Opioid antagonism in haemorrhagic shock

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The role of endogenous opioids and opioid-receptor antagonism in shock has just begun to unfold. Injection of the opioid antagonist naloxone following physiological perturbations such as shock and trauma evokes a number of useful and life-saving responses in experimental animals. This has provided valuable insights into the role of the endogenous opioid system in shock. Extrapolation of the experimental findings to the clinic has yielded promising results, supporting a therapeutic role for naloxone in humans in many types of shock. Naloxone appears to be a promising pharmacological agent, and a controlled, randomized and well-designed clinical trial may help in confirming the usefulness of this opioid-receptor antagonist in haemorrhagic shock.

The recent interest in opioids, for medical scientists and laymen alike, reflects the unique therapeutic value of these agents and the mystery about their mode of action. The discovery of endogenous opioid peptides has opened up many scientific areas and posed questions, many of which are still in an early stage of exploration. The term opioid refers to any directly acting compound whose effects are stereospecifically antagonized by naloxone. It is now clear that at least three different families of endogenous opioid peptides exist, viz. endorphins, enkephalins and dynorphins. These peptides may function as neuromodulators, neurotransmitters or hormones. Contrary to the previous observation that there was only one opiate receptor, at present at least nine opiate receptor subtypes have been identified.

Endorphin-positive neurons are largely restricted to the arcuate nucleus of the hypothalamus, with long axonal projections extending to the nucleus tractus solitarius, reticular midbrain and limbic regions. The anatomical distribution of these neurons is also correlated with that of areas that may control the cardiovascular system. The enkephalins and dynorphins are present in neuronal cell bodies at every central nervous system level from the spinal cord to the brain and appear to be contained within the terminals of shorter interneurons. Many of these neurons project to areas within the brain and spinal cord that are known to control autonomic functions. Opioid peptides are also present within the peripheral nervous system, in areas such as myenteric plexus of the gut, cervical and mesenteric ganglia, and the adrenal medulla. Outside the central nervous system the highest concentration of β-endorphin is found in the pituitary gland and of enkephalins in the adrenal medulla. A neuroendocrine role has been postulated for pituitary and adrenal opioid peptide hormones, since they are released in circulation in response to stress and other physiological stimuli.

The endogenous opioid peptides may exert suppressive effects on two principal stress axes, viz. the hypothalamo-pituitary-adrenal axis and the sympathoadrenal-medullary system. It is important to note that these endogenous opioid systems are normally inactive and opioid antagonists such as naloxone have little or no effect in control of the homeostatic mechanism in organisms. However, once they are activated by physiological perturbations such as shock or trauma, they are capable of evoking a number of responses. They can suppress sympathetic-nerve activity, cardiovascular function, respiratory function, renal function, gastrointestinal transit, and vital tissue perfusion. These effects are reversed after naloxone administration (Figure 1).

Role of opioids in shock

The role of opioids and opiate receptors in 'shock', still an enigma to the medical world, has just begun to unfold. Both exogenous (morphine) and endogenous (β-endorphin) opioids produce systemic hypotension and bradycardia after intravenous administration. β-Endorphin is stored with adrenocorticotropic hormone (ACTH) in the anterior pituitary and is released in blood, as is ACTH, during stress. This endogenous opioid peptide released during haemorrhagic stress may also contribute to the cardiovascular suppression associated with it. This hypothesis was tested by administering the opiate-receptor antagonist naloxone in many types of shock models, including haemorrhagic shock. Naloxone did indeed reverse the hypotension seen in haemorrhagic shock as well. In this article we review the effect of the opiate antagonist naloxone on various parameters that are altered in haemorrhagic shock.

The dramatic results shown by naloxone in haemorrhagic shock were first reported by Faden and Holaday.
in 1979 in conscious rats. They observed that administration of naloxone after 20 min of haemorrhage, which resulted in a mean arterial pressure (MAP) of 40 mm Hg, caused prompt and sustained increase in MAP and improved survival (assessed up to 24 h).

Vargish et al.28-30 provided further insight by conducting studies on canine haemorrhagic shock models. In their studies naloxone showed a significant increase in the inotropic function of the heart by showing improvement in MAP and cardiac output (CO). Guril et al.31,32 have shown dose-related improvement in haemodynamic variables and survival in dogs subjected to haemorrhagic shock after naloxone treatment even without reinfusion of the shed blood.

These haemodynamic effects of naloxone have been confirmed by many other investigators33-36. In our laboratory it was observed that there was sustained improvement in MAP for one hour after 1 mg kg⁻¹ of intravenous bolus of naloxone was administered17. This improvement in MAP was comparable with that in groups of dogs which were receiving either noradrenaline (2 μg kg⁻¹ min⁻¹) or dopamine (10 μg kg⁻¹ min⁻¹) by intravenous infusion for one hour. Curtis and Lefèr37,38 studied the effect of naloxone on haemorrhagic shock in cats. It was reported that naloxone reduced release of lysosomal enzymes and, concentration of myocardial depressant factor (MDF) released during shock. Feuerstein et al.39 have shown sustained improvement in MAP in anephric cats as well as in cats with intact kidney, with similar doses of naloxone after acute haemorrhage.

The effect of naloxone on the cardiovascular, haematologic and metabolic derangement associated with endotoxic and haemorrhagic shock was studied in unanaesthetized horses by Weld et al.40. Their results suggest that endogenous opioids are involved in the pathogenesis of shock and naloxone appears to attenuate some of the haematologic and metabolic responses associated with shock. We have found improved metabolic status, by way of decreased lactic acid and increased bicarbonate level in the blood, after administration of naloxone41. The improvement in metabolic status and survival was better in dogs subjected to haemorrhagic shock after naloxone (1 mg kg⁻¹) treatment compared to that after treatment with clinically used drugs like dopamine (10 μg kg⁻¹ min⁻¹) and noradrenaline (2 μg kg⁻¹ min⁻¹). An evaluation of naloxone as a gastric cytoprotective agent during haemorrhagic shock has also been studied by Moran et al.42, who found that naloxone had no apparent effect on local vascular resistance during haemorrhagic shock.

Renal-function deterioration in haemorrhagic shock is primarily due to decrease in renal blood flow. This is quite understandable when one considers the fact that the kidney normally receives about one-fourth of the normal cardiac output. Therefore administration of any drug that improves renal function during haemorrhagic shock will be of immense value in such conditions. Although, in an earlier study, Schadt et al.43 did not find any significant change in renal resistance after naloxone administration in rabbits subjected to haemorrhage, compared to controls which received only saline, studies from our laboratory have shown encouraging effects on kidney function after naloxone treatment in haemorrhagic shock. This study, in dogs showed that all the parameters of renal function, such as inulin clearance, PAH clearance and urine flow, which were depressed during haemorrhage, improved significantly after naloxone (1 mg kg⁻¹ i.v. bolus) administration17. The improvement seen after naloxone treatment was much better than that after treatment with dopamine. An angiohistopathological study44 of the kidney revealed partial patency of the majority of glomeruli in the cortical region of the kidney, shown by the presence of India ink injected through the renal artery, after one hour of treatment with naloxone in haemorrhaged dogs.

Even in primates like baboons, McIntosh et al.45 investigated the possible involvement of endogenous
opioid peptides in the cardiovascular depression associated with hypovolemic shock. The increased plasma levels of β-endorphin seen during haemorrhagic shock were correlated well with a decrease in cardiac output. Single-bolus administration of naloxone (2 or 5 ng kg⁻¹) produced a transient but significant improvement in MAP and CO.

Extrapolation of these experimental findings to the clinic has yielded promising evidence for a therapeutic role for naloxone in humans in spinal and septic shock.⁴⁵⁻⁴⁸. There are several anecdotal reports of improvement after naloxone injection in patients with septic shock and it is interesting that most of these patients failed to respond to conventional resuscitative measures, including administration of dopamine, dobutamine and steroids, and volume administration. Though there are evidences that opioid antagonists may reverse the hypotension associated with different types of shock in man, results of randomized double-blind trials in haemorrhagic shock are awaited.

Mechanism of action of naloxone

Cardiovascular status

From the available literature, the mechanism of action of naloxone in improving cardiovascular status in haemorrhagic shock is not clear. Normal animals treated with naloxone demonstrated no significant difference in MAP compared to a control group of animals perfused only with ringer solution.⁴¹⁲. According to Faden and Holaday β-endorphin released during haemorrhagic shock might contribute to the hypotension and bradycardia seen in shock, and naloxone did indeed reverse this effect. β-Endorphin level in the blood is increased in experimental animals subjected to haemorrhagic shock.⁹,⁴⁴. Lehner et al.⁴⁶,⁴⁹,⁵⁰ demonstrated that naloxone appears to improve the cardiovascular status by potentiating the effect of released catecholamines, but does not increase the sympathoadrenal discharge. They found that the increases in MAP, CO and LV (dp/dt) due to naloxone in haemorrhagic shock are unaffected by cardiac denervation but are attenuated by α- and β-adrenergic blockade. Prior infusion of α- and β-adrenergic agonists completely restored the cardiovascular responses to naloxone abolished by adrenal denervation and ganglionic blockade.

As for the site of action of naloxone in the improvement of cardiovascular status in haemorrhagic shock, there are conflicting views. Some workers have demonstrated in animal studies that the action of naloxone is centrally mediated via the pituitary.²⁸⁻⁵¹. They have suggested that the beneficial effect of naloxone in haemorrhagic shock is mediated through central opioid receptors as it is seen only in animals with intact pituitary. They have also found that neither intracerebroventricular nor intraventricular administration of naloxone in hypophysectomized rats gave any improvement in cardiovascular function after haemorrhagic shock. But Gurll et al.⁵² argue that opiate receptor-mediated cardiovascular depression seen in shock is mediated centrally only in endotoxic shock and is peripheral in haemorrhagic shock. The small dose of 0.1 mg kg⁻¹ of naloxone was effective when given directly into the coronary circulation during haemorrhagic shock, but was not effective when given into the ventriculocisternal system of the brain. This suggests a peripheral site of (cardiac) action of naloxone in canine haemorrhagic shock. However, it appears that further studies are required to confirm the mechanism of action of naloxone on the cardiovascular system.

Renal function

The beneficial effect of naloxone on kidney function seems to be a consequence of generalized improvement in MAP. Schadt et al.⁵⁵ found no change in renal vascular resistance after naloxone injection in rabbits. While there are many physiological findings⁵³⁻⁵⁵ that sympathetic activity and peripheral resistance are increased by acute haemorrhagic hypotension after a sufficient period of haemorrhage, others have reported that there is a decrease in sympathetic activity and vascular resistance.¹⁴,⁵⁶,⁵⁷. Endorphins released during shock might contribute towards inhibition of sympathetic outflow during the later stages.⁵⁸. Although naloxone does not increase renal resistance, it can prevent its decline in the later stages of shock by maintaining the sympathetic tone, as indicated by the partial patency of glomerular capillaries in the cortical region of the kidney.⁵³. Infusion of small doses of naloxone (0.1 mg kg⁻¹) through the renal artery of haemorrhaged dogs did not improve renal function (unpublished work from this laboratory), indicating that there was no direct action of naloxone on renal blood vessels. Since naloxone does not improve MAP at this small dose, improvement of renal function at a higher dose (1 mg kg⁻¹) of naloxone might be due to generalized improvement in renal blood flow because of the increased MAP and maintenance of renal resistance.

Metabolic status

Metabolic acidosis is evident in haemorrhagic shock. This is indicated by increased lactate acid concentration, with a concomitant fall in blood pH, bicarbonate concentration and pCO₂. A significant decrease in
arterial lactic acid level and a recovery in bicarbonate level and pCO₂ after naloxone treatment suggest effective restoration of tissue perfusion, aerobic metabolism and rapid utilization of lactic acid. Lechner et al.\textsuperscript{59} reported increased blood flow to vital organs, and we have seen significant increase in the PAH clearance and inulin clearance after naloxone treatment in canine haemorrhagic shock, which indicate increased blood flow to kidney\textsuperscript{17}. Matheus and Engelbrecht\textsuperscript{60} demonstrated increased metabolic activity in tissues, especially of liver and lungs, after naloxone treatment in haemorrhaged rabbits. Adequate central and peripheral perfusion and prompt restoration of acid–base balance are essential for reversibility of shock. Naloxone seems to have met these requirements to some extent in many of the experimental studies, as shown by the increased survival of shocked animals\textsuperscript{22,41}.

Conclusions

The clinical relevance of these findings are far-reaching. The opioid-receptor antagonist naloxone may be used as a better adjunct to blood transfusion in haemorrhagic shock. Even today circulatory shock is a major therapeutic problem. Although haemorrhagic shock in human beings and other species is best treated with prompt readministration of fluid, which may be sufficient to restore adequate tissue perfusion, there are occasions during emergency medical care when biological fluids or technical expertise for their administration are unavailable. In these situations a single-bolus administration of naloxone provides initial stabilization, until such time that conventional therapies such as volume replacement could be made. Controlled, randomized and well-designed clinical trials of this promising pharmacological agent may help in confirming the usefulness of this opioid receptor antagonist in haemorrhagic shock.