Review Article

Naloxone: New therapeutic roles

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The narcotic antagonist naloxone, the n-allyl derivative of oxymorphone, is used widely by anaesthetists to reverse opiate-induced respiratory depression. However, the discovery that there are endogenous opiate-like substances in the central nervous system and other tissues, and that they are involved in regulation of general physiological phenomena, has raised the possibility that naloxone may have wider therapeutic uses. Possible uses include the treatment of septic and hypovolemic shock, spinal cord injury, stroke, respiratory depression, drug overdose, and a number of other disease states ranging from the hypothalamic syndrome to chronic constipation. In addition, naloxone-induced reversal of the hypotensive and analgesic effects of various anaesthetics demonstrated by some investigators suggests that certain endogenous opiates may be released during anaesthesia. The potential use of naloxone in the above conditions raises the possibility that the endogenous opiates may be involved in physiological mechanisms other than pain. A general review which highlights the potential use of naloxone in several disorders is presented.

Conventional use of naloxone

Naloxone is used commonly for the reversal of

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opiate induced respiratory depression. It is also indicated for the diagnosis of suspected acute opiate overdose or physical dependence on opioid drugs. It is thought to be a relatively pure narcotic antagonist and its main advantage over other n-allyl narcotic antagonists is that it does not produce respiratory depression. Naloxone is used by anaesthetists primarily in the treatment of postanaesthetic respiratory depression due to opiates. In neonates it is frequently used to reverse the effects of opiates administered to the mother. Total doses for the adult are usually in the range of 0.1 to 0.4 mg intravenously. Titration of naloxone in $100 \mu\text{g}$ or $1 \mu\text{g}\cdot\text{kg}^{-1}$ IV doses every two to three minutes is recommended to reverse respiratory depression as sudden arousal with the onset of acute pain may lead to problems. Several reports indicate that naloxone when used as a narcotic antagonist may induce adverse effects such as hypertension, pulmonary oedema, atrial and ventricular arrhythmias, or cardiac arrest.¹ These adverse effects are thought to be due to the sudden release of endogenous catecholamines with the return of postoperative pain. Recurrence of respiratory depression may also occur after administration of naloxone due to the relatively short half-life of the drug and therefore an intravenous infusion may be required to antagonize large doses of opiates. Many reports of complications following naloxone use have involved patients with coronary artery disease, and thus naloxone should be used with caution in these patients. In such patients postoperative ventilation is an alternative to naloxone reversal.¹⁻³

Shock

Holaday and Faden⁴ initially reported that naloxone ($10 \text{ mg}\cdot\text{kg}^{-1}$ IV) reversed endotoxic hypotension in conscious rats and also demonstrated that naloxone ($1.0 \text{ mg}\cdot\text{kg}^{-1}$ IV) rapidly increased mean arterial pressure following acute blood loss in rodents.⁵

Vargish *et al.*⁶ reported naloxone ($2 \text{ mg} \cdot \text{kg}^{-1}$ IV plus $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hour}$) reversal of hypovolemic shock in dogs, demonstrating a prompt increase in arterial pressure and cardiac output. Also, blockade of opiate receptors with naloxone has been found to improve survival and cardiac performance in canine endotoxic shock.⁷ Since these reports, the beneficial effect of naloxone in septic and hypovolemic shock has been confirmed in other studies and in other species,⁸⁻¹¹ including man. In man there are several reports indicating beneficial effects of naloxone in septic shock, anaphylactic shock and shock associated with hepatic failure.¹²⁻¹⁸ Peters *et al.*¹⁶ reported on the pressor effect of naloxone in septic shock with eight patients experiencing an increase of 45 per cent in systolic blood pressure within minutes after receiving naloxone ($0.4-1.2 \text{ mg}$). This effect lasted for at least 45 minutes.

The mechanism of action of naloxone in shock is not clear. It has been theorized that naloxone reverses the effect of the opiate peptide, β -endorphin, which is released in stress.^{19,20} This endogenous opioid peptide is stored together with ACTH in the pituitary and is released during stressful states. Like classical opiate analgesics in clinical use, β -endorphin is reported to cause hypotension.²¹ In fact it has been suggested that the efficacy of corticosteroids in the management of shock may be due to their inhibitory effect on the release of pituitary β -endorphin.⁴ Koyama's observations suggest that at least part of the beneficial cardiovascular actions of naloxone in endotoxic shock involves activation of the efferent sympathetic nervous system.²² Others have reported that naloxone's effects are mediated by an integrated response of both parasympathetic and sympathetic systems.²³

The discovery that the endogenous opiate system may be involved in shock states is important. In addition to their wide distribution in the brain and dorsal horn of the spinal cord, opiate peptides such as enkephalins are also found in other tissues including the sympathetic ganglia and adrenal gland,²⁴ sites which are involved in the shock state. In many of the studies that have been performed with naloxone, this agent has been used in doses that may be considered to be excessive when compared with those employed clinically for the reversal of opioid effects. These high doses of the drug may be necessary due to a relative

lower affinity of certain opiate receptors for naloxone.^{25,26} While naloxone can hardly be expected to replace the infusion of crystalloid or colloid solutions in the clinical treatment of hypovolemic shock, its potential use in optimizing the treatment of endotoxic shock is a distinct possibility. The rather short duration of action of naloxone could be overcome by constant infusion of this drug or by use of a narcotic antagonist such as naltrexone, which has a longer plasma half-life.

Spinal injury

Naloxone therapy has been reported to be beneficial in reversing hypotension, hypothermia and hypoventilation and improving neurological outcome following experimental spinal injury.²⁷⁻²⁹ Since naloxone has been found to improve spinal cord blood flow in the injured region,^{30,31} it has been postulated that the therapeutic action of naloxone results from its ability to reverse the post-traumatic reduction in spinal cord blood flow. Thyrotropin-releasing hormone, a peptide which acts as a partial physiologic opiate antagonist and spares analgesic systems, was also found to be beneficial in spinal cord injury in experimental animals.³² Unlike naloxone, this hormone does not reverse the analgesic action of narcotics. Thus endogenous opiates appear to play a role in the pathophysiology of experimental spinal injury and therefore opiate antagonists might be of benefit in reducing the manifestations of spinal injury in humans. The use of naloxone in spinal injury is still very much experimental in nature and no human trials have been performed nor has the safety of such trials been established.

Stroke

Naloxone has been reported to improve neurologic recovery after ischaemic cerebral insult. Hosobuchi *et al.*³³ reported that stroke induced by carotid occlusion in gerbils was reversed by intraperitoneal injection of naloxone ($1 \text{ mg} \cdot \text{kg}^{-1}$) for up to 30 minutes. While placebo-treated stroked gerbils died within 48 hours, 40 per cent of gerbils implanted with naloxone pellets survived over two weeks without significant neurologic deficit. Intravenous naloxone was also reported by Hosobuchi to produce transient reversal of hemiplegia in two patients with neurologic deficit from cerebral ischaemia. In addition, in the incremental air embolization model

of stroke in dogs, where air was injected as a bolus, with additional increments, into a catheter placed in the right internal carotid artery, naloxone ($2 \text{ mg} \cdot \text{kg}^{-1}$ IV plus $2 \text{ mg} \cdot \text{kg}^{-1}$ per hour) significantly improved cortical somatosensory-evoked response and had a beneficial effect on cerebral blood flow.³⁴ Faden *et al.* also found that naloxone-treated stroked animals maintained blood flow to all regions above critical threshold values and had a substantially better cortical somatosensory-evoked response recovery. It has been postulated that release of endorphins during cerebral ischaemia may be an important contributing factor in the pathophysiology of stroke, and that naloxone may have some specific effect on the cerebral microvasculature.³⁴ Alternatively naloxone may exert beneficial effects through non-opioid actions, e.g., by acting as an antioxidant, affecting calcium flux or cyclic adenosine monophosphate.³³

On the basis of experimental studies it appears that naloxone may have the ability to improve blood flow to compromised cerebral areas, and as Sugar has stated, "It certainly would appear worthy of trial for those cases of postangiographic and postoperative hemiplegias that might not respond to hypertensive agents, and which do carry some risks."³⁵

Non-opiate-induced respiratory depression

Since it is well recognized that opiates produce respiratory depression it seems logical that endogenous opiates would be involved in the control of respiration. Opiate receptors are widely distributed throughout the brain and medullary respiratory centres,³⁶ and methionine and leucine enkephalin-like material has been found in carotid body type I cells.³⁷ This notion is further supported by the findings that naloxone apparently restores the ventilatory response to added inspiratory loads in some patients with chronic airflow obstruction. It has been suggested that naloxone may have some value in decompensated patients with chronic obstructive pulmonary disease in whom restoration of respiratory drive to a neuromechanical stimulus might make the difference between success or failure of conservative management.³⁸ The drug has also been shown to markedly decrease the duration of primary apnoea produced by asphyxia in the newborn rabbit.³⁹ Chernick *et al.* suggested that endogenous opiates released during asphyxia are a major factor in the suppression of medullary neuronal discharge

during primary apnoea.^{40,41} In addition, the action of intracerebroventricular naloxone in improving respiratory rates following spinal cord transection in the rat is stereospecific.⁴² A child with respiratory failure and cor pulmonale secondary to obesity hypoventilation was found to have abnormal CSF and serum β -endorphin levels, and in this patient a single IV dose of naloxone ($10 \mu\text{g} \cdot \text{kg}^{-1}$) resulted in dramatic improvement.⁴³ In this case improvement was maintained by a continuous infusion of the drug. Ayers *et al.*⁴⁴ treated a 58-year-old man with acute on chronic respiratory failure with an infusion of naloxone which produced an improvement in O_2 saturation. Endorphins may also be involved in high altitude pulmonary oedema. Dramatic improvement of hypoxaemia and clinical course was reported in a patient with this form of oedema and with raised plasma β -endorphin level following naloxone administration.⁴⁵

There may be an overproduction of endorphins or an increased sensitivity to their effects in acute respiratory failure. Whether endogenous opiates are released as a result of the stress of asphyxia, or whether they have a more direct role in respiration is not yet known. The possibility has been raised that endogenous opiates may be involved in neonatal apnoea, sudden infant death, acute respiratory failure, chronic obstructive pulmonary disease, obesity hypoventilation and high altitude pulmonary oedema. Although theoretically naloxone would appear to be an ideal drug for these conditions, it may not be a very specific agent. It is now recognized that there are sub-types of opiate receptors²⁶ and specific antagonists acting at such receptors may have a greater therapeutic potential than naloxone.

Non-specific arousal

Arousal with naloxone treatment has been reported following ingestion of diazepam, alcohol, combinations of barbiturates with alcohol and diazepam, and non-narcotic anaesthesia. Bell reported a case of a 27-month-old girl presenting in coma resulting from ingestion of diazepam which was reversed with 0.1 mg naloxone subcutaneously.⁴⁶ Similarly, naloxone in doses of up to 3.2 mg IV caused an increase in pupillary size and respiratory rate in a patient with anoxic and metabolic encephalopathy and diazepam consumption.⁴⁷ No traces of narcotics were found by the toxicology lab in either

case. Mackenzie reported a case of alcohol-induced coma which was quickly reversed by naloxone and suggested that there is a place for this agent in pure alcohol poisoning, or in selected cases of suspected head injury complicated by alcoholic intoxication.⁴⁸ A case of naloxone reversal of apnoea occurring after combined barbiturate, alcohol and diazepam consumption was also cited in this report.⁴⁸ Also, 12 patients with ethanol-induced coma were given intravenous naloxone, 0.4–0.6 mg and all regained normal consciousness within several minutes.⁴⁹ Aldrete *et al.* found return to consciousness and occurrence of incisional pain in patients after non-narcotic anaesthesia within one minute of naloxone (0.8 mg) injection.⁵⁰ In the same study patients receiving doxapram also developed increase in consciousness and spontaneous activity, but no incisional pain. On the other hand, a controlled clinical trial by Christensen examining the reversibility of diazepam-induced sedation by naloxone (0.4 mg IV), was unable to demonstrate antagonism of diazepam with naloxone.⁵¹ The failure of Christensen to demonstrate naloxone antagonism of diazepam-induced sedation may be due to the low dose of naloxone (0.4 mg) utilized in that study.

The ability of naloxone to apparently antagonize a number of central depressants that are non-opioid in their nature may be due to the possibility that such agents cause a release of endogenous opioids. This type of mechanism is supported by the observation that diazepam produces changes in enkephalin levels in the striatum and hypothalamus.⁵² On the other hand a non-specific analeptic action of naloxone may also underlie this antagonism. In the case of alcoholic intoxication, naloxone may act by antagonizing the effect of certain condensation products (e.g., isoquinoline alkaloids) resulting from ethanol metabolism that apparently exert opiate-like actions.⁴⁹

Anaesthesia

Antagonism of the analgesic and hypotensive action of certain anaesthetic agents by naloxone has led to the suggestion that endogenous opiates released by anaesthetics contribute to their effects. Naloxone has been shown to reverse the effects of nitrous oxide on pain,^{53–57} locomotor activity,⁵⁸ and cerebral evoked potentials.⁵⁹ Recent studies also show that arterial hypotension, bradycardia, de-

pressed baroreceptor responses and EEG synchronization associated with halothane anaesthesia were reversed in animals when naloxone was perfused through the fourth ventricle. More significantly, the inactive stereoisomer (+) naloxone in similar tests failed to antagonize the circulatory effects of halothane.^{60,61}

On the other hand, some investigators have reported that inhaled anaesthetics do not interact with opiate receptors and that the effect of naloxone on anaesthetic requirements is the result of its nonspecific analeptic action. Harper *et al.* found that intravenous naloxone (up to 250 mg·kg⁻¹) did not alter halothane requirements (MAC) in rats.⁶² Naloxone also failed to antagonize nitrous oxide anaesthesia when anaesthetic potency was measured using loss of righting reflex as a non-painful stimulus.⁶³ Thus, some controversy still exists in this area and it needs to be further resolved. Although naloxone may appear to be useful in reversing anaesthesia-induced depression, its therapeutic use in this regard is limited because of associated reversal of analgesia. Again, development of more specific antagonists, that would preserve analgesia but would effectively reverse other effects, may provide a more rational approach.

Miscellaneous

Naloxone has also been used, with varying degrees of success, in such diverse disease states as schizophrenia, tardive dyskinesia, organic psychosis, idiopathic constipation, episodic and climacteric flushing, non-specific pruritis and hypothalamic syndrome.^{64–72}

Conclusions

The beneficial effects of naloxone observed in a number of pathophysiological states are based on the premise that there is overactivity of the endorphin system in such states. As the endorphins increasingly are being implicated in a variety of pathophysiological states, naloxone or similar opioid antagonists are likely to be employed as therapeutic agents to modify the function of endorphins. However, it must be noted that to date most of the results with naloxone in these states are based on animal studies and there is a marked paucity of human clinical data. Due to species differences, experimental results obtained from animal studies

are not always applicable to humans. Additionally, the action of naloxone is short in duration. Naltrexone, a longer acting antagonist, or perhaps a more receptor specific endogenous opiate antagonist, if developed, may be of value in shock, spinal cord injury, stroke, respiratory failure and drug overdose. More human studies will be required to confirm the validity of animal experiments performed using naloxone. It is clear that the physiologic roles of the endogenous opiates, other than their analgesic properties, are not fully understood and naloxone or related agents are likely to hold clinical interest in the foreseeable future.

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