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THE EFFECTS OF NALOXONE ON ENDOTOXIC AND HEMORRHAGIC SHOCK IN HORSES

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ABSTRACT

The effects of naloxone on the cardiovascular, hematologic and metabolic derangements associated with endotoxic and hemorrhagic shock were studied in unanesthetized horses. In the first of 3 experiments blood glucose and lactate levels, hematocrit, white, red and differential white cell counts, rectal temperature and clinical signs were obtained before and after endotoxin (10 μg/Kg) administration in 5 horses. In the second experiment, two groups of 3 horses received either intravenous naloxone (0.04 mg/Kg) or saline, 7 minutes prior to endotoxin. In a third experiment two groups of 4 horses received either saline or naloxone (0.20 mg/Kg) immediately following acute hemorrhage. In the second and third experiments, pulse, mean arterial and right ventricular pressures, and heart rate were also observed.

Endotoxin and acute hemorrhage produced hypothermia, leukopenia, lymphopenia, neutropenia, elevations in hematocrit, blood glucose and blood lactate, and clinical signs of shock. Naloxone (0.040 mg/Kg IV) significantly lowered endotoxin-induced increases in right ventricular pressure and heart rate, and at a higher dose (0.20 mg/Kg) antagonized the decrease in pulse and heart rate, and tachycardia observed after acute hemorrhage. These results suggest endogenous opioids are involved in the pathogenesis of shock. Naloxone appeared to attenuate some of the cardiovascular responses associated with shock and thus may be of therapeutic value in shock management.

INTRODUCTION

Shock is a life threatening condition characterized by an acute reduction in effective circulating blood volume, hypotension and impaired tissue perfusion. A variety of hematologic and metabolic changes often occur in concert with these cardiovascular disturbances. Shock may result from overwhelming infection, severe hemorrhage, dehydration, anaphylaxis, anesthesia or severe physical trauma. Regardless of the cause, if uncompensated, shock eventually results in death of the organism.

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It has recently been suggested that endorphins (endogenous opioid peptides) may be involved in the hypotension associated with shock (Holaday and Faden, 1978; Faden and Holaday, 1979a; Faden and Holaday, 1979b; Faden and Holaday, 1980). According to this hypothesis, endorphins are released in response to the stress of shock and mediate the observed decrease in systemic blood pressure. Both centrally (Bolme et al., 1978) and systemically (Lemaire et al., 1978) administered β-endorphins produce a vasodepressor response which is antagonized by the opiate antagonist naloxone. In addition, the hypotension associated with hypovolemic and endotoxic shock has been reversed to varying degrees by naloxone in species other than the horse (Holaday and Faden, 1978; Faden and Holaday, 1979a; Faden and Holaday, 1979b; Faden and Holaday, 1980; Janssen and Lutherer, 1980; Reynolds et al., 1980).

In this study, the effect of naloxone on the cardiovascular, hematologic and metabolic sequelae of shock were examined in healthy, unanesthetized horses with no prior experimental exposure to endotoxin. Shock was induced (1) by the systemic administration of bacterial endotoxin, which has been implicated in the pathogenesis of shock associated with intestinal torsions, strangulations and obstructions (Nelson et al., 1968) and (2) by hypovolemia produced through controlled hemorrhage.

METHODS

Adult unanesthetized Standardbred and Thoroughbred mares and geldings (400-500 Kg) were used in 3 separate experiments. In the first experiment 5 horses were monitored for 2 days. On day 1, serial blood samples were obtained 1 hour prior to, and 0.25, 0.5, 1, 2, 3, 4, 6, 8 and 24 hours after intravenous saline (10 ml) administration. Serum glucose (Kadish et al., 1968) and plasma lactate (Marback et al.,

1968) and plasma lactate (Marback et al., 1967) levels were measured, and hematocrit, white, red and differential white cell counts (Coulter Counter, Coulter Electronics) were determined on each sample. Rectal temperature was monitored every 0.5 hours for eight hours, and at 24 hours. On day 2, E. coli endotoxin (Difco Laboratories, Detroit, MI) was administered (10 µg/Kg) intravenously to the same group of horses. Blood samples and rectal temperatures were obtained and analyzed according to the methods described above.

In a second experiment, 6 horses received an intravenous injection of endotoxin (15 µg/Kg). Three of these horses were treated with intravenous saline (10 ml) and the remaining 3 with intravenous naloxone (Naloxone hydrochloride, courtesy Endo Laboratories, Garden City, NJ) (0.04 mg/Kg/10 ml), 7 minutes prior to endotoxin administration. In these animals, blood pressure was measured by insertion of a catheter (Deseret Intracath, The Deseret Co., Sandy, UT) into the carotid artery. Right ventricular pressure was measured by advancing a catheter through the left jugular vein into the right ventricle. Both catheters were connected to pressure transducers (Gould Statham P23ID, Gould Inc., Oxnard, CA) and a polygraph (Grass Model 7 Polygraph, Grass Instrument Co., Quincy, MA). Pulse pressure and heart rate were calculated from polygraph tracings of arterial pressure. A stable baseline was obtained for 45 minutes before endotoxin administration. Rectal temperatures and blood samples were obtained according to methods described in the first experiment.

In a third experiment, 8 horses were acutely hemorrhaged by incising the jugular vein under local anesthesia (Carbocaine, Geigy, Ardsey, NY). Blood flow from the incision was controlled by an elastic

bandage and tourniquet around the neck. Ten to 15 L of blood were removed from each animal, which lowered mean arterial blood pressure by approximately 50 mm Hg. The incision was sutured to prevent further blood loss. Four of the hemorrhaged animals were intravenously treated with naloxone (0.2 mg/Kg/10 ml) and the remaining four (control group) with an equal volume of saline. Cardiovascular parameters were recorded 30 minutes prior to, during, and 90 minutes after hemorrhage. A t-value was determined for paired or unpaired values at various times before and after treatment. Statistically significant results were reported when $P<0.05$.

RESULTS

Endotoxin (10 µg/Kg IV) produced significant hyperthermia, leukopenia, lymphopenia, neutropenia, and an increase in hematocrit. These responses were prolonged, generally lasting 8 hours or more and peaked 2–4 hours after endotoxin administration. Peak elevations in blood glucose and blood lactate levels were similarly observed 2-4 hours after endotoxin administration. Changes in gross behavior became apparent 20–30 minutes after endotoxin treatment and consisted of excitement, restlessness, increased locomotor activity and abdominal checking. Additional signs which included spreading diapharesis, diarrhea, hypothermic extremities, gingival ischemia, weakness and, in some animals, collapse occurred around one hour after treatment.

The slightly higher dose of endotoxin (15 µg/Kg) employed in the second (cardiovascular) experiment, produced a rapid onset and prolonged increase in right ventricular pressure (Fig 1A) and heart rate (Fig 1B). An increase in arterial blood pressure (Fig 1D) and pulse pressure (Fig 1C) with comparatively later onset and shorter duration,

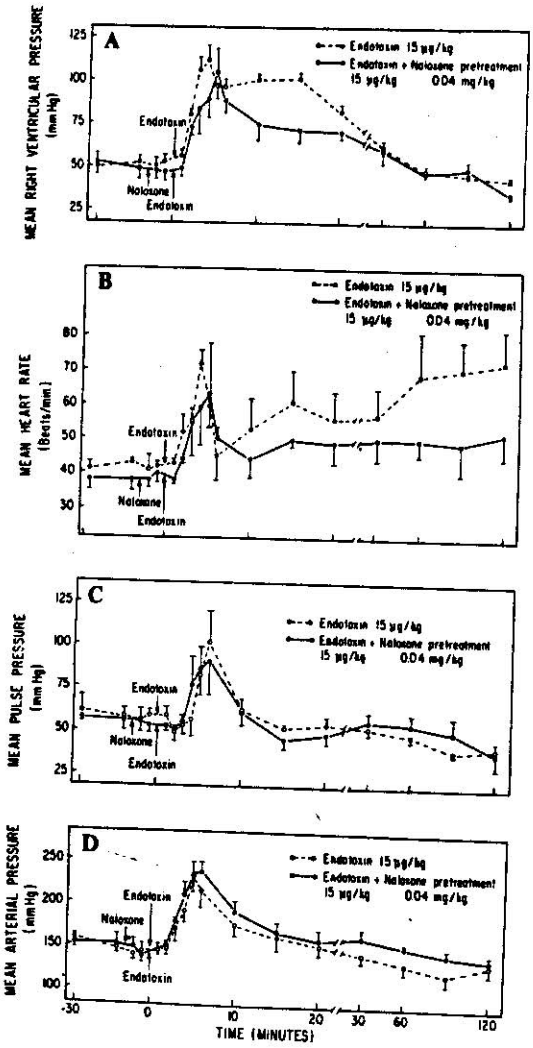

Fig. 1. The effects of endotoxin administered alone (open circles), and 7 minutes after naloxone (solid circles) and (A) right ventricular pressure, (B) heart rate, (C) pulse pressure, and (D) arterial blood pressure. Each point represents the mean response of 3 horses (± SEM).

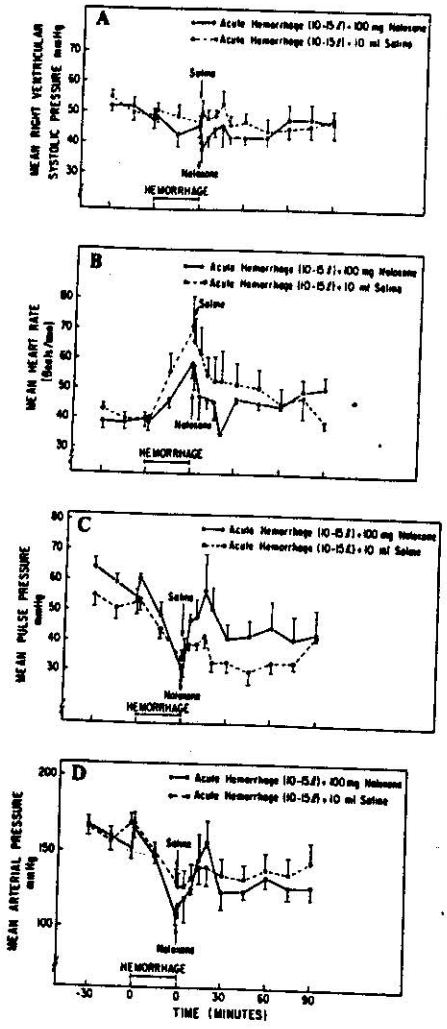

Fig. 2. The effects of naloxone (closed circles) and saline (open circles) on post-hemorrhage changes in (A) right ventricular pressure, (B) heart rate, (C) pulse pressure, and (D) arterial pressure. Each point is the mean response of 4 horses (± SEM).

were also observed. Endotoxin produced a significantly ($P<0.05$) smaller increase in right ventricular pressure ($P<0.05$) and heart rate in the naloxone pretreated groups than in the saline-treated groups (Fig 1A and B). However, naloxone failed to alter endotoxin-induced changes in arterial blood pressure, pulse pressure, body temperature, behavior or any hematologic parameter.

Acute hemorrhage produced a cardiovascular syndrome which differed from that observed after endotoxin administration. Removal of 10-15 L of blood produced immediate decreases in arterial and pulse pressures (Fig 2D and C), an increase in heart rate (Fig 2B), and no change in right ventricular pressure (Fig 2A) during the hemorrhagic period. Immediately post-hemorrhage, naloxone (0.2 mg/Kg) or an equal volume of saline (10 ml) was administered. Heart rate (Fig 2B) remained depressed and pulse pressure (Fig 2C) remained elevated 30-60 minutes post-hemorrhage in the saline-treated group. However, these parameters returned to baseline levels within 20 minutes in the naloxone-treated animals. A statistically significant difference ($P<0.05$) in heart rate and pulse pressure was noted for the 60-minute post-treatment periods between the saline and naloxone-treated groups. Recovery from post-hemorrhage mean arterial hypotension was not influenced by naloxone. Right ventricular pressure did not change significantly during or after hemorrhage, or after saline or naloxone administration.

Naloxone alone (0.04 mg/Kg) did not significantly alter heart rate or arterial pulse or right ventricular pressure.

DISCUSSION

The administration of endotoxin (15 µg/Kg) produced the hematologic, metabolic and behavioral responses typically associated with

shock (Burrows, 1981). However, our endotoxin shock model did not produce the marked degree of hypotension or cardiovascular compromise reported by others who used larger endotoxin doses and terminal models in conscious (Burrows, 1971) and anesthetized ponies (Burrows and Cannon, 1970; Burrows, 1970; Bottoms et al., 1981; Moore et al., 1983). While increasing doses of endotoxin might have produced sustained hypotension, these higher doses (>15 μg/Kg) were lethal in our experiments and would have raised short and long term mortality to an unacceptable level. The dose of endotoxin employed in this study, however, produced consistent and reproducible increases rather than decreases in heart rate, pulse pressure and right ventricular and arterial blood pressure. Although blood flow through various organs was not measured, the observed cardiovascular augmentations may have, in part, been a compensatory response to extensive dilation of the gastrointestinal vasculature. Reduced resistance and increased blood flow through this region has been reported after endotoxin administration in anesthetized ponies (Bottoms et al., 1981; Moore et al., 1981). Increased resistance to cerebral blood flow has also been reported (Moore et al., 1983). Therefore, redistributed blood flow to intestinal vasculatures, together with compromised cerebral perfusion, could have been an adequate stimulus for activating compensatory sympathetic reflexes resulting in the observed hypertension and tachycardia.

Naloxone pretreatment significantly attenuated the endotoxin-induced increases in right ventricular pressure and heart rate which may have clinical import in the pathogenesis and treatment of endotoxic shock. Reduced arterial blood flow to the lungs and increased pulmonary vascular resistance has been reported after endotoxin administration in

anesthetized ponies (Moore et al., 1983). This increase in resistance has been attributed to marked sequestration of neutrophils and disruption of pulmonary endothelium (Moore et al., 1981; Kux et al., 1972). In the presence of local tissue damage, neutrophils release serotonin, histamine, kinins, prostaglandins and other vasoactive substances, (Croweder et al., 1969; Hsueh et al., 1980) which probably contribute to pulmonary congestion and hypertension. Partial antagonism of this hypertensive response by naloxone suggests that endogenous opioids are involved in endotoxin-induced changes in lung perfusion. Our data suggests that naloxone lowers pulmonary vascular resistance and consequently right ventricular pressure in response to endotoxin. This could be interpreted as an improvement in lung perfusion, although this parameter was not directly measured in our study. The ability of naloxone to improve lung perfusion appears controversial since Moore et al (1983) were unable to demonstrate any change after naloxone. However, anesthetized ponies and higher doses of naloxone and endotoxin were used in their studies making direct comparisons difficult. In our study, naloxone pretreatment also reduced the late onset tachycardia produced by endotoxin and tended to stabilize heart rate over time. This suggests that endogenous opioids may also mediate the effects of endotoxin or cardiac rhythm. Although the mechanism for these effects is not apparent, naloxone's value may be in its ability to reduce cardiac work and improve pulmonary circulation.

Since endotoxin failed to produce hypotension, a hemorrhagic shock model was used to test naloxone's anti-hypotensive ability. Acute hemorrhage produced decreases in pulse and arterial blood pressure which reflected the effects of reduced circulating blood volume. The

tachycardia represented a compensatory reflex recruited to maintain cardiac output and blood pressure. The lack of change in right ventricular pressure suggests that vascular changes occurred predominantly in the peripheral rather than pulmonary circulation. These responses were different from those observed after endotoxin, suggesting that the lung perfusion was less severely compromised. Although naloxone failed to significantly antagonize post-hemorrhage arterial hypotension, it significantly antagonized both post-hemorrhage tachycardia and elevated pulse pressure. These data suggest that following acute hemorrhages, endogenous opioids are released which exert vasodepressive effects, or interfere with certain compensatory responses to sudden hypovolemia. Hypotensive responses to centrally (Bolme et al., 1978) and systemically (Lemaire et al., 1978) administered opioids has been demonstrated in the rat. However, since pulse pressure and heart rate were more rapidly restored after naloxone, it would appear that stroke volume and cardiac output were preserved.

These experiments support current hypotheses that endogenous opioids are released as a consequence of endotoxic and hemorrhagic shock. However, the actions of naloxone, and possibly the opioids, differ between the two models presented. Naloxone may be therapeutically beneficial in the treatment of shock by lowering some indices of cardiac work demand and pulmonary vascular resistance during the acute stages of shock.

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