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Effects of intravascular volume expansion on the cardiovascular response to naloxone in a canine model of severe endotoxin shock

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1 The specific opiate receptor antagonist, naloxone, can produce haemodynamic improvement and increased survival in experimental shock. The efficacy of naloxone therapy in a canine model of endotoxin shock has been evaluated both with and without intravascular volume replacement.

2 Animals were anaesthetized with α-chloralose and allowed to breathe spontaneously. A large bolus dose of endotoxin was followed by a continuous infusion, and treatment was instituted one hour after the endotoxin bolus.

3 In the absence of volume replacement, naloxone caused only limited and transient increases in mean arterial pressure (MAP) and left ventricular (LV) *dp/dt max*, with little effect on cardiac index (CI). Total peripheral resistance index (TPRI) tended to rise in both control and naloxone-treated dogs.

4 In volume-replaced animals, naloxone produced substantial and sustained increases in the MAP and LV *dp/dt max* with an associated rise in the CI. TPRI rose initially in this series and then fell progressively. Further analysis of the improvements in the CI showed an increase in stroke index with a tendency for heart rate to fall.

5 These findings suggest a myocardial action of naloxone in endotoxin shock, which is augmented by volume replacement. An initial, transient vasoconstrictor effect cannot, however, be excluded. Further work is required to determine the mechanism of the effects described.

Introduction

There is increasing evidence for the involvement of endogenous opioid systems in shock. Cardiovascular depression can be produced in experimental animals by central or intravenous administration of endogenous opioid peptides (Laubie *et al.*, 1977; Florez & Mediavilla, 1977; Lemaire *et al.*, 1978). In addition, the specific opiate receptor antagonist, naloxone, has been shown to produce cardiovascular improvement in animal models of haemorrhagic shock (Vargish *et al.*,1980; Gurll *et al.*, 1982a), spinal shock (Holaday & Faden, 1980) and endotoxin shock (Holaday & Faden, 1978; Reynolds *et al.*, 1980; Gahos *et al.*, 1982). Furthermore, the effects of naloxone in a rat model of endotoxin shock were shown to be stereospecific (Faden & Holaday, 1980). More recently, improvement in the cardiovascular status of dogs with haemorrhagic shock has been produced with a newer opiate antagonist, naltrexone (Gurll *et al.*, 1982b). In a number of these models, opiate receptor blockade was also found to prolong survival (Reynolds *et al.*, 1980; Vargish *et al.*, 1980; Gurll *et al.*, 1982a,b).

Previous studies of the effects of naloxone in endotoxin shock have used models in which a single bolus dose of endotoxin was given to barbiturate-anaesthetized animals (Holaday & Faden, 1978; Reynolds *et al.*, 1980). Spontaneous recovery of cardiovascular function occurs within about 30 min of an endotoxin bolus (Gilbert, 1960), and barbiturate anaesthesia can itself result in significant cardiovascular depression (Lumb, 1963) which might be exacerbated by positive pressure ventilation. Furthermore, naloxone was given before (Holaday & Faden, 1978) or very shortly after (Reynolds *et al.*,

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1980) the administration of endotoxin. This is in contrast to the clinical situation, in which such treatment is usually given relatively late to patients in severe shock unresponsive to more conventional measures.

A more rigorous assessment of the efficacy of naloxone has therefore been performed using the new canine model of severe endotoxin shock described in the previous paper. The influence of intravascular volume replacement on the cardiovascular response to naloxone has also been evaluated.

Methods

The shock model used has been described fully in our preceding paper (Evans *et al.*, 1984).

Twenty animals were used in this study, mean weight 19.5 ± 0.8 (± s.e.mean) kg.

In an initial series of 10 dogs (series 1), intravascular volume replacement was not given and treatment was instituted 60 min after induction of shock. One group of 5 animals was treated with a bolus dose of naloxone hydrochloride (0.5% solution), 2 mg kg^{-1} followed by a continuous infusion at 1.5 mg $kg^{-1} h^{-1}$. A control group of 5 dogs received an equivalent volume of 0.9% w/v NaCl solution (isotonic saline).

In this series, cardiovascular measurements were made during the baseline period at 30 and 15 min before administration of endotoxin, and at 5, 30, 45, 65, 90, 120, 150 and 180 min thereafter.

In a second series of experiments, again using two groups of five dogs (series 2), intravascular volume was replaced 1 h after the induction of shock with a bolus of colloidal gelatin solution (Haemaccel, Hoechst) 10 ml kg^{-1}, followed by a continuous intravenous infusion of 10 ml $kg^{-1} h^{-1}$. Naloxone or isotonic saline was administered 15 min after the start of volume replacement.

In series 2 animals, baseline cardiovascular measurements were made 15 min and immediately before giving endotoxin, and at 5, 30, 45, 60, 75, 80, 105, 135, 165 and 195 min thereafter.

In both series, packed cell volume (PCV) was measured at each time interval. In addition to the measured cardiovascular variables, derived values: cardiac index (CI, ml $min^{-1} kg^{-1}$) and total peripheral resistance index (TPRI, mmHg l^{-1} min kg^{-1}) were calculated using standard formulae, as in the previous paper. In both series, animals were randomly allocated to control or treatment groups and the experiments were performed blind.

Tests of statistical significance were performed using a two sample Student's *t* test for between-group analyses and a paired *t* test for within-group comparisons.

Table 1 Baseline cardiovascular measurements in anaesthetized animals

	Series 1				*Series 2*			
	Control group		*Treatment group*		*Control group*		*Treatment group*	
	t = −30	t = −15	t = −30	t = −15	t = −15	t = 0	t = −15	t = 0
MAP (mmHg)	137 ± 12.1	137 ± 16.0	148 ± 14	144 ± 16	127 ± 5.8	135 ± 5.2	145 ± 8.5	142 ± 7.5
CI (ml $min^{-1} kg^{-1}$)	210 ± 50	200 ± 50	170 ± 30	170 ± 20	200 ± 20	180 ± 20	180 ± 40	170 ± 40
PCWP (mmHg)	5.8 ± 1.0	5.0 ± 1.3	6.0 ± 1.0	7.6 ± 0.7	5.4 ± 1.9	4.6 ± 1.6	6.2 ± 0.5	6.0 ± 0.6
LV dp/dt max ($mmHg\,s^{-1} \times 10^3$)	3.1 ± 0.8	3.2 ± 0.6	3.1 ± 0.8	3.0 ± 0.8	4.3 ± 0.5	4.3 ± 0.5	3.9 ± 0.6	4.0 ± 0.5
TPRI (mmHg 1 $min kg^{-1}$)	655 ± 60	683 ± 70	878 ± 75	823 ± 64	678 ± 83	769 ± 90	826 ± 102	852 ± 87
PCV (%)	41.4 ± 2.2	41.0 ± 1.9	46.6 ± 3.4	46.8 ± 3.4	45.6 ± 0.4	45.6 ± 0.8	45.4 ± 1.8	45.4 ± 1.6

Results show mean ± s.e.mean for 5 animals in each group; t = time in min before administration of endotoxin. MAP: mean arterial pressure; CI: cardiac index; PCWP: pulmonary capillary wedge pressure LV: left ventricle; TPRI: total peripheral resistance index; PCV: packed cell volume.

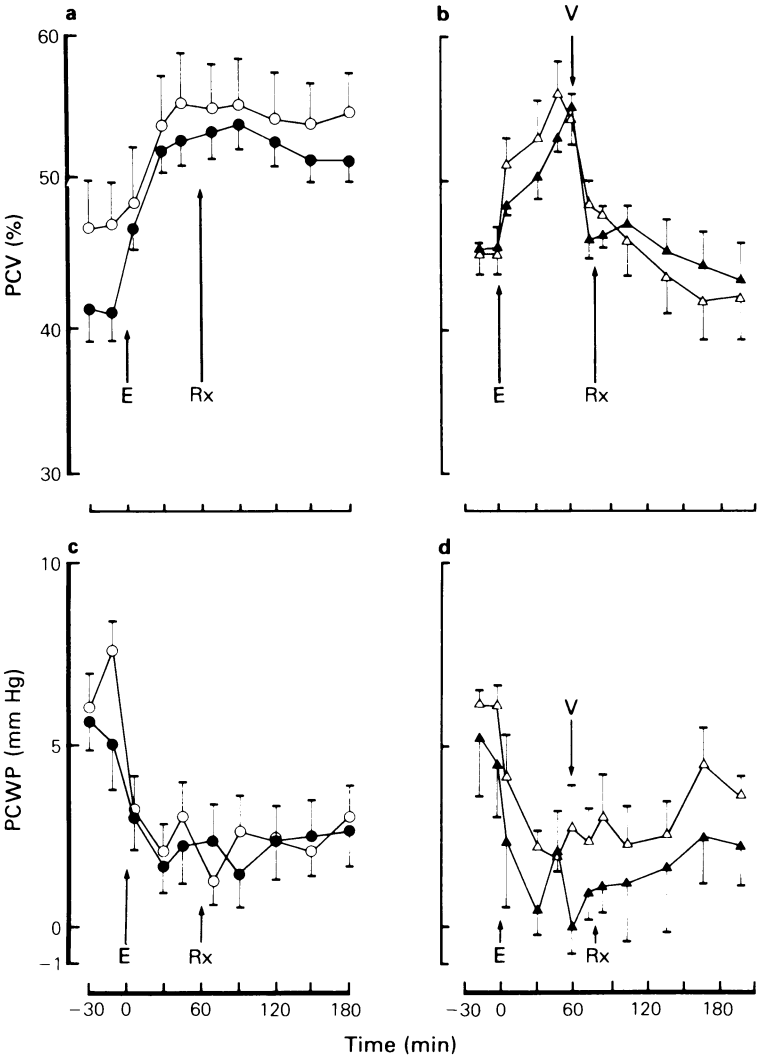

Figure 1 Values of (a and b) packed cell volume (PCV) and (c and d) pulmonary capillary wedge pressure (PCWP) in endotoxin-shocked, anaesthetized dogs treated with naloxone or vehicle. Series 2 animals were given volume replacement (V; b and d). Rx indicates time of treatment with naloxone or vehicle and E, endotoxin administration. Results show mean values, with vertical line representing s.e.mean, for 5 dogs in each group. (●) Series 1 control group; (○) series 1 treatment group; (▲) series 2 control group; (△) series 2 treatment group.

Results

There were no significant differences in measured or derived cardiovascular values between control and treatment groups in either series during the baseline period (Table 1).

Administration of endotoxin resulted in severe cardiovascular depression in all animals, and in the control groups this was maintained throughout the experimental period. The initial haemodynamic responses to endotoxin of the control and treatment groups in both series were not significantly different.

Endotoxin shock was accompanied by haemoconcentration and a fall in pulmonary capillary wedge pressure (PCWP) which became maximal about 60 min after giving endotoxin (Figure 1). In the first series of animals PCV and PCWP showed no further change after this time. In the second series volume replacement returned PCV to levels statistically indistinguishable from baseline. PCWP tended to rise,

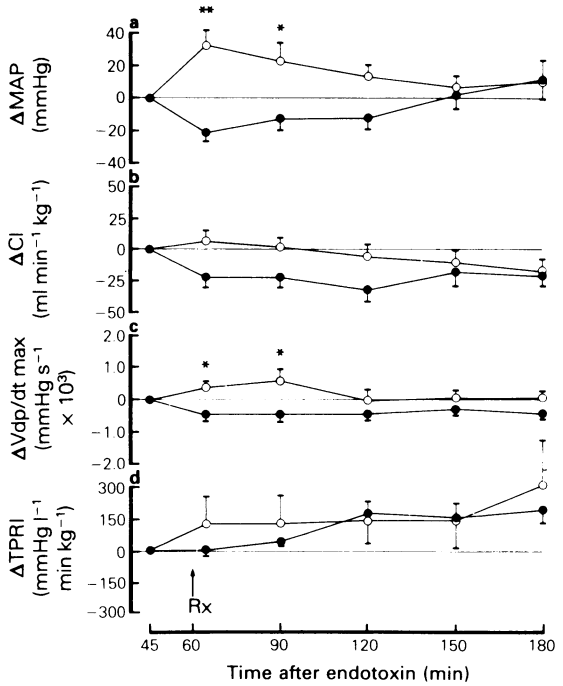

Figure 2 Changes in (a) mean arterial pressure (MAP) (b) cardiac index (CI);(c) left ventricular (LV) *dp/dt max* and (d) total peripheral resistance index (TPRI) after naloxone without prior volume expansion (series 1 animals). Results are calculated as mean changes from pretreatment value, with vertical lines showing s.e.mean, for 5 dogs in each group. Rx indicates time of treatment with naloxone or vehicle.(●) Control group; (○) treatment group.

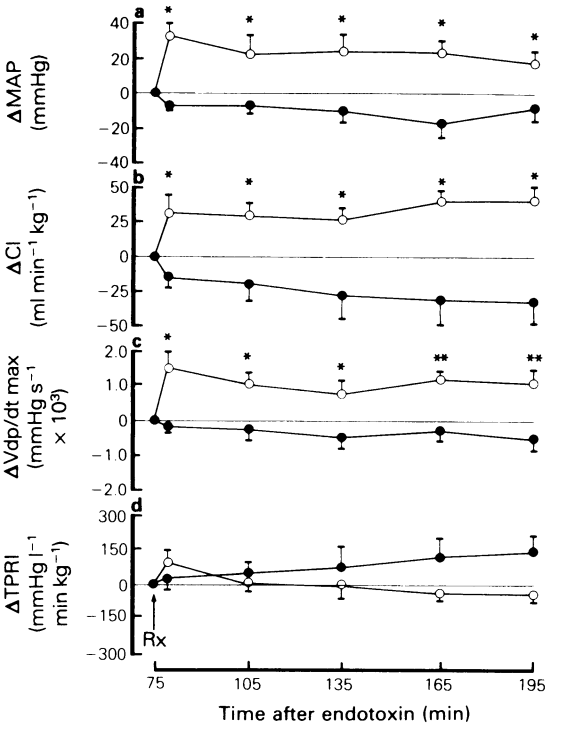

Figure 3 Changes in (a) mean arterial pressure (MAP), (b) cardiac index (CI), (c) left ventricular (LV) *dp/dt max* and (d) total peripheral resistance index (TPRI) after naloxone with prior volume expansion (series 2 animals). Results are calculated as mean changes from pretreatment values, vertical lines show s.e.mean, for 5 dogs in each group. Rx indicates time of treatment with naloxone or vehicle. (●) Control group; (○) treatment group.

although this did not achieve statistical significance (Figure 1).

Series 1 experiments

Administration of naloxone to non-volume-replaced dogs resulted in a transient but statistically significant increase in mean arterial pressure (MAP) and left ventricle (LV) *dp/dt max*. Although in comparison to control animals further falls in CI appeared to be prevented, this effect was also transient and did not achieve statistical significance (Figure 2). There was a tendency for stroke index (SI)to rise and heart rate (HR) to fall in treated animals, but again this was not significant.

TPRI tended to increase progressively in both groups and initially this rise appeared to be greater in those given naloxone, although neither of these changes was statistically significant (Figure 2). PCWP remained unchanged (Figure 1) and was not influenced by naloxone therapy.

Series 2 experiments

In volume-replaced animals the haemodynamic response to naloxone was greater, with significant increases in MAP, LV *dp/dt max* and CI (Figure 3). Furthermore, this improvement in cardiovascular function was sustained throughout the experimental period. Again the increase in CI was associated with a tendency for HR/SI to rise and to fall.

TPRI continued to rise in the control animals as in series 1. Naloxone-treated dogs showed an initial increase in TPRI with a subsequent fall, although differences between control and treatment groups did not achieve statistical significance (Figure 3). PCWP tended to rise in both control and treatment groups as volume replacement was given, but, as in series 1 animals, PCWP was uninfluenced by naloxone.

Discussion

This study has confirmed the efficacy of naloxone in a canine model of severe endotoxin shock. However, in the absence of intravascular volume replacement, the haemodynamic effects of naloxone were small and transient, whilst expansion of the circulating volume augmented and prolonged the response.

In previously published studies, naloxone was given before or shortly after the administration of endotoxin (Holaday & Faden, 1978; Reynolds *et al.*, 1980). In these studies a single bolus dose of endotoxin was given without the subsequent addition of a continuous infusion, and, as a result, some haemodynamic variables exhibited spontaneous recovery during the first 30 min after endotoxin. In addition, previous workers have used barbiturate anaesthesia, which may itself cause cardiovascular depression (Lumb, 1963).

In this study, spontaneous recovery from cardiovascular depression was largely prevented by the use of a continuous intravenous infusion of endotoxin in addition to a large bolus dose. Haemodynamic changes attributable to anaesthesia were minimized by the use of α-chloralose as the principal anaesthetic agent (Cox, 1972) and by allowing the animals to breathe spontaneously. Furthermore, treatment was not instituted in either of our series of animals until one hour after induction of endotoxin shock, at which time the animals were in a stable, severe, hypodynamic shock state. This more closely simulates the clinical situation, in which such treatment is only likely to be given relatively late to patients in shock refractory to other treatment.

Naloxone was given as a bolus of 2 mg kg^{-1} since this dose was found previously to improve survival in a less severe shock model (Reynolds *et al.*, 1980). The bolus was followed by an infusion at 1.5 mg kg^{-1} h^{-1}. This dose was chosen to produce approximately constant blood levels, as the serum half life of naloxone in the dog is of the order of 70 min (Pace *et al.*, 1979).

Administration of naloxone to non-volume-replaced dogs caused transient rises in MAP and LV *dp/dt max*, with very little effect upon CI (Figure 2). Analysis of the CI changes revealed an initial, but statistically insignificant, increase in SI and fall in HR in naloxone-treated animals. These changes were of very short duration, and subsequently SI tended to fall and HR tended to rise in both control and treatment groups.

In both series 1 and series 2 animals the haematocrit rose and there was a tendency for PCWP to fall (Figure 1). Although in dogs splenic contraction may contribute to haemoconcentration, a reduction in plasma volume has been demonstrated in a primate endotoxin shock model (Cavanagh *et al.*, 1970) and the limited response to naloxone seen in series 1 animals was almost certainly due to hypovolaemia. Furthermore, plasma volume depletion is an important feature of septic shock in humans, and in the clinical situation immediate fluid replacement therapy is essential.

Series 2 animals therefore received volume replacement. This returned PCV to baseline levels and there was a tendency for PCWP to rise, although this was not statistically significant (Figure 1). Interpretation of PCWP changes is, however, complicated by the influence of alterations in venous capacitance and ventricular compliance occurring after volume replacement, and these probably masked an effective increase in pre-load.

In volume-replaced animals, haemodynamic improvement following naloxone was more dramatic and was sustained throughout the measurement period. In particular, there was a significant and persistent elevation of CI which was accompanied by increases in LV *dp/dt max* and MAP (Figure 3). The increase in CI was mainly attributable to an increased SI, as HR tended to fall in both control and treatment groups.

Although in both series of experiments TPRI tended to be higher in the naloxone-treated animals immediately after treatment, there were no significant differences in the TPRI changes between control and treatment groups in either series. However, whereas in series 1 animals TPRI continued to increase following treatment in both control and naloxone-treated groups (Figures 2 and 3), in the volume-replaced animals, after an initial rise mirroring the control group, TPRI fell in those given naloxone (Figure 3). It seems likely that this delayed fall in TPRI was secondary to the increased flow produced by the improvement in cardiac output.

These findings suggest that naloxone improves myocardial function in endotoxin shock and corroborate the findings of Reynolds and his colleagues (Reynolds *et al.*, 1980). It is also possible that naloxone produces an immediate, but transient, vasoconstriction. The mechanisms whereby naloxone produced these cardiovascular changes have yet to be elucidated.

In conclusion, we have demonstrated significant and sustained haemodynamic improvement in severe canine endotoxin shock only when naloxone therapy is accompanied by adequate intravascular volume replacement. In this respect, naloxone behaves in the same way as other clinically available inotropic drugs.

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