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Comparison of the cardiovascular effects of meptazinol and naloxone following haemorrhagic shock in rats and cats

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1 The cardiovascular effects of the opioid mixed agonist-antagonist, meptazinol, and the opioid antagonist, naloxone, have been evaluated in conscious rats, anaesthetized rats and anaesthetized cats following the induction of haemorrhagic shock.

2 The mean arterial pressure of conscious rats decreased by 17–29 mmHg following a haemorrhage of 20% of blood volume. Meptazinol (17 mg kg^{-1}, i.m.) administered after haemorrhage evoked a rapid and sustained increase in mean arterial pressure to pre-haemorrhage levels. Naloxone (10 mg kg^{-1}, i.v.) also increased mean arterial pressure to a level significantly higher than post-haemorrhage values.

3 Neither haemorrhage nor subsequent drug treatments evoked significant changes in the heart rates of conscious rats.

4 In anaesthetized rats, 20% haemorrhage evoked decreases in mean arterial pressure, heart rate and cardiac output. Blood flow to the heart, skin, skeletal muscle, kidneys, spleen and liver (arterial) was decreased. Meptazinol and naloxone increased blood pressure and total peripheral resistance, but did not significantly alter heart rate or cardiac output. Hepatic arterial flow decreased further in both drug and vehicle treated groups. In addition meptazinol slightly reduced skeletal muscle flow.

5 In anaesthetized cats 40% haemorrhage decreased mean arterial pressure by 46 ± 3 mmHg. An intravenous infusion of either meptazinol or naloxone (cumulative 2 mg kg^{-1}, i.v.) partially restored blood pressure.

6 In experimental animal models of haemorrhagic shock, meptazinol has a similar cardiovascular profile to naloxone. The established analgesic activity of meptazinol may confer an advantage in some shock states.

Introduction

In hypovolaemic subjects morphine has been reported to produce a further decrease in blood pressure and a severe metabolic acidosis which can be fatal (Chasnow *et al.*, 1964). In contrast, the opioid antagonist naloxone produces an elevation of blood pressure, increased cardiac output and increased survival in various shock states (Holaday & Faden, 1978; Curtis & Lefer, 1980; Reynolds *et al.*, 1980) whilst having no significant cardiovascular effects in normal animals and man.

Meptazinol [*m*-(3-ethyl-l-methyl-hexahydro-lH-azepin-3-yl)] phenol hydrochloride is an opioid mixed agonist-antagonist which possesses good analgesic activity in man and animals without significantly altering cardiovascular variables (Stephens *et al.*, 1978). However, in animals subjected to endotoxic and anaphylactic shock, the drug showed marked pressor activity (Paciorek *et al.*, 1983; 1985). The actions of meptazinol on blood pressure and heart rate have now been compared with those of naloxone in conscious rats and anaesthetized cats subjected to haemorrhagic shock. In addition their effects on haemodynamics and regional blood flow have been evaluated in hypovolaemic anaesthetized rats. Preliminary accounts of part of this study have been previously reported (Chance *et al.*, 1981; Chance & Waterfall, 1982).

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Methods

Haemorrhagic shock in conscious rats

Groups of 5 female Sprague Dawley rats (200–280 g) were prepared under halothane anaesthesia with indwelling left carotid arterial and right jugular venous cannulae. After a 2 h recovery period the rats were placed in perspex tubes and mean arterial pressure (MAP) recorded from the carotid cannula (Statham P23 blood pressure transducer; Grass model 7 polygraph). The pulse pressure signal was used to trigger a tachometer for the measurement of heart rate. The blood volume of each rat was calculated from the value of 62 ml kg^{-1} body weight given by Wang (1959). Aliquots of 5% of the calculated total blood volume were removed over 90 s at 5 min intervals until a total of 20% had been bled from each animal via its carotid cannula. MAP and heart rate were monitored for 20 min following the removal of the last aliquot of blood.

Rats received meptazinol (17 mg kg^{-1}, i.m.), naloxone (1 or 10 mg kg^{-1}, i.v.) or an equivalent volume of 0.9% w/v NaCl (1 ml kg^{-1}). The dose of meptazinol chosen was one which produced 80% non-responders to a noxious stimulus during a predetermined latency in tail flick tests (unpublished observations). The dose of naloxone was that shown by Faden & Holaday (1979) to facilitate rapid recuperation of arterial pressure following haemorrhagic hypovolaemia. MAP and heart rate were monitored for a further 1 h after drug or vehicle administration.

Results were analysed within groups and between groups by analysis of variance. Within groups, post-haemorrhage values were compared with pre-haemorrhage values and post-treatment values with post-haemorrhage values. Comparisons between groups were made using the differences between post-treatment and post-haemorrhage values. In all cases t values were derived when F ratios reached the 5% level of significance.

Haemodynamic effects in anaesthetized rats after haemorrhagic shock

Anaesthesia was induced with halothane in groups of 5 female Sprague Dawley rats (220–270 g) and cannulae implanted in the left femoral vein for drug administration and in the left femoral artery for the withdrawal of reference blood samples. The right carotid artery was cannulated and the cannula was advanced until the tip entered the left ventricle as indicated by a sudden change in the pressure wave form. The cannula was then carefully withdrawn until an arterial pulse re-appeared. MAP and heart rate were monitored continuously throughout the experiment (Bell and Howell blood pressure transducer; Lectromed M2 pen recorder). On completion of the operative procedures, halothane was discontinued and anaesthesia maintained with urethane (9.6%) and chloralose (1.2%) in 0.9% NaCl (7.5 ml kg^{-1}). Rats were allowed to stabilize for 30 min before regional blood flow measurements were made.

One group of rats was used to determine cardiac output and regional blood flows before and after haemorrhage. A well-mixed suspension of ^{57}Co microspheres (9 μm) in 0.9% w/v NaCl to which Tween 80 (0.25%) had been added was injected via the carotid cannula over a period of 30 s. The microsphere injection contained between 20,000 and 40,000 spheres in a volume of 0.2 ml. At the same time, blood was withdrawn from the femoral artery for 60 s (1.3–1.5 ml min^{-1}; Watson Marlow 501 peristaltic pump). Ten minutes later 20% of the blood volume was removed as described above and MAP and heart rate monitored for 20 min. Cardiac output and regional blood flows were then re-assessed by use of ^{113}Sn-labelled microspheres.

The remaining groups were used to assess the effect of drug treatment upon cardiac output and regional blood flows after haemorrhage. The ^{57}Co microspheres were injected and blood withdrawn as described above at 20 min after haemorrhage. Ten minutes later meptazinol (17 mg kg^{-1}, i.m.), naloxone (10 mg kg^{-1}, i.v.) or saline (1 ml kg^{-1}) was administered. After a further 5 min cardiac output and regional blood flows were measured again using ^{113}Sn labelled microspheres.

The rats were killed, the position of the carotid cannula was verified visually and the organs selected for blood flow measurement were dissected out, blotted, placed in weighed vials and the vials re-weighed. The carotid cannula was removed and flushed with 0.9% w/v NaCl into a vial to determine residual activity. Volumes of the microsphere suspensions equivalent to those administered were included for counting to determine the counts injected. Radioactivity was measured with a Packard gamma counter (energy window settings: ^{57}Co, 80–140 KeV; ^{113}Sn, 350–425 KeV). Samples were counted for 1 min. Counts were corrected for background activity.

Cardiac output, regional distribution of the cardiac output and organ blood flows were calculated by the method of McDevitt & Nies (1976). Statistical analysis was made within groups using paired t tests.

Haemorrhagic shock in anaesthetized cats

Female cats (2.0–2.5 kg) were anaesthetized with chloralose (80 mg kg^{-1}) and pentobarbitone sodium (6 mg kg^{-1}) in saline (8 ml kg^{-1} i.p.). The right femoral artery was cannulated and blood pressure recorded (Statham P23 pressure transducer; Grass model 7 polygraph). Heart rate was monitored from a

tachograph triggered by the blood pressure signal. The right femoral vein was cannulated for i.v. drug administration and the trachea intubated to facilitate spontaneous respiration. Deep body temperature was maintained at 37 ± 0.5°C with a heated blanket.

Each cat was left for 20 min post-operatively to allow heart rate and blood pressure to stabilise. The index of blood volume to body weight of the cat was taken as 55.5 ml kg^{-1} (Farnsworth *et al.*, 1960). To induce a haemorrhagic shock state, 10% aliquots of blood were removed at 5 min intervals until 40% of the calculated blood volume had been removed. Twenty minutes after the 40% haemorrhage, meptazinol, naloxone (0.5 mg kg^{-1} min^{-1}) or saline vehicle (0.2 ml min^{-1}) was administered for 4 min via the right femoral vein using a continuous infusion pump. Blood pressure and heart rate were monitored throughout the experimental period and for 30 min following the injection of the test agents.

Results were analysed using analysis of variance and *t* values derived where appropriate.

Materials

Meptazinol hydrochloride (Wyeth) and naloxone hydrochloride (Endo Laboratories Inc) were administered in saline (0.9% w/v NaCl; 1 ml kg^{-1}). Drug doses were calculated as base. ^{57}Co and ^{113}Sn radiolabelled microspheres, 9 μm diameter, were suspended in saline with 0.1% Tween 80 to prevent aggregation (New England Nuclear).

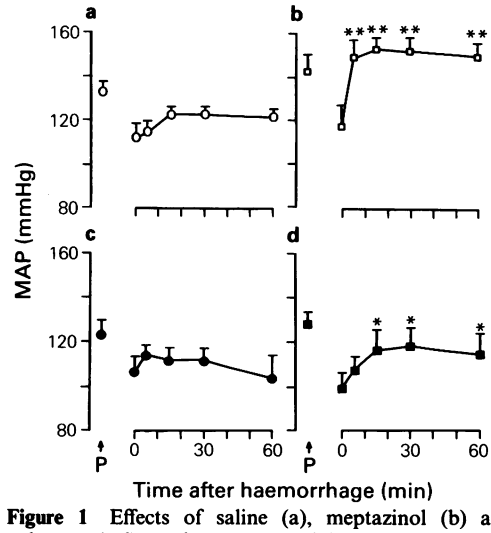

Figure 1 Effects of saline (a), meptazinol (b) and naloxone (c,d) on the mean arterial pressure (MAP) of conscious rats subjected to haemorrhagic shock. In (a) rats received 1 ml kg^{-1} saline, in (b) 17 mg kg^{-1} meptazinol, in (c) 1 mg kg^{-1} naloxone and in (d) 10 mg kg^{-1} naloxone. Each point represents the mean of 5 results with s.e.mean shown by vertical lines. P indicates MAP before induction of haemorrhage. In all cases 20% haemorrhage induced a highly significant ($P < 0.01$) decrease in MAP. Drugs or vehicle were given at time zero, 20 min after the final aliquot of blood was withdrawn. Asterisks indicate significant differences from the zero time reading: $*P < 0.05$; $**P < 0.001$ (analysis of variance).

Results

Haemorrhagic shock in conscious rats

In all groups a 20% haemorrhage evoked a highly significant reduction in MAP ($P < 0.01$). The decrease varied from 17–29 mmHg (Figure 1). Pulse pressure also tended to decrease after haemorrhage but the effect was significant only in the group subsequently treated with saline vehicle (39 ± 4.1 to 29.8 ± 2.6 mmHg; $P < 0.05$). Rats given saline vehicle after haemorrhage showed a small (~10 mmHg) increase in MAP over 15 min; the final pressure was not significantly different from that recorded before the vehicle was given and MAP did not return to control levels (Figure 1). Meptazinol evoked a rapid and sustained rise of MAP to pre-haemorrhage levels. The blood pressure at all time points was significantly

Table 1 Effects of saline, meptazinol and naloxone on heart rates of conscious rats subjected to haemorrhagic shock

		Heart rate (beats min^{-1})					
		Pre-haemorrhage	*20 min post-*	*Time after treatment* (min)			
Treatment	*Dose* (mg kg^{-1})	*control*	*haemorrhage*	5	15	30	60
Saline	Vol	402 ± 11	413 ± 23	417 ± 28	433 ± 21	426 ± 17	426 ± 20
Meptazinol	17	437 ± 15	403 ± 34	379 ± 21	432 ± 22	412 ± 19	413 ± 21
Naloxone	1	403 ± 9	387 ± 14	390 ± 17	401 ± 16	404 ± 16	400 ± 17
Naloxone	10	397 ± 30	348 ± 40	345 ± 34	377 ± 40	382 ± 29	393 ± 24

Values are means ± s.e.mean of 5 experiments.
There were no significant changes within or between the treatment groups (analysis of variance).

Table 2 Pretreatment values for organ blood flows in urethane/chloralose anaesthetized rats in comparison with data from other published studies

	Organ blood flow (ml min^{-1} g^{-1})				
Organ	*Current study*†	*Hafström et al.** (1979)	*McDevitt & Nies** (1976)	*Malik et al.** (1978)	*Saini & Somani*† (1979)
Heart	9.73 ± 2.72	10.9 ± 2.1	—	4.75 ± 0.83	3.28 ± 0.26
Brain	0.88 ± 0.10	—	—	0.40 ± 0.05	—
Liver	0.41 ± 0.06	0.7 ± 0.1	0.3 ± 0.1	—	0.24 ± 0.03
Spleen	2.15 ± 0.23	0.8 ± 0.1	2.2 ± 0.2	0.61 ± 0.22	0.42 ± 0.08
Skin	0.18 ± 0.03	0.03 ± 0.01	—	—	0.03 ± 0.007
Skeletal muscle	0.09 ± 0.02	0.1 ± 0.02	—	0.09 ± 0.01	0.14 ± 0.01
L. Kidney	6.99 ± 0.82	3.9 ± 0.9	5.5 ± 0.3	4.21 ± 0.73	1.66 ± 0.25
R. Kidney	6.97 ± 0.61	3.8 ± 0.7		3.86 ± 0.49	
Small intestine	1.75 ± 0.17	—	—	1.17 ± 0.19	0.49 ± 0.11

Values are means ± s.e.mean.
Data from previously published studies derived from rats anaesthetized with pentobarbitone.
*15 μm microspheres.
†9μm microspheres.

higher than the pre-dose level and overall the response was significantly greater than that of the control group ($P < 0.05$). Naloxone (1 mg kg^{-1}) had no significant effects, but a higher dose (10 mg kg^{-1}) produced a slow elevation of blood pressure over 15 min. Although the blood pressure was significantly higher at 15–60 min after naloxone than the value recorded before treatment, the effects of naloxone did not achieve statistical significance from those of the vehicle alone.

None of the treatments significantly changed pulse pressure from the values obtained after haemorrhage although the data for meptazinol indicated an upwards trend in this parameter (31.2 ± 4.3 mmHg post-haemorrhage to 40.4 ± 1.9 mmHg at 60 min after meptazinol; $P > 0.05$). Heart rate was not significantly altered by haemorrhage, vehicle or drug treatment (Table 1).

Haemodynamic effects after haemorrhagic shock in anaesthetized rats

The percentages of microspheres trapped in the lungs of the 4 treatment groups were 5.1 ± 0.6 (haemorrhage alone), 3.9 ± 1.1 (vehicle), 3.4 ± 0.6 (meptazinol) and 4.2 ± 0.4 (naloxone) for the first administration (^{57}Co

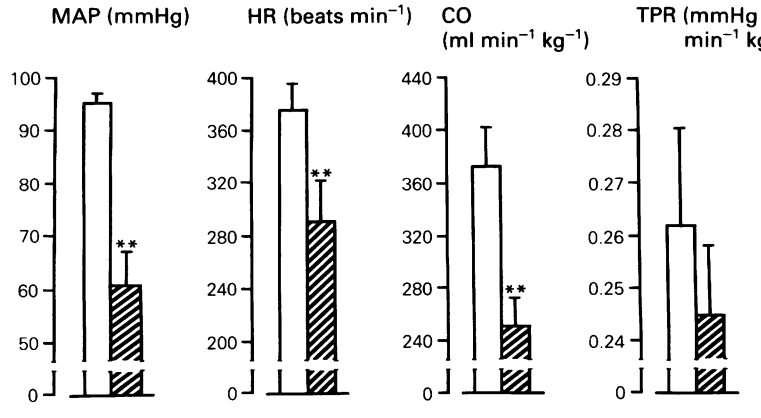

Figure 2 Effects of haemorrhage on the mean arterial pressure (MAP), heart rate (HR), cardiac output (CO) and total peripheral resistance (TPR) of anaesthetized rats. Open columns depict the data recorded before haemorrhage; hatched columns show the results obtained 20 min after removal of 20% of the blood volume. Values are means of 5 determinations with s.e.mean shown by vertical lines. **$P < 0.01$ (paired t test).

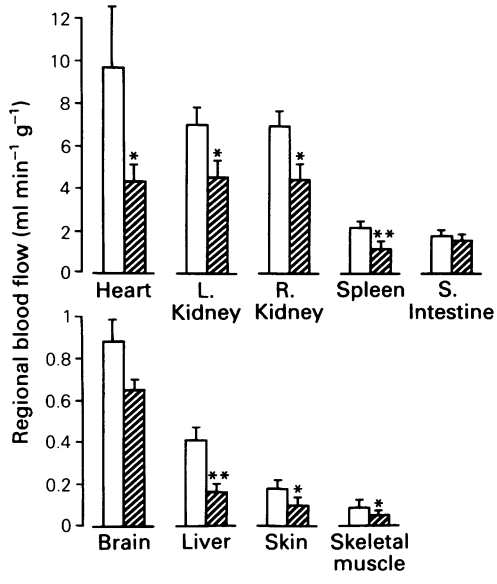

Figure 3 Effects of haemorrhage on regional blood flow in anaesthetized rats. Open columns depict the data recorded before haemorrhage; hatched columns show the results obtained 20 min after removal of 20% of the blood volume. Values are means of 5 determinations with s.e.mean shown by vertical lines. $*P<0.05$; $**P<0.01$ (paired t test).

microspheres). For the second administration (^{113}Sn microspheres) the corresponding percentages were 1.0 ± 0.3, 1.4 ± 0.5, 1.3 ± 0.4 and 1.6 ± 0.2. There were no significant differences in lung entrapment between the treatment groups for either set of microspheres, but entrapment of the ^{113}Sn microspheres was significantly lower than for ^{57}Co spheres in all groups except for that treated with vehicle.

Pre-haemorrhage organ blood flows for the group of rats that did not receive drug or vehicle treatment are shown in Table 2 together with control data from other published studies in anaesthetized rats. The blood flows to the heart, liver, spleen and skeletal muscle derived in the present study fall within the range of the published data whereas values for the kidney and small intestine were slightly higher and that for skin substantially higher.

Haemorrhage evoked significant reductions in MAP, heart rate and cardiac output in anaesthetized rats, but the derived reduction in total peripheral resistance did not achieve statistical significance (Figure 2). Pulse pressure was not significantly changed by haemorrhage (21.2 ± 2.1 to 24.4 ± 3.7 mmHg; $P>0.05$). Blood flows to the heart, skin, skeletal muscle, kidneys, spleen and liver (arterial) were decreased, but perfusion of the brain and small intestine was not significantly changed (Figure 3). Cardiac output distribution was significantly decreased to the liver (0.4 ± 0.06 to $0.2 \pm 0.04\%\ g^{-1}$; $P<0.01$) and significantly increased to the small intestine (1.8 ± 0.2 to $2.3 \pm 0.4\%\ g^{-1}$; $P<0.05$). Distribution to the brain was slightly increased (0.9 ± 0.1 to $1.0 \pm 0.04\%\ g^{-1}$) and distribution to the heart was slightly decreased (9.9 ± 2.5 to $6.6 \pm 0.7\%\ g^{-1}$) but these effects were not statistically significant. No other changes in cardiac output distribution were detected.

Following haemorrhage, meptazinol ($17\ mg\ kg^{-1}$) and naloxone ($10\ mg\ kg^{-1}$) increased MAP and total peripheral resistance but did not alter heart rate or cardiac output (Figure 4). There were no significant haemodynamic changes in the vehicle control group and none of the treatments modified pulse pressure. Further decreases in hepatic arterial blood flow occurred in drug and vehicle treated groups and splenic flow was reduced in the vehicle treated group (Figure 5). In addition, meptazinol reduced skeletal muscle flow. None of the treatments significantly

Table 3 The effects of saline, meptazinol or naloxone on heart rates of anaesthetized cats during haemorrhagic shock

		Heart rate (beats min^{-1})		
	Time (min)	*Saline* ($0.2\ ml\ min^{-1}$)	*Meptazinol* ($0.5\ mg\ kg^{-1}\ min^{-1}$)	*Naloxone* ($0.5 mg\ kg^{-1}\ min^{-1}$)
Pre-haemorrhage	0	193 ± 18	194 ± 10	179 ± 11
40% haemorrhage	20	178 ± 11	176 ± 12	191 ± 13
	30	191 ± 13	173 ± 15	197 ± 18
Infusion commenced	40	203 ± 14	184 ± 17	210 ± 14
Post-treatment	50	214 ± 16	216 ± 18	206 ± 9
	60	$22/*\pm 15$	223 ± 15	$209 \pm 8*$
	70	235 ± 11	$218 \pm 13*$	$209 \pm 8**$

Values are means ± s.e.mean; $n = 4$ for each group.
Times are from start of experiment.
$*P<0.05$; $**P<0.01$ from saline control group (analysis of variance).

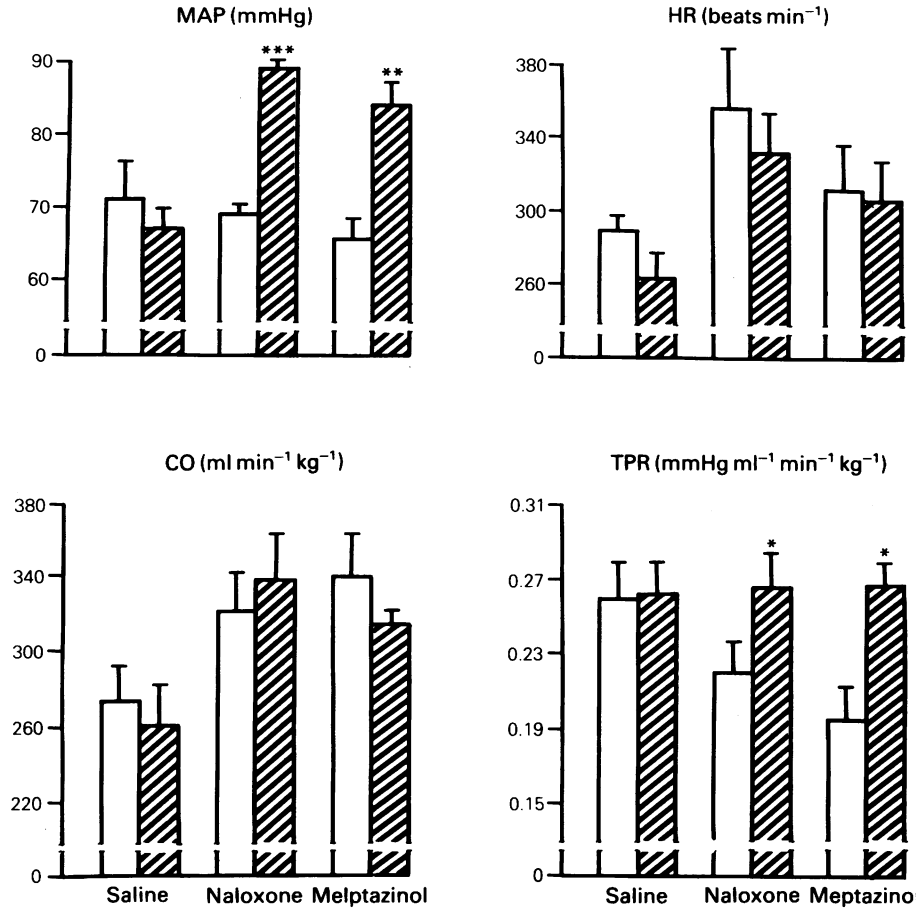

Figure 4 Effects of saline, naloxone and meptazinol on the mean arterial pressure (MAP), heart rate (HR), cardiac output (CO) and total peripheral resistance (TPR) of anaesthetized rats subjected to haemorrhagic shock. Open columns depict the data recorded 20 min after removal of 20% of the blood volume; hatched columns show the results obtained 5 min after administration of saline (1 ml kg^{-1}), naloxone (10 mg kg^{-1}) or meptazinol (17 mg kg^{-1}). Values are means of 5 determinations with s.e.means shown by vertical lines. $*P<0.05$; $**P<0.01$; $***P<0.001$ (paired t test).

affected blood flow to the heart, brain, kidneys, small intestine or skin. The only significant changes in cardiac output distribution noted were further decreases to the spleen and liver (arterial) in the vehicle and naloxone treated groups. Neither the drugs nor the vehicle significantly altered distribution of the cardiac output to the heart or brain.

Haemorrhagic shock in anaesthetized cats

Removal of 40% of the calculated blood volume from anaesthetized cats reduced MAP by 46 ± 3 mmHg at 20 min after haemorrhage. Meptazinol (0.5 mg kg^{-1} min^{-1} for 4 min) raised MAP by 19–27 mmHg in shocked cats. Blood pressure remained significantly higher than that of the vehicle-treated control group ($P<0.001$) over the 30 min observation period (Figure 6). Naloxone (0.5 mg kg^{-1} min^{-1} for 4 min) evoked a rapid increase in MAP of 18–29 mmHg over 30 min (Figure 6). MAP remained significantly higher than that of the control group at all time points ($P<0.001$). Saline vehicle evoked a slow rise in MAP of 1–8 mmHg over 30 min. Heart rate in all 3 groups gradually increased after haemorrhage (Table 3). The increases were significantly less than those of the control group in cats given meptazinol (30 min after infusion) and naloxone (20 and 30 min after infusion).

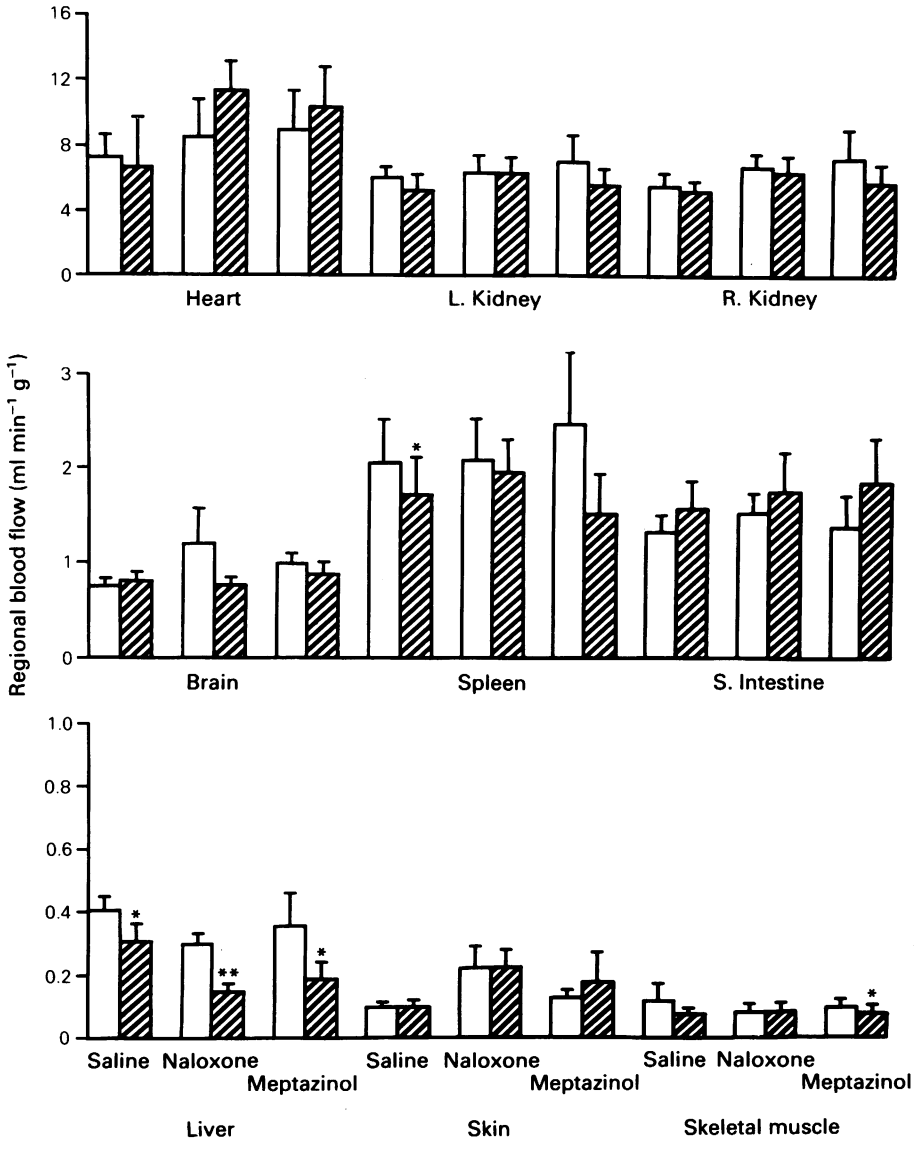

Figure 5 Effects of saline, naloxone and meptazinol on regional blood flow in anaesthetized rats subjected to haemorrhagic shock. Open columns depict the data recorded 20 min after removal of 20% of the blood volume; hatched columns show the results obtained 5 min after administration of saline (1 ml kg^{-1}), naloxone (10 mg kg^{-1}) or meptazinol (17 mg kg^{-1}). Values are means of 5 determinations with s.e.mean shown by vertical lines. $*P < 0.05$; $**P < 0.01$ (paired t test).

Discussion

The hypovolaemia caused by severe haemorrhage results in decreased venous return, cardiac output and arterial pressure leading to impaired regional blood flows. Compensatory mechanisms include baroreceptor activation, enhanced secretion of adrenomedullary catecholamines (Glaviano *et al.*, 1960) and stimulation of the renin-angiotensin system (Bunag *et al.*, 1966). Despite baroreceptor-mediated increases in sympathetic nerve activity, the heart rate response to haemorrhage is variable as chemoreceptor stimulation (Daly &

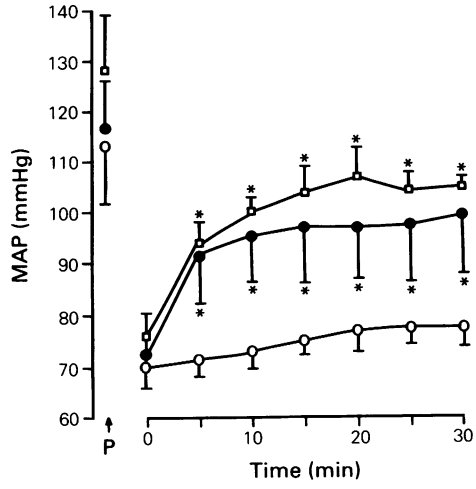

Figure 6 The effects of a 4 min infusion of saline vehicle (0.2 ml min^{-1}; O), naloxone (0.5 mg kg^{-1} min^{-1}; ●) and meptazinol (17 mg kg^{-1} min^{-1}; □) on the mean arterial pressure (MAP) of anaesthetized cats subjected to haemorrhagic shock, induced by removal of 40% of blood volume. Each point represents the mean of 4 determinations with s.e.means shown by vertical lines. P indicates pre-haemorrhage MAP. Drug or vehicle infusion was started at time zero. $*P < 0.001$ (analysis of variance).

Scott, 1959) and the cardiodepressant effects of increased central and peripheral endogenous opioid levels evoked by stress (Madden *et al.*, 1977; Rossier *et al.*, 1977) lead to bradycardia and a reduction in cardiac output (Laubie *et al.*, 1977).

In conscious rats the opiate antagonist, naloxone, increased arterial pressure after haemorrhage. The beneficial effect of naloxone in shock has been reported previously from studies both in animals (Holaday & Faden, 1978) and man (Peters *et al.*, 1981). In animals, naloxone raised blood pressure and facilitated recovery after haemorrhagic (Curtis & Lefer, 1980), endotoxic (Holaday & Faden, 1978), hypoglycaemic (Huidobro-Toro & Musacchio, 1981) and traumatic shock following spinal cord injury (Faden *et al.*, 1981b). Naloxone has also been shown to improve survival in mice following anaphylactic shock (Amir, 1982). The action of naloxone in shock may be due to either central or peripheral antagonism of cardiodepressant endogenous opiates (Holaday & Faden, 1980) with resultant alterations in autonomic efferent activity (Montastruc *et al.*, 1981). Hughes *et al.* (1975) have described inhibitory opioid receptors on noradrenergic nerve endings which are activated by morphine and by [Met] and [Leu]enkephalins. The physiological relevance of these receptors remains to be clarified; however, in theory, opioid antagonists could block the action of endogenous opioids at these receptors, enhancing the release of noradrenaline and increasing peripheral resistance. Other mechanisms which may be important include the stabilization of lysosomal membranes (Curtis & Lefer, 1980), or release of adrenal medullary catecholamines (Schadt & York, 1981) although Feuerstein *et al.* (1981) could not detect any significant effects of naloxone on plasma noradrenaline, adrenaline or dopamine levels after acute haemorrhage. The usefulness of naloxone in haemorrhagic shock where trauma has occurred may be limited since it will block the actions of opioid analgesic agents.

Meptazinol completely reversed the fall in blood pressure associated with hypovolaemia in conscious rats, even though it has minimal effects on the cardiovascular system of normovolaemic animals and man (Stephens *et al.*, 1978). Pulse pressure was slightly increased relative to post-haemorrhage values, owing to a greater increase in systolic than in diastolic pressure after meptazinol. Meptazinol is an example of an opioid mixed agonist/antagonist analgesic agent. Recent studies have shown that it behaves as a μ_1-receptor agonist in rat striatum but as a μ_2-receptor antagonist in the rat cerebral cortex (Ennis & Wyllie, 1985). It has been tentatively suggested that the high affinity (μ_1) opioid binding site might mediate the supraspinal analgesic actions of opioids whereas their cardiorespiratory effects, including those activated by circulatory shock, occur at low affinity (μ_2 or δ) sites (Pasternak *et al.*, 1983; Holaday *et al.*, 1983). This hypothesis could explain why meptazinol can act both as an analgesic agent and as an antagonist of the circulatory effects of haemorrhagic shock. In addition, meptazinol like naloxone, stabilizes lysosomal membranes *in vitro* (Paciorek *et al.*, 1983). In the same study it was shown that meptazinol increased, in a dose-dependent manner, the release of noradrenaline from synaptosomes both under basal conditions and under conditions of potassium-induced depolarization whereas naloxone only enhanced basal release. Studies in a rat model of anaphylactic shock have shown that the ability of meptazinol to reverse the adverse circulatory changes is dependent upon the integrity of the sympathetic nervous system (Paciorek *et al.*, 1985).

The microsphere technique is based on the assumptions that the spheres are homogeneously distributed in the blood before becoming impacted in the peripheral vessels, are impacted in the first pass through the circulation, are distributed in proportion to the cardiac output and do not disturb haemodynamic function. In this study 9 μm diameter microspheres were used. Smaller spheres have several advantages over larger ones in that they are distributed more like red blood cells, occlude less of the vascular bed, are less variable in size and can be given in large numbers

without adverse haemodynamic consequences, allowing a more accurate measure of flow to less well vascularised regions to be made (Buckberg *et al.*, 1971).

Adequate mixing and distribution was ensured by injecting the microspheres close to the left ventricle. Identical distribution of radioactivity in the kidneys provides a means of demonstrating the uniformity of mixing of microspheres before they reach the aorta (Malik *et al.*, 1976) and in the present study the blood flows in the left and right kidneys were similar in all groups.

Criticism of the use of 9 μm microspheres has been made on the grounds that recirculation is more likely to occur than with larger spheres. Thus Hof & Hof (1981) have shown that in the rabbit, 9 μm microspheres were poorly extracted by most vascular beds, 26% being found in the lungs after administration into the left atrium. Thus in the majority of tissues their use markedly underestimated tissue blood flows compared with those derived from use of 15 μm spheres. In the rat, however, 9 μm spheres were preferred to 15 μm spheres by Saini & Somani (1979). In the present study, lung entrapment was taken as a measure of microsphere recirculation. With the first injection (^{57}Co microspheres) the percentage in the lungs was between 3.4 and 5.1% and there were no significant differences between the 4 treatment groups. With the second injection of microspheres (^{113}Sn), lung entrapment was 1–1.6% and was again consistent between the 4 groups. Since part of the radioactivity in the lungs can be accounted for by left ventricular distribution via the bronchial circulation, the degree of recirculation of 9 μm microspheres in rats of ~250 g is very small.

The accuracy of the microsphere technique also depends upon there being sufficient spheres in each sample counted to avoid large random variability of distribution. Ishise *et al.* (1980) have suggested a minimum number of 200 microspheres as being appropriate for the rat. In the present study the lowest mean number of counts was in skeletal muscle (358) a figure well in excess of the suggested minimum. Although no comparable data exist for urethane/chloralose anaesthetized rats, literature values for cardiac output and organ blood flows in rats anaesthetized with pentobarbitone vary widely. Thus for cardiac output, a range of 121–388 ml min^{-1} kg^{-1} has been quoted (McDevitt & Nies, 1976). Values from the current study were towards the upper end of this range. Except for skin flow, the organ blood flows derived for urethane/chloralose anaesthetized rats were similar to or slightly greater than the values quoted by other authors using 9 or 15 μm spheres (Table 2). Where disparities exist, therefore, it is unlikely that they could be accounted for by recirculation of the microspheres, which would tend to underestimate flow to a given vascular bed. Thus the experimental model chosen would appear to be suitable for evaluating induced changes on haemodynamics and blood flow.

Induction of haemorrhage in anaesthetized rats evoked a rapid decrease in blood pressure, heart rate and cardiac output. The expected increase in peripheral resistance did not occur, possibly as a result of the chloralose/urethane anaesthetic used. In this context, it has recently been reported that urethane (1.2 g kg^{-1}, i.p.) inhibits cardiovascular responses mediated via central and peripheral α_2-adrenoceptors (Armstrong *et al.*, 1982). Although the dose of urethane used in the present study was smaller (0.72 g kg^{-1} i.p.), the impairment of cardiovascular reflexes cannot be ruled out. Haemorrhage reduced blood flow to a number of major areas including the heart, kidneys, spleen, liver (arterial), skin and skeletal muscle; brain and small intestinal blood flow were not significantly affected. Similar data on the effects of haemorrhage on rat organ blood flow were obtained by Sapirstein *et al.* (1960) except that in their study cerebral flow was also reduced. These data taken together suggest that the absolute levels of cerebral and cardiac blood flow may not be maintained during moderate haemorrhage. Other authors have shown that whilst absolute levels of flow are reduced, the proportion of the cardiac output supplying the brain and heart is increased after haemorrhage (Forsyth *et al.*, 1970). There was a slight increase in cardiac output distribution to the brain but not to the heart in the present study.

Meptazinol and naloxone significantly increased mean arterial pressure after haemorrhage in anaesthetized rats. This effect appears to have been brought about by an increase in peripheral resistance as cardiac output was not significantly changed by either drug. The microsphere experiments did not give a clear indication of which vascular beds were the principal contributors to the rise in peripheral resistance as the experiments were designed primarily to investigate changes in vital organ flow. Thus, cerebral, cardiac and renal blood flows were maintained in both meptazinol- and naloxone-treated rats but skeletal muscle flow was slightly decreased by meptazinol. Hepatic arterial blood flow decreased further in both vehicle- and drug-treated animals, presumably a manifestation of the continued development of the shock syndrome. Total hepatosplanchnic blood flow was not assessed in this study.

In the anaesthetized cat, meptazinol and naloxone increased arterial pressure during haemorrhagic shock although the response was more variable for meptazinol as reflected by the larger standard errors around the mean values. Neither drug completely restored mean arterial pressure to its level before haemorrhage. Curtis & Lefer (1980) have previously

demonstrated that haemorrhaged cats treated with naloxone maintained post-reinfusion arterial pressure at a higher level than cats treated with vehicle. Faden *et al.* (1981b) have shown that, after traumatic injury to the spine of cats, naloxone reversed the fall in MAP caused by the injury and promoted neurological recovery. The benefits of naloxone may be partially due to its effect on MAP maintaining spinal blood flow and thus reducing ischaemic damage. Meptazinol, by virtue of its pressor action, may also prove useful in this situation. Dopamine may be involved in the cardiovascular response to shock in the cat since, following spinal cord transection, the reversal of the hypotension by naloxone is blocked by domperidone and the administration of naloxone is accompanied by a rise in the circulating plasma dopamine concentration (Faden *et al.*, 1981a).

In conclusion, meptazinol and naloxone showed similar profiles of cardiovascular activity in animal models of haemorrhagic shock. Both drugs raised mean arterial pressure in conscious rats without significantly affecting heart rate. In anaesthetized rats, blood pressure was raised as a result of a change in peripheral resistance but neither drug further compromised vital organ flow. In the cat study, both drugs partially restored mean arterial pressure. Since naloxone has already shown clinical promise in a number of shock states these experiments suggest that meptazinol would have a similar cardiovascular profile whilst retaining the important advantage of providing effective analgesia.

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