Drug Safety 1998 Sep; 19 (3): 173-189
0114-5916/98/0009-0173/$08.50/0

Adverse Effects of Opioid Agonists and Agonist-Antagonists in Anaesthesia

T. Andrew Bowdle

Department of Anaesthesiology, University of Washington, Seattle, Washington, USA

Contents

Abstract

The traditional view of opioids held that the individual opioid agonists shared the same mechanism of action, differing only in their potency and pharmacokinetic properties. However, recent advances in opioid receptor pharmacology have made this view obsolete. Distinguishing features of the synthetic opioid agonists are related, at least in part, to variation in affinity and intrinsic efficacy at multiple opioid receptors.

Respiratory depression is the opioid adverse effect most feared by anaesthesiologists. Specific κ-receptor agonists produce analgesia with little or no respiratory depression. There are a number of commercially available κ-receptor partial agonist drugs, the so-called agonist-antagonist or nalorphine-like opioids, which appear to have a limited effect on breathing.

Within the series of fentanyl analogues there are differences in behaviour towards particular opioid receptors and there is evidence for subtle differences in respiratory depressant effects.

Pethidine (meperidine) causes histamine release and myocardial depression, while the fentanyl analogues do not. Pethidine has atropine-like effects on heart rate, while fentanyl analogues reduce heart rate by a vagomimetic action. Severe bradycardia or even asystole is possible with fentanyl analogues, especially in conjunction with the vagal stimulating effects of laryngoscopy.

Fentanyl analogues often produce minor reductions in blood pressure, and occasionally severe hypotension by centrally mediated reduction in systemic vascular resistance. Muscle rigidity and myoclonic movement occurs frequently during induction of anaesthesia with larger doses of opioids. Fentanyl and alfentanil have been reported to produce localised temporal lobe electrical seizure activity in patients with complex partial epilepsy.

There are probably fewer biliary effects with agonist-antagonist opioids than the agonist opioids. The mechanism of adverse effects after spinal administration is distinctly different for morphine, which is very water soluble, compared with more lipid-soluble opioids. The systemic absorption of morphine after intrathecal or epidural administration is very slow, resulting in long duration of analgesia and low plasma concentrations, while lipid-soluble opioids are rapidly absorbed into the circulation and redistributed to the brain.

The serotonin syndrome may result from coadministration of pethidine, dextromethorphan, pentazocine or tramadol with monoamine oxidase inhibitors (MAOIs) or selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs). There are clinically important interactions between opioids and hypnosedatives, resulting in synergistic effects on sedation, breathing and blood pressure.

Opioids are the mainstay of pain therapy. No other class of drugs currently combines the analgesic potency of opioids, with an acceptable profile of adverse effects. Certainly other classes of drugs are useful, especially local anaesthetics and nonsteroidal analgesics. α_2-Agonists, such as dexmedetomidine,[1] and calcium antagonists, such as the selective N-type neuronal voltage-sensitive calcium antagonist ziconotide (SNX-111),[2] are promising agents for the future.

The clinical choice of an individual opioid depends upon the duration and severity of pain, the route of administration, the desired speed of onset and duration of action and the adverse effect profile.

This article will review the adverse effects of opioids, with comparisons between individual opioids when this information is available and relevant. Throughout this review the assumption will be made that the desired effect of an opioid is analgesia, and all other effects are adverse effects, realising that opioid adverse effects are sometimes used for therapeutic purposes.

1. Opioid Receptors

Although a detailed review of opioid receptor pharmacology is beyond the scope of this review, an appreciation for the complexity of opioid receptors is helpful in understanding opioid adverse effects. The traditional view of opioids held that the individual agonists shared the same mechanism of action, differing only in potency and pharmacokinetic properties. Recent advances in opioid receptor pharmacology have made this view obsolete. Opioid receptor pharmacology is evolving rapidly, stimulated by recent cloning of cDNAs for μ-, κ- and δ-opioid receptors. Assuming that the analogy to other classes of drug receptors holds, a substantial number of opioid receptors and receptor subtypes will eventually be revealed. Undoubtedly, many clinical differences between opioid agonists are related to variation in affinity and intrinsic efficacy at multiple opioid receptors.

Three major types of opioid receptors have been recognised.[3] μ-Receptors mediate the major effects of morphine-like agonists, such as the fentanyl analogues and are associated with analgesia and respiratory depression (table I). κ-Receptors convey analgesia, sedation and dysphoria, but not respiratory depression and have greater affinity for a distinct set of agonists which includes the nalorphine-like drugs, such as pentazocine, butorphanol and nalbuphine (table I). μ- and κ-receptors each have several subtypes which have been identified pharmacologically. δ-Receptors are associated with endogenous opioid peptides: the role of these receptors in the effects of nonpeptide opioids is not clear.

In addition to the μ-, κ- and δ-opioid receptors, there is evidence for additional opioid receptors, including morphine-6-glucuronide receptors, orphan opioid receptors and peripheral opioid receptors. These most recently discovered opioid receptors will be discussed very briefly, to further illustrate the complexity of opioid pharmacology.

Table I. Common synthetic opioids classified by receptor actions

μ-Receptor agonists	Agonist-antagonists[a]	μ-Receptor partial agonists
Fentanyl	Butorphanol	Tramadol
Alfentanil	Nalbuphine	Meptazinol
Sufentanil	Buprenorphine	
Remifentanil	Dezocine	

a μ-Receptor partial agonist/κ-receptor partial agonist.

1.1 Morphine-6-Glucuronide Receptors

Pasternak and Standifer[4] have used antisense probes to demonstrate that morphine-6-glucuronide, an extremely potent morphine metabolite, acts through a novel opioid receptor which may be a splice variant of the gene which encodes the μ-opioid receptor.[5] They also found no cross-tolerance in CD-1 mice between morphine and either diamorphine (heroin), 6-acetylmorphine (diamorphine metabolite) or morphine-6-glucuronide, further supporting the notion of a novel opioid receptor.[6] Moreover, CXBK mice, which are insensitive to morphine, are sensitive to diamorphine, 6-actylmorphine, morphine-6-glucuronide, fentanyl and etonetazene.

1.2 Orphan Opioid Receptors

A 7 transmembrane domain, $G_{i/o}$-coupled receptor with a high degree of homology to the μ-, δ- and κ-opioid receptors has recently been cloned[7] and is known as opioid receptor-like 1 (ORL1). There is currently no definitive name for this 'orphan' receptor. An endogenous peptide ligand has been identified, known as 'nociceptin' or alternatively as 'orphanin FQ'. Despite the similarity of structure, the pharmacology of this receptor is unlike the classical opioid receptors. For example, naloxone has no affinity for it, while etorphine and lofentanil have agonist activity for it. The orphan opioid receptor appears to be

involved in nociception, although the physiological role is not clear.

1.3 Peripheral Opioid Receptors

There is evidence that opioid receptors on peripheral afferent neurons may mediate analgesia, especially in the setting of inflammation.[8,9] Khoury et al.[10] compared analgesia with intra-articular morphine to intra-articular bupivacaine following knee surgery. Analgesia with morphine was superior and of longer duration.

Opioid binding sites have been identified in microglial cells, astrocytes, Kupffer cells, peripheral blood monocytes and macrophages.[11] These receptors bind morphine and morphine-6-glucuronide, but not opioid peptides or fentanyl. The endogenous ligand for these receptors may be morphine itself.[12] Morphine, codeine and thebaine have been identified in mammalian tissues and mammalian cytochrome P450 enzymes are able to catalyse the transformation of thebaine to codeine and morphine.[13] The physiological significance of these receptors is unclear, but a role in the immune system has been postulated.[14]

2. Respiratory Depression

2.1 Nalorphine-like Agonist Antagonist Opioids

Respiratory depression is the opioid adverse effect most feared by anaesthesiologists. The traditional view held that the extent of respiratory depression was strictly proportional to the extent of analgesia. This concept preceded the discovery of multiple opioid receptors. Specific κ-receptor agonists produce analgesia with little or no respiratory depression,[15,16] suggesting that respiratory depression might be minimised or avoided entirely. Unfortunately, commercial development of κ-receptor agonists has been largely unsuccessful because these drugs also produce dysphoria.[17] However, there are a number of commercially available κ-receptor partial agonist/μ-receptor partial agonist drugs which appear to have a limited effect on breathing, the so-called agonist-antagonist or nalorphine-like opioids, such as pentazocine, butorphanol and nalbuphine.[18] The maximum respiratory depressant effects are generally less than full μ-receptor agonists.

Keats studied the respiratory effects of pentazocine, nalorphine, nalbuphine and dezocine in human volunteers, using the ventilatory response to carbon dioxide as a measure of respiratory depression.[19-21] Gal and DiFazio[22] also studied dezocine. Nalorphine, nalbuphine and dezocine were found to have a 'ceiling' for respiratory depression equivalent to about 30mg/70kg of morphine. At lower doses, the respiratory depression was dose related. Higher doses produced no additional depression of CO_2 response. The pentazocine respiratory dose-effect curve was less steep than that for morphine, but a plateau could not be demonstrated because intense dysphoria in the volunteers limited the maximum dose.[19] Nagashima et al.[23] found that the dose-effect curve for respiratory depression for butorphanol was less steep than that for morphine, but doses large enough to establish a true ceiling were not studied. Zucker et al.[24] compared the respiratory effects of butorphanol 0.17 mg/kg to nalbuphine 0.86 mg/kg, in a blinded, randomised study of patients anaesthetised with thiopental sodium (for induction) and nitrous oxide. The authors suggested that these doses probably produced the 'ceiling' or maximum respiratory depression. Butorphanol produced significantly greater depression of minute ventilation and CO_2 response.

The respiratory effects of buprenorphine have not been fully characterised. Buprenorphine appears to be a partial agonist at μ- and κ-receptors.[25] Slow dissociation from μ-receptors and an unusual 'bell' shaped dose response curve give buprenorphine a unique pharmacological profile.[26] Because of the tight binding to receptors, the respiratory depression caused by buprenorphine may not always be antagonised by naloxone; doxapram, a short-acting analeptic drug that stimulates ventilation, has been suggested as an alternative antidote.[27] Unusually large doses of naloxone (5 to 10mg) have also been tried and may be effective.[28]

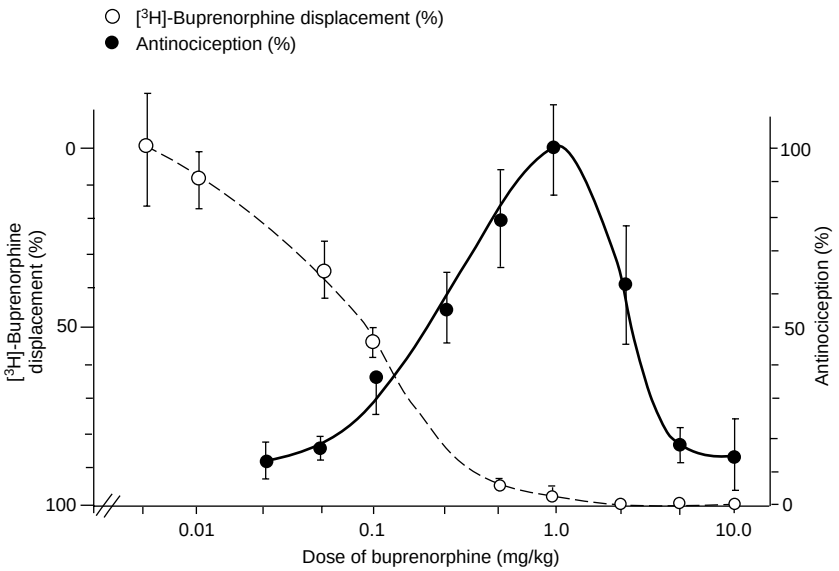

Fig. 1. Buprenorphine dose *vs* antinociception in rats. The curve is bell-shaped. Buprenorphine binding to brain receptors is shown for the same range of buprenorphine doses (left axis), showing that receptor binding corresponds to the antinocieptive effects (reproduced from Dum & Herz,[26] with permission).

Dum and Herz[26] examined the antinociceptive effects of buprenorphine in rats and found that doses of buprenorphine up to about 0.5 mg/kg produced the expected dose-related analgesia but doses greater than 0.5 mg/kg resulted in a paradoxical reduction in antinociception (fig. 1). The opioid antagonist naltrexone shifted the buprenorphine dose-effect curve symmetrically to the right, suggesting that the bell shape is related to opioid receptor activity. The explanation for the shape of the buprenorphine dose-response curve is unknown, although theoretical explanations for bell shaped dose-response curves have been presented.[29]

Comparable dose-effect studies of buprenorphine in humans are not available, however it is interesting to consider a case report of two patients with severe postoperative pain after balanced anaesthesia with buprenorphine and nitrous oxide.[30] The anaesthesiologists were aware of the bell shaped dose-effect curve and reasoned that the patients had received too much buprenorphine, placing them on the downsloping side of the curve (dose-related reduction in analgesia). Administration of naloxone to these patients resulted in 'total pain relief', consistent with a shift to the right of a bell shaped dose-effect curve.

The main thrust in the development of agonist-antagonist and partial agonist opioids was to devise drugs with fewer adverse effects; particularly less respiratory depression and less risk of addiction, compared with morphine-like μ-receptor agonists. How has this worked out in practice? Although agonist-antagonist opioids may have a 'ceiling' for analgesia, multiple studies have shown that agonist-antagonist opioids produce post-operative analgesia comparable to μ-receptor agonists such as morphine and pethidine.[31] On the one hand, an argument could be made that agonist-antagonists are preferable to full μ-receptor agonists for post-operative pain, based upon a ceiling for respiratory depression and a lower potential for abuse. On the other hand, surgical patients are not at high risk for developing opioid addiction: a low abuse potential may not be a high priority in drug selection. Also, the dysphoria and sedation mediated by κ-receptors,

that probably contributes to the lower abuse potential, can also be considered an undesirable adverse effect. A reduced risk of respiratory depression would certainly be advantageous. However, most of the agonist-antagonist drugs produce dose-related respiratory depression when given in typical analgesic doses. Thus, the 'ceiling' for respiratory depression may not be a practical advantage in many situations.

2.2 Fentanyl Analogues

There is evidence for subtle differences in respiratory depression between fentanyl analogues. Perhaps this is surprising, given the clinical similarity of the μ-receptor agonist opioids. However, the complexity of the μ-receptor, the existence of several receptor subtypes and the apparent role of peripheral μ-receptors in respiratory depression (see section 2.4) makes significant differences between μ-receptor agonists more plausible. Within the series of fentanyl analogues there are significant differences in behaviour towards particular opioid receptors. Yeadon and Kitchen[32] studied affinity of fentanyl analogues for rat μ- and δ-receptors and found that the more potent analogues, such as sufentanil, lofentanil and carfentanil had approximately equal affinity for μ- and δ-receptors, while the less potent analogue alfentanil (as well as morphine) had much greater affinity for μ- than for δ-receptors.

Sufentanil produced less depression of CO_2 responsiveness compared with fentanyl, relative to a common level of analgesia in surgical patients[33] and healthy volunteers.[34] Differences were also apparent in animal models. Bilateral vagotomy in rats reduced the respiratory depressant effects of fentanyl, alfentanil and sufentanil. However, sufentanil respiratory depressant effects were reduced to a much greater extent compared to fentanyl or alfentanil, suggesting that the peripherally mediated respiratory depressant effects of sufentanil are relatively more important.[35]

2.3 μ-Receptor Partial Agonist Opioids

Meptazinol and tramadol are partial μ-receptor agonist opioids that do not have the partial κ-receptor agonist actions of the nalorphine-like opioids. The respiratory effects of meptazinol[36] and tramadol[37,38] appear to be less than morphine-like opioids. Houmes et al.[39] performed a blinded, randomised comparison of tramadol and morphine for postoperative pain control following gynaecological surgery. Under the conditions of their study, analgesia was clinically acceptable with either drug, although there was a trend for morphine to be more effective in patients with severe pain. Oxygen saturation was measured by pulse oximetry as a measure of respiratory depression; supplemental oxygen was not given during the study. In the morphine group, 13% of patients had oxygen saturation <86%, compared with 0% in the tramadol group. The authors suggested that tramadol was preferable to morphine because of this apparent difference in respiratory effects.

2.4 Peripherally-Mediated Respiratory Depression

Opioid receptors have been identified in mammalian lung.[40] Sapru and colleagues[41] found that administration of a stable enkephalin analogue into the right atrium of rats produced apnoea that was prevented by vagotomy or naloxone. They hypothesised that opioid-induced apnoea was mediated by pulmonary J receptor stimulation. Yeadon and Kitchen[35] reported that respiratory depression in rats given fentanyl analogues was mediated through peripheral μ-receptors and centrally through μ- and non–μ-receptors. The apnoea response was abolished by either bilateral vagotomy or the quaternary opioid agonist *N*-methyl levallorphan (which acts peripherally).

A recent report from Ohtani et al.[42] has suggested yet another layer to the complexity of buprenorphine effects on breathing, involving peripheral opioid receptors. They found that the buprenorphine metabolite, norbuprenorphine, was a much more potent respiratory depressant in rats

than the parent drug. The respiratory effects of norbuprenorphine were antagonised by the specific μ-receptor antagonist β-funaltrexamine. Interestingly, norbuprenorphine had low permeability into the brain and the respiratory depression resulting from norbuprenorphine was much greater after intravenous administration compared with central intra-arterial administration (bypassing the lungs), suggesting a peripheral rather than a central respiratory depressant effect.

3. Cardiovascular Effects

3.1 Histamine Release

Histamine release is a well known cause of hypotension following rapid administration of larger doses of morphine. Pethidine also causes histamine release. Flacke et al.[43] administered equipotent doses of pethidine (4.3 mg/kg), morphine (0.6 mg/kg), fentanyl (7 μg/kg) or sufentanil (1.3 μg/kg) for induction of anaesthesia. Plasma histamine levels were elevated in 31% of patients receiving pethidine compared to 10% in patients receiving morphine and in 0% of patients receiving fentanyl or sufentanil. Plasma histamine level was inversely correlated with blood pressure and directly correlated with elevation of heart rate and circulating epinephrine (adrenaline). The fentanyl analogues, fentanyl, sufentanil, alfentanil and remifentanil do not release histamine.

3.2 Myocardial Depression

Fentanyl analogues do not produce direct myocardial depression at clinically relevant concentrations. In contrast, pethidine has significant myocardial depressant effects. Pethidine 2.5 mg/kg produced severe cardiovascular depression in dogs and higher doses of approximately 35 mg/kg produced rapid cardiac arrest.[44] Although the myocardial depressant effects of pethidine are not critical in the range of doses used for postoperative analgesia, the usefulness of pethidine as a primary anaesthetic agent is limited by cardiovascular adverse effects. Dezocine 20 mg/kg produced severe hypotension and death in dogs anaesthetised with enflurane;[45] whether dezocine is capable of producing serious cardiovascular depression in humans is unknown.

3.3 Heart Rate

Fentanyl analogues typically reduce heart rate by a vagomimetic action that is antagonised by atropine. Severe bradycardia or even asystole is possible, especially in conjunction with the vagal stimulating effects of laryngoscopy. This author has seen one case of asystolic cardiac arrest prior to laryngoscopy in a healthy patient following administration of a moderate sized bolus of fentanyl (approximately 10 μg/kg) that was given during induction of anaesthesia and several cases of asystolic arrest during laryngoscopy following administration of larger boluses of fentanyl analogues (e.g. sufentanil 1.5 μg/kg), demonstrating the importance of vigilance during the use of these drugs. However, the heart rate lowering effects of fentanyl analogues are usually beneficial, particularly in patients with coronary disease, where lower hearts rates improve the balance between coronary oxygen supply and demand.[46] Pethidine was originally studied as an anticholinergic agent and tends to increase heart rate by an atropine-like effect.[47]

3.4 Blood Pressure

Fentanyl analogues often produce minor reductions in blood pressure and occasionally severe hypotension, despite the absence of direct cardiovascular depressant effects. The probable mechanism is centrally mediated reduction in systemic vascular resistance. Flacke et al.[48] showed that fentanyl produced no cardiovascular depression in dogs previously deprived of sympathetic tone by subarachnoid block. They also showed that the cardiovascular depressant effects of fentanyl in dogs were antagonised by naloxone and that clonidine prevented naloxone from reversing fentanyl's cardiovascular effects, presumably by decreasing central sympathetic outflow.[49] Hypotension caused by opioids can usually be treated with intravenous fluid, which is particularly important in hypovolaemic

patients, and α-adrenergic agonist drugs, which restore systemic vascular resistance. Coadministration of hypnosedatives tends to exaggerate the cardiovascular effects of opioids. This interaction is synergistic. Tomicheck et al.[50] showed that diazepam and fentanyl coadministration produced dramatic reductions in systemic vascular resistance and blood pressure, whereas fentanyl or diazepam alone had minimal effects.

3.5 Cardiovascular Stimulation

Paradoxically, fentanyl may occasionally produce cardiovascular stimulation. Thomson et al.[51] administered fentanyl 50 μg/kg for induction of anaesthesia and found that a minority of patients experienced substantial increases in heart rate, blood pressure, pulmonary artery pressure and cardiac index. The agonist-antagonist opioids pentazocine and nalorphine may also produce cardiovascular stimulation.

3.6 Potency and Cardiovascular Effects

Interestingly, the cardiovascular depressant effects of opioids appear to be inversely related to analgesic potency. The therapeutic indices [ratio of lethal dose to effective dose (LD_{50}/ED_{50})] in rats are 4.8 for pethidine, 70 for morphine, 277 for fentanyl and 26 700 for sufentanil, the same rank order as potency.[52] That a high degree of μ-receptor specificity and efficacy, as with sufentanil, should confer a greater margin of cardiovascular safety suggests that severe cardiovascular toxicity may be mediated by other than μ-receptors.

4. Rigidity and Other Neuroexcitatory Effects

4.1 Rigidity

Muscle rigidity occurs frequently during induction of anaesthesia with larger doses of opioids. Benthuysen et al.[53] have shown that opioid rigidity affects virtually all of the major muscle groups in the body, with the onset occurring first in the upper body (sternocleidomastoid, deltoid, biceps, forearm). The only practical and reliable treatment for rigidity is neuromuscular blocking drugs. α_2-Agonists attenuate opioid-induced rigidity in rodents.[54,55] However, intravenous α_2-agonists are not currently available for use in humans. Studies in rodents suggest that opioid rigidity is mediated by μ-receptors[56] in brainstem midline nuclei and the basal ganglia.[57] There is no convincing evidence that any particular opioid drug is intrinsically more prone to produce rigidity than any other. However, opioids with very fast equilibrium between blood and brain, such as alfentanil and remifentanil, probably appear clinically to be more likely to produce rigidity because of relatively high peak brain concentrations following rapid bolus administration.

Although opioid induced rigidity is usually observed during induction of anaesthesia, there are case reports of rigidity occurring either immediately upon emergence from anaesthesia, or delayed until 3 to 5 hours postoperatively.[58] Naloxone administration dramatically relieved the rigidity in those cases where it was tried, implicating an opioid mechanism. The explanation for delayed rigidity is unknown.

4.2 Myoclonus

Opioids have been associated with tonic-clonic movements, or myoclonus, in addition to tonic rigidity. Opioid-induced myoclonus may be quite dramatic, resembling generalised seizures (epileptic convulsions). However, there appears to be no electroencephalogram (EEG) evidence that opioids produce generalised, cortical seizure activity in humans (with the exception of norpethidine, see section 4.4), despite many studies in which EEG recordings have been made.[59] On the contrary, myoclonus has been observed during simultaneous EEG recording, in the absence of EEG evidence of seizure activity.[60] The mechanism of opioid-induced myoclonus may be closely related to opioid-induced tonic rigidity.

4.3 Localised Seizure Activity

Fentanyl (mean dose 25 μg/kg)[61] and alfentanil (50 μg/kg)[62] have been reported to produce

localised temporal lobe electrical seizure activity not accompanied by motor activity in patients with complex partial epilepsy. The clinical significance of this phenomenon, particularly for patients without epilepsy, is unknown.

4.4 Norpethidine (Normeperidine)

The *N*-demethylated metabolite of pethidine, norpethidine (normeperidine) is capable of producing CNS excitation and generalised seizures, which are not antagonised by naloxone.[63] Norpethidine is eliminated by the kidney and by hydrolysis to norpethidinic acid, with a half-life of 15 to 40 hours. Patients with impaired renal function are at increased risk for toxicity.

5. Cerebral Blood Flow and Intracranial Pressure

Tradition maintains that opioids produce no change or only modest reductions in cerebral blood flow and cerebral metabolic oxygen consumption. However, Milde et al.[64] reported in 1990 that sufentanil caused substantial increases in cerebral blood flow in anaesthetised dogs, without a change in cerebral metabolic oxygen consumption, implying that sufentanil was dilating cerebral vessels directly. Subsequently, reports were published suggesting that fentanyl analogues could increase intracranial pressure under certain circumstances. Furthermore, some investigators hypothesised that the effects of the various fentanyl analogues on cerebral haemodynamics were not identical. This complicated area of research has been recently reviewed by Artru,[65] who concluded that the effects of fentanyl analogues on cerebral blood flow and intracranial pressure are probably due primarily to changes in blood pressure, such that a decrease in blood pressure produced by the opioid may result in cerebral vasodilation (due to autoregulation) and an increase in intracranial pressure if intracranial compliance is critically impaired. However, feline cerebrovascular smooth muscle was reported to dilate in response to direct microapplication of μ- or δ-receptor agonists,[66] suggesting a possible direct effect of opioids on cerebral vessels. There is also the hypothetical possibility that neuroexcitatory effects of opioids, such as the localised seizure activity noted in section 4.3,[61,62] could affect cerebral blood flow under certain circumstances.

Anaesthesiologists have generally not reported clinical problems from opioids given to neurosurgical patients during anaesthesia, suggesting that effects on electrical activity, cerebral blood flow or intracranial pressure are usually not of great clinical significance.

6. Gastrointestinal Effects

Virtually all commonly used opioids produce gastrointestinal adverse effects, by a combination of central and peripheral actions. Intestinal motility is generally reduced, contributing to constipation. Increased tone of the sphincter of Oddi and increased pressure in the biliary ducts may result in right upper quadrant pain.[67] Opioid-induced spasm of the sphincter of Oddi may prevent radiographic dye from entering the duodenum during intraoperative cholangiography, simulating the presence of a gallstone in the common bile duct. While some anaesthesiologists avoid opioids during cholecystectomy because of the possibility of interfering with the cholangiogram, this is a relatively uncommon problem[68] and may be resolved by administering glucagon (alternatively, naloxone or nalbuphine) which relaxes the sphincter of Oddi. Obstruction of the common bile duct that persists after glucagon administration is unlikely to be related to opioid effects.

Several studies have suggested that the biliary effects of the nalorphine-like agonist-antagonist drugs, such as butorphanol,[69,70] nalbuphine[70] and pentazocine[67,71] are less than comparable doses of the morphine-like drugs, such as morphine, pethidine and fentanyl. Staritz et al.[72] reported that the opioid partial-agonists buprenorphine and tramadol had no effect on sphincter of Oddi motor activity measured by ERCP manometry, while pentazocine increased sphincter pressure. Whether the differences in biliary effects among

the opioids are clinically significant or useful is unclear.

7. Nausea and Vomiting

Opioids commonly produce nausea and vomiting.[73] The neurophysiology and pharmacology of nausea and vomiting is very complex. The vomiting centre in the medulla receives input from the cerebral cortex, the gut, the vestibular system and the chemoreceptor trigger zone. The chemoreceptor trigger zone is located in the floor of the fourth ventricle, outside the blood-brain barrier. The chemoreceptor trigger zone contains many types of receptors, including opioid receptors, that promote vomiting. Experiments in cats have suggested that opioids actually have an antiemetic effect on the vomiting centre that is reversible by naloxone.[74] Thus, opioids appear to have opposite effects in the vomiting centre (antiemetic) and the chemoreceptor trigger zone (emetic). Intracerebroventricular injection of naloxone prevented opioid induced emesis, but intravenous administration of naloxone did not, suggesting that the vomiting centre was much more sensitive to intravenous naloxone than the chemoreceptor trigger zone. Intravenous naloxone appeared to reverse the antiemetic effects of opioids on the vomiting centre, but not the emetic effect of opioids on the chemoreceptor trigger zone, thereby promoting emesis. For example, fentanyl did not produce emesis in cats until they were pretreated with intravenous naloxone.[74] This is consistent with clinical observations by Longnecker et al.[75] that naloxone frequently resulted in vomiting when administered to antagonise morphine.

Clinical lore suggests that nausea and vomiting is more frequent with particular opioid drugs (codeine and alfentanil are commonly mentioned). Anecdotal evidence suggests that individual patients may be highly sensitive to the emetogenic effects of a particular opioid, while having much less trouble with others. However, there is little scientific evidence to document these clinical experiences. Nausea and vomiting are notoriously difficult to study because there are so many factors which affect the outcome. Comparisons of studies performed under different circumstances are difficult to interpret. Several studies have suggested that nausea and vomiting after anaesthesia are more common when opioids are given, than when opioids are avoided.[73]

8. Spinal Opioids

8.1 Neurotoxicity

The possibility of direct neurotoxicity must be considered for any drug that will be administered spinally, whether intrathecal or epidural.[76] While many opioids have been given spinally, regulatory agencies in the US have officially sanctioned only morphine and sufentanil. Despite the lack of formal approval, the use of spinal fentanyl is so widespread that there is virtually no controversy regarding safety. Practitioners should give careful consideration prior to spinal administration of other, unapproved opioids, particularly if animal toxicology is not available to demonstrate safety.[76]

8.2 Spinal Morphine

The mechanism of adverse effects after spinal administration is distinctly different for the more water soluble opioids, such as morphine, compared with the more lipid soluble opioids, such as the fentanyl analogues.[77] The systemic absorption of morphine after intrathecal or epidural administration is very slow, resulting in long duration of analgesia and low plasma concentrations. The effects of spinal morphine are mediated primarily by direct penetration into the spinal cord, not by absorption into the circulation and subsequent redistribution to the brain. Intrathecal morphine 0.3mg produced a peak plasma concentration of 4.5 μg/L (minimum analgesic concentration in plasma 20 to 40 μg/L), while concentration in CSF was 6410 μg/L.[78]

8.3 Lipid Soluble Spinal Opioids

Very lipid soluble opioids, such as the fentanyl analogues, are much more rapidly absorbed into the circulation after neuraxial administration,

resulting in relatively short duration of action and clinically significant plasma concentrations. Continuous infusion of fentanyl in the epidural space resembles intravenous administration; epidural infusion and intravenous infusion of fentanyl following knee surgery produced similar plasma fentanyl concentrations and comparable analgesia.[79] Camman et al.[80] have reviewed the literature and concluded that the effects of lipophilic opioids in general are substantially the same whether given intravenously or spinally.

8.4 Adverse Effects of Spinal Opioids

The adverse effects of spinal opioids (encompassing both epidural and intrathecal routes of administration) have been recently reviewed.[77,81] The major adverse effects of spinal opioids are respiratory depression, pruritus, nausea and urinary retention. A variety of other less common adverse effects are also possible. The pharmacodynamics of spinal opioids are not fundamentally different from other routes of administration. However, there are unique aspects of spinal opioid pharmacokinetics. Morphine spreads in a cephalad direction in cerebrospinal fluid (CSF), where it may eventually reach critical areas of the brain, resulting in respiratory depression, pruritus and nausea. Lipid soluble opioids also spread in CSF. However, rapid absorption into the systemic circulation and redistribution to the brain is the predominant route by which drugs such as fentanyl cause adverse effects.

Respiratory depression from epidurally administered lipid soluble opioids typically occurs within 2 hours (so-called 'early' respiratory depression) because of rapid absorption into the systemic circulation. Early respiratory depression is very unlikely to occur with any type of intrathecal opioid, because of the small size of conventional intrathecal doses. Respiratory depression from spinal morphine is usually delayed for more than two hours (so-called 'delayed' respiratory depression), typically occurs at 6 to 12 hours, but is highly variable. The delay in onset reflects the time required for bulk movement of drug in CSF to the respiratory centres of the brain stem.

The reported incidence of clinically significant respiratory depression from spinal opioids varies considerably. However, it is probably similar to intravenous or intramuscular opioids. As with any other route of administration, respiratory depression from spinal opioids may be life threatening. There is a positive relationship between opioid dose and the likelihood of significant respiratory depression.

The incidence of nausea and vomiting following spinal opioids may be no different from the incidence associated with intravenous opioids.[79,82] In contrast, the incidence and severity of pruritus is greater with spinal opioids compared with intramuscular or intravenous routes. Pruritus may be treated by administration of naloxone, demonstrating that the mechanism involves opioid receptors. Small doses of naloxone (e.g. 40μg) may effectively antagonise pruritus while preserving analgesia.

Urinary retention is much more common with spinal opioids compared with other parenteral routes of administration and is probably mediated in the sacral spinal cord. Naloxone will antagonise urinary retention. However, larger doses may be required, resulting in reversal of analgesia as well. Therefore, opioid-related urinary retention is usually treated by urethral catheterisation.

Spinal opioids have been associated with recurrence of herpes simplex infections, although the causal relationship between opioids and herpes simplex recurrence has been questioned.[83]

Opioids have complex effects on thermoregulation, that are heavily influenced by ambient temperature. Epidural or intrathecal opioids administered to parturients in a cool environment have been associated with a fall in temperature.[84,85]

9. Drug Interactions

9.1 Serotonin Syndrome

The serotonin syndrome occurs with the use of serotomimetic drugs alone or in combination with

monamine oxidase inhibitors (MAOIs), which block the enzymatic degradation of serotonin in the synaptic cleft, or selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs), which block the reuptake of serotonin into nerve terminals.[86,87] The syndrome was first described in animals, which became hypermetabolic, with fever, myoclonus, stiffness in the hindlimbs, tremor, stereotyped movements and autonomic instability. The first reported clinical case was reported in 1955, in a patient treated with iproniazid (an MAOI) and pethidine.[88] The clinical manifestations of the serotonin syndrome are analagous to the syndrome in animals. However, a remarkably large range of signs and symptoms have been reported. Several fatalities have occurred. Treatment is supportive. An extensive review of the clinical syndrome and case reports is available.[89]

The serotonin syndrome should be distinguished from the neuroleptic malignant syndrome, although there is significant overlap of signs and symptoms.[86] Neuroleptic malignant syndrome is a rare condition resulting from treatment with antipsychotics, consisting of mental status changes, severe hyperthermia, muscle rigidity and autonomic instability.

The synthetic opioids pethidine,[86] dextromethorphan,[90] pentazocine[91] and tramadol[92] block reuptake of serotonin and have been associated with the serotonin syndrome. Other commonly used opioids have not been implicated and are probably acceptable to use in patients taking MAOIs or SSRIs.

Attention should be paid to the fact that many of the MAOIs and SSRIs have an extremely long duration of action and effects may persist for some time following discontinuation of the drugs.[86] Most MAOIs act irreversibly and replacement of depleted MAO can take 2 weeks following discontinuation of the MAOI. An interval of 4 to 6 weeks has been suggested between discontinuation of MAOIs and administration of a serotomimetic agent.[86] A new class of drugs that reversibly inhibits MAO-A may be less problematic. The prototype drug of this class, moclobemide, has a half-life of 1 to 3 hours and duration of MAO inhibition is closely related to the elimination half-life.[93,94] Some of the SSRIs have prolonged half-lives and may require weeks to months to be cleared following discontinuation.

Given the wide use of pethidine, MAOIs and SSRIs, the relative rarity of the serotonin syndrome is interesting and suggests the possibility that an idiosyncratic mechanism may be involved, beyond the pharmacology outlined above. Nevertheless, clinicians are well advised to avoid combining pethidine, dextromethorphan, pentazocine or tramadol with MAOIs or SSRIs.

Tramadol is a particularly interesting analgesic which has only recently been approved in the US after extensive use in Germany.[95] A synthetic analogue of codeine, tramadol has weak μ-receptor agonist activity and also modulates analgesia in monoaminergic pathways by blocking serotonin and norepinephrine (noradrenaline) reuptake. The analgesic effects of tramadol are only partially antagonised by naloxone, while the α_2-adrenoceptor antagonist yohimbine produces more complete reversal.[96] The combination of tramadol and MAOIs has been fatal to experimental animals.[92]

9.2 Benzodiazepines

There are synergistic interactions between opioids and hypnosedatives which result in greater than additive effects on sedation, breathing and blood pressure. These interactions are clinically very significant. The interactions between benzodiazepines and opioids have been most thoroughly studied, although similar interactions may occur with nonbenzodiazpine hypnosedative drugs.[97,98] As combinations of opioids and benzodiazepines are widely used for conscious sedation by gastroenterologists, oral surgeons, cardiologists, emergency physicians and other nonanaesthesiologists, these interactions have broad clinical significance.

Vinik et al. determined that the ED_{50} for unconsciousness for alfentanil was 0.13 mg/kg without midazolam and 0.028 mg/kg after midazolam 0.07 mg/kg, i.e. an 80% reduction in dose requirement for alfentanil (fig. 2).[99]

This figure is not available for online viewing

Fig. 2. Dose-effect curves for induction of anaesthesia with alfentanil (**A**) plus saline (**S**) [right] or alfentanil plus midazolam (**M**), 0.07 mg/kg (left). Midazolam reduced the alfentanil ED_{50} for unconsciousness by about 80% (from Vinik et al.,[99] with permission). **ED** = effective dose; ↑ = data points are >95%; ↓ = data points are <59%.

Tomicheck et al.[50] evaluated the haemodynamic effects of fentanyl 50 μg/kg administered for cardiac surgery, in combination with 0.125 to 0.5 mg/kg of diazepam. Fentanyl or diazepam alone produced insignificant haemodynamic effects, while the combination resulted in dramatic reduction of systemic vascular resistance and blood pressure. Flacke et al.[48] found that coadministration of fentanyl and diazepam produced no cardiovascular depression in dogs when autonomic tone was blocked, suggesting that the synergistic effects of fentanyl and diazepam on blood pressure result from a reduction in sympathetic tone, rather than direct effects on the heart or blood vessels.

Small doses of fentanyl or benzodiazepines alone produce only minor effects on breathing. However, coadministration can produce profound respiratory depression. Bailey et al.[100] administered midazolam 0.05 mg/kg and fentanyl 2 μg/kg to healthy volunteers. Fentanyl alone produced hypoxaemia (breathing room air) in 6/12 study participants and no apnoea. Midazolam alone produced no hypoxaemia or apnoea. Coadministration of fentanyl and diazepam produced hypoxaemia in 11/12 volunteers and apnoea in 6/12 volunteers. Coadministration of opioids and midazolam were the cause of a large number of deaths reported to the US Food and Drug Administration soon after the release of midazolam and the study of Bailey and colleagues probably explains the mechanism of these deaths. Therefore coadministration of benzodiazepines and opioids should only be undertaken with adequate cardiopulmonary monitoring (such as pulse oximetry) and immediate availability of supplemental oxygen, resuscitative equipment and trained personnel.

10. Novel Routes of Administration

Beyond the standard parenteral routes of administration, there are commercially available forms for transnasal butorphanol and transdermal fen-

tanyl.[101] A transnasal form of buprenorphine is under development.

10.1 Nasal Butorphanol

Nasal butorphanol has been popular for the treatment of severe headache.[102] The limited potential for respiratory depression and addiction[103] may be particularly valuable in these applications, although butorphanol was recently rescheduled in the US to Schedule IV of the Controlled Substances Act, reflecting concern about abuse. Butorphanol 1% nasal spray is marketed in a multiple dose pump sprayer that can deliver a total of 14 to 15mg, the usual dose being 1 to 2mg. What happens if a patient self-administers the entire sprayer as a single dose? An intravenous bolus dose of 15mg would have profound effects that could be life-threatening. Fortunately, the absorption of nasal butorphanol is not proportional to dose because of the limited surface area available for absorption and the peak plasma concentration after nasal administration of 14mg is less than 20% of the equivalent intravenous dose.[104] The butorphanol which is not absorbed nasally is apparently swallowed and eliminated by first-pass clearance.

10.2 Transdermal Fentanyl

Transdermal fentanyl has proved to be useful in the treatment of cancer pain. Attempts to treat postoperative pain with transdermal fentanyl have been less successful. The relatively slow onset, requiring 17 to 48 hours to reach peak plasma fentanyl concentrations, is poorly suited to the rapidly changing requirements of acute postoperative pain. Moreover, an incidence of hypoventilation of 4% was noted in the trials of the fentanyl patch for postoperative pain. Respiratory depression appears to be less of a problem in cancer patients, perhaps because of long term exposure and tolerance to opioids.[101]

11. Conclusion

Opioids are highly efficacious and remarkably well tolerated agents. While there are a large number of potential adverse effects, most are not serious. In the practice of anaesthesia, the most dangerous adverse effect of opioids is respiratory depression, which can be life-threatening. Potent analgesic drugs with efficacy equivalent to opioids, but not producing significant respiratory depression, have long been sought after. However, at this time there are no viable alternatives for opioids in the treatment of severe pain. Although α_2-receptor agonists have shown some promise, development of highly selective opioid agonists which target analgesia receptors, while avoiding receptors that mediate respiratory depression, may be the solution to this problem.

References

1. Hayashi Y, Maze M. Drugs affecting adrenoceptors: alpha-2 agonists. In: Bowdle T, Horita A, Kharasch E, editors. The pharmacologic basis of anesthesiology. New York: Churchill Livingstone, 1994: 607-779
2. Bowersox SS, Gadbois T, Singh T, et al. Selective N-type neuronal voltage-sensitive calcium channel blocker, SNX-11, produces spinal antinociception in rat models of acute, persistent and neuropathic pain. J Pharmacol Exp Ther 1996; 279: 1243-9
3. Pasternak GW. Basic pharmacology of opioids. In: Bowdle T, Horita A, Kharasch E, editors. The pharmacologic basis of anesthesiology. New York: Churchill Livingstone, 1994: 19-36
4. Pasternak GW, Standifer KM. Mapping of opioid receptors using antisense oligodeoxynucleotides: correlating their molecular biology and pharmacology. Trends Pharmacol Sci 1995; 16: 344-50
5. Rossi GC, Pan Y-X, Brown GP, et al. Antisense mapping the MOR-1 opioid receptor: evidence for alternative splicing and a novel morphine-6beta-glucuronide receptor. FEBS Lett 1995; 369: 192-6
6. Rossi GC, Brown GP, Leventhal L, et al. Novel receptor mechanisms for heroin and morphine-6beta-glucuronide analgesia. Neurosci Lett 1996; 216: 1-4
7. Henderson G, McKnight AT. The orphan opioid receptor and its endogenous ligand-nociceptin/orphanin FQ. Trends Pharmacol Sci 1997; 18: 293-300
8. Stein C. Peripheral mechanisms of opioid analgesia. Anesth Analg 1993; 76: 182-91
9. Kolesnikov YA, Jain S, Wilson R, et al. Peripheral morphine analgesia: synergy with central sites and a target of morphine tolerance. J Pharmacol Exp Ther 1996; 279: 502-6
10. Khoury GF, Chen ACN, Garland DE, et al. Intraarticular morphine, bupivacaine, and morphine/bupivacaine for pain control after knee videoarthroscopy. Anesthesiology 1992; 77: 263-6
11. Dobreni K, Makman MH, Stefano GB. Occurrence of the opiate alkaloid-sensitive mu_3 receptor in mammalian microglia, astrocytes and Kupffer cells. Brain Res 1995; 686: 239-48
12. Stefano GB, Scharrer B. Endogenous morphine and related opiates, a new class of chemical messengers. Adv Neuroimmunol 1994; 4: 57-67

13. Kodaira H, Spector S. Transformation of thebaine to oripavine, codeine, and morphine by rat liver, kidney, and brain microsomes. Proc Natl Acad Sci USA 1988; 85: 1267-71
14. Stefano GB, Digenis A, Spector S, et al. Opiate-like substances in an invertebrate, an opiate receptor on invertebrate and human immunocytes, and a role in immunosuppression. Proc Natl Acad Sci USA 1993; 90: 11099-103
15. Freye E, Hartung E, Schenk GK. Bremazocine: an opiate that induces sedation and analgesia without respiratory depression. Anesth Analg 1983; 62: 483-8
16. Castillo R, Kissin I, Bradley E. Selective kappa opioid agonist for spinal analgesia without the risk of respiratory depression. Anesth Analg 1986; 65: 350-4
17. Millan MJ. Kappa-opioid receptors and analgesia. Trends Pharmacol Sci 1990; 11: 70-6
18. Bowdle TA, Nelson WL. Partial agonist, mixed agonist-antagonist, and antagonist opioids. In: Bowdle T, Horita A, Kharasch E, editors. The pharmacologic basis of anesthesiology. New York: Churchill Livingstone, 1994
19. Keats AS, Telford T. Studies of analgesic drugs X. Respiratory effects of narcotic antagonists. J Pharmacol Exp Ther 1966; 112: 126-32
20. Romagnoli A, Keats AS. Ceiling effect for respiratory depression by nalbuphine. Clin Pharmacol Ther 1980; 27: 478-85
21. Romagnoli A, Keats AS. Ceiling respiratory depression by dezocine. Clin Pharmacol Ther 1984; 35: 367-73
22. Gal TJ, DiFazio CA. Ventilatory and analgesic effects of dezocine in humans. Anesthesiology 1984; 61: 716-22
23. Nagashima H, Karamanian A, Malovany R, et al. Respiratory and circulatory effects of intravenous butorphanol and morphine. Clin Pharmacol Ther 1976; 19: 738-45
24. Zucker JR, Neuenfeldt T, Freund PR. Respiratory effects of nalbuphine and butorphanol in anesthetized patients. Anesth Analg 1987; 66: 879-81
25. Pick CG, Peter Y, Schreiber S, et al. Pharmacological characterization of buprenorphine, a mixed agonist-antagonist with $kappa_3$ analgesia. Brain Res 1997; 744: 41-6
26. Dum JE, Herz A. In vivo receptor binding of the opiate partial agonist, buprenorphine, correlated with its agonistic and antagonistic actions. Br J Pharmacol 1981; 74: 627-33
27. Orwin JM. The effect of doxapram on buprenorphine induced respiratory depression. Acta Anaesthsiol Belg 1977; 2: 93-105
28. Gal TJ. Naloxone reversal of buprenorphine-induced respiratory depression. Clin Pharmacol Ther 1989; 45: 66-71
29. Rovati GE, Nicosia S. Lower efficacy: interaction with an inhibitory receptor or partial agonism? Trends Pharmacol Sci 1994; 15: 140-1
30. Pedersen JE, Chraemmer-Jorgensen B, Schmidt JF, et al. Naloxone – a strong analgesic in combination with high-dose buprenorphine? Br J Anaesth 1985; 57: 1045-6
31. Hoskin PJ, Hanks GW. Opioid agonist-antagonist drugs in acute and chronic pain states. Drugs 1991; 41: 326-44
32. Yeadon M, Kitchen I. Comparative binding of mu and delta selective ligands in whole brain and pons/medulla homogenates from rat: affinity profiles of fentanyl derivatives. Neuropharmacology 1988; 27: 345-8
33. Clark NJ, Meuleman T, Liu W, et al. Comparison of sufentanil-N20 and fentanyl-N20 in patients without cardiac disease undergoing general surgery. Anesthesiology 1987; 66: 130-5
34. Bailey PL, Streisand JB, East KA, et al. Differences in magnitude and duration of opioid-induced respiratory depression and analgesia with fentanyl and sufentanil. Anesth Analg 1990; 70: 8-15
35. Yeadon M, Kitchen I. Multiple opioid receptors mediate the respiratory depressant effects of fentanyl-like drugs in the rat. Gen Pharmacol 1990; 21: 655-64
36. Jones JG. The respiratory effects of meptazinol. Postgrad Med J 1983; 59 (Suppl. 1): 72-7
37. Seitz W, Lubbe N, Fritz K, et al. Effects of tramadol on respiratory CO2 response and mouth occlusion pressure. Anaesthesist 1985; 34: 241-6
38. Vickers MD, O'Flaherty D, Szekely SM, et al. Tramadol: pain relief by an opioid without depression of respiration. Anaesthesia 1992: 291-6
39. Houmes RM, Voets MA, Verkaaik A, et al. Efficacy and safety of tramadol versus morphine for moderate and severe postoperative pain with special regard to respiratory depression. Anesth Analg 1992; 74: 510-4
40. Hughes J, Kosterlitz AW, Smith TW. The distribution of methionine-enkephalin and leucine-enkephalin in the brain and peripheral tissues. Br J Pharmacol 1977; 61: 639-47
41. Sapru HN, Willette RN, Krieger AJ. Stimulation of pulmonary J receptors by an enkephalin-analog. J Pharmacol Exp Ther 1981; 217: 228-34
42. Ohtani M, Kotaki H, Nishitateno K, et al. Kinetics of respiratory depression in rats induced by buprenorphine and its metabolite, norbuprenorphine. J Pharmacol Exp Ther 1997; 281: 428-33
43. Flacke JW, Flacke WE, Bloor BC, et al. Histamine release by four narcotics: a double-blind study in humans. Anesth Analg 1987; 66: 723-30
44. Freye E. Cardiovascular effects of high dosages of fentanyl, meperidine, and naloxone in dogs. Anesth Analg 1974; 53: 40-7
45. Hall RI, Murphy MR, Szlam F, et al. Dezocine-MAC reduction and evidence for myocardial depression in the presence of enflurane. Anesth Analg 1987; 66: 1169-74
46. Buffington CW. Hemodynamic determinants of ischemic myocardial dysfunction in the presence of coronary stenosis in dogs. Anesthesiology 1985; 63: 651-62
47. Jaffe JH, Martin WR. Narcotic analgesics and antagonists. In: Goodman L, Gilman A, Koelle G, editors. The pharmacological basis of therapeutics. 5th ed. New York: MacMillan, 1975: 245-83
48. Flacke JW, Davis LJ, Flacke WE, et al. Effects of fentanyl and diazepam in dogs deprived of autonomic tone. Anesth Analg 1985; 64: 1053-9
49. Flacke JW, Flacke WE, Bloor BC, et al. Effects of fentanyl, naloxone and clonidine on hemodynamics and plasma catecholamine levels in dogs. Anesth Analg 1983; 62: 305-13
50. Tomicheck RC, Rosow CE, Philbin DM, et al. Diazepam-fentanyl interaction-hemodynamic and hormonal effects in coronary artery surgery. Anesth Analg 1983; 62: 881-4
51. Thomson IR, Putnins CL, Friesen RM. Hyperdynamic cardiovascular responses to anesthetic induction with high-dose fentanyl. Anesth Analg 1986; 65: 91-5
52. Janssen PAJ. The past, present and future of opioid analgesics in anesthesia. In: Estafanous F, ed. Opioids in anesthesia II. Boston: Butterworth-Heinemann, 1991: xvi
53. Benthuysen JL, Smith NT, Sanford TJ, et al. Physiology of alfentanil-induced rigidity. Anesthesiology 1986; 64: 440-6
54. Weinger MB, Segal IS, Maze M. Dexmedetomidine, acting through central alpha-2 adrenoceptors, prevents opiate-induced muscle rigidity in the rat. Anesthesiology 1989; 71: 242-9
55. Weinger MB, Chen D-Y, Lin T, et al. A role for CNS alpha-2 adrenergic receptors in opiate-induced muscle rigidity in the rat. Brain Res 1995; 669: 10-8

56. Vankova ME, Weinger MB, Chen D-Y, et al. Role of central mu, delta-1, and kappa-1 opioid receptors in opioid-induced muscle rigidity in the rat. Anesthesiology 1996; 85: 574-83
57. Weinger MB, Cline EJ, Smith NT, et al. Localization of brainstem sites which mediate alfentanil-induced muscle rigidity in the rat. Pharmacol Biochem Behav 1988; 29: 573-80
58. Bowdle TA, Rook GA. Postoperative myoclonus and rigidity after anesthesia with opioids. Anesth Analg 1994; 78: 783-6
59. Smith NT, Benthuysen JL, Bickford RG, et al. Seizures during opioid anesthetic induction - are they opioid-induced rigidity? Anesthesiology 1989; 71: 852-62
60. Bowdle TA. Myoclonus following sufentanil without EEG seizure activity. Anesthesiology 1987; 67: 593-5
61. Tempelhoff R, Modica PA, Bernardo KL, et al. Fentanyl-induced electrocorticographic seizures in patients with complex partial epilepsy. J Neurosurg 1992; 77: 201-8
62. Cascino GD, So EL, Sharbrough FW, et al. Alfentanil-induced epileptiform activity in patients with partial epilepsy. J Clin Neurophysiol 1993; 10: 520-5
63. Armstrong PJ, Bersten A. Normeperidine toxicity. Anesth Analg 1986; 65: 536-8
64. Milde LN, Milde JH, Gallagher WJ. Effects of sufentanil on cerebral circulation and metabolism in dogs. Anesth Analg 1990; 70: 138-46
65. Artru AA. Effects of fentanyl, sufentanil, and alfentanil on epileptiform EEG activity, cerebral blood flow, and intracranial pressure. In: Hines R, Bowdle TA, editors. Anesthesiology clinics of North America annual of anesthetic pharmacology. Philadelphia: WB Saunders, 1997: 117-54
66. Wahl M. Effects of enkephalins, morphine and naloxone on pial arteries during perivascular microapplication. J Cereb Blood Flow Metab 1985; 5: 451-7
67. Radnay PA, Brodman E, Mankikar D, et al. The effect of equianalgesic doses of fentanyl, morphine, meperidine and pentazocine on common bile duct pressure. Anaesthesist 1980; 29: 26-9
68. Jones RM, Detmer M, Hill AB, et al. Incidence of choledochoduodenal sphincter spasm during fentanyl-supplemented anesthesia. Anesth Analg 1981; 60: 638-40
69. Radnay PA, Duncalf D, Novakovic M, et al. Common bile duct pressure changes after fentanyl, morphine, meperidine, butorphanol, and naloxone. Anesth Analg 1984; 63: 441-4
70. McCammon RL, Stoelting RK, Madura JA. Effects of butorphanol, nalbuphine, and fentanyl on intrabiliary tract dynamics. Anesth Analg 1984; 63: 139-42
71. Economou G, Ward-McQuaid JN. A cross-over comparison of the effect of morphine, pethidine, pentazocine, and phenazocine on biliary pressure. Gut 1971; 12: 218-21
72. Staritz M, Poralla T, Manns M, et al. Effect of modern analgesic drugs (tramadol, pentazocine, and buprenorphine) on the bile duct sphincter in man. Gut 1986; 27: 567-9
73. Watcha M, White PF. Postoperative nausea and vomiting: its etiology, treatment and prevention. Anesthesiology 1992; 77: 162-84
74. Costello DJ, Borison HL. Naloxone antagonizes narcotic self-blockade of emesis in the cat. J Pharmacol Exp Ther 1977; 203: 222-30
75. Longnecker DE, Grazis P, Eggers GWN. Naloxone antagonism of morphine induced respiratory depression. Anesth Analg 1973; 52: 447-52
76. Yaksh TL, Collins JG. Studies in animals should precede human use of spinally administered drugs. Anesthesiology 1989; 70: 4-6
77. Sandler AN. Clinical pharmacology and applications of spinal opioids. In: Bowdle TA, Horita A, Kharasch ED, editors. The pharmacologic basis of anesthesiology. New York: Churchill Livingstone, 1994: 149-78
78. Sjostrom S, Tamsen A, Persson MP, et al. Pharmacokinetics of intrathecal morphine and meperidine in humans. Anesthesiology 1987; 67: 889-95
79. Loper KA, Ready B, Downey M, et al. Epidural and intravenous fentanyl infusions are clinically equivalent after knee surgery. Anesth Analg 1990; 70: 72-5
80. Camann WR, Loferski BL, Fanciullo GJ, et al. Does epidural administration of butorphanol offer any clinical advantage over the intravenous route? Anesthesiology 1992; 76: 216-20
81. Chaney M. Side effects of intrathecal and epidural opioids. Can J Anaesth 1995: 891-903
82. Sandler AN, Stringer D, Panos L, et al. A randomized, double-blind comparison of lumbar epidural and intravenous fentanyl infusions for post-thoracotomy pain relief: analgesic, pharmacokinetic and respiratory effects. Anesthesiology 1992; 77: 626-34
83. James CF. Recurrence of herpes simplex virus blepharitis after cesarean section and epidural morphine. Anesth Analg 1996; 82: 1094-6
84. Kavee EH, Ramanathan S. The hypothermic action of epidural and subarachnoid morphine in parturients. Region Anesth 1991; 16: 325-8
85. Sevarino FB, Johnson MD, Lema MJ, et al. The effect of epidural sufentanil on shivering and body temperature in the parturient. Anesth Analg 1989; 68: 530-3
86. Bodner RA, Lynch T, Lewis L, et al. Serotonin syndrome. Neurology 1995; 45: 219-23
87. Kam PCA, Chang GWM. Selective serotonin reuptake inhibitors: Pharmacology and clinical implications in anaesthesia and critical care medicine. Anaesthesia 1997; 52: 982-8
88. Mitchell RS. Fatal toxic encephalitis occurring during iproniazid therapy in pulmonary tuberculosis. Ann Intern Med 1955; 42: 417-24
89. Sternbach H. The serotonin syndrome. Am J Psychiatry 1991; 148: 705-13
90. Rivers N, Homer B. Possible lethal interaction between Nardil and dextromethorphan. Can Med Assoc J 1970; 103: 85
91. Hansen TE, Dieter K, Keepers GA. Interaction of fluoxetine and pentazocine. Am J Psychiatry 1990; 147: 949-50
92. Sinatra RS, Scramcik JL. Tramadol: its use in pain management. In: Hines R, Bowdle TA, editors. Anesthesiology clinics of North America annual of anesthetic pharmacology. Philadelphia: WB Saunders, 1998: 53-69
93. Amrein R, Guntert TW, Dingemanse J, et al. Interaction of moclobemide with concomitantly administered medication: evidence from pharmacological and clinical studies. Psychopharmacology 1992; 106: S24-31
94. Sternberg TL. All monoamine oxidase inhibitors are not equal. Anesth Analg 1997; 84: 938
95. Lee CR, McTavish D, Sorkin EM. Tramadol: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute and chronic pain states. Drugs 1993; 313-340
96. Raffa RB, Friderichs E, Reimann W, et al. Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic. J Pharmacol Exp Ther 1992; 260: 275-85
97. Bowdle TA, Ward RJ. Induction of anesthesia with small doses of sufentanil or fentanyl: dose versus EEG response,

speed of onset and thiopental requirement. Anesthesiology 1989; 70: 26-30
98. Vinik HR. Intravenous anaesthetic drug interactions: practical applications. Eur J Anaesthesiol 1995; 12 Suppl. 12: 13-9
99. Vinik HR, Bradley EL, Kissin I. Midazolam-alfentanil synergism for anesthetic induction in patients. Anesth Analg 1989; 69: 213-7
100. Bailey PL, Pace NL, Ashburn MA, et al. Frequent hypoxemia and apnea after sedation with midazolam and fentanyl. Anesthesiology 1990; 73: 826-30
101. Jeal W, Benfield P. Transdermal fentanyl: a review of its pharmacological properties and therapeutic efficacy in pain control. Drugs 1997; 53: 109-38
102. Bowdle TA, Galer BS. Agonist-antagonist and partial agonist opioids: pharmacologic mechanisms and clinical application in the treatment of headache. Headache Q 1993; 4: 322-36
103. Preston KL, Sullivan JT, Testa M, et al. Psychopharmacology and abuse potential of transnasal butorphanol. Drug Alcohol Depend 1994; 35: 159-67
104. Rosow CE, Connors PM, Hennessy D, et al. Bioavailability of nasal butorphanol. Anesthesiology 1996; 85: A314

Correspondence and reprints: Dr *T. Andrew Bowdle*, Department of Anaesthesiology, Box 356540, Room RR 444, University of Washington, Seattle, WA, USA 98195.
E-mail: bowdle@u.washington.edu