Naloxone, the n-allyl derivative of oxymorphone, has gained widespread use in anaesthesia for the purpose of antagonizing opioid-induced respiratory depression and sedation. Although naloxone has been regarded traditionally as a pure opioid antagonist without agonist activity, following the discovery of the endogenous opioid system (originating with Hughes and his colleagues (1975)) evidence has accumulated to suggest that this may not be so. Within anaesthetic practice, the prime indication for the use of naloxone is the presence of unwanted opioid effects, predominantly respiratory depression in the immediate postoperative period. However, it is well known that the offset of clinical effect seen after a single bolus of naloxone is rapid and usually occurs within 30 min following a typical dose of 0.1–0.4 mg i.v. This clinical duration of action mirrors the decay in plasma concentration which is most rapid over the first 30 min following i.v. administration, although the terminal elimination half-life is approximately 150 min (Aitkenhead et al., 1984). Thus, in order to prevent the re-emergence of opioid agonist effects, it has been suggested that either supplementary doses i.m. or an infusion i.v. should be administered to prolong the duration of opioid antagonism.

Recent information has suggested the need for caution in the use of naloxone by i.v. bolus. There have been reports of ventricular dysrhythmia (Andree, 1980), hypertension (Azar and Turndorf, 1979), and pulmonary oedema (Flacke, Flacke and Williams, 1977) following naloxone 0.4 mg i.v. More recently, two cases of acute pulmonary oedema have been reported after 0.1 mg i.v. in healthy young patients (Prough et al., 1984). It is likely that in all these reports the underlying mechanism comprised acute arousal leading to centrally-mediated catecholamine release, with neurogenic pulmonary oedema in the most extreme cases.

In the light of these reports we suggest that, when tempted to use naloxone i.v. to reverse opioid effects, the anaesthetist should administer the drug slowly in dilute form in order to titrate the minimum dose possible against the result required. In the less acute situation, the i.m. route may be safer.

After the administration of opioids by the subarachnoid or extradural routes, respiratory depression may occur following a variable latent period (3–18 h). This may be treated successfully by the parenteral administration of naloxone, but repeated doses may be necessary. In contrast to its use following parenteral opioids, naloxone does not appear to reverse the analgesic component of extradural/subarachnoid opioids. This is thought to be the result of the high local concentration of opioid in proximity to spinal cord opioid receptors, while the receptors which affect respiratory control are more cephalad—in the region of the brainstem. Cousins and Mather (1984) have suggested that circulating CSF concentrations of opioids around this site are of paramount importance in the mechanism of respiratory depression following subarachnoid or extradural opioid administration.

Since 1975, at least four sub-types of opioid receptor—mu, kappa, sigma and delta—have been defined in the central nervous system (Yaksh, 1984), but these may be only a fraction of those to be discovered in the future. Although it is still not possible to identify those specific effects which result from stimulation of individual receptors, there are clear actions associated with some receptor sub-types, for example analgesia appears to be mediated via the mu/kappa system and dysphoria is thought to be sigma-mediated.

Naloxone binds competitively to opioid receptors and thus occupation of the site by an agonist (either endogenous or exogenous) is prevented, although this is dependent on the local concentra-
tion of each agent at the biophase. It is of particular significance, however, that the affinity of naloxone for each receptor population is not equal, the binding of naloxone to mu sites being much more stronger than to kappa or delta. These specificities are relative, rather than absolute, and it is known that in high local concentrations binding to non-preferred sites can occur.

In addition to the antagonism of opioid-induced respiratory depression and sedation, naloxone has been used therapeutically in the treatment of hypotensive states, stroke, spinal cord injury and other miscellaneous conditions. This may seem paradoxical at first sight for an agent viewed traditionally as a pure opioid antagonist.

In hypotensive states it has been shown in animal models that naloxone increases arterial pressure in both endotoxic and hypovolaemic shock. Some reports have confirmed a similar effect in patients (Peters et al., 1981), although the effect was not observed in patients who were hypoadrenocortico-trophic or receiving high-dose corticosteroids, which indicates that pituitary beta-endorphin plays a role in the hypotensive state (see review by Pinnock (1985)). Weisglass (1983) has shown that naloxone does not produce its effect by a direct action on the myocardium and the following mechanisms have been proposed: centrally mediated increase in sympathetic tone, central inhibition of parasympathetic output, peripheral antagonism of opioid peptides released in shock states or a cellular action of stabilization of lysosomes. Certainly, administration of naloxone may be accompanied by a sharp increase in circulating catecholamine concentrations especially in patients with phaeochromocytoma (Manelli et al., 1983). The discovery of opioid peptides in intimate relationship with the splanchnic nerve in the adrenal medulla has led to speculation that these may play a regulatory neurotransmitter role with regard to the release of catecholamines. In addition, a number of opioid peptides have been discovered within the adrenal gland, although their role and significance remain obscure.

Naloxone has been shown to reduce neurological deficit in animals after cerebral and spinal cord ischaemia. Hosobuchi, Baskin and Woo (1981) found that, in gerbils, the clinical signs of stroke produced by carotid occlusion were reversed by intraperitoneal naloxone, although this effect lasted only 30 min. Subsequently, naloxone i. v. was reported to reverse hemiplegia in two patients with stroke, although this effect was again transient. Although one recent report has implicated the vehicle rather than the active drug as the mechanism whereby naloxone exerts its effect in the gerbil model (Crockard et al., 1983), a large body of other experimental data from animal work has confirmed that naloxone may ameliorate the neurological deficit following a cerebral ischaemic insult (see review by Milne and Jhamandas, 1984).

The mechanism of a beneficial effect of naloxone following spinal cord injury defies elucidation, but possible explanations involve an improvement in local blood supply to the ischaemic site, either by a reduction of local oedema or by a direct vascular effect (Faden, 1983).

It seems certain that naloxone can cause an increase in cerebral and spinal cord blood flow, a finding which is consistent with the presence of opioid receptors on CNS vessels. However, there is sufficient conflict in the conclusions drawn from laboratory studies in this area to suggest that considerably more research is required before extrapolations can be made from the experimental to the clinical situation. Data on the clinical use of naloxone in this area are largely anecdotal and the results of controlled studies are required before any recommendations can be made.

Naloxone has been used successfully to treat overdosage with benzodiazepines, alcohol and barbiturates. In the case of alcohol, condensation products resulting from metabolism (the isoquinolines) have opioid-like actions, which may explain this particular antagonist effect. In respect of the benzodiazepines and barbiturates it is possible that a non-specific analeptic action may account for the mechanism of action of naloxone. However, it has been postulated that there is an interaction of the opioid neurotransmitter system with other systems (notably gamma amino butyric acid) and, thus, possibly with the benzodiazepine receptor also, which could provide an alternative explanation.

In addition to these major areas of interest to the anaesthetist, naloxone has also been used in a number of unrelated conditions with apparently beneficial results including: schizophrenia, chronic idiopathic constipation, intractable pruritus and thalamic pain syndrome.

It is clear, therefore, that naloxone cannot be regarded as a simple antagonist of opioid-induced respiratory depression. Whilst many of its diverse and apparently paradoxical actions have now become explicable on the basis of the endogenous opioid peptide system, some await clarification, particularly those actions which are not stereospecific
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(such as the reversal of the inhibition of spinal neurones caused by GABA).

There is little doubt that the rapid progress currently being made in the elucidation of opioid physiology will provide the basis for understanding many of the complex effects of this agent. The development of receptor-specific antagonists will provide the key to further elucidation of the endogenous opioid system and may also provide the anaesthetist with a drug which will antagonize respiratory depression without the unwanted effects of naloxone, particularly antagonism of analgesia.

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REFERENCES


