmHg after), heart rate (187 ± 12 to 169 ± 7), left ventricular d*P*/d*t max* (3750 ± 420 to 3580 ± 40 mmHg/s), LVEDP (8 ± 1 to 9 ± 1 mmHg), cardiac output (4.1 ± 0.4 to 4.0 ± 0.4 l/min), external cardiac work (4.5 ± 0.5 to 4.9 ± 0.6 kgm/min), myocardial O_2 extraction (41 ± 6 to 37 ± 6%), peripheral vascular resistance (37 ± 2 to 38 ± 2 arbitrary units) and whole body O_2 consumption (134 ± 15 to 114 ± 10 ml/minute).

Prenylamine lactate (5 mg/kg; 6 dogs) also caused an immediate fall in blood pressure (a reduction of 46 ± 10 mmHg in diastolic pressure) but in contrast to MG 8926, this was accompanied by transient but significant increases in heart rate (from 168 ± 11 to 202 ± 7 beats/min; $P < 0.05$) and in left ventricular d*P*/d*t max* (mean increase 667 ± 80 mmHg/second). Pulmonary artery pressure was initially increased from 18 ± 3 mmHg systolic, (9 ± 1 diastolic) to 24 ± 4 mmHg systolic (13 ± 1 mmHg diastolic) ($P < 0.05$). Like MG 8926, prenylamine lactate also caused a transient increase in cardiac output (4.3 ± 0.2 to 5.5 ± 0.2 litres/min, $P < 0.05$) and a marked decrease in myocardial O_2 extraction (38 ± 5 to 22 ± 3%; $P < 0.05$). As with MG 8926, all parameters had returned to control levels 10 min after the injection of prenylamine.

A constant finding with prenylamine was the production of dysrhythmias on injection. These dysrhythmias were ventricular in origin and lasted 5–10 minutes. In contrast, MG 8926 altered cardiac rhythm, and that transiently, on only one occasion.

The effects of MG 8926 and prenylamine lactate on the immediate dysrhythmias ensuing after acute coronary artery ligation

The results of this investigation are presented and compared with previous results in control animals in Table 2. Ventricular dysrhythmias are common in this preparation especially in the 10–20 min post-ligation period and in 4 out of the 12 control dogs ventricular fibrillation occurred during this time. In contrast, significantly fewer dysrhythmias were seen during this crucial period in dogs pretreated with either MG 8926 or prenylamine, both given in an intravenous dose of 5.0 mg/kg, 20 min before ligation. None of the animals given MG 8926, and only one animal given prenylamine, succumbed to ventricular fibrillation but in 5 of the treated dogs (3 given MG 8926, 2 given prenylamine) there were sustained runs of ventricular

Table 1 The immediate haemodynamic changes (mean ± s.e.) resulting from the intravenous administration of MG 8926 in anaesthetized closed-chest greyhounds

	Dose of MG 8926 (mg/kg)					
	(n=3) 0.5		*(n=6) 2.5*		*(n=5) 5.0*	
	Pre	*Post*	*Pre*	*Post*	*Pre*	*Post*
Systolic blood pressure (mmHg)	208 ± 8	198 ± 16	201 ± 8	165 ± 12*	190 ± 8	130 ± 10*
Diastolic blood pressure (mmHg)	142 ± 2	143 ± 9	145 ± 6	112 ± 9*	138 ± 5	79 ± 7*
Heart rate (beats/min)	197 ± 27	200 ± 31	199 ± 10	215 ± 8	185 ± 11	200 ± 13
Cardiac output (1/min)	2.7 ± 1.4	2.7 ± 1.7	2.6 ± 0.6	3.5 ± 0.6*	2.6 ± 0.4	3.6 ± 0.5*
External cardiac work (kgm/min)	3.0 ± 1.2	2.9 ± 1.5	3.0 ± 0.7	3.5 ± 0.8	3.1 ± 0.5	4.4 ± 0.4*
Peripheral resistance (units)	78 ± 30	93 ± 38	73 ± 16	50 ± 15	68 ± 9	38 ± 6*
Myocardial blood flow (ml 100 g^{-1} min^{-1})	112 ± 24	101 ± 21	99 ± 12	121 ± 9*	110 ± 9	133 ± 19*
Myocardial oxygen extraction (%)	44 ± 4	46 ± 4	46 ± 6	38 ± 6	53 ± 9	34 ± 8*
Myocardial oxygen consumption (ml 100 g^{-1} min^{-1})	14.5 ± 3.1	12.7 ± 2.5	11.8 ± 2.5	12.1 ± 3.4	12.5 ± 5.1	10.1 ± 6.4
Myocardial vascular resistance (units)	1.4 ± 0.2	1.8 ± 0.3	2.0 ± 0.1	1.3 ± 0.1*	1.5 ± 0.1	0.9 ± 0.1*

*$P < 0.05$

Table 2 Analysis of the number of ventricular ectopic beats at various times after acute coronary ligation in control (untreated) dogs and in dogs pretreated with either MG 8926 or prenylamine

Group	*0–5 min*	*6–10 min*	*11–15 min*	*16–20 min*	*21–25 min*	*26–30 min*	*Total*	*Fibrillation*
Control	120±42	150±60	94±67	286±92	96±38	52±21	904±260	4/12
MG 8926 5 mg/kg	69±34	55±29*	84±59	118±82*	2± 2*	2± 1*	329±150*	0/6
Prenylamine 5 mg/kg	131±32	52±47*	42±31	43±23*	85±54	20±19	372±196*	1/6

Values are means ± s.e. All dogs breathed 100% O_2.
* Significantly different from control; $P < 0.05$.

Table 3 The haemodynamic effects of acute coronary artery ligation in control dogs and in dogs pretreated with either MG 8926 or prenylamine

	Controls (n=8)		*MG 8926 (n=6)*		*Prenylamine (n=6)*	
	Pre	*30 min post*	*Pre*	*30 min post*	*Pre*	*30 min post*
Heart rate (beats/min)	176± 5	182± 6	174± 3	183± 9	160± 10	176± 7
Mean blood pressure (mmHg)	130± 4	124± 6	152± 9	136± 10	150± 13	137± 13
LV d*P*/d*t max* (mmHg/s)	2910±280	2600±190	3350±340	2716±490	2240±192	2100±201
LVEDP (mmHg)	6± 1	11± 2*	8± 1	10± 2*	7± 2	14± 2*
Cardiac output (l/min)	3.2±0.4	2.2±0.2*	3.7±0.3	2.7±0.2*	4.1±0.1	3.2±0.3*
External cardiac work (kgm/min)	5.8±0.8	3.4±0.5*	4.7±0.5	3.2±0.1*	5.2±0.3	3.3±0.4*

Values are mean ± s.e.
* $P < 0.05$.

Table 4 Changes in coronary sinus and coronary vein, P_{CO_2} and pH, and in myocardial O_2 extraction, before and 30 min after, coronary artery ligation in control dogs and in dogs treated with either MG 8926 or prenylamine

	Controls		*MG 8926*		*Prenylamine*	
	Pre	*Post*	*Pre*	*Post*	*Pre*	*Post*
Coronary sinus						
O_2 extraction (%)	52 ± 3	54 ± 4	37 ± 6	45 ± 7	41 ± 7	48 ± 9
P_{CO_2} (mmHg)	46 ± 2	48 ± 2	51 ± 4	50 ± 4	50 ± 2	51 ± 2
pH (units)	7.350 ± 0.016	7.345 ± 0.020	7.321 ± 0.010	7.326 ± 0.013	7.344 ± 0.032	7.341 ± 0.033
Coronary vein						
O_2 extraction (%)	54 ± 3	69 ± 3*	39 ± 5	48 ± 8*	47 ± 8	61 ± 12*
P_{CO_2} (mmHg)	45 ± 2	60 ± 3*	49 ± 4	54 ± 3*	47 ± 8	61 ± 5*
pH (units)	7.347 ± 0.014	7.265 ± 0.023*	7.325 ± 0.017	7.313 ± 0.009	7.350 ± 0.034	7.310 ± 0.043*

Values are mean ± s.e.; $n = 6$.
*$P < 0.05$.

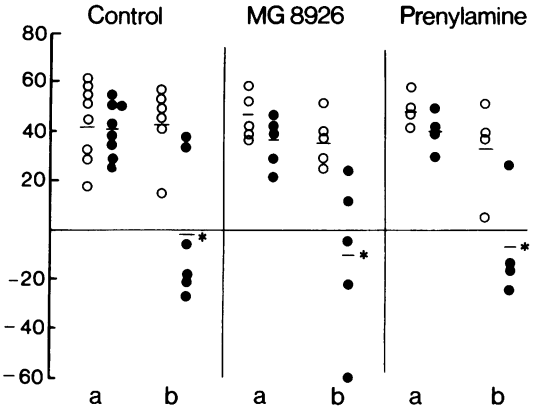


Figure 1 The effects of coronary artery ligation on lactate extraction coefficients (A–V%) calculated using samples of blood from the coronary sinus (draining both areas of heart; (O) and coronary vein (draining the ischaemic zone; (●), in control dogs and in dogs pretreated with either MG 8926 or prenylamine (5.0 mg/kg). Negative values for A–V indicate lactate production. Samples were taken immediately before (a) and 30 min after coronary artery ligation (b). Note that lactate production was evident in blood draining from the ischaemic myocardium in all three groups of animals.

tachycardia. There were no dysrhythmias in any dog after 30 minutes. The reduced incidence of dysrhythmias in dogs pretreated with MG 8926 or prenylamine was remarkable since the area of the left ventricular wall served by the ligated artery was significantly greater (33 ± 2 and 32 ± 2% respectively) than that in control dogs (21 ± 2%).

Haemodynamic and metabolic consequences of acute coronary artery ligation in dogs pretreated with MG 8926 or prenylamine

The haemodynamic consequences of acute coronary artery ligation in this experimental model have been described previously (Marshall *et al.*, 1974). The haemodynamic effects of ligation in this series of animals, given MG 8926 or prenylamine, were essentially similar (Table 3) and included a decrease in cardiac output and external cardiac work. These changes are probably secondary to a decreased cardiac contractility, as manifested by transient decreases in left ventricular d*P*/d*t* *max* with more sustained increases in LVEDP (Table 3).

When a major branch of the left anterior descending coronary artery is ligated, metabolic changes occur in the venous blood draining the acutely ischaemic region which do not occur in blood draining the remaining, essentially normal areas; these

changes in untreated dogs have been described in detail by Ledingham *et al.* (1974) and include reductions in coronary venous P_{O_2}, O_2 content, pH and lactate extraction and an increase in P_{CO_2}. Changes in these parameters induced by coronary artery ligation in dogs pretreated with either MG 8926 or prenylamine (5.0 mg/kg) are shown in Table 4, and the effects on lactate extraction illustrated in Figure 1. Clearly, neither drug significantly modified these metabolic consequences of coronary artery ligation, although the changes in coronary vein O_2 content, P_{CO_2} and pH were rather less than those seen in the control animals (Table 4).

Another metabolic change induced by coronary ligation is loss of potassium from ischaemic cardiac cells (Thomas, Shulman & Opie, 1970; Marshall & Parratt, 1975). In a series of untreated dogs, coronary vein potassium rose significantly from 3.5 ± 0.3 (pre-ligation) to 4.4 ± 0.2 mEq/litre, 30 min after ligation, although arterial and coronary sinus levels remained unchanged. In the dogs pretreated with MG 8926 the increase in coronary vein potassium (3.4 ± 0.2 to 3.9 ± 0.3 mEq/litre respectively) was significantly less than in the control animals. Similar results were obtained in the prenylamine-treated animals; coronary vein potassium rising from 3.0 ± 0.2 to 3.4 ± 0.2 mEq/litre ($P < 0.05$).

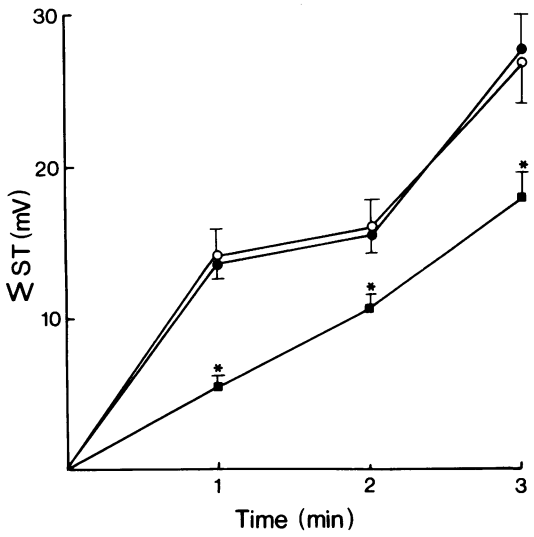


Figure 2 Total ST-segment elevation in nine epicardial electrocardiographic leads at varying times after the occlusion of the anterior descending branch of the left coronary artery, 40 min before (●), 10 min before (○), and 10 min after (■) the intravenous administration of MG 8926 (5.0 mg/kg). Each point is the mean of five observations; vertical lines show s.e. mean. *$P < 0.05$.

The haemodynamic effects of MG 8926 when administered intravenously, 1 to 2 h after acute coronary artery occlusion

When administered 1 to 2 h after coronary artery ligation MG 8926 (5.0 mg/kg administered to 6 dogs) caused essentially similar effects to those seen before ligation. The drug caused an immediate, but transient, fall in blood pressure (mean diastolic change 63 ± 4 mmHg) and increased cardiac output (mean 34%) and both coronary sinus P_{O_2} (29 ± 3 to 56 ± 7 mmHg; $P < 0.05$) and coronary vein P_{O_2} (30 ± 1 to 49 ± 5

Table 5 Haemodynamic changes induced by the intravenous injection of MG 8926 (5.0 mg/kg), 1 to 2 h after acute coronary artery ligation

	Pre-drug	*10 min post-drug*
Heart rate (beats/min)	170 ± 10	145 ± 8*
Systolic arterial blood pressure (mmHg)	164 ± 9	167 ± 6
Diastolic arterial blood pressure (mmHg)	119 ± 6	123 ± 5
Systolic pulmonary artery pressure (mmHg)	17 ± 1	19 ± 1
Diastolic pulmonary artery pressure (mmHg)	8 ± 1	9 ± 1
LV dP/dt max (mmHg/s)	2140 ± 261	1870 ± 245*
LVEDP (mmHg)	7 ± 2	12 ± 4*
Cardiac output (l/min)	2.4 ± 0.3	2.6 ± 0.6
External cardiac work (kgm/min)	2.65 ± 0.21	3.40 ± 0.44
Myocardial O_2 extraction (normal zone %)	54 ± 6	50 ± 7
Myocardial O_2 extraction (ischaemic zone – %)	54 ± 4	52 ± 4

Values are mean ± s.e.; $n = 6$.
*$P < 0.05$.

Table 6 Comparison of the effects of saline, MG 8926 and prenylamine on ouabain-induced cardiac arrhythmias in the anaesthetized guinea-pig; the mean amounts of ouabain (μg/kg) required to produce the stated effects are given (±s.e.)

	Unequal intervals	*Extrasystoles*	*Ventricular tachycardia*	*Ventricular fibrillation*	*Cardiac arrest*
Saline (control) $n=7$	71 ± 4	92 ± 6	120 ± 11	7/7 143 ± 11	165 ± 14
MG 8926 1.0 mg/kg $n=6$	90 ± 11	113 ± 15	153 ± 6*	3/6 208 ± 63*	250 ± 38*
Prenylamine 1.0 mg/kg $n=6$	63 ± 7	94 ± 10	130 ± 16	3/6 158 ± 35	169 ± 24

*$P<0.05$ compared with saline controls.

mmHg; $P<0.05$). Although all these parameters had returned to control levels 10 min after injection, there were at this time significant decreases in heart rate and dP/dt *max* and increases in LVEDP (Table 5).

The effect of intravenously administered MG 8926 on ST-segment changes of epicardial electrocardiograms

The observation, in dogs treated with MG 8926, that the metabolic changes following coronary artery ligation were less marked than those seen in control animals prompted us to examine the effects of the drug on the extent and severity of myocardial ischaemia as assessed by epicardial electrocardiograms. The effects of prophylactically administered MG 8926 (5.0 mg/kg) on ST-segment elevation after acute occlusion of the LAD are shown in Figure 2. It is clear that, at this dose, MG 8926 decreases ST-segment elevation at all times after occlusion. In addition, the number of sites showing more than 2 mV ST-segment elevation, 3 min after occlusion, was significantly reduced (from 4.5 ± 0.6 to 2.5 ± 0.6; $P<0.05$).

The effects of MG 8926 (5 mg/kg; five experiments) were also examined on ST-segment elevation in dogs in which the LAD had been ligated 1 to 2 h previously. The mean ST-segment elevation from all the seven sites varied in individual dogs (from 1.6 ± 0.9 to 5.1 ± 1.9 mV) but remained constant in each preparation over the 30 min preceding the injection of MG 8926. Particular attention was paid to the effect of MG 8926 on the border areas between normal and clearly ischaemic regions (usually leads 2, 3 and 4). In six such border sites, MG 8926 reduced mean ST-segment elevation from 4.3 ± 0.3 to 2.4 ± 0.6 mV ($P<0.05$). This decrease in ST-segment elevation was still evident 20–30 min after administration of MG 8926. The results from one of these experiments are illustrated in Figure 3.

The effects of MG 8926 and prenylamine on ouabain-induced dysrhythmias in the anaesthetized guinea-pig

The concentrations of ouabain required to produce (a) the first signs of rhythm abnormality (unequal R-R intervals), (b) ventricular extrasystoles, (c) sustained ventricular tachycardia, (d) ventricular fibrillation and (e) cardiac arrest in animals treated with either saline, MG 8926 (1 mg/kg) or prenylamine (1 mg/kg) are shown in Table 6. Injection of saline (<0.5 ml) had no significant effect on heart rate (320 ± 10 to 324 ± 9 beats/min, 30 s after injection). All control animals (saline-treated) developed ventricular fibrillation compared with only half of those treated with either MG 8926 or prenylamine. In addition MG 8926 (1 mg/kg) significantly increased the amount of ouabain necessary to induce ventricular tachycardia, ventricular fibrillation and cardiac arrest (Table 6). This dose of MG 8926 caused a significant decrease in

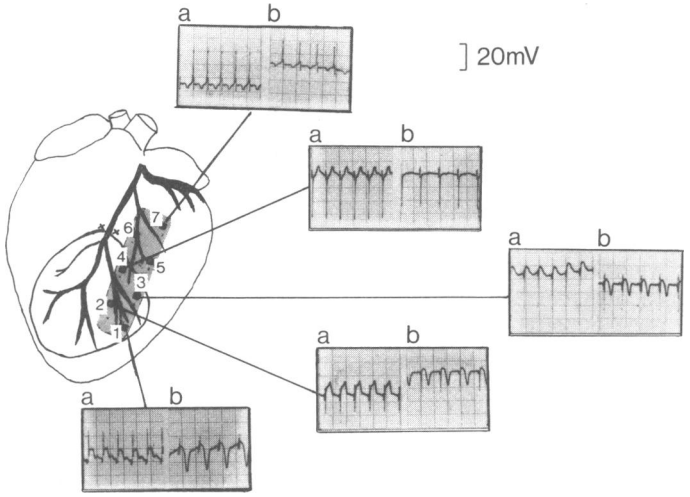


Figure 3 Schematic diagram showing the siting of the epicardial leads in relation to the ischaemic portion of left ventricle produced by ligation of the anterior descending branch of the left coronary artery (X--X). Also shown are actual pairs of tracings from one dog (from leads 1, 2, 3, 4 & 7) taken immediately before (a) and 20 min after (b) injection of MG 8926 (5 mg/kg). Note that ST-segment elevation (indicative of ischaemia) is only present in leads 1, 2, 3 and 4 and that MG 8926 reduced the amount of ST-elevation in these leads.

heart rate from 353 ± 9 to 317 ± 9 beats/minute. In contrast, in animals treated with prenylamine (1 mg/kg intravenously), the amounts of ouabain needed to cause each type of dysrhythmia did not differ from those in the control animals. Prenylamine at this dose did not affect heart rate (312 ± 16 beats/min before and 295 ± 16 beats/min 5 min after injection). An attempt was made to investigate the effects of higher doses but both MG 8926 and prenylamine at an intravenous dose of 5 mg/kg caused such marked changes in the electrocardiogram that no investigation into possible antiarrhythmic effects at this dose level was possible. These toxic effects of both drugs were manifested first as severe bradycardia with T-wave reversal followed by conduction block and arrest.

The effects of MG 8926 and prenylamine on isolated electrically driven left atria of guinea-pigs

Both MG 8926 (2.7–27 μM) and prenylamine (2.4–24 μM) caused dose-dependent decreases in developed tension of electrically driven guinea-pig atrial muscle. However at the lower concentrations this negative inotropic effect of both drugs was preceded by a transient increase in developed tension; dysrhythmias often occurred. A higher concentration of both drugs (>200 μM) caused sustained contracture.

Both MG 8926 and prenylamine significantly decreased the maximum driving frequency of atrial muscle. The magnitude of this effect was critically dependent on the time the drug was in contact with the tissue (Figure 4).

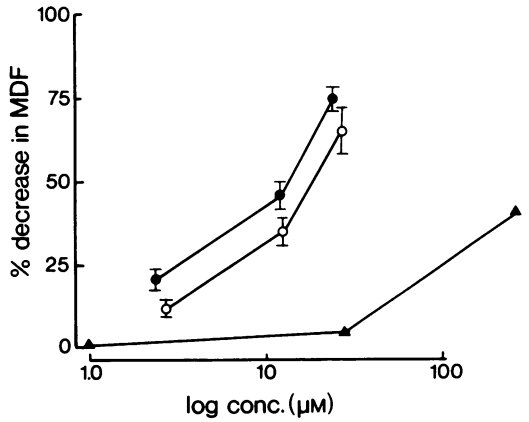


Figure 4 The effects of MG 8926 (O) and prenylamine (●) on maximal driving frequency (MDF) of electrically driven guinea-pig atrial muscle. The ordinate scale represents percentage decrease in MDF and the abscissa scale is log concentration (μM). The contact time was 20 min except for (▲) which indicates effects of MG 8926 with contact time of 10 minutes. Note that the effect produced by MG 8926 is crucially dependent on this contact time.

Discussion

Although previous experimental studies have demonstrated that prenylamine is capable of suppressing dysrhythmias induced either by hypothermia (Nielsen & Owman, 1967), or by the application of various chemicals (Lindner, 1963; Szekeres & Papp, 1971), there is no information available on the efficacy of prenylamine (or compounds, like MG 8926, of similar structure) in suppressing the early dysrhythmias that occur in the acute phase of experimental myocardial infarction. This information is of some importance since it is known that 61% of electrical deaths arising from myocardial infarction among patients younger than 65 occur within one hour of onset (Gordon & Kannel, 1971). The results obtained in this study have shown that both MG 8926 and prenylamine, when given intravenously in a dose of 5 mg/kg 20 min before ligation, protect anaesthetized greyhounds from the initial (30 min) burst of ventricular dysrhythmias which, in control dogs, are frequently fatal. For example, in this study, 4 out of 12 untreated dogs fibrillated within this crucial half hour period. None of the animals given MG 8926 and only one given prenylamine showed fibrillation during this period.

The protective effects of MG 8926 and prenylamine against ouabain-induced arrhythmias in anaesthetized guinea-pigs were much more equivocal. At a dose of 1 mg/kg only MG 8926 significantly increased the amount of ouabain required to cause ventricular tachycardia, ventricular fibrillation and cardiac arrest although both compounds reduced the incidence of fibrillation induced by the glycoside. The reasons for these equivocal findings are not immediately apparent but of possible relevance are the findings of Lindner (1963) who showed, in anaesthetized guinea-pigs, that although prenylamine (2–13 mg/kg, intravenously) protected against the arrhythmias induced by digoxin, no protection was afforded when ouabain was used to induce arrhythmias.

In theory, there are several possible explanations for the anti-arrhythmic properties shown by prenylamine and related compounds. First, prenylamine is known to cause a partial depletion of catecholamine stores in cardiac adrenergic nerves (Schone & Lindner, 1962). This effectively reduces cardiac sympathetic drive which has been implicated in the genesis of early arrhythmias induced either by coronary ligation (Harris, Estandia & Tillotson, 1951; Harris & Bisteni, 1955; Shanks & Dunlop, 1967) or by infusion of cardiac glycosides (Dohadwalla *et al.*, 1969). Secondly, prenylamine causes direct effects on various phases of the cardiac action potential. Thus it has been shown that prenylamine slows the maximum rate of rise (phase 0), increases the threshold potential, increases refractory period and depresses pacemaker activity (Lindner, 1963). These direct effects of prenylamine are now thought to be due to depression of the inward sodium and/or calcium currents involved in cell depolarization processes (Haas, Kern, Benninger & Einwachter, 1975). It would seem probable, but has not yet been established, that MG 8926 possesses at least some of these properties of prenylamine. Certainly in this study, MG 8926 increased the effective refractory period of electrically-driven guinea-pig atrial muscle, in concentrations similar to those needed with prenylamine.

At dose levels which were clearly antidysrhythmic, both MG 8926 and prenylamine caused only transient haemodynamic changes. The major immediate effects common to both drugs were decreases in blood pressure and increases in cardiac output and coronary blood flow. Since O_2 extraction was considerably reduced, neither drug changed myocardial O_2 consumption. The vasodilatation induced by MG 8926 and prenylamine may be due, like that seen with verapamil, to inhibition of the depolarization-induced calcium influx in the smooth muscle of the peripheral and the coronary arteries (Peiper, Griebel & Wende, 1971). The transient but considerable increases in cardiac output caused by both drugs may also be due to an effect on cardiac calcium flux.

It has been demonstrated in anaesthetized cats, and rat isolated perfused hearts, that prenylamine is capable of releasing substantial amounts of noradrenaline (Grobecker, Palm & Holtz, 1968). In this present investigation, further circumstantial evidence that prenylamine causes noradrenaline release is available from the fact that, immediately on injection, it increased heart rate and myocardial contractility (as measured by dP/dt *max*) and evoked marked ventricular ectopic activity. Interestingly, MG 8926 did not cause positive chronotropic or inotropic effects *in vivo*, nor did it induce ectopic activity.

On guinea-pig isolated atrial muscle, both compounds (2–30 μM) decreased developed tension, in a dose-dependent manner. This was usually preceded by a transient positive inotropic effect. These results confirm previous findings with prenylamine (Fleckenstein, Kammermeier, Döring & Freund, 1967; Lindner, 1969). The view has recently been presented that this inotropic effect of prenylamine may be due to an inhibition of active calcium transport within the cell, leading to transient increases in available calcium (Haas *et al.*, 1975).

It has been shown that, by means of epicardial ECG mapping of the ischaemic area of cardiac muscle, that it is possible to evaluate the extent and severity of damage caused by coronary artery ligation (Maroko, Kjekshus, Sobel, Watanabe, Covell, Ross & Braunwald, 1971; Wendt, Canavan & Michalak, 1974). With this technique it has recently been demonstrated that verapamil, a calcium antagonist drug, is capable of reducing both the extent and severity of ischaemia induced by ligation of a

coronary artery (Smith, Singh, Nisbet & Norris, 1975; Wende, Bleifeld, Meyer & Stühlen, 1975). In the present investigation there was some evidence that MG 8926 (administered either before or after occlusion) was capable of favourably influencing the balance between myocardial O_2 supply and demand (as assessed by epicardial ST-segment changes) especially in border areas surrounding the developing infarct. The mechanism behind this reduction in ischaemia seen after MG 8926 may involve both bradycardia and a reduction in the resistance to blood flow in the ischaemic zone. It has certainly been established that a decrease in heart rate is important for the beneficial effects of β-adrenoceptor antagonists in myocardial ischaemia (Gross & Winbury, 1973; Marshall & Parratt, 1976) and that propranolol decreases the degree of ischaemia-induced ST-segment elevation largely by slowing heart rate (Wendt *et al.*, 1974). In this study it was observed that MG 8926 only reduced heart rate when administered after coronary artery occlusion, a fact which may be related to the effects of the drug on the increased sympatho-adrenal outflow produced by myocardial ischaemia (Staszewska-Barczak & Ceremuzynski, 1968).

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