USE OF NARCOTIC ANTAGONISTS IN ANAESTHESIA

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- 1 The introduction of morphine antagonists into anaesthesiology has aroused great scientific interest, increased our knowledge of analgesia, and opened new frontiers for therapeutics.
- 2 The advantages and disadvantages of these compounds are described and assessed.
- 3 The best choices for treatment of pain are the most potent and long-acting drugs of this group with a wide safety margin. As an antidote to narcotic agonists, naloxone seems to be the most suitable drug in the majority of cases, although in certain conditions drugs having less rapid onset of action and of longer duration may be more desirable.
- 4 In all cases of treatment after anaesthesia when antagonists to narcotic analgesics are used, drug administration must depend on careful control, which necessitates specific and prolonged patient care by specifically trained and competent staff.

Introduction

THE interest of anaesthetists in morphine antagonists has developed in parallel with their interest in analgesia and in analgesic anaesthesia. Indeed, practical application of this group of drugs has developed in anaesthesia in two directions: they are used in anaesthesiology for either their analgesic (agonist) properties, or for their narcotic antagonist properties (Table 1).

The products that are available at present or that are in an advanced stage of clinical investigation are butorphanol, naloxone, nalorphine, pentazocine and buprenorphine. As nalorphine and pentazocine are well-known drugs, this review will concentrate on a discussion of naloxone, butorphanol and buprenorphine, three typical products among the recent acquisitions to this group of drugs.

Agonist properties of narcotic antagonists

Pure antagonists

Naloxone, a pure antagonist, has no characteristic activity of its own when it is used at clinical dosages of 0.4–4 mg in the absence of a previously administered narcotic (Evans, 1974; Foldes, 1969; Jacob, 1974; Longnecker, 1973).

Mixed agonist-antagonists

Such compounds generally show all the effects of the pure agonist drugs but with a profile of potency, toxicity and kinetics characteristic for each product.

The effects, as with all morphine-like drugs, consist of a mixture of excitation phenomena and depression although with certain agents (for example, cyclazocine) the excitatory effects (dysphoria, nalorphine-like effects) are dominant at clinical doses, and this makes them less suited for use in anaesthetics. The depressive effects of the agonist-antagonists (analgesia, sedation, somnolence, respiratory depression, anti-tussive action, and so on) are a result of CNS depression, which also manifests itself in changes in EEG patterns similar to those observed for the pure agonists such as morphine (reviewed in De Castro, 1978).

The analgesic potency of this group of compounds varies greatly. Of particular interest are two recently developed drugs — butorphanol and buprenorphine — which are more potent than morphine (Houde, 1979). The duration of action of most of the agents in this class is of the same order as that of morphine. Buprenorphine is an exception, showing greater duration of action (Houde, 1979).

The agonist-antagonists, especially the less potent products, have a relatively low epileptogenic threshold. For example, convulsions are produced in the dog after a lower dose of nalorphine (110 mg/kg intravenously) than for morphine (180 mg/kg intravenously), although the analgesic potency of these two compounds is similar (De Castro *et al.*, 1978). The therapeutic index becomes more favourable in the more potent agents (De Castro *et al.*, 1978). Thus the agonist-antagonists are similar to the pure agonists in that their safety margin increases with their analgesic potency.

Table 1 Uses of morphine antagonists in anaesthesiology

As analgesics and anti-tussive drugs:	
Analgesic component in anaesthesia	
(1) Pre-operative	Premedication
(2) Per-operative	Pure analgesic anaesthesia
	Potentialised analgesic anaesthesia
	General anaesthesia; "balanced anaesthesia"
	Analgo-sedation
	Complement to local-regional anaesthesia
(3) Post-operative	Post-operative analgesia
Treatment of severe pain	Acute pain
	Chronic pain
As anti-tussive drug during mechanical ventilation	
As antagonists of opioids:	
Treatment of intoxication by opioids	Unwanted overdosage
	Deliberate overdosage: in obstetrics
Treatment of respiratory depression after anaesthesia with opioids	Sequential analgesic anaesthesia
	Potentialised analgesic anaesthesia

Antagonist properties of narcotic antagonists

As well as their usefulness as analgesics, compounds with narcotic antagonist action can also be used in the treatment of all forms of overdosage with opiates. Thus, in anaesthesia they are useful in reversing respiratory depression after analgesic anaesthesia, that is, in sequential analgesic anaesthesia. The characteristics of these agents which are important in this field are antagonist potency, the kinetic profile of the antagonist action, and the absence of secondary effects such as dysphoria.

Techniques of analgesic anaesthesia differ according to the importance given to the narcotic in the mixture of anaesthetics. Sequential analgesic anaesthesia consists of the use of pure analgesic anaesthesia during the surgical intervention and reversal of the excess of analgesia and of the respiratory depression at the end of the intervention by the sequential use of a pure antagonist or an analgesic with narcotic antagonist action. The most suitable pure antagonist in this field is certainly naloxone, although this agent has disadvantages in that the reversal of narcotic effects with naloxone is very rapid and complete. An acute abstinence syndrome can appear when reversal takes place so abruptly, accompanied by a metabolic stimulation directly proportional to the dose of opiate used, to the interval which precedes the reversal, to the dose of antagonist used, to the speed of antagonist administration, and to the rapidity of its antagonist action (De Castro, 1976). For example, a serious imbalance between myocardial oxygen requirement and available oxygen (MVO_2 demand/ MO_2 supply)

can result in ischemia in coronary patients (Patschke, 1977).

Buprenorphine when used as an antagonist is of slower onset, with the result that acute withdrawal effects, though apparent, are attenuated with this agent. The use of buprenorphine as an antagonist in this situation has the added advantage of ensuring a long-lasting, pain-free postoperative period (De Castro, 1976).

The use of a morphine antagonist at the end of anaesthesia should never be routine. In many cases prolongation of mechanical ventilation represents the best treatment of post-anaesthetic respiratory depression.

Conclusions

The best choices for the treatment of pain are the most potent and long-acting drugs (buprenorphine and butorphanol) which possess a wide safety margin. As an antagonist of the pure narcotics, naloxone seems to be the most suitable drug in the majority of cases, although in certain conditions drugs of less rapid onset of action and of longer duration, such as buprenorphine, may be more desirable. In all cases of treatment after anaesthesia, when narcotic antagonists are used, drug administration must depend on most careful control, which necessitates specific and prolonged patient care by specifically trained and competent staff.

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