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THE CARDIOVASCULAR RESPONSE TO DIMAPRIT, A SELECTIVE HISTAMINE H_2-RECEPTOR AGONIST

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1 The cardiovascular responses to dimaprit (S-(3-dimethylaminopropyl) isothiourea), a selective histamine H_2-receptor agonist have been studied in anaesthetized cats, dogs, rats and rabbits.

2 Dimaprit lowered systemic arterial blood pressure in all species whether given by intravenous injection or by continuous infusion. Intra-arterial injections or infusions caused vasodilatation in the femoral vascular bed.

3 In the cat, continuous intravenous infusions of dimaprit lowered blood pressure without any significant change in heart rate or cardiac output. The fall in blood pressure was thus due to a decrease in peripheral vascular resistance.

4 Dimaprit, given intravenously, increased coronary and gastric blood flows and there were associated marked reductions in vascular resistance. Small reductions in vascular resistance occurred in skeletal muscle, in the intestine and the kidneys.

5 The histamine H_2-receptor antagonists, metiamide and cimetidine, antagonized the depressor and vasodilator responses to dimaprit.

Introduction

The cardiovascular response to histamine has been shown to involve both histamine H_1- and H_2-receptors (e.g. Black, Owen & Parsons, 1975; Tucker, Weir, Reeves & Grover, 1975; Powell & Brody, 1976). The identification of histamine receptors in the cardiovascular system, and elsewhere, has been based predominantly on the use of selective histamine receptor antagonists and confirmed with relatively selective receptor agonists (e.g. Owen, 1975; Powell & Brody, 1976.

Until recently, the most selective histamine H_2-receptor agonist described was 4-methylhistamine (Black, Duncan, Durant, Ganellin & Parsons, 1972) and, although this compound shows marked selectivity for H_2-receptors some residual H_1-receptor activity remains (Durant, Ganellin & Parsons, 1975) and the depressor responses to large doses are due in part to interaction with histamine H_1-receptors (Owen, 1975).

A more selective histamine H_2-receptor agonist, dimaprit, S-(3-dimethylaminopropyl) isothiourea, has recently been described (Parsons, Owen, Durant & Ganellin, 1977). Dimaprit increases the rate of beating of isolated right atria of guinea-pigs, stimulates gastric acid secretion in cats, rats and dogs and elicits depressor and vasodilator responses in cats (Parsons *et al.*, 1977). These responses to dimaprit are due to interaction with H_2-receptors; responses to dimaprit independent of histamine H_2-receptors have not been observed. This paper describes some cardiovascular effects of dimaprit in a number of species.

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Methods

Cats

The effects of dimaprit on blood pressure, heart rate and femoral vascular resistance were determined in cats anaesthetized with sodium pentobarbitone (60 mg/kg intraperitoneally). The trachea was cannulated. Blood pressure was measured from the right femoral artery, with a Statham P23A blood pressure transducer, and monitored on a Devices recorder. Heart rate was measured from the blood pressure pulse. Drugs were administered via cannulae in the right femoral vein or right brachial vein. Dose-response curves were constructed for dimaprit by intravenous injection of increasing doses at intervals of 5 min or by continuous intravenous infusion at 0.2 ml/minute.

The vasodilator effects of dimaprit were determined in the acutely denervated left hind-limb. Systemic blood pressure was measured from a cannula in the right common carotid artery. The left hind-limb was acutely denervated by severing the sciatic nerve bundle in the popliteal cavity. The cat was given heparin 100 iu/kg. The right femoral artery was cannulated and blood pumped through silicone rubber tubing by a Watson-Marlow flow inducer at constant pulsatile flow into the left femoral artery. A small segment of thick rubber tubing was inserted into the external perfusion circuit before the pump for injection of drugs. The perfusion pressure was measured by a blood pressure transducer from a side arm in the perfusion circuit between the pump and the perfused hind-limb. At the start of the experiment the rate of flow was adjusted so that the perfusion pressure was approximately equal to systemic blood pressure and was kept constant at this rate for the duration of the experiment. Dimaprit was administered by intra-arterial injection into the external perfusion circuit before the pump in a volume of 10–20 µl or by continuous intra-arterial infusions at 0.06 ml/minute.

The H_2-receptor agonist activity of dimaprit relative to histamine in causing depressor and vasodilator responses was measured in cats treated with mepyramine, 2.5×10^{-5} mol/kg, to abolish the H_1-receptor responses to histamine.

The effects of infusions of dimaprit on blood pressure, heart rate, cardiac output, stroke volume, total peripheral resistance and regional blood flow were determined in 6 cats anaesthetized by an intraperitoneal injection of urethane, 700 mg/kg, and chloralose, 60 mg/kg. The trachea was cannulated. Blood pressure was measured from the right brachial artery. Heart rate was measured from the blood pressure trace. Cardiac output and regional blood flow were measured using radioactive microspheres (25 µm diameter) by the method described by Johnston & Owen (1977). A catheter was placed in the left ventricle of the heart via the right carotid artery to allow injection of microspheres into the heart. A second catheter was tied into the right femoral artery for withdrawal of blood at a known rate, 5 ml/min, during the injection of microspheres.

Microspheres suspended in 0.5 ml of 0.9% w/v NaCl solution (saline) and labelled with one of two different nucleides were injected, approximately 100,000 microspheres each time. Initially, cardiac output and tissue blood flows were measured under control conditions using microspheres labelled with ^{46}Sc. A second determination of cardiac output and tissue blood flows was made, 30 min after the start of infusions of dimaprit, 5×10^{-7} mol kg^{-1} min^{-1}, with the infusion still running, using microspheres labelled with ^{85}Sr. On completion of the experiments the animals were killed by an overdose of sodium pentobarbitone and the organs of interest were dissected free of surrounding tissue, weighed and transferred to vials to permit measurement of tissue radioactivity in a Nuclear Enterprise 8312 Detector. The channels on the detector were set to provide optimal differential counting conditions for both nucleides. The lungs were counted for radioactivity. The number of microspheres in the lungs did not exceed 5% of the injected total, indicating that very few of the microspheres were not trapped in capillary beds downstream from the site of injection. The even distribution of microspheres was indicated by the close correlation between blood flow to both kidneys. (See Table 1). The microspheres were purchased from the 3M Company.

Dogs

Experiments were carried out in Beagle dogs anaesthetized with intravenous sodium pentobarbitone, 30 mg/kg. Supplementary doses of sodium pentobarbitone were given as required. The dogs were intubated. Blood pressure was measured from the right femoral artery and drugs given via the left femoral vein and the right brachial vein.

Rats

Rats of either sex, 200–250 g, were anaesthetized by an intraperitoneal injection of allobarbitone, 100 mg/kg, plus urethane 400 mg/kg. The trachea was cannulated. Blood pressure was recorded from the right common carotid artery and drugs were administered via cannulae in either femoral vein.

Rabbits

Rabbits of either sex were anaesthetized by intraperitoneal injection of a mixture of urethane, 700 mg/kg plus sodium pentobarbitone, 40 mg/kg. The trachea was cannulated. Blood pressure was measured from one femoral artery and drugs given via the opposite femoral vein.

Drugs

Dimaprit, metiamide, cimetidine, diphenylpyraline hydrochloride, chlorpheniramine maleate and mepyramine maleate were used. Solutions of metiamide and cimetidine were prepared by dissolving the base in a small quantity of 0.1 N HCl, neutralizing by addition of 0.1 N NaOH and made up to volume with saline. The other compounds were prepared in saline.

Results

Intravenous administration

Dimaprit decreased blood pressure in cats, dogs, rats and rabbits. The quantitative nature of this response has been studied in cats.

Intravenous injections of dimaprit to cats caused dose-dependent falls in blood pressure over the dose-range 1×10^{-8} to 1×10^{-6}6 mol/kg (Figure 1). This hypotension was associated with a large increase in pulse pressure and usually persisted longer than the hypotension induced by histamine. Unlike the depressor responses to histamine, which are usually followed by a secondary pressor response, dimaprit did not cause any secondary increase in blood pressure after the initial depressor response (Figure 1). The secondary pressor responses to histamine were usually associated with increases in heart rate; dimaprit did not cause any consistent changes in heart rate.

The depressor responses to dimaprit were unaltered by the administration of the histamine H_1-receptor antagonists, mepyramine, up to 2.5×10^{-5} mol/kg, chlorpheniramine, up to 3.6×10^{-5} mol/kg or diphenylpyraline, up to 3.1×10^{-5} mol/kg. Histamine H_2-receptor blockade with either metiamide or cimetidine caused dose-dependent parallel displacement of the dimaprit dose-response curves to the right (Figure 2). Infusion of metiamide, 4×10^{-7} mol kg^{-1} min^{-1}, caused displacement of the dimaprit dose-response curve with a dose-ratio of 5.7 (3.0–9.8, 95% confidence limits); cimetidine, 4×10^{-7} mol $kg^{-1}min^{-1}$, caused displacement of the dimaprit curve with a dose-ratio of 7.9 (3.4–18.5).

Increasing the infusion rate of both metiamide and cimetidine to 2×10^{-6} mol kg^{-1} min^{-1} increased the dose-ratio to 55.7 (32.3–96.1) for metiamide and to 119.0 (51.1–278) for cimetidine. Even after the administration of either of the H_2-receptor antagonists, when large doses of dimaprit were needed to elicit depressor responses, no further displacement of the dimaprit dose-response curve occurred after histamine H_1-receptor blockade. Relative to histamine, dimaprit has 18.2% (9.9–33.6) the activity to cause depressor responses.

In cats, infusions of dimaprit caused sustained falls in blood pressure. The threshold infusion rate was approximately 1×10^{-7} mol kg^{-1} min^{-1} when diastolic pressure fell, usually with little or no change in systolic pressure. Larger doses of dimaprit, up to 1×10^{-6} mol kg^{-1} min^{-1} reduced both systolic and diastolic

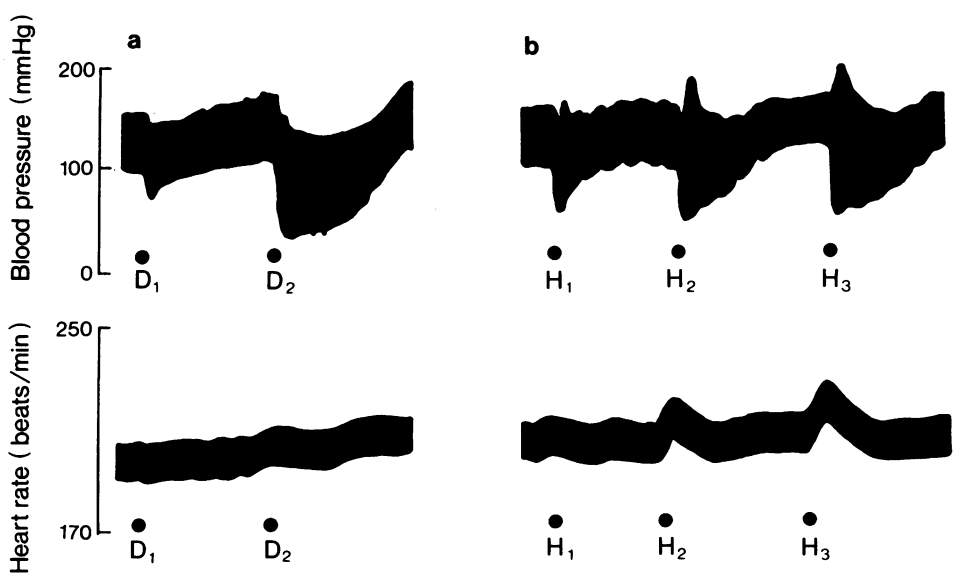

Figure 1 Blood pressure and heart rate responses in an anaesthetized cat. The left hand panels show reductions in blood pressure after intravenous injections of dimaprit, 1×10^{-7} mol/kg at D_1 and 1×10^{-6} mol/kg at D_2. These doses of dimaprit had no effect on heart rate. The right hand panels show comparable falls in blood pressure (and increases in heart rate) after injection of histamine, 1×10^{-9} mol/kg at H_1, 1×10^{-8} mol/kg at H_2 and 1×10^{-7} mol/kg at H_3. Unlike histamine, dimaprit does not cause any secondary increase in systolic blood pressure.

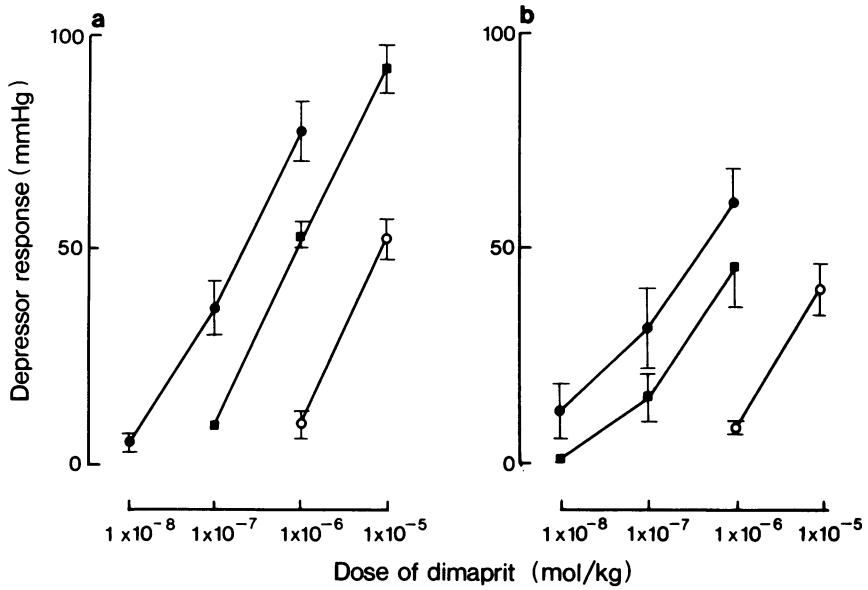

Figure 2 Blood pressure responses to dimaprit in anaesthetized cats. (a) Shows the effect of metiamide and (b) the effect of cimetidine on the dimaprit dose-response curve. Responses in untreated cats (●), during treatment with metiamide or cimetidine, 4×10^{-7} mol kg^{-1} min^{-1} (■), and during treatment with metiamide or cimetidine 2×10^{-6} mol kg^{-1} min^{-1} (○). Each point is mean from 4 cats. Vertical lines show s.e. means.

pressures although the decrease in diastolic pressure always exceeded that of the systolic pressure and pulse pressure was thus increased. Administration of either metiamide or cimetidine during the continuous intravenous infusion of dimaprit (5×10^{-7} mol kg^{-1} min^{-1}) caused a dose-dependent reversal of the depressor response to dimaprit. Both antagonists were roughly equipotent. Complete antagonism of the response to dimaprit occurred after about 1×10^{-5} mol/kg of either antagonist. The dose required for 50% blockade was about 1×10^{-6} mol/kg.

In rats, intravenous injections of dimaprit, 1×10^{-6} mol/kg and 1×10^{-5} mol/kg caused dose-dependent reductions in blood pressure. The responses to both these doses were abolished during infusions of metiamide, 2×10^{-6} mol kg^{-1} min^{-1} although increasing the dose of dimaprit to 1×10^{-4} mol/kg restored depressor responses. In rats, intravenous infusions of dimaprit in excess of 1×10^{-7} mol kg^{-1} min^{-1} caused sustained depressor responses.

In dogs, intravenous infusions of dimaprit, 1×10^{-7} mol kg^{-1} min^{-1} caused a small fall in diastolic blood pressure without any change in systolic pressure. Increasing the dose to 1×10^{-6} mol kg^{-1} min^{-1} caused a large fall in diastolic pressure with a smaller fall in systolic pressure. Administration of cimetidine, 1×10^{-5} mol/kg during continuous infusion of dimaprit abolished the response to dimaprit.

In rabbits, unlike other species studied, histamine causes a biphasic change in blood pressure characterized by an initial increase in pressure, due to histamine H_1-receptor interaction followed by a histamine H_2-receptor depressor response (Parsons & Owen, 1973). Dimaprit, 1×10^{-6} mol/kg, caused a fall in blood pressure with no initial pressor phase. Administration of metiamide 2×10^{-6} mol kg^{-1} min^{-1} abolished this response to dimaprit.

Intravenous infusions of dimaprit, 5×10^{-7} mol kg^{-1} min^{-1} in cats caused a significant fall in blood pressure, mean blood pressure fell from 129 ± 8 mmHg before the infusion to 77 ± 6 mmHg during the infusion ($n = 6$). The fall in blood pressure during the infusion of dimaprit was due totally to a fall in total peripheral resistance; resistance was 0.65 ± 0.04 mmHg ml^{-1} min^{-1} before dimaprit and 0.38 ± 0.03 mmHg ml^{-1} min^{-1} during the infusion. Dimaprit did not significantly change heart rate (240 ± 16 beats/min to 242 ± 14 beats/min), cardiac output (470 ± 42 ml/min to 476 ± 38 ml/min), or stroke volume (1.98 ± 0.17 ml to 1.8 ± 0.25 ml).

Significant increases in blood flow occurred in the heart and stomach; there were no significant changes in blood flow to the intestine, to the muscles of the calf or to skin sample. Significant reductions in blood flow occurred in the brain, liver, kidneys and adrenal glands. These changes in regional blood flow occurred during systemic hypotension; calculation of vascular resistance indicated marked reductions in the

Table 1 The effect of infusion of dimaprit, 5×10^{-7} mol kg^{-1} min^{-1} on regional blood flow and vascular resistance

Region	*Blood flow (ml/min)*		*Vascular resistance (mmHg ml^{-1} min)*	
	Before infusion	*During infusion*	*Before infusion*	*During infusion*
Brain	20.11 ± 0.88	10.5 ± 0.58*	6.47 ± 0.51	7.37 ± 0.55
Right kidney	33.42 ± 4.40	26.48 ± 3.38*	4.08 ± 0.46	3.05 ± 0.34*
Left kidney	33.40 ± 3.71	26.07 ± 3.18*	4.05 ± 0.45	3.10 ± 0.35*
Heart	26.57 ± 1.78	57.37 ± 5.05*	4.89 ± 0.23	1.38 ± 0.15*
Stomach	8.45 ± 2.22	34.13 ± 6.87*	24.44 ± 8.74	2.54 ± 0.32*
Small intestine	44.97 ± 5.78	53.32 ± 5.57	3.01 ± 0.28	1.74 ± 0.52*
Large intestine	15.28 ± 1.99	19.27 ± 2.75	9.20 ± 1.50	4.45 ± 0.84*
Liver	97.25 ± 8.37	43.18 ± 7.83*	1.36 ± 0.12	2.05 ± 0.33
Adrenal glands	2.45 ± 0.35	1.48 ± 0.23*	57.28 ± 8.17	55.66 ± 6.51
Calf muscle	3.30 ± 0.57	5.37 ± 1.16	43.49 ± 5.71	17.78 ± 3.67*
Skin (sample only)	4.05 ± 0.71	3.28 ± 1.34	25.58 ± 5.23	35.19 ± 6.58

* Indicates values during dimaprit infusion significantly different from pre-infusion values (paired t test) $P < 0.05$.

stomach, heart, calf muscle, intestine and kidneys; there were no changes in resistance in the brain, liver or skin. The values for regional blood flow and vascular resistance before and during the dimaprit infusions are shown in Table 1.

Intra-arterial administration

Dimaprit caused dose-related dilatation in the acutely denervated femoral vascular bed in cats over the dose-range 1×10^{-9} to 1×10^{-7} mol/kg. Administration of

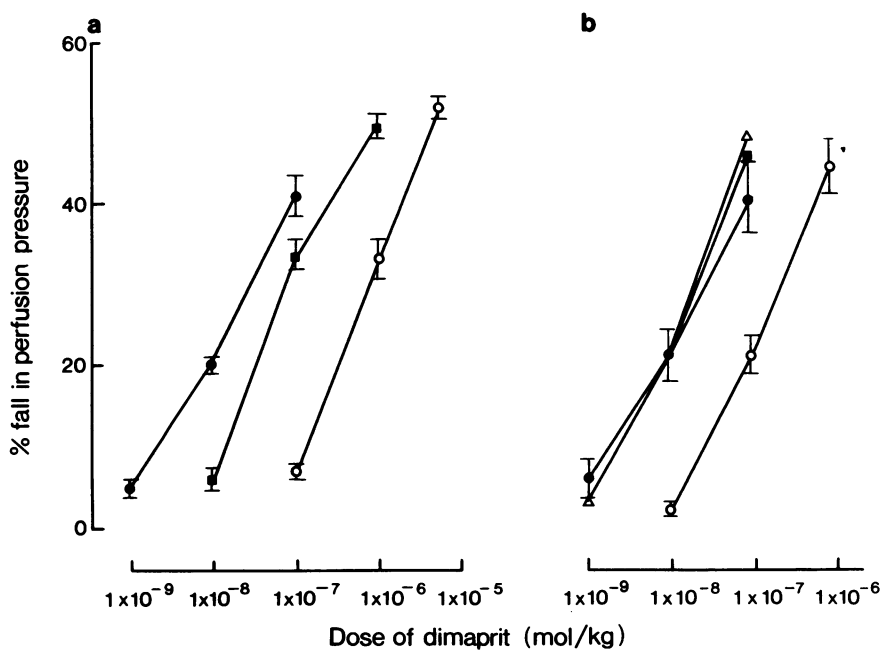

Figure 3 Vasodilatation induced by dimaprit in the femoral vascular bed in anaesthetized cats. (a) Shows displacement of the dimaprit dose-response curve in untreated cats (●) by administration of metiamide, 4×10^{-7} mol kg^{-1} min^{-1} (■), and 2×10^{-6} mol kg^{-1} min^{-1} (○). (b) Shows the failure of mepyramine, 2.5×10^{-6} mol kg (■) or 2.5×10^{-5} mol kg (△) to modify the responses to dimaprit (●). Subsequent administration of metiamide, 4×10^{-7} mol kg^{-1} min^{-1} (○), displaced the dose-response curve to the right.

metiamide caused dose-dependent displacement of the dose-response curve to the right with dose-ratios of 2.74 (1.85–4.05) and 23.2 (15.7–34.4) at 4×10^{-7} mol $kg^{-1} min^{-1}$ and 2×10^{-6} mol $kg^{-1} min^{-1}$ respectively. Subsequent administration of mepyramine 2.5×10^{-6} mol/kg had no further effect on the dimaprit dose-response curve (Figure 3a). Administration of mepyramine alone, up to 2.5×10^{-5} mol/kg, had no effect on the dimaprit dose-response curve (Figure 3b). Dimaprit has 18.6% (16.0–24.0) the vasodilator activity of histamine in the mepyramine-treated cat.

Continuous intra-arterial infusions of dimaprit caused vasodilator responses which persisted throughout the infusion. In 6 cats, an infusion rate of 1×10^{-9} mol $kg^{-1} min^{-1}$ reduced resistance by $8.0 \pm 2.3\%$, 1×10^{-8} mol $kg^{-1} min^{-1}$ reduced resistance by $42.0 \pm 4.9\%$, 1×10^{-7} mol $kg^{-1} min^{-1}$ reduced resistance by $66.0 \pm 3.9\%$ and 1×10^{-6} mol $kg^{-1} min^{-1}$ reduced resistance by $64 \pm 4.9\%$.

Discussion

In the present study cardiovascular responses to dimaprit have been shown to involve only H_2-receptors. The responses could be abolished by either of the H_2-receptor antagonists, metiamide or cimetidine and quantitative assessment of this interaction of metiamide or cimetidine indicated that marked and parallel displacements of the dose-response curves to dimaprit occurred. From the use of dose-ratios, it would appear that there is little difference in potency between metiamide and cimetidine. In addition, the dose of either antagonist required to reverse the depressor response to dimaprit was approximately the same as that required to inhibit either histamine or dimaprit-induced gastric acid secretion, Thus the effective dose for 50% inhibition of the dimaprit depressor response was approximately 1×10^{-6} mol/kg. This value is similar to the ED_{50} for metiamide against dimaprit-induced gastric acid secretion in rats (Parsons *et al.*, 1977).

The potency of dimaprit as an H_2-agonist in the cat, relative to histamine, was similar both for depressor and vasodilator responses and similar to their relative potencies in causing gastric acid secretion in the rat and for inhibiting electrically induced contractions of the rat uterus (Parsons *et al.*, 1977).

Like histamine, dimaprit lowered systemic arterial blood pressure when given intravenously. The response differed from that to histamine in that it was more persistent and was never followed by a secondary rise in blood pressure, an effect first observed by Burn & Dale (1926) and due to an H_1-receptor mediated release of catecholamines from the adrenal medulla (Emmelin & Muren, 1949; Black *et al.*, 1975). The greater persistence of the depressor responses to dimaprit almost certainly reflects the absence of catecholamine release opposing the direct depressor effects, although the relative rates of metabolism of dimaprit and histamine may also be important.

Dimaprit usually did not change heart rate despite causing marked systemic hypotension. This failure to elicit reflex tachycardia is consistent with our experience using other vasodilator compounds such as hydralazine (Fielden, Owen & Taylor, 1974) and may, in part, be due to the effect of anaesthesia (Kirchheim, 1976). Although H_2-receptor agonists have been shown to increase sinus rate in isolated cardiac tissue (Black *et al.*, 1972; Broadley, 1975; Levi, Capurro & Lee, 1975), tachycardia in response to H_2-receptor agonists *in vivo* has not been demonstrated. Tachycardia induced by histamine in anaesthetized cats is due, in part, to release of catecholamines from chromaffin tissue (Owen, unpublished) and this is a histamine H_1-receptor phenomenon (Emmelin & Muren, 1949). Dimaprit would not be expected to release catecholamines from chromaffin tissue.

The pattern of depressor responses after dimaprit administration is consistent with results obtained with histamine in mepyramine-treated animals (Black *et al.*, 1975; Flynn & Owen, 1975; Owen 1975; Johnston & Owen, 1977). The response to H_2-receptor agonists consists of dilatation of resistance vessels leading to a decreased vascular resistance. The major sites of dilatation during systemic administration are the coronary, splanchnic and skeletal muscle vasculature. The changes in blood flow in other vascular beds mainly reflect changes in arterial perfusion pressure more than local vascular responses.

In conclusion, this paper characterizes some effects of dimaprit on the cardiovascular system. Dimaprit is likely to prove more valuable than 4-methylhistamine as a tool for examination of histamine H_2-receptor characteristics, because unlike 4-methylhistamine it has no detectable H_1-receptor agonist activity (Parsons *et al.*, 1977).

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