ADVERSE EFFECTS OF OPIOID ANALGESIC DRUGS

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An “opioid” is a drug with morphine-like actions. It may reproduce some of the effects of the endogenous peptides, enkephalins, endorphins and dynorphins, which occur naturally in the central nervous system, and act through multiple receptors. The desired clinical effects are usually relief of pain and diarrhoea or suppression of cough. Opioid antagonist drugs bind receptors without producing an effect. There are partial agonists and opioid agonist/antagonist drugs which, as their name suggests, have intermediate effects.

All opioids share the side effects of respiratory depression, cough suppression, reduced intestinal motility, nausea, vomiting and urinary retention. Tolerance to their effects and both physical and psychological dependence may develop. Hypersensitivity reactions have been reported rarely after i.v. injection. Teratogenic and carcinogenic effects have not been described.

EPIDEMIOLOGY OF THE USE OF OPIOIDS

Opioid analgesics are used widely in hospital practice. In the Boston Collaborative Drug Surveillance Program, 29.7% of 39946 patients in hospital received at least one opioid analgesic preparation. In a study of 628 patients made over 6 months in 15 intensive care units, sedative and analgesic drugs were prescribed more frequently than any other groups of drugs (Farina, Levati and Tognoni, 1981). Morphine was prescribed to 35% of 200 critically ill patients, who received an average of seven different drugs (Buchanan and Cane, 1978).

In anaesthesia, opioids are used frequently for premedication, intraoperative and postoperative analgesia. In the Western Infirmary, Glasgow, a computerized anaesthetic record system has been in operation for 6 years (Todd, Duthie and Spence, 1983). From April 1980 to June 1984, records of 64645 anaesthetics reveal that 41% of patients received opioid premedication and 28% were given opioids during operation to supplement anaesthesia. Volatile anaesthetic agents were used in 94% of all anaesthetic procedures recorded.

EXAMPLES OF OPIOID ANALGESIC DRUGS

The British National Formulary lists 12 opioid drugs under “Narcotic and other analgesics for severe pain” and three “Narcotic analgesics for mild to moderate pain” (table I). Naloxone is the only “opioid antagonist for respiratory depression”, although naltrexone and nalmefene are available on clinical trial.

PHARMACOLOGICAL EFFECTS

Mechanisms of Action of the Opioid Analgesics

Opioids dull the appreciation of pain without loss of consciousness. The affective response to pain is altered such that the perception of pain may be preserved whilst the threshold of pain tolerance is increased markedly. The sites of action for analgesic effects are located principally in the brainstem and spinal cord. Endogenous sensory control systems are activated to filter sensory inputs at the level of the spinal cord (Jordan, 1984). Other sites may be responsible for the effects that opioids have on mood and the behavioural response to pain.

Opioids act centrally at both pre- and postsynaptic sites. They inhibit selectively the release of excitatory transmitters from terminals of nerves carrying nociceptive stimuli. Neurones are hyperpolarized, which suppresses spontaneous discharge and evoked responses (Duggan and North, 1983). Opioids do not block nerve conduction in primary afferent fibres at concentrations likely to be achieved after systemic adminis-
Opioid receptors have been demonstrated near the dorsal root ganglion (Fields, Emson and Leigh, 1980) and opioids are placed at this site in high concentration by extradural or intrathecal administration. What effect opioids have on afferent neurones at these sites is still unresolved.

Opioid effects are mediated through multiple opioid receptors (Martin et al., 1976) (table II). Drugs may act at more than one opioid receptor, with varying effects. For example, pentazocine is a weak μ antagonist, but a strong κ agonist. Naloxone is an antagonist at both receptors, but has a greater affinity for the μ receptor (Pleuvry, 1983). Subpopulations of receptors have been proposed. Work in isolated animal tissues, such as guineapig myenteric plexus—longitudinal muscle and mouse vas deferens, has provided a wealth of data. These data are sometimes conflicting and difficult to relate to the clinical effects of opioids.

The adverse effects of opioids result either from a direct toxic effect of the drug or from recognized actions mediated through opioid receptors. An opioid with an action specific for one receptor subtype, with an appropriate affinity and receptor binding holds theoretical advantages for specificity of action with reduced side effects.

The opioid antagonists, naloxone, naltrexone and nalmefene are effective in reversing the adverse effects of opioids, but restore acutely the awareness of painful stimuli. Naloxone and naltrexone have no agonist effects when given on their own in clinical doses (McNicholas and Martin, 1984). Nalmefene exhibits a prolonged duration of action, which appears to be dose related (Gal and DiFazio, 1986).

**Relationship Between Plasma Concentration and Effects**

Steep concentration–effect curves have been demonstrated for pethidine. In 95 observations in nine patients after intra-abdominal or joint surgery, there was only a difference of 50 ng ml\(^{-1}\) between the mean plasma pethidine concentration at which severe pain was experienced (410 ng ml\(^{-1}\)) and the mean, minimum plasma pethidine concentration at which pain was relieved (460 ng ml\(^{-1}\)) (Austin, Stapleton and Mather, 1980a).

Plasma concentrations of opioid which provide effective analgesia after abdominal surgery vary considerably between individuals. The coefficients of variation in minimum effective analgesic concentration were as high as 39% after hysterectomy when pain was relieved by i.m. pethidine (Austin, Stapleton and Mather, 1980a) and 57% after intra-abdominal surgery, relieved by morphine i.v. from a patient controlled analgesia device (Dahlström et al., 1982). Doubts about the accuracy and reproducibility of the available methods for assaying opioids have been expressed (Faulding and Hall, 1984). Analytical errors may explain inconsistencies in the results of pharmacokinetic studies obtained in different laboratories.

Although significant, the variation between patients in concentration and effect is slight compared with the pharmacokinetic variation in the plasma concentration obtained from a dose of opioid, by whichever route it is given (Hug, 1984). Following i.m. injection of pethidine 100 mg to 10 patients who had undergone hysterectomy or cholecystectomy, there was a five-fold variation in the peak plasma pethidine concentration measured (240–1210 ng ml\(^{-1}\)), and a seven-fold variation in the time taken for the peak concentration to be reached (15 min–1.8 h) (Austin, Stapleton and Mather, 1980b). Morphine 0.15 mg kg\(^{-1}\) given i.m. either as premedication or as postoperative analgesia to 41 surgical patients resulted in peak plasma morphine concentrations which varied from 30 to 160 ng ml\(^{-1}\) and were achieved between 4 and 60 min after injection (Rigg et al., 1978).

Minimizing the pharmacokinetic variation by constant infusion of opioid to steady state is possible in the time opioids are given after surgery. After two loading infusion rates, i.v. infusion of pethidine 24 mg h\(^{-1}\) for 32 h in 10 hysterectomy patients has produced stable plasma pethidine concentrations and excellent pain control.
### Table II. Opioid receptors

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Effect</th>
<th>Agonist</th>
<th>Antagonist</th>
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<tr>
<td>mu, µ</td>
<td>Analgesia (supraspinal)</td>
<td>Morphine</td>
<td>Naloxone</td>
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<td></td>
<td>Ventilatory depression</td>
<td>-partial</td>
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<td>Depression of temperature regulation</td>
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<td>Miosis</td>
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<td>Euphoria</td>
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<td>Indifference to the environment</td>
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<td>Bradycardia</td>
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<td>Physical dependence (morphine type)</td>
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<tr>
<td>kappa, κ</td>
<td>Analgesia (spinal)</td>
<td>Morphine</td>
<td>Naloxone</td>
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<td></td>
<td>Sedation</td>
<td>Pentazocine</td>
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<td></td>
<td>Miosis</td>
<td>Butorphanol</td>
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<td></td>
<td>?Respiratory depression</td>
<td>-partial</td>
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<td></td>
<td>Physical dependence (distinct from morphine)</td>
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<td>sigma, σ</td>
<td>Dysphoria, delerium</td>
<td>Butorphanol</td>
<td>Naloxone</td>
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<td></td>
<td>Hallucinations</td>
<td>(Nalbuphine)</td>
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<td>Muscle tone</td>
<td>(Nalorphine)</td>
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<td>Tachycardia</td>
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<td>Ventilatory stimulation</td>
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<td>Vasomotor stimulation</td>
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<td>Mydriasis (not analgesia)</td>
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<tr>
<td>delta, δ</td>
<td>? Respiratory depression</td>
<td>D-Ala, D-Leu-enkephalin (DADL)</td>
<td>Naloxone</td>
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Adverse Effects

Adverse effects may be classified as: (1) Predictable: a dose-related extension of pharmacological effects; or (2) Unpredictable.

Predictable adverse effects, such as respiratory depression and nausea and vomiting are documented well in the literature. Unpredictable effects have been reported usually as isolated case histories or small, uncontrolled series. Examples of adverse effects according to body system are given below.

Respiratory system

Mechanisms of opioid respiratory depression. The respiratory depressant effects of opioid analgesics are dose related and linked intimately to their analgesic effects. Opioids exert direct depressant effects on the pontine and bulbar brainstem respiratory centres. Patients have to rely on hypoxic drive to stimulate ventilation, similar to patients with chronic obstructive airways disease,
whose arterial carbon dioxide tensions are increased persistently above normal (Bewley and Ghodse, 1984).

Increased reliance on hypoxic drive after opioid therapy is illustrated in a case report of one patient who developed respiratory depression requiring assisted ventilation after bilateral carotid endarterectomy and morphine 6 mg i.m. The same dose had been given to the patient before endarterectomy without ill effect. Damage to the nerve or vascular supply to the carotid bodies was considered to be the cause of the increased sensitivity to the respiratory depressant effects of morphine (Lee et al., 1981). The reduced response to hypoxia following carotid endarterectomy may persist for up to 10 months (Wade et al., 1970).

The respiratory stimulant, almitrine, enhances ventilation by an effect on the peripheral chemoreceptors of the aortic and carotid bodies. It has no central effects on the brain stem. The respiratory depressant effects of fentanyl 6.6 μg kg⁻¹ i.v. were antagonized in five female patients before surgery by almitrine 0.5 mg i.v. Tidal volume, respiratory rate and expired minute volume were all reduced significantly in five control patients who received fentanyl alone. There were no significant changes in tidal volume and respiratory rate in the five patients who were given fentanyl and almitrine. Expired minute volume did decrease in these patients, but by half as much as in those who received fentanyl alone (Gaudy, Dauthier and Fourgeaux, 1982).

Pain is an effective antagonist to the respiratory depressant effects of opioids. Abolition of pain by cervical anterolateral cordotomy (Wells, Lipton and Lahuerta, 1984) or neural blockade (Hanks, Twycross and Lloyd, 1981) in patients treated with opioids for painful conditions has been followed by respiratory depression as a result of persisting unopposed opioid action.

**Measurement of respiratory depression.** The effects of drugs on respiration have been quantified by measurement of the stimulus to ventilation provided by an increased partial pressure of carbon dioxide in inspired gas. The results are plotted to give alveolar ventilation–alveolar Pco₂ response curves. An increased or decreased threshold of the respiratory centre to carbon dioxide is represented by parallel displacement of the response curve to the right or left respectively. The gradient of the response curve is related directly to the sensitivity of the respiratory centre to carbon dioxide (Read, 1967). The respiratory pattern following opioid administration is often irregular. Breathing rate must be measured over at least 1 min in order to avoid inaccuracies from sampling errors in a respiratory pattern resembling Cheynes–Stokes breathing.

Airway occlusion pressures in response to carbon dioxide stimulation are increased when patients experience pain. After extradural morphine, airway occlusion pressures are reduced, but not below control measurements made before anaesthesia and surgery. Supporting patients in a 45° elevated position makes no difference to occlusion pressures measured in the postoperative period (Molke Jensen et al., 1984).

Morphine 10 mg and phenoxyperidine 1.5 mg reduced expired minute volume by 20–35% but, concurrently, reduced oxygen consumption by 20–30%. Minute volume changed in response to both drug action and metabolic requirements (Jennett, Barker and Forrest, 1968). Arterial or end-tidal carbon dioxide tensions must therefore be measured to determine the adequacy of ventilation in relation to carbon dioxide production (Jordan, 1982).

**Clinical examples of opioid respiratory effects.** In 17 surgical patients morphine 0.15 mg kg⁻¹ i.m. before surgery caused a significant increase in mixed venous carbon dioxide tensions and displaced the carbon dioxide response curve to the right. These changes correlated poorly with plasma morphine concentrations (Rigg, 1978).

Although the analgesic and ventilatory effects of opioid partial agonist drugs are related, the maximal effects of these drugs are less than those of pure agonists. Excessive doses of pentazocine, butorphanol, buprenorphine and nalbuphine cause moderately severe respiratory depression unlike the apnoea that is produced by pure agonists (Bellville and Green, 1965; Heel et al., 1978, 1979; Romagnoli and Keats, 1980). In 23 volunteers, nalbuphine 30 mg produced respiratory depression similar to that from morphine 20 mg. However, the dose–response curve for respiratory depression was flatter for nalbuphine than for morphine. Increasing the dose of nalbuphine to 60 mg produced respiratory depression no greater than that produced by nalbuphine 30 mg (Romagnoli and Keats, 1980). This “ceiling effect” for respiratory depression with nalbuphine has been demonstrated for another opioid partial agonist, nalorphine (Keats and Telford, 1966).
Opioid partial agonists have been used to antagonize the respiratory depression caused by pure opioid agonists. Large doses of pure agonists are used during anaesthesia to take advantage of the cardiovascular stability of these drugs. Partial agonists are then used instead of pure antagonists to antagonize respiratory depression, but not analgesia. For example, increments of nalbuphine up to 150 μg kg⁻¹ were effective initially in reversing respiratory depression in patients who had received fentanyl 90–120 μg kg⁻¹ during anaesthesia, but some recurrent respiratory depression did occur (Moldenhauer et al., 1985). In 53 elderly orthopaedic patients, pentazocine was effective in reversing respiratory depression from fentanyl without any further important side effects (Rifat, 1972).

Respiratory depression occurs after extradural injection of opioids, but may be delayed some hours (Hammond, 1984). In 1200 patients receiving extradural morphine 2 mg in saline 10 ml there was only one report of respiratory depression, which was antagonized on two occasions by naloxone 0.2 mg i.v. without loss of analgesia. A second dose of extradural morphine elicited no respiratory depression in this patient (Reitz and Westberg, 1980). Respiratory depression by extradural opioids may be antagonized by opioid partial agonists in addition to pure antagonists. Nalbuphine has reversed delayed respiratory depression after extradural diamorphine without return of pain (Hammond, 1984). The duration of analgesia provided by extradural opioids is said be dose related. However, a morbidly obese patient who received an accidental overdose of extradural morphine did not develop respiratory difficulties. She received two doses of morphine 50 mg, which provided analgesia for only 10 and 23 h respectively (Robinson, 1984).

The respiratory depressant effects of opioids are antagonized by both opioid antagonists and physostigmine. Physostigmine preserves the analgesic action of opioids and is effective after systemic opioid administration (Weinstock et al., 1982; Snir-Mor et al., 1983).

Cough suppression. Codeine is an effective cough suppressant and is prescribed for this effect when constant coughing serves no useful purpose, is irritating and prevents sleep. Codeine has a low affinity for opioid receptors and its analgesic properties may depend on prior conversion to morphine. The potent antitussive actions of codeine have prompted suggestions that there are opioid receptors which mediate cough suppression, distinct from receptors mediating analgesia and for which codeine has a high affinity.

Cough suppression is a side effect common to all opioid analgesics. It impairs the clearing of sputum and inhaled secretions effectively from the lungs and predisposes to pulmonary infection (Jaffe and Martin, 1985).

Cardiovascular system

Histamine release. Following opioid administration, orthostatic hypotension may occur, especially with hypovolaemia, by direct and indirect mechanisms (Lowenstein, Whiting and Bitter, 1972). Venous capacitance may be increased directly (Hsu, Hickey and Forbes, 1979) whereas, indirectly, histamine release is implicated with morphine and pethidine, but not after methadone and fentanyl (Gardocki and Yelnosky, 1964; Thompson and Walton, 1966). The cardiovascular effects of fentanyl are less than morphine, even in patients with severe cardiac disease (Stanley and Webster, 1978).

Histamine released by opioid drugs is associated with pruritis, urticaria, hypotension and a decrease in systemic vascular resistance (Philbin et al., 1981). In human mast cells derived from skin, morphine, in concentrations of 1.5 × 10⁻⁴ and 5 × 10⁻⁴ mol litre⁻¹ was responsible for the release of histamine in vitro. Calcium 1–4 mmol litre⁻¹ was necessary for histamine release, which increased with increasing morphine concentration up to a maximum at morphine 5 × 10⁻⁴ mol litre⁻¹. No histamine release was demonstrable in basophils and the opioid oxymorphone, chemically similar to morphine, produced no such effect (Hermens et al., 1985).

In 45 surgical patients, histamine release was four times as likely in patients given pethidine 4.3 mg kg⁻¹ than in those given morphine 0.6 mg kg⁻¹. The newer synthetic opioids, fentanyl and sufentanil, had no such effect, which may explain the cardiovascular stability of these drugs (Flacke, Van Etten and Flacke, 1983). In eight patients before cardiopulmonary bypass, morphine 1 mg kg⁻¹ increased mean plasma histamine concentrations seven-fold and was associated with an average reduction in mean arterial pressure of 27 mm Hg and a 42% reduction in systemic vascular resistance. The decrease in systemic vascular resistance correlated well with the plasma histamine concentration. Seven other patients
given fentanyl 50 \mu g \text{ kg}^{-1} demonstrated no change in plasma histamine concentration and no reduction in mean arterial pressure or systemic vascular resistance (Rosow et al., 1982).

Clinically, the effects of histamine release by morphine were antagonized by a combination of \text{H}_1- and \text{H}_2-receptor antagonists such as diphenhydramine and cimetidine, without obting the increase in plasma histamine concentrations. On their own, they offered little protection to the decrease in systemic vascular resistance and diastolic pressure and increase in cardiac index associated with marked increases in plasma histamine concentrations (Philbin et al., 1981). Naloxone does not stimulate histamine release from mast cells \textit{in vitro} and does not inhibit histamine release produced by morphine. There is no increase in lactate dehydrogenase associated with histamine release from mast cells (Hermens et al., 1985).

Histamine release, therefore, is considered to be a displacement reaction, related to the dose and molar concentration of morphine or pethidine and not a non-specific effect of opioids, related to analgesic potency. It is not determined by opioid receptor binding and is not related to cell membrane damage.

\textit{Response to intubation.} Analgesic doses of opioid drugs in normovolaemic patients with adequate cardiac function are unlikely to affect the cardiovascular system adversely. One cardiovascular effect of benefit to the anaesthetist is the attenuation of the pressor response to tracheal intubation. Fentanyl 3 \mu g \text{ kg}^{-1} \text{i.v.} before induction of anaesthesia is sufficient to prevent increases in systemic arterial pressure and heart rate during tracheal intubation in geriatric patients (Chung and Evans, 1985).

Indirect effects may occur via the sympathetic nervous system. Small doses of opioids are associated with increased plasma concentrations of adrenaline and noradrenaline, which increase heart rate and arterial pressure. This response is accompanied by increases in blood glucose and antidiuretic hormone concentrations (Hasbrouck, 1970). Such plasma catecholamine changes are not seen with the high doses of opioids used in anaesthesia for cardiac surgery (Stanley et al., 1980).

\textit{Vagus nerve.} Opioids may exert effects via the vagus nerve (Reitan et al., 1978). Pethidine has been implicated when heart block developed in a patient with an inferior myocardial infarct (Gershengorn and Haft, 1972). In rabbits, propoxyphene and norpropoxyphene prolong atrioventricular conduction and slow heart rate (Lund-Jacobson, 1978). The same effect with morphine is disputed. In a survey of 154 patients with proven myocardial infarction who received morphine, the four sustained hypotensive episodes which occurred were considered to result from an inappropriate heart rate in response to a reduction in arterial pressure and not from a primary conduction defect. These episodes followed first administration of morphine and were not apparent with repeat doses. There was no association with inferior myocardial infarction (Semenkovich and Jaffe, 1985). Direct chronotropic and inotropic effects are not important in doses of opioids used clinically (Eckenhoff and Oech, 1960).

\textit{Opioid antagonists.} Naloxone can cause hypertension, pulmonary oedema and ventricular fibrillation when given to antagonize the effects of opioids (Tanaka, 1974; Flacke, Flacke and Williams, 1977; Azar and Turndorf, 1979; Cuss, Colaco and Baron, 1984; Prough et al., 1984). Although found usually in patients with pre-existing cardiopulmonary disease, cardiac arrest has been reported in previously healthy patients (Andree, 1980), as has pulmonary oedema, even when naloxone was given i.v. in small increments (Taff, 1983). It is not clear if these are drug effects or if they result from the experience of severe pain.

Naloxone may partially antagonize the hypotension associated with shock of varied aetiology, possibly by antagonism of the effects of endogenous opioids (Holaday, 1983). No changes in arterial pressure are seen when normotensive and hypertensive subjects are given clinical doses of naloxone (Estilo and Cottrell, 1982), but hypotension has been induced in a patient given a total of naloxone 26 mg i.v. over 2.5 h. This hypotension was antagonized by concurrent administration of clonidine, which produced profound hypotension when given alone (Levin et al., 1985).

\textit{Miscellaneous.} Gangrene has been produced by accidental i.a. injection of pethidine, pentazocine, diamorphine and dextropropoxyphene. Arterial injection of crushed codeine tablets has caused gangrene, but it was the microcrystalline cellulose, not codeine which was the responsible ingredient. This ingredient is present in formulations of oral
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methadone, oxycodone, paracetamol, aspirin with
codeine and dextropropoxyphene (Goldberg,
Bahir and Yosipovitch, 1984).

Gastrointestinal system

Gastro-oesophageal reflux. Decreased lower
oesophageal pressure has been demonstrated in
35 volunteers given doses of opioids i.v., just
sufficient to induce drowsiness. Morphine
7–10 mg and pethidine 40–50 mg decreased lower
oesophageal pressure and increased the severity of
reflux in those with pre-existing spontaneous
oesophageal reflux (Hall et al., 1975). Similar
effects were produced in volunteers by pethidine
1–3 mg (Hey et al., 1981). By decreasing lower
oesophageal pressure, opioid drugs make regurgi-
tation and aspiration of gastric contents more
likely (Cotton and Smith, 1984).

Gastric emptying and intestinal transit. Opioids
reduce gastrointestinal motility with an increase
in tone in the gastric antrum and the first part of
the duodenum. Longitudinal propulsive peristalsis
is reduced, whereas contractility and sphincter
tone are increased.

Ileus after surgery results from neurogenic
inhibition of gastrointestinal motility mediated by
non-cholinergic, non-adrenergic vagal inhibition
of the stomach and sympathetic inhibition
throughout the gastrointestinal tract (Lisander
and Stenqvist, 1985). Systemic opioid drugs may
aggravate postoperative ileus by constricting
smooth muscle, delaying gastrointestinal transit,
and inhibiting gastric emptying (Nimmo, Wilson
and Prescott, 1975; Nimmo et al., 1975).

Gastric emptying in seven patients, measured
24 h after hysterectomy, was significantly reduced
by diamorphine 5 mg i.m. given every 6 h to
relieve pain. Gastric emptying was assessed by
measurement of the rate of paracetamol absorption
following oral administration of the drug. There
was little difference from normal in gastric
emptying when the patients’ pain was relieved by
extradural lignocaine (Nimmo et al., 1978). In 30
chloralose anaesthetized cats, extradural fentanyl
counteracted sympathetic inhibition of gastroin-
testinal motility, assessed by measurement of
gastric volume. This effect was reversed by
extradural naloxone and not reproduced by i.v.
fentanyl (Lisander and Stenqvist, 1985). Both
avoiding systemic opioid drugs and relieving the
sympathetic inhibition of gastrointestinal motility
appear to be effective in minimizing ileus after
surgery.

Naloxone antagonizes opioid–induced delay in
gastric emptying and drug absorption, but can
itself affect gastric motility. Naloxone 2 mg
delayed gastric emptying of solids in healthy
volunteers (Champion et al., 1982).

Decreased colonic motility as a result of opioids
doesesicated faeces and constipation. This is
reversed by naloxone, but analgesia is forfeited.
By diminishing intestinal secretion and peristaltic
activity, opioids are effective antidiarrhoeal
agents (Awouters, Niemegeers and Janssen,
1983).

Constipation may be prevented by anthraquinone
cathartics (senna, cascara, danthron and aloe).
These drugs must undergo transformation in the
colon to active metabolites and therefore are
effective on the distal colon only (Hardcastle and
Wilkins, 1970). They act directly on the wall of
the colon to stimulate longitudinal peristalsis. A
dose of 3.75 mg of total sennosides is effective in
reversing the constipation produced by codeine
60 mg or its equivalent (Maguire, Yon and Miller,

Gastrointestinal secretions. Opioids reduce gas-
tric, biliary and pancreatic secretions and can
inhibit secretions provoked by secretagogues such
as prostaglandin E2 (Turnberg, 1983). The
volume and pH of gastric contents of surgical
patients, when aspirated immediately after tra-
cheal intubation, were no different 2 h after oral
naloxone or placebo (Molke Jensen, Thiessen and
Christensen, 1986).

Together, these effects can cause symptoms of
abdominal pain, vomiting, weight loss and
apparent intestinal obstruction after repeated
opioid administration (Sandgren, McPhee and
Greenberger, 1984). Clonidine is effective in
alleviating such symptoms by enhancing intestinal
motility (Lechin and van der Dijs, 1983) and
promoting fluid and electrolyte absorption
(McArthur et al., 1982).

Blood flow. The effects opioids have on
gastrointestinal blood flow vary according to the
drug and the dose at which it is given. In dogs,
fentanyl demonstrates a dose-dependent decrease
in intestinal vascular resistance, an increase in
flow and a decrease in oxygen uptake. The net
effect is an increase in hepatic oxygen supply.
Morphine 1 mg kg$^{-1}$ produced no change in total
intestinal blood flow, but the proportion directed through nutritive exchange vessels increased, possibly as a result of histamine release. At five times this dose, morphine increased vascular resistance mediated by adrenaline released from the adrenal gland (Tverskoy et al., 1983).

**Entero-systemic circulation of opioids.** Secondary peaks are seen often in plasma concentration-time graphs during pharmacokinetic studies of the more lipid soluble opioids. Increased plasma concentrations long after opioid administration has ceased may explain reports of delayed respiratory depression associated with opioids (Adams and Pybus, 1978; Sebel et al., 1984). Controversy exists over whether or not this results from absorption of opioid, first sequestered in the acidic gastric juices then absorbed from the small intestine. Opioid drugs are subjected to a high first pass clearance from the gastrointestinal tract, which must be overcome for entero-systemic circulation to affect plasma concentrations. In dogs, gastric sequestration of fentanyl has been demonstrated, but a small fraction only of the dose administered appeared in the stomach. Hepatic extraction failed to prevent recirculation, but the dose of fentanyl was 100 μg kg⁻¹ (Clark et al., 1985).

**Liver and biliary system**

**Hepatocellular damage.** Increased plasma liver enzyme concentrations and centrilobular hepatic necrosis have been demonstrated in spontaneously breathing mice and rats after subanaesthetic doses of fentanyl. These changes are similar to those seen with volatile anaesthetic agents under the same conditions (Baden et al., 1985). Liver damage increases with increasing doses of fentanyl in hypoxic rats (Shingu et al., 1983). It occurs with small doses of fentanyl injected to the cerebral ventricles and is prevented by simultaneous naloxone administration (Needham et al., 1981). The mechanism proposed is liver hypoxia rather than a direct toxic effect (Shingu et al., 1983). Increases in liver enzyme concentrations were the same for cirrhotic and non-cirrhotic animals (Baden et al., 1985).

In dogs, fentanyl improved intestinal blood flow and decreased oxygen uptake, improving liver oxygen supply. However, the lungs of these dogs were ventilated artificially (Tverskoy et al., 1985). The conflicting findings of hypoxic liver damage and improved hepatic oxygenation, both attributed to fentanyl, may result from a species difference or the prevention of hypoxia by artificial ventilation of the lungs.

**Biliary function.** The tone of the choledochoduodenal sphincter is increased by opioid analgesics. Opioid premedication in patients with biliary disease may cause sphincter pain severe enough to mimic acute cholecystitis or myocardial infarction (Lang and Pilon, 1980). Opioid drugs have been held responsible for preventing contrast medium reaching the duodenum during cholangiography (McCammon et al., 1978). However, in doses used during balanced anaesthesia, only 3% of abnormal cholangiograms were attributable to the anaesthetic technique (Jones et al., 1981). In two groups of 112 patients undergoing cholecystectomy either with or without a fentanyl supplement, only three patients, drawn from both groups, demonstrated sphincter spasm (Chisolm et al., 1983).

Pentazocine, unlike tramadol and buprenorphine, increases intrabiliary pressure and prolongs sphincter closure time, thus reducing bile flow through the ampulla of Vater (Staritz et al., 1985). The partial agonists nalbuphine and butorphanol decrease biliary flow rate and increase intrabiliary pressure less than morphine (McCammon, Stoe- tting and Madura, 1984). Naloxone and glucagon (Jones, Fiddian-Green and Knight, 1980) reverse the effects of opioids on the choledochoduodenal sphincter.

**Central nervous system**

**Tolerance and dependence.** Tolerance to the analgesic effects of opioid analgesics, and their ability to induce physical and psychological dependence is well known (Jaffe and Martin, 1985). In the clinical use of opioids during anaesthesia and for the relief of pain after surgery, reports of acute tolerance and dependence to opioid analgesics are rare. In the Boston Collaborative Drug Surveillance Program, dependence was documented in only four of 11882 patients who received an opioid analgesic drug and had no previous history of addiction (Porter and Jick, 1980). Hydromorphone, percodan and pethidine (twice) were the opioids responsible in these four cases of dependence, only one of which was considered “major”.

Acute tolerance to methadone was proposed when patients, who underwent orthopaedic surgery under local anaesthetic extradural blockade,
demanded more methadone i.v. after surgery than others, who had received methadone during the procedure as part of a balanced anaesthetic technique (Porter et al., 1983). Patients after cholecystectomy who received morphine by infusion for 24 h to provide a background of analgesia, demanded more morphine i.m. in the subsequent 24 h than those given a placebo infusion (Marshall et al., 1985). Animal studies have demonstrated that acute tolerance to fentanyl develops when opioids are given without painful stimuli, but not when pain is experienced at the time of opioid administration (Colpaert et al., 1980).

Patients anticipate pain after surgery and vary greatly in their analgesic requirements. Patients whose pain is treated effectively immediately after surgery by neural blockade or opioid infusion may be dissatisfied with a subsequent inferior analgesic regimen. Whether the greater demands for opioids reported in certain groups of patients resulted from acute tolerance to opioids or a greater expectation of success from analgesic therapy is unresolved.

**Cerebral toxicity.** Pethidine therapy can cause excitatory toxic effects in the central nervous system. Jitteriness, tremors, myoclonus and convulsions occur in progression proportional to the plasma concentration of norpethidine, an active metabolite of pethidine (Goetting and Thirman, 1985). Electroencephalographic (EEG) changes of slow wave activity and epileptiform discharges resolve when norpethidine is excreted, unless an underlying cause for seizures persists (Kaiko et al., 1983).

After therapeutic doses, high voltage, low frequency changes are seen in the electroencephalogram, as occur during natural sleep. At the high doses of opioids used in opiate anaesthesia for cardiac surgery, marked EEG effects are apparent. Fentanyl 30–70 μg kg\(^{-1}\) and sufentanil 15 μg kg\(^{-1}\) produce massive increases in the delta power of the EEG, when analysed by computerized three-dimensional power spectral analysis. High voltage, slow delta waves of 0.5–2.5 Hz were characteristic and the total power decreased with time. Although isolated sharp wave activity was seen over the frontotemporal region initially, no other excitatory activity was apparent (Sebel et al., 1981; Bovill et al., 1982). The effects of high dose opioids are depressive predominantly.

The pharmacokinetics of pethidine influence its cerebral toxicity. Pethidine undergoes extensive first pass metabolism when given orally (Mather and Tucker, 1976). An oral dose produces lower plasma concentrations of pethidine and higher concentrations of norpethidine than the same dose given parenterally (Stambaugh, Wainer and Stanstead, 1976). Norpethidine is cleared from plasma by the kidney. The oral route and renal impairment both increase the susceptibility of patients to cerebral toxicity from pethidine by increasing plasma concentrations of norpethidine (Kaiko et al., 1983).

Perceptual disturbances occur in 7–10% of patients taking pentazocine. Visual hallucinations are more common than auditory and reaction to these experiences varies from pleasure to intense dislike (Wood et al., 1974). Opioids affect motor function by central actions. Methadone can induce choreic movements of the upper limbs and torso and disordered speech. An interaction between methadone and opioid receptors is thought to influence the release of neurotransmitters such as dopamine, in the brain (Wasserman and Yahr, 1980). These effects resolved once methadone was withdrawn. More than 12 mg of extradural morphine in a day may cause opisthotonos, rigidity, spasticity and miosis, which is antagonized by naloxone, and does not affect cardiovascular and respiratory function (Engquist, Chraemmer-Jørgensen and Andersen, 1980).

Depression of conscious level by opioids is reversible by both opioid antagonists and physostigmine. Physostigmine has the advantage of maintaining the analgesic effects of opioids whilst restoring consciousness. It is effective after both systemic (Weinstock et al., 1982) and extradural (Schulman, Sandler and Brebner, 1984) opioid administration.

**Nausea and vomiting.** All opioids used clinically produce nausea and vomiting by direct stimulation of the chemoreceptor trigger zone in the area postrema of the medulla. The effect is dose-related and tolerance to it develops rapidly. Nausea and vomiting are frequent despite opioids having also a depressant effect on the vomiting centre (Clark, 1984). The emetic effect of morphine may be treated by anticholinergics and phenothiazines, especially those which are antagonists at dopamine receptors (Jaffe and Martin, 1985).
Morphine as premedication increased the incidence of nausea, retching and vomiting in patients undergoing uterine curettage from 22% in controls to 65%. When morphine was combined with atropine the incidence was 35% (Riding, 1960). A biphasic dose–response curve has been proposed for the effect pethidine has on nausea and vomiting (Bellville, 1961). Premedication with pethidine less than 1 mg kg$^{-1}$ i.m. was associated with an antiemetic effect, whereas at doses greater than 1 mg kg$^{-1}$, pethidine caused nausea and vomiting.

Stimulation of the vestibular apparatus is a potent cause of nausea and vomiting during opioid therapy. Walking, sitting up in bed and turning the head to follow a conversation are sufficient to provoke vomiting (Rubin and Winston, 1950). Pain itself can elicit nausea and vomiting. In a survey of 104 patients undergoing abdominal surgery, 59% of patients suffered concomitant pain and nausea, whereas nausea was provoked by only 3.4% of morphine injections (Andersen and Krohg, 1976).

Not only are nausea, vomiting and retching unpleasant and likely to be painful for patients with surgical wounds, but aspiration into the lungs of vomited gastric contents may be fatal (Brahams, 1984).

**Pupillary effects.** Most opioid agonists at μ and κ receptors cause constriction of the pupil by stimulation of the Edinger–Westphal nucleus of the third cranial nerve. Pinpoint pupils are pathognomonic of opioid toxicity until hypoxia supervenes and mydriasis develops (Jaffe and Martin, 1985).

**Genitourinary system**

Opioid analgesics cause an increase in urinary sphincter pressure and a decrease in central inhibition of detrusor tone (Doyle and Briscoe, 1976). Retention of urine is a frequent finding with opioids after extradural, i.m. (Petersen et al., 1982) and sublingual (Murray, 1983) administration. In 56 patients whose pain after upper abdominal surgery was relieved by i.m. or two regimens of extradural morphine, the incidence of acute retention of urine within the first 24 h was 35%, 33% and 50% respectively. These differences were not significant, but patients received two to three times the dose of morphine by the i.m. route than by the extradural route during the first 24 h after surgery (Petersen et al., 1982). Naloxone antagonizes these effects, promoting an increase in detrusor contractility with a reduction in functional bladder capacity (Murray and Feneley, 1982).

The influence of opioids on the autonomic control of bladder function may be mediated through opioid receptors found on neurones within the thoracic spinal cord (Murray, 1984). The site of maximum pressure in the urethra of males with prostatic hypertrophy is within the prostatic urethra. The bladder neck is not closed and the external sphincter is inhibited. All these findings are altered by bladder decompression and blockade of sympathetic alpha adrenoceptors (Cain and Perlberg, 1977). Phenoxybenzamine is effective in preventing urinary retention in women, who have had pain after Caesarean section relieved by extradural morphine (Evron, Magora and Sadowsky, 1984). Changes in prostatic urethral pressure cannot explain the effects of phenoxybenzamine in women. The proposed site of action of opioids and alpha sympathomimetic antagonists in regulating bladder function is in the thoracic spinal cord, where some preganglionic sympathetic neurone cell bodies are surrounded by terminals containing enkephalins and substance P (Murray, 1984).

Failure to ejaculate after lumbar extradural morphine has been described (Torda et al., 1980). A similar effect has been found in rats after intrathecal morphine. This was reversed by naloxone and was not demonstrated when morphine was given i.p. (Wiesenfeld-Hallin and Södersten, 1984). Opioids may produce this effect by modification of the sympathetic response to sexual stimuli. Extradural opioids may be of use in the treatment of premature ejaculation (Pybus et al., 1984).

Morphine should be used with caution in the harvesting of ova for in vitro fertilization. Abnormal fertilization and development of up to 33% of eggs have been demonstrated in in vitro fertilization of sea urchin eggs incubated with morphine (Cardasis and Schuel, 1976). No inhibition or abnormal development was demonstrated using fentanyl at concentration at or higher than those to which ova are exposed during balanced anaesthesia (Bruce, Hinckley and Norman, 1985). All opioids enhance the release of prolactin, which may interfere with the subsequent endometrial implantation of the fertilized egg (Watson, 1986).
ADVERSE EFFECTS OF OPIOIDS

Endocrine system

Endocrine response to trauma. Injury to the body from surgical or other causes is followed by a recognized endocrine and metabolic response, which is related to the severity of the trauma (Traynor and Hall, 1981). The hormonal changes involved are affected by opioid drugs and in some patients have been prevented by them.

In 28 gynaecology patients undergoing tubal reconstruction, increases in blood glucose, plasma cortisol and growth hormone concentrations seen under balanced anaesthesia were abolished by anaesthesia involving fentanyl 50 µg kg⁻¹ (Hall et al., 1978). However, in 30 patients having more major gynaecological surgery, the increase in plasma cortisol concentrations was not obtunded in three groups who received fentanyl 13, 12 and 25 µg kg⁻¹, respectively (McQuay et al., 1979). Similarly, fentanyl 10–15 µg kg⁻¹ with a subsequent infusion of mean dose 2.9 µg kg⁻¹ h⁻¹ was insufficient to prevent hyperglycaemia in 25 patients undergoing repair of abdominal aortic aneurysms (Florence, 1978). The long-term benefits of a high-dose opioid technique remain unproven and the disadvantage of prolonged respiratory depression after surgery make it unsuitable for large numbers of patients.

The release of vasopressin in response to an osmotic challenge of hypertonic saline in fit volunteers was inhibited by an analogue of met-enkephalin. This analogue produced a diuresis in water deprived volunteers, which was attenuated by naloxone (Grossman et al., 1980). Morphine 2 mg kg⁻¹, but not 1 mg kg⁻¹, was effective in preventing a significant increase in plasma antidiuretic hormone concentrations in six patients undergoing cardiac surgery (Philbin and Coggins, 1978). Opioids appear to be able to cause a diuresis by suppression of osmotically mediated release of vasopressin, and prevent antidiuretic secretion in response to surgery.

Adrenal insufficiency. Adrenal insufficiency has been demonstrated in methadone addicts. In five methadone addicts, basal plasma cortisol concentrations were no different from controls, but the cortisol secretion following ACTH 0.25 mg i.m. was blunted. This was attributed to a deficiency in ACTH and β-endorphin secretion in addicts causing secondary hypoadrenalism (Dackis et al., 1982). However, measurement of ACTH concentration in 10 methadone addicts and five others who had been weaned from the drug for over 6 months suggested that adrenal insufficiency resulted from compensated primary hypoadrenalism. Again there were no differences in basal cortisol concentrations between the two groups, but addicts had ACTH concentrations that were 60% higher than ex-addicts. These data suggest that methadone is responsible for an effect in the adrenal cortex and not in ACTH or β-endorphin production (Pullan et al., 1983).

Haemopoietic system

Thrombocytopenia, from a drug-related immunological mechanism, has been described in heroin addicts (Adams et al., 1978). Although the effects of chronic sepsis in these patients cannot be discounted, antiplatelet antibodies have been detected (Fishmann, 1981). Morphine i.m. has caused thrombocytopenia 7 days after elective surgery. The platelet count returned to normal when morphine was discontinued (Cimo, Hammond and Moake, 1982).

Agranulocytosis has been induced by pentazocine (Marks and Abramson, 1980; Sheehan, Hyland and Norman, 1985). After 4–6 weeks, there was an abrupt onset of rigors and localized infection with a neutropenia, which resolved when pentazocine was discontinued. This pattern is consistent with destruction of leucocytes in the peripheral blood by antibodies generated in response to drug sensitivity (Pisciotta, 1978).

Large doses of fentanyl 50–100 µg kg⁻¹ used in anaesthesia for open heart surgery can cause haemolysis. Serum haemoglobin concentrations are significantly greater in patients whose anaesthesia is induced by fentanyl rather than volatile anaesthetic agents. In adult patients, from 70 to more than 100 ml of fentanyl solution 50 µg ml⁻¹ are used and this volume of hypotonic solution, injected rapidly, is likely to be responsible (Furuya and Okumura, 1986).

Musculo-skeletal system and skin

Muscle rigidity. Muscular rigidity is induced in all muscle groups by the large doses of opioids used in opioid anaesthesia for cardiac surgery. Morphine 2 mg kg⁻¹, fentanyl 17 µg kg⁻¹ and alfentanil 175 µg kg⁻¹ have all produced muscle rigidity. There are marked increases in voltage detected by surface electromyographic recordings, but no associated electroencephalographic changes (Sebel et al., 1981; Bovill et al., 1982; Scott and Sarnquist, 1985). Central venous pres-
sure increases and there is resistance to artificial ventilation of the lungs from decreased chest wall compliance and upper airway obstruction. Adduction of the vocal cords and supraglottic obstruction by soft tissues have been suggested as reasons for airway obstruction (Scamman, 1983; Benthuysen et al., 1986). This effect on muscle tone is likely to be a central effect at a site above the spinal cord (Freund et al., 1973). Neuromuscular blocking drugs effectively abolish all muscle tone and are appropriate at induction of anaesthesia.

In case reports of muscular rigidity after initial recovery from anaesthesia, both neuromuscular blocking drugs and naloxone have been used (Christian, Waller and Moldenhauer, 1983; Goldberg et al., 1985). In uncontrolled reports of prompt, successful treatment of life-threatening emergencies, it is less clear whether respiratory depression or muscle rigidity is the problem than when electromyographic monitoring has been available for studies performed at induction of anaesthesia. Because of the adverse haemodynamic effects of acute antagonism of opioid drugs, neuromuscular blocking agents free from hypotensive effects have been advocated as the preferred treatment of opioid-induced muscle rigidity (Wangler and Gupta, 1983).

Histamine release after morphine has been demonstrated in connective tissues but not in basophils (Hermens et al., 1985). It is not an effect common to all opioids, related to analgesic potency, rather an adverse effect of morphine and pethidine.

Pruritis. Facial pruritis following extradural injection of opioids is attributed variously to histamine release, an effect of opioid spreading to the medulla or fourth ventricle, or opioid action in the substantia gelatinosa of the spinal cord, referring pruritis to a distant site by neuronal transmission (Scott and Fischer, 1982a). Three patients had facial pruritis, which arose 2–5 h after spinal morphine or diamorphine 1 mg, relieved without return of pain by naloxone 0.4 mg i.v. These patients suffered no further itching when subsequent intrathecal opiate was given together with 0.25% bupivacaine (Scott and Fischer, 1982b).

Miscellaneous effects. Alopecia areata in the occipital area has been reported in a patient after 3 days of extradural morphine, which was complicated by widespread itching (Andersen, 1984). This was thought not to result from pressure and to be unlike temporary telogen effluvium described 1 month after anaesthesia and surgery (Desai and Roaf, 1984).

Fixed drug reactions from opioids are uncommon, but have occurred with morphine, opium and codeine (Derbes, 1964). Smoking and inhaling vapours of heroin and methaqualone has resulted in macular pigmentation of the tongue (Westerhof et al., 1983).

Repeated, superficial injection of pentazocine has led to sclerosis, inflammatory nodules and ulceration of the skin surrounded by a halo of hyperpigmentation. Precipitation of the acidic pentazocine in alkaline extracellular fluid may initiate this reaction (Schlicher, Zuehlke and Lynch, 1971).

Fibrous myopathy with contractures has developed after repeated i.m. injection of pethidine and pentazocine. This appears at the site of injection and leaves distal muscle groups unaffected (Mastalgia, Gardner-Medwin and Hudson, 1971; Adams, Horowitz and Sundstrom, 1983).

Hyperkalaemia associated with heroin overdose may occur by ischaemic muscle injury (Pearce and Cox, 1980).

Self poisoning

Accidental and deliberate self poisoning with opioid analgesics is common. Dextropropoxyphene, formulated in combination with paracetamol, is the drug most commonly associated with death after self poisoning (OPCS, 1982). Only 4% of those poisoned required treatment to prevent liver damage from paracetamol poisoning, and a proportion similar to that in self poisoning with paracetamol alone. Death was more likely to be attributable to respiratory depression and sudden cardiovascular collapse, possibly as a result of depression of atrioventricular conduction by dextropropoxyphene (Lund-Jacobson, 1978).

Drug interactions

Opioids exhibit both pharmacodynamic and pharmacokinetic interactions with other drugs. For example, additive effects occur with central nervous system and respiratory depressants and the analgesic effects of methadone are reduced by rifampicin, because of liver enzyme induction (British National Formulary, 1985).

Two types of interaction between monoamine oxidase inhibitors and pethidine have been
described. The first is characterized by respiratory depression, hypotension and depressed consciousness. It resembles pethidine overdose and is antagonized by naloxone. It may be explained by inhibition of pethidine metabolism by monoamine oxidase inhibitors. The second is an idiosyncratic reaction involving central nervous system excitation, hypertension, tachycardia, pyrexia, rigidity and convulsions. This interaction has not been regularly, that recognition and treatment of respiratory problems are an integral part of their craft and that opioid antagonists are effective in reversing respiratory depression.

### Diagnostic tests

Therapeutic plasma concentrations of morphine may interfere with the measurement of amylase, lipase, lactate dehydrogenase, creatine phosphokinase in serum or plasma and glucose in urine (Benedicts) (Hansten, 1979).

### SUMMARY

Opioids were available in clinical practice since before the birth of modern anaesthesia—Setürner isolated morphine in 1806. They have a record of safety which is reflected in their high therapeutic ratios, especially the synthetic opioids introduced recently (table III). The most serious immediate adverse effect, respiratory depression, is a predictable effect related closely to analgesia. It is fortunate for anaesthetists who use opioids regularly, that recognition and treatment of respiratory problems are an integral part of their craft and that opioid antagonists are effective in reversing respiratory depression.

### REFERENCES


Andersen, P. T. (1978). Delayed respiratory phine may interfere with the measurement of pethidine, morphine and pentazocine in mice and convulsions. This interaction has not been


### Table III. Therapeutic indices of opioid analgesics in rats and mice

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic index (LD₉₀/ED₉₀)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufentanil</td>
<td>25211</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>277</td>
</tr>
<tr>
<td>Phenoperidine</td>
<td>166</td>
</tr>
<tr>
<td>Morphine</td>
<td>69</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>31</td>
</tr>
<tr>
<td>Pethidine</td>
<td>5</td>
</tr>
</tbody>
</table>

### ADVERSE EFFECTS OF OPIOIDS

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