Review Article

Side effects of intrathecal and epidural opioids

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The purpose of this article is to review the literature on the side effects of intrathecal and epidural opioids. English-language articles were identified through a MEDLINE search and through review of the bibliographies of identified articles. With the increasing utilization of intrathecal and epidural opioids in humans during the 1980s, a wide variety of clinically relevant side effects have been reported. The four classic side effects are pruritus, nausea and vomiting, urinary retention, and respiratory depression. Numerous other side effects have also been described. Most side effects are dose-dependent and may be more common if the opioid is administered intrathecally. Side effects are less common in patients chronically exposed to either intrathecal, epidural, or systemic opioids. Some side effects are mediated via interaction with specific opioid receptors while others are not. It is concluded that the introduction of intrathecal and epidural opioids marks one of the most important breakthroughs in pain management in the last two decades. However, a wide variety of clinically relevant non-nociceptive side effects may occur. All physicians utilizing intrathecal and epidural opioids must be aware of these side effects, for while most are minor, others are potentially lethal.

Ce travail constitue un survol de la littérature portant sur les effets secondaires des morphiniques sous-arachnoïdiens et épiduraux. Les articles en langue anglaise ont été identifiés grâce à une recherche sur Medline et une revue des bibliographies des articles trouvés de cette façon. Avec l'utilisation croissante des morphiniques sous-arachnoïdiens et épiduraux débutée dans les années 80, on a décrit avec pertinence une grande variété d'effets secondaires convaincants. Les quatres effets secondaires classiques sont le prurit, les nausées et les vomissements, la rétention urinaire et la dépression respiratoire; ce ne sont toutefois pas les seuls effets secondaires rapportés. La plupart dépendent de la dose et sont plus fréquents lorsque le morphinique est administré par la voie sous-arachnoïdienne. Les effets secondaires surviennent moins souvent chez les patients exposés de façon chronique à des morphiniques sous-arachnoïdiens, épiduraux ou systémiques. Quelques-uns des effets secondaires résultent de l'interaction de récepteurs morphiniques spécifiques mais pas tous. Les auteurs concluent que l'introduction des morphiniques sous-arachnoïdiens et épiduraux représente la percée la plus importante des deux dernières décennies dans le domaine du traitement de la douleur. Cependant, des effets secondaires multiples de nature non-nociceptive sont susceptibles de survenir. Tous les médecins utilisateurs de morphinique sous-arachnoïdiens et épiduraux doivent connaître ces effets secondaires qui sont mineurs pour la plupart, alors que d'autres sont potentiellement létaux.

Key words
ANALGESIA: postoperative;
ANALGESIA: morphine, fentanyl, sufentanil.

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Pure antinociception without side effects has long been an elusive goal. In the 1970s, the discovery of highly specific opioid receptors in the central nervous system, in particular their existence in the spinal cord, created new enthusiasm for the possible realization of this goal. Subsequent demonstration that small amounts of intrathecal or epidural opioids produced profound antinociception only heightened enthusiasm. However, with increasing universal application of the technique in humans in the 1980s, a wide variety of clinically relevant non-nociceptive side effects have been reported.[1,2] Because of the profound antinociception obtained and despite the non-nociceptive side effects, spinal application of opioids remains very popular and effective in the treatment of many pain states.

Opioids are perhaps the oldest and most studied of drugs. Opium use, for its euphoric effects, can be traced back over 4000 yr and its respiratory depressant effects were first noted approximately 600 yr ago. It was not until 1971, however, that highly specific opioid receptors were discovered.[3] In 1973, opioid receptors were localized in mammalian brain[4] and in 1976 they were found to exist in primate spinal cord.[5] Also in 1976, Yaksh and Rudy first demonstrated the effectiveness of intrathecal

opioids in abolishing experimental pain in an animal model.[6] In 1979, initial reports of intrathecal[7] and epidural[8] use of morphine in humans appeared in the literature.

Intrathecal and epidural opioids produce profound segmental antinociception in doses much smaller than would be required for comparable antinociception if administered systemically. Antinociception may be prolonged; when morphine is utilized, it may persist for days following a single injection.[9] Unlike the response to local anaesthetics, there is no motor, sensory, or autonomic blockade. Paralysis and hypotension, therefore, are absent. Another critical advantage over local anaesthetics is the availability of a specific opioid receptor antagonist, naloxone.

Pharmacokinetics of intrathecal and epidural opioids

Side effects of intrathecal and epidural opioids are caused by presence of the drug in either cerebrospinal fluid or blood. Therefore, following administration of intrathecal and epidural opioids, side effects will be profoundly affected by their pharmacokinetic behaviour. Fentanyl and sufentanil are, respectively, approximately 800 and 1600 times as lipid-soluble as morphine. When administered intrathecally or epidurally, therefore, morphine will exhibit slower onset and longer duration of antinociception and a higher incidence of some side effects.

Intrathecal administration of opioids immediately produces high cerebrospinal fluid concentrations of drug that are dose-dependent.[10] Vascular reabsorption of opioids following intrathecal administration does occur to some degree, but is clinically irrelevant.[11-13] Fentanyl and sufentanil penetrate the spinal cord quickly, leaving little drug to ascend cephalad in cerebrospinal fluid. In contrast, morphine penetrates the spinal cord slowly, allowing considerable amounts of drug to ascend cephalad in cerebrospinal fluid. Following lumbar intrathecal morphine administration, appreciable cervical cerebrospinal fluid concentrations occur one to five hours after injection, while cervical cerebrospinal fluid concentrations of a highly lipophilic opioids, similarly administered, are minimal.[14,15] The underlying cause of ascension of morphine is bulk flow of cerebrospinal fluid. Cerebrospinal fluid ascends in a cephalad direction from the lumbar region, reaching the cisterna magna by one or two hours and the fourth and lateral ventricles by three to six hours.[16] Although coughing, sneezing, or straining can affect movement of cerebrospinal fluid, body position does not.[16] Highly lipophilic opioids are removed from cerebrospinal fluid rapidly secondary to vascular reabsorption and spinal cord penetration.[17] In contrast, morphine persists in cerebrospinal fluid for prolonged periods and may depend on reabsorption through arachnoid granulations for elimination.[18] The terminal elimination half-life of morphine in cerebrospinal fluid is similar to that in plasma, two to four hours.[10,17]

Epidural administration of opioids also produces considerable cerebrospinal fluid concentrations of drug. Penetration of the dura is considerably influenced by lipophilicity, but molecular weight may also play an important role.[19] Following epidural administration, cerebrospinal fluid concentrations of fentanyl peak in 10 to 20 min[20] while sufentanil concentrations peak in about six minutes.[21] In contrast, cerebrospinal fluid concentrations of morphine, following epidural administration, peak in one to four hours.[22,23] Furthermore, only about 3% of the dose of morphine administered epidurally crosses the dura to enter cerebrospinal fluid.[22,23] The epidural space contains an extensive venous plexus. Therefore, vascular reabsorption following epidural administration of opioids is extensive. Epidural administration of morphine, fentanyl, or sufentanil produces opioid blood concentrations that are similar to an intramuscular injection of an equivalent dose. Following epidural administration, fentanyl blood concentrations peak at about five to ten minutes[24,25] while sufentanil blood concentrations peak even faster.[13,26] In contrast, blood concentrations of morphine following epidural administration peak at about 10 to 15 min.[22,23,27,28]

TABLE I Side effects of intrathecal and epidural opioids

Pruritus
Nausea and vomiting
Urinary retention
Respiratory depression
Mental status changes
Central nervous system excitation
Hyperalgesia
Herpes simplex labialis virus reactivation
Neonatal morbidity
Sexual dysfunction
Ocular dysfunction
Gastrointestinal dysfunction
Thermoregulatory dysfunction
Water retention
Cardiac dysrhythmia
Hair loss
Neurotoxicity
Anaphylaxis

Side effects of intrathecal and epidural opioids

Side effects of intrathecal and epidural opioids are listed in Table I. The four classic side effects are pruritus, nausea and vomiting, urinary retention, and respiratory depression. Numerous other side effects have also been described. In general, most side effects of intrathecal and

epidural opioids are dose-dependent and may be more common if the opioid is administered intrathecally. Side effects are less common in patients chronically exposed to either intrathecal, epidural, or systemic opioids.[29] Some side effects are mediated via interaction with specific opioid receptors while others are not.

Pruritus

The most common side effect of intrathecal and epidural opioids is pruritus. It may be generalized but is more likely to be localized to the face, neck, or upper thorax.[1,2] The incidence varies widely, from 0 to 100%, and it is often elicited only after direct questioning. Severe pruritus is rare, occurring in only about 1% of patients. Pruritus usually occurs within a few hours of injection and may precede the onset of antinociception.[30,31] The incidence may[32] or may not[30] be related to the dose of opioid administered, may be higher when the intrathecal route is utilized[33] and is lower following subsequent doses.[29] Pruritus is more likely to occur in obstetric patients[32] which may result from an interaction of oestrogen with opioid receptors.[34,35]

Although opioids may liberate histamine from mast cells, this does not appear to be the mechanism underlying pruritus. Opioids can produce naloxone-reversible pruritus without affecting plasma histamine concentrations.[36] Furthermore, rash following intrathecal and epidural opioid administration is very rare.[37] Paradoxically, antihistamines may be effective treatment for pruritus, likely secondary to their sedative effects. Pruritus also does not appear to be related to systemic absorption of opioid.[31]

Pruritus induced by intrathecal and epidural opioids is likely due to cephalad migration of the drug in cerebrospinal fluid and subsequent interaction with the trigeminal nucleus located superficially in the medulla.[38] Opioid receptors are present in the trigeminal nucleus and trigeminal nerve roots.[39] In fact, the most common location of induced pruritus is in the facial areas innervated by the trigeminal nerve.[38] Animal studies support the concept of an "itch centre" located in the lower medulla[40] and indicate that the trigeminal nucleus is involved in the itch reflex.[41] Injection of opioid into the cisterna cerebellomedullaris of cats promotes itching.[40] In humans, naloxone has been used successfully in treatment of intractable idiopathic pruritus[42] and cerebral tumours infiltrating the fourth ventricle cause itching in facial areas innervated by the trigeminal nerve.[43]

Altered central nervous system perception of pain may also play a role in pruritus induced by intrathecal and epidural opioids.[44] The trigeminal nucleus descends into the cervical region of the spinal cord and becomes continuous with the substantia gelatinosa of the dorsal horn. Opioid interaction in the substantia gelatinosa may thus initiate an "itch reflex" through indirect action on the trigeminal nucleus.[44] Pruritus may be a clinical symptom in patients who experience sensory modulation disturbances; examples include multiple sclerosis,[45] diabetes,[46] and differential neural blockade.[47]

Nausea and vomiting

The incidence of nausea and vomiting following intrathecal and epidural opioids is approximately 30%. Although the underlying mechanism is not related to systemic absorption of drug,[31] the incidence of nausea and vomiting following intravenous opioids is the same.[1,2] Nausea usually occurs within four hours of injection and vomiting soon thereafter.[31] The incidence may[30,48,49] or may not[32,50] be related to the dose of opioid administered and may be higher when intrathecal morphine is utilized.[1,2] Nausea and vomiting are more frequent in women than in men experiencing pain.[50] Paradoxically, for reasons unknown, the epidural administration of opioids may decrease the incidence of perioperative nausea and vomiting.[51]

Nausea and vomiting induced by intrathecal and epidural opioids are likely the result of cephalad migration of drug in cerebrospinal fluid and subsequent interaction with opioid receptors located in the area postrema.[39,52] Sensitization of the vestibular system to motion[53] and decreased gastric emptying[54] produced by opioids may also play a role in nausea and vomiting induced by intrathecal and epidural opioids.

Urinary retention

The incidence of urinary retention following intrathecal and epidural opioids varies widely, from 0 to 80%, and occurs most often in young male volunteers.[2,31] The incidence is not related to the dose of opioid administered[30,48,50,55] and may be higher when intrathecal morphine is utilized.[33] The underlying mechanism is not related to systemic absorption of drug.[31] Urinary retention following intrathecal and epidural opioids is much more common than after intravenous or intramuscular administration of equivalent doses of opioid.[55-57]

Urinary retention induced by intrathecal and epidural opioids is likely related to interaction with opioid receptors located in the sacral spinal cord.[55] This interaction promotes inhibition of sacral parasympathetic nervous system outflow which causes detrusor muscle relaxation and an increase in maximal bladder capacity leading to urinary retention. In humans, epidural morphine causes marked detrusor muscle relaxation within 15 min of injection that persists for up to 16 hr and is readily reversed with naloxone.[55] Endogenous opioids likely play an important role in normal control of bladder function via

modulation of parasympathetic nervous system outflow at the sacral spinal cord level.[58-61]

Respiratory depression

The most feared side effect of intrathecal and epidural opioids is respiratory depression.[62] Only four months after initial utilization of intrathecal and epidural opioids in humans, life-threatening respiratory depression was reported.[63-65] Clinically important respiratory depression has been reported following intrathecal morphine,[66] epidural morphine,[50] intrathecal fentanyl,[67] epidural fentanyl,[68] intrathecal sufentanil,[69] and epidural sufentanil.[70] Respiratory depression may occur within minutes of injection of opioid or may be delayed for hours. The incidence of respiratory depression depends on how it is defined.[71] The incidence of respiratory depression requiring intervention following conventional doses of intrathecal and epidural opioids is approximately 1%, which is the same as that following conventional dosing of intramuscular and intravenous opioids.[32,33,50,66,72]

Early respiratory depression occurs within two hours of injection of opioid. Most reports of clinically important early respiratory depression involve administration of epidural fentanyl or epidural sufentanil[26,68,70,73,74] and is very rare following the intrathecal use of fentanyl or sufentanil.[67,69] Respiratory depression induced by epidural fentanyl and sufentanil likely results from systemic absorption of drug, since blood concentration of opioid is proportional to the magnitude of respiratory depression.[26,73] However, cephalad migration of opioid in cerebrospinal fluid may also initiate early respiratory depression. Following epidural administration of sufentanil, cisternal cerebrospinal fluid concentrations of opioid are measurable within one minute.[21] Apnoea within one minute of injection of epidural sufentanil has been reported.[75] Although sensitive tests of respiratory depression reveal that epidural morphine induces early respiratory depression, it is clinically irrelevant.[76,77] Clinically important early respiratory depression following intrathecal use of morphine has never been described.

Delayed respiratory depression occurs more than two hours after injection of opioid. All reports of clinically relevant delayed respiratory depression involve administration of intrathecal or epidural morphine.[50,66] Clinically important delayed respiratory depression following a single injection of intrathecal or epidural fentanyl or sufentanil has never been described. However, continuous infusions or repeated doses of a lipophilic opioid may possibly initiate clinically relevant delayed respiratory depression.[73] Delayed respiratory depression results from cephalad migration of opioid in cerebrospinal fluid and subsequent interaction with opioid receptors located in the ventral medulla.[78] High concentrations of opioid receptors exist in the ventral medulla and are important in normal regulation of respiration.[79] Minute amounts of opioid directly applied to the medulla induce significant respiratory depression.[80] Following lumbar intrathecal morphine administration, respiratory depression is maximal when peak concentration of morphine is attained in the medulla.[81] Delayed respiratory depression characteristically occurs 6 to 12 hr following intrathecal or epidural administration of morphine yet may persist 24 hr.[30,76,77]

TABLE II Factors increasing risk of respiratory depression

High doses of opioid
Repeated doses of opioid
Intrathecal utilization
Morphine
Intravenous sedatives
Advanced age
Co-existing disease
Lack of opioid tolerance
Thoracic epidural placement
General anaesthesia
Increased intrathoracic pressure
Patient position

Detection of respiratory depression induced by intrathecal and epidural opioids may be difficult. Classic bradypnoea may[33] or may not[72] be present and hypercarbia may develop despite a normal respiratory rate.[82] Bradypnoea appears to be a more reliable clinical sign of early respiratory depression following intrathecal or epidural use of fentanyl or sufentanil.[67,68,70,73] Pulse oximetry may be valuable[30] but must be interpreted cautiously if supplemental oxygen is being administered.[83] The most reliable clinical sign of respiratory depression appears to be a depressed level of consciousness, possibly caused by hypercarbia.[62,72,82] Inhalation of carbon dioxide mixtures by healthy volunteers causes somnolence and loss of consciousness at $PaCO_2$ of 80 mmHg.[84] Characteristically, early respiratory depression develops rapidly, whereas, delayed respiratory depression develops slowly and progressively.[50] Protocols for monitoring the development of respiratory depression following intrathecal and epidural opioids vary among institutions. Most assess patients hourly for four to six hours if fentanyl or sufentanil has been administered and for 18 to 24 hr after morphine.[72] Clinically important respiratory depression developing 24 hr after the last injection of intrathecal or epidural morphine has never been described.

Certain factors are known to increase the risk of respiratory depression following intrathecal and epidural opioids (Table II). Concomitant use of any intravenous sedative increases the risk and should be avoided, if possible. Coughing may affect movement of cerebrospinal

fluid[16] and may be associated with the development of respiratory depression.[77] Although body position does not affect movement of cerebrospinal fluid,[16] it may[85] or may not[86] increase the risk of respiratory depression. Obstetric patients appear to be at less risk for respiratory depression, perhaps because of increased blood concentration of progesterone, a respiratory stimulant.[87]

Mental status changes

Sedation, the most common mental status change following intrathecal and epidural opioids, occurs frequently with all opioids but is most commonly associated with the use of sufentanil.[88] The degree of sedation appears to be related to the dose of opioid administered.[30,49] Central nervous system depression may be profound and coma has been described.[89,90] Any time sedation occurs following intrathecal or epidural administration of opioids, respiratory depression must be suspected.[91]

Mental status changes other than sedation may also occur after intrathecal and epidural opioids. Naloxone-reversible paranoid psychosis[92] and catatonia[33,93] have been reported. Others have described the development of euphoria, anxiety, and hallucinations.[66]

Mental status change caused by intrathecal and epidural opioids likely results from cephalad migration of drug in cerebrospinal fluid and subsequent interaction with opioid receptors located in the brain. Possible mechanisms include interactions with opioid receptors located in the thalamus, limbic system, and cerebral cortex.[94] Other behavioural changes may be caused by interaction with opioid receptors located in the amygdala.[39] Of interest, animal studies indicate that opioid receptors in the brain may play a role in certain forms of mental illness.[95]

Central nervous system excitation

Tonic muscle rigidity resembling seizure activity is a well known side effect of large doses of intravenous opioids.[96] Rarely, similar activity may be observed following administration of intrathecal or epidural opioids. Myoclonic activity following both intrathecal and epidural opioids has been reported.[97,98] Muscle rigidity has also been observed after administration of epidural morphine[93,99] and intrathecal sufentanil.[100] Deep tendon reflexes may become hypertonic following epidural morphine.[101] In animals, large doses of intrathecal opioids induce hindlimb stiffness and rigidity.[102,103]

The mechanism of central nervous system excitation caused by intrathecal and epidural opioids does not appear to be mediated by opioid receptors.[102] A spinal cord mechanism may be involved[104] but cephalad migration of opioid in cerebrospinal fluid and subsequent interaction with non-opioid receptors in the brainstem or basal ganglia is more likely.[96] In animals, administration of opioids into the cerebral ventricles induces behavioural excitation that is not reversible with naloxone.[105,106] The central nervous system excitation may be caused by the ability of opioids to block glycine or gamma-aminobutyric acid-mediated inhibition.[107]

Although large doses of opioids reliably induce seizure activity in animals, clinically relevant doses of intravenous, intrathecal, or epidural opioids have never been observed to induce generalized cortical seizure activity in humans.[96]

Hyperalgesia

Paradoxically, large doses of intrathecal morphine will cause hyperalgesia in laboratory animals.[103,107-109] Hyperalgesia has also been reported in refractory cancer pain patients administered large doses of intrathecal morphine.[110,111]

Hyperalgesia caused by intrathecal morphine is not mediated by opioid receptors and is not affected by even large doses of naloxone.[103,107-109] Alteration of spinal cord coding of sensory information via a non-opioid receptor mechanism may play a role.[103,109] Hyperalgesia may be caused by the ability of morphine to block glycine or gamma-aminobutyric acid-mediated inhibition.[107,108] Conjugated metabolites of morphine, several hundred times more potent at producing behavioural excitation, may also be involved.[106] Unlike morphine, opioids that do not undergo conjugation are incapable of producing hyperalgesia.[38]

Herpes simplex labialis virus reactivation

A link exists between the use of epidural morphine in obstetric patients and reactivation of herpes simplex labialis virus.[112,113] Reactivation of the herpes virus typically occurs two to five days after epidural administration of opioid.[113,114] Manifestation of symptoms characteristically occurs in the same sensory innervation area as the primary infection, which is usually facial areas innervated by the trigeminal nerve.[113] A similar link between the use of intrathecal opioids in young patients and reactivation of the herpes virus has been suggested.[115,116] At present, no evidence exists supporting a link between use of any other opioid by any other route and reactivation of herpes simplex labialis virus.[112]

The underlying mechanism causing herpes virus reactivation likely involves cephalad migration of opioid in cerebrospinal fluid and subsequent interaction with the trigeminal nucleus.[117] Reactivation of the herpes virus may be initiated by stimulation of opioid receptors located in the trigeminal nucleus, where the virus is known to reside in latent form.[113] Itching, with associated mechanical irritation of the skin, induced by intrathecal or epidural opioids, may also indirectly reactivate the latent

herpes virus.[112-114,117,118] It is interesting to note that the most common areas of both pruritus and reactivation of herpes virus following intrathecal and epidural opioids is in facial areas innervated by the trigeminal nerve. Physiological changes normally associated with pregnancy, including depression of some aspects of cell-mediated immunity and alterations in hormone levels, may also be involved in reactivation of the herpes virus.[118] Most likely, the underlying mechanism causing herpes simplex labialis virus reactivation is multifactorial and may involve all, some, or none of the above proposed mechanisms.[113,118]

Neonatal morbidity

Neonatal morbidity is possible when intrathecal or epidural opioids are used in obstetric patients for pain relief during labour or Caesarean section. Following intrathecal or epidural administration of opioid to the mother, vascular reabsorption of drug occurs. Once present in the maternal blood, the opioid may then be transferred across the placenta to the fetus. Immediately after birth, neonatal blood concentrations of opioid are detectable following maternal administration of intrathecal morphine,[119] epidural morphine,[120] epidural fentanyl,[121,122] and epidural sufentanil.[123] Clinically important respiratory depression has developed in neonates following administration of epidural morphine[120] and epidural fentanyl[121] to the mother. Furthermore, neurological signs of drug-induced depression in neonates have been observed following epidural sufentanil.[124] However, multiple investigations involving large numbers of patients have revealed that intrathecal and epidural opioids are safe for the mother and neonate provided that conventional doses are used.[25,119,122,123,125-129]

The use of intrathecal or epidural opioids in obstetric patients may affect the neonate in ways other than placental transfer of drug. For a variety of reasons, intrathecal morphine may either inhibit[130,131] or enhance[132] the progress of labour. Following administration of epidural fentanyl or epidural sufentanil to obstetric patients, breast milk concentration of opioid is negligible.[133]

Sexual dysfunction

In healthy male volunteers, administration of epidural morphine may lead to sustained erection and inability to ejaculate.[55,134] In male rats, intrathecal morphine increases while intrathecal naloxone decreases the number of intromissions prior to orgasm.[135] These properties may make intrathecal or epidural opioids viable treatment options for premature ejaculation.[135,136] Erection is under the influence of the parasympathetic nervous system whereas ejaculation and termination of erection are under the influence of the sympathetic nervous system.[136] Therefore, sustained erection and inability to ejaculate may be secondary to an opioid-induced decrease in sympathetic nervous system response to sexual stimulation.[136] It appears that this effect occurs in the spinal cord, for sustained erection and inability to ejaculate is not observed in males administered intravenous or intramuscular opioids.[55,134,135]

In female rats, intrathecal morphine inhibits while intrathecal naloxone enhances sexual receptivity.[135] Opioids may also inhibit ovulation in rats.[137] Amenorrhoea and sterility are commonly observed in human female morphine addicts.[138]

Ocular dysfunction

Naloxone-reversible nystagmus has been reported following administration of intrathecal morphine[139] and epidural morphine.[140] A naloxone-reversible Ménière-like syndrome has also been reported following administration of epidural morphine.[141] Vertigo has been observed after use of epidural morphine.[142] The time course of symptom development and the fact that they are naloxone-reversible indicate cephalad migration of opioid in cerebrospinal fluid and subsequent interaction with opioid receptors in the brain is likely involved.[141,142]

Like intravenous opioids, intrathecal and epidural opioids may initiate miosis. When miosis occurs following administration of intrathecal or epidural opioids, it indicates drug is present in cerebrospinal fluid at the midbrain level and thus may be an early warning sign of impending respiratory depression.[143,144]

Gastrointestinal dysfunction

Intravenous and intramuscular opioids are known for their ability to alter gastrointestinal motility. Intrathecal and epidural opioids may also delay gastric emptying and prolong intestinal transit time.[54,102] In human volunteers, administration of epidural morphine delays gastric emptying.[145] In mice, intrathecal morphine causes dose-dependent, naloxone-reversible prolongation of small bowel transit time.[146] Patients administered intrathecal or epidural opioids may exhibit signs and symptoms of ileus which may, in turn, lead to nausea and vomiting.[54,97,102,145] The cause of the decrease in gastrointestinal motility following intrathecal or epidural opioids is not related to systemic absorption of drug[145] and appears to be caused by interaction with opioid receptors located in the spinal cord.[145,146]

Thermoregulatory dysfunction

Opioids induce alterations in body temperature, an effect that depends on species, route of administration, dosage, and ambient temperature.[147,148] In rats, intrathecal morphine causes a dose-dependent, naloxone-reversible increase in body temperature, which appears to be caused

by interaction with opioid receptors located in the spinal cord.[149] However, alterations in body temperature may also be initiated by cephalad migration of drug in cerebrospinal fluid and subsequent interaction with opioid receptors located in the hypothalamus. In animals, administration of opioid into the cerebral ventricles may cause hyperthermia or hypothermia.[95,150,151] In humans, administration of epidural sufentanil may induce hypothermia, an effect likely caused by the ability of the opioid to decrease shivering.[152-154]

Water retention

Oliguria and water retention leading to peripheral oedema have been reported following administration of intrathecal and epidural morphine.[97,155] The water retention is likely caused by release of vasopressin, stimulated by cephalad migration of opioid in cerebrospinal fluid and subsequent interaction with opioid receptors located in the posterior pituitary. The posterior pituitary does possess opioid receptors[156] and release of vasopressin is stimulated in animals administered opioids.[157] In humans, administration of epidural morphine stimulates release of vasopressin despite effective analgesia.[155]

Cardiac dysrhythmia

New left bundle branch block has occurred in one patient 45 min after receiving an inadvertent overdose of epidural morphine.[158] Five minutes after intravenous naloxone, the left bundle branch block disappeared and the ECG reverted to the patient's usual pattern.

Hair loss

Unexplained hair loss, resembling alopecia areata, has occurred in one patient after receiving epidural morphine for three days.[159] The hair loss was associated with widespread itching.

Neurotoxicity

Damage to the spinal cord may occur following administration of intrathecal or epidural opioids. After intrathecal injection of morphine, 2.5 mg, the cerebrospinal fluid concentration of drug is 4000 times that seen after intravenous injection of 1.0 $mg \cdot kg^{-1}$.[160] In sheep, epidural morphine causes spinal cord necrosis[161] and intrathecal sufentanil induces inflammatory changes in the meninges.[162] In cats, intrathecal sufentanil induces inflammatory changes in the spinal cord.[103] Furthermore, these animals exhibited hindlimb dysfunction in the form of stiffness and weakness.[103,161,162] In monkeys, however, no spinal cord damage was detected following administration of intrathecal morphine.[163] In humans, intrathecal morphine[33,97,164] and epidural morphine[33] have been implicated as possible causes of spinal cord damage. Clinical manifestations in these patients included sensory and motor neurological dysfunction,[33,164] myoclonic spasms,[97] paresis,[33] and paralysis.[97] On the other hand, administration of large doses of intrathecal morphine for prolonged periods of time has proved to be safe.[29,165,166] Intrathecal morphine has been administered for as long as 90 days and epidural morphine for as long as 450 days without problems.[29] Inadvertent overdose of epidural morphine has also occurred without sequela.[158] Postmortem examination of spinal cords from patients who had received prolonged infusions of intrathecal morphine revealed no damage.[165] In summary, spinal cord damage following administration of intrathecal or epidural opioids may occur but is extremely rare if conventional doses of opioids are utilized.

The spinal cord possesses only marginal blood flow and is susceptible to ischaemia if vasoconstriction occurs. Several studies have demonstrated opioid receptor-mediated effects on blood vessels *in vitro*.[167] Although no studies have been performed in humans, it appears from animal studies that intrathecal morphine does not affect spinal cord blood flow.[168]

Some opioid preparations contain preservatives which, if injected intrathecally or epidurally, may cause spinal cord damage.[169,170] In humans, inadvertent use of drugs with preservatives has caused paralysis following intrathecal[171] and epidural[172] injection.

Anaphylaxis

True anaphylaxis following administration of opioids, by any route, is extremely rare. It has been reported once following administration of epidural fentanyl.[173] A previous exposure to fentanyl was documented and hypersensitivity was later confirmed by intradermal testing.

Treatment and prophylaxis of side effects

Essentially, all side effects of intrathecal and epidural opioids are mediated via opioid receptors. Treatment, therefore, involves administration of an opioid receptor antagonist, usually naloxone. The most common clinically encountered side effects (pruritus, nausea and vomiting, urinary retention, respiratory depression) are all readily antagonized with administration of naloxone. Unfortunately, when antagonizing side effects with naloxone, analgesia may[174-176] or may not[50,177,178] be preserved. Administration of an opioid agonist-antagonist to treat side effects instead of an opioid antagonist may preserve analgesia.[179,180] During treatment of respiratory depression caused by intrathecal or epidural morphine, it may reappear later if only a single dose of naloxone is utilized.[181] Oral naltrexone, a long-acting opioid antagonist, may be useful if one wants to avoid the time and expense involved in maintaining a naloxone infusion.[182] Even though nal-

oxone crosses the placenta, it appears to cause no neonatal morbidity and thus may be utilized to treat side effects in obstetric patients.[183] Drugs other than opioid receptor antagonists have been used to treat side effects of intrathecal and epidural opioids with occasional success. Antiemetics are often useful in treating nausea and vomiting yet unwanted sedation may aggravate respiratory depression.[184]

Prophylactic administration of opioid receptor antagonists has occasionally been effective in decreasing the incidence of some side effects. However, the dose of naloxone that will antagonize side effects while at the same time preserve analgesia is uncertain at best.[30] Most physicians believe that prophylactic administration of opioid antagonists to decrease the incidence of side effects is not justified and treatment should be reserved for those patients who manifest symptoms.[179,185] In theory, intrathecal or epidural administration of an opioid agonist-antagonist should be associated with a lower incidence of side effects than a pure opioid agonist similarly administered. However, this may[76] or may not[186] occur and analgesia is inferior to that produced by opioid agonists. Other drugs have been used prophylactically in attempts to decrease the incidence of side effects of intrathecal and epidural opioids with occasional success. Prophylactic transdermal scopolamine decreases the incidence of nausea and vomiting associated with epidural morphine.[53,187]

Summary

The introduction of intrathecal and epidural opioids marks one of the most important breakthroughs in pain management in the last two decades. Profound segmental antinociception is obtained with doses much smaller than would be required if administered systemically. However, a wide variety of clinically relevant non-nociceptive side effects may occur. All physicians utilizing intrathecal and epidural opioids must be aware of the non-nociceptive side effects for while some are minor, others are potentially lethal.

References

1 *Cousins MJ, Mather LE.* Intrathecal and epidural administration of opioids. Anesthesiology 1984; 61: 276–310.

2 *Morgan M.* The rational use of intrathecal and extradural opioids. Br J Anaesth 1989; 63: 165–88.

3 *Goldstein A, Lowney LI, Pal BK.* Stereospecific and nonspecific interactions of the morphine congener levorphanol in subcellular fractions of mouse brain. Proc Natl Acad Sci U S A 1971; 68: 1742–7.

4 *Pert CB, Snyder SH.* Opiate receptor: demonstration in nervous tissue. Science 1973; 179: 1011–4.

5 *LaMotte C, Pert CB, Snyder SH.* Opiate receptor binding in primate spinal cord: distribution and changes after dorsal root section. Brain Res 1976; 112: 407–12.

6 *Yaksh TL, Rudy TA.* Analgesia mediated by a direct spinal action of narcotics. Science 1976; 192: 1357–8.

7 *Wang JK, Nauss LA, Thomas JE.* Pain relief by intrathecally applied morphine in man. Anesthesiology 1979; 50: 149–51.

8 *Behar M, Magora F, Olshwang D, Davidson JT.* Epidural morphine in treatment of pain. Lancet 1979; 1: 527–8.

9 *Mathews ET, Abrams LD.* Intrathecal morphine in open heart surgery (Letter). Lancet 1980; 2: 543.

10 *Nordberg G, Hedner T, Mellstrand T, Dahlström B.* Pharmacokinetic aspects of intrathecal morphine analgesia. Anesthesiology 1984; 60: 448–54.

11 *Chauvin M, Samii K, Schermann M, Sandouk P, Bourdon R, Viars P.* Plasma pharmacokinetics of morphine after i.m., extradural and intrathecal administration. Br J Anaesth 1982; 54: 843–7.

12 *Hansdottir, Hedner T, Woestenborghs R, Nordberg G.* The CSF and plasma pharmacokinetics of sufentanil after intrathecal administration. Anesthesiology 1991; 74: 264–9.

13 *Ionescu TI, Taverne RHT, Houweling PL, Drost RH, Nuijten S, Van Rossum J.* Pharmacokinetic study of extradural and intrathecal sufentanil anaesthesia for major surgery. Br J Anaesth 1991; 66: 458–64.

14 *Max MB, Inturrisi CE, Kaiko RF, Grabinski PY, Li CH, Foley KM.* Epidural and intrathecal opiates: cerebrospinal fluid and plasma profiles in patients with chronic cancer pain. Clin Pharmacol Ther 1985; 38: 631–41.

15 *Payne R, Inturrisi CE.* CSF distribution of morphine, methadone and sucrose after intrathecal injection. Life Sci 1985; 37: 1137–44.

16 *Di Chiro G.* Observations on the circulation of the cerebrospinal fluid. Acta Radiol 1966; 5: 988–1002.

17 *Sjöström S, Tamsen A, Persson MP, Hartvig P.* Pharmacokinetics of intrathecal morphine and meperidine in humans. Anesthesiology 1987; 67: 889–95.

18 *Davies GK, Tolhurst-Cleaver CL, James TL.* Respiratory depression after intrathecal narcotics. Anaesthesia 1980; 35: 1080–3.

19 *Moore RA, Bullingham RES, McQuay HJ, et al.* Dural permeability to narcotics: *in vitro* determination and application to extradural administration. Br J Anaesth 1982; 54: 1117–28.

20 *Gourlay GK, Murphy TM, Plummer JL, Kowalski SR, Cherry DA, Cousins MJ.* Pharmacokinetics of fentanyl in lumbar and cervical CSF following lumbar epidural and intravenous administration. Pain 1989; 38: 253–9.

21 *Stevens RA, Petty RH, Hill HF, et al.* Redistribution of sufentanil to cerebrospinal fluid and systemic circulation after epidural administration in dogs. Anesth Analg 1993; 76: 323–7.

22 *Ionescu TI, Taverne RHT, Drost RH, Roelofs JMM,*

Winckers EKA, Van Rossum JM. Epidural morphine anesthesia for abdominal aortic surgery - pharmacokinetics. Reg Anesth 1989; 14: 107–14.

23 *Sjöström S, Hartvig P, Persson MP, Tamsen A.* Pharmacokinetics of epidural morphine and meperidine in humans. Anesthesiology 1987; 67: 877–88.

24 *Ahuja BR, Strunin L.* Respiratory effects of epidural fentanyl. Anaesthesia 1985; 40: 949–55.

25 *Justins DM, Knott C, Luthman J, Reynolds F.* Epidural versus intramuscular fentanyl. Anaesthesia 1983; 38: 937–42.

26 *Koren G, Sandler AN, Klein J, et al.* Relationship between the pharmacokinetics and the analgesic and respiratory pharmacodynamics of epidural sufentanil. Clin Pharmacol Ther 1989; 46: 458–62.

27 *Gourlay GK, Cherry DA, Cousins MJ.* Cephalad migration of morphine in CSF following lumbar epidural administration in patients with cancer pain. Pain 1985; 23: 317–26.

28 *Gourlay GK, Cherry DA, Plummer JL, Armstrong PJ, Cousins MJ.* The influence of drug polarity on the absorption of opioid drugs into CSF and subsequent cephalad migration following lumbar epidural administration: application to morphine and pethidine. Pain 1987; 31: 297–305.

29 *Arnér S, Rawal N, Gustafsson LL.* Clinical experience of long-term treatment with epidural and intrathecal opioids - a nationwide survey. Acta Anaesthesiol Scand 1988; 32: 253–9.

30 *Bailey PL, Rhondeau S, Schafer PG, et al.* Dose-response pharmacology of intrathecal morphine in human volunteers. Anesthesiology 1993; 79: 49–59.

31 *Bromage PR, Camporesi EM, Durant PAC, Nielsen CH.* Nonrespiratory side effects of epidural morphine. Anesth Analg 1982; 61: 490–5.

32 *Fuller JG, McMorland GH, Douglas MJ, Palmer L.* Epidural morphine for analgesia after Caesarean section: a report of 4880 patients. Can J Anaesth 1990; 37: 636–40.

33 *Rawal N, Arnér S, Gustafsson LL, Allvin R.* Present state of extradural and intrathecal opioid analgesia in Sweden. Br J Anaesth 1987; 59: 791–9.

34 *DuPont A, Barden N, Cusan L, Mérand Y, Labrie F, Vaudry H.* β-endorphin and Met-enkephalins: their distribution, modulation by estrogens and haloperidol, and role in neuroendocrine control. Federation Proceedings 1980; 39: 2544–50.

35 *LaBella FS, Kim RS, Templeton J.* Opiate receptor binding activity of 17-alpha estrogenic steroids. Life Sci 1978; 23: 1797–1804.

36 *Bernstein JE, Grinzi RA.* Butorphanol-induced pruritus antagonized by naloxone (Letter). J Am Acad Dermatol 1981; 5: 227–8.

37 *Hales P.* Pruritus after extradural morphine (Letter). Lancet 1980; 2: 204.

38 *Ballantyne JC, Loach AB, Carr DB.* Itching after epidural and spinal opiates. Pain 1988; 33: 149–60.

39 *Snyder SH.* Opiate receptors in the brain. N Engl J Med 1977; 296: 266–71.

40 *Koenigstein H.* Experimental study of itch stimuli in animals. Archives of Dermatology and Syphilology 1948; 57: 828–49.

41 *Hu JW, Dostrovsky JO, Sessle BJ.* Functional properties of neurons in cat trigeminal subnucleus caudalis (medullary dorsal horn). I. Responses to oral-facial noxious and non-noxious stimuli and projections to thalamus and subnucleus oralis. J Neurophysiol 1981; 45: 173–92.

42 *Bernstein JE, Swift R.* Relief of intractable pruritus with naloxone. Arch Dermatol 1979; 115: 1366–7.

43 *Andreev VC, Petkov I.* Skin manifestations associated with tumours of the brain. Br J Dermatol 1975; 92: 675–8.

44 *Scott PV, Fischer HBJ.* Intraspinal opiates and itching: a new reflex? BMJ 1982; 284: 1015–6.

45 *Osterman PO.* Paroxysmal itching in multiple sclerosis. Br J Dermatol 1976; 95: 555–8.

46 *Koski DW, Fraser JG.* Pruritus following spinal anesthesia. Anesth Analg 1980; 59: 157–8.

47 *Nathan PW.* Observations on sensory and sympathetic function during intrathecal analgesia. J Neurol Neurosurg Psych 1976; 39: 114–21.

48 *Martin R, Salbaing J, Blaise G, Tétrault J-P, Tétreault L.* Epidural morphine for postoperative pain relief: a dose-response curve. Anesthesiology 1982; 56: 423–6.

49 *Samii K, Chauvin M, Viars P.* Postoperative spinal analgesia with morphine. Br J Anaesth 1981; 53: 817–20.

50 *Stenseth R, Sellevold O, Breivik H.* Epidural morphine for postoperative pain: experience with 1085 patients. Acta Anaesthesiol Scand 1985; 29: 148–56.

51 *Vincent RD Jr, Chestnut DH, Choi WW, Ostman PLG, Bates JN.* Does epidural fentanyl decrease the efficacy of epidural morphine after cesarean delivery? Anesth Analg 1992; 74: 658–63.

52 *Wang SC, Borison HL.* The vomiting center. Archives of Neurology and Psychiatry 1950; 63: 928–41.

53 *Loper KA, Ready LB, Dorman BH.* Prophylactic transdermal scopolamine patches reduce nausea in postoperative patients receiving epidural morphine. Anesth Analg 1989; 68: 144–6.

54 *Wattwil M.* Postoperative pain relief and gastrointestinal motility. Acta Chir Scand 1988; 550: 140–5.

55 *Rawal N, Möllefors K, Axelsson K, Lingårdh G, Widman B.* An experimental study of urodynamic effects of epidural morphine and of naloxone reversal. Anesth Analg 1983; 62: 641–7.

56 *Lanz E, Theiss D, Riess W, Sommer U.* Epidural morphine for postoperative analgesia: a double-blind study. Anesth Analg 1982; 61: 236–40.

57 *Peterson TK, Husted SE, Rybro L, Schurizek BA, Wern-*

berg M. Urinary retention during i.m. and extradural morphine analgesia. Br J Anaesth 1982; 54: 1175–8.

58 *de Groat WC, Kawatani M, Hisamitsu T, et al.* The role of neuropeptides in the sacral autonomic reflex pathways of the cat. J Autonon Nerv Syst 1983; 7: 339–50.

59 *Dray A, Metsch R.* Spinal opioid receptors and inhibition of urinary bladder motility in vivo. Neurosci Lett 1984; 47: 81–4.

60 *Drenger B, Magora F, Evron S, Caine M.* The action of intrathecal morphine and methadone on the lower urinary tract in the dog. J Urol 1986; 135: 852–5.

61 *Roppolo JR, Booth AM, de Groat WC.* The effects of naloxone on the neural control of the urinary bladder of the cat. Brain Res 1983; 264: 355–8.

62 *Etches RC, Sandler AN, Daley WD.* Respiratory depression and spinal opioids. Can J Anaesth 1989; 36: 165–85.

63 *Glynn CJ, Mather LE, Cousins MJ, Wilson PR, Graham JR.* Spinal narcotics and respiratory depression (Letter). Lancet 1979; 2: 356–7.

64 *Liolios A, Anderson FH.* Selective spinal analgesia (Letter). Lancet 1979; 2: 357.

65 *Scott DB, McClure J.* Selective epidural analgesia (Letter). Lancet 1979; 1: 1410–1.

66 *Gustafsson LL, Schildt B, Jacobsen K.* Adverse effects of extradural and intrathecal opiates: report of a nationwide survey in Sweden. Br J Anaesth 1982; 54: 479–86.

67 *Palmer CM.* Early respiratory depression following intrathecal fentanyl-morphine combination. Anesthesiology 1991; 74: 1153–5.

68 *Brockway MS, Noble DW, Sharwood-Smith GH, McClure JH.* Profound respiratory depression after extradural fentanyl. Br J Anaesth 1990; 64: 243–5.

69 *Hays RL, Palmer CM.* Respiratory depression after intrathecal sufentanil during labor. Anesthesiology 1994; 81: 511–2.

70 *Stienstra R, Pannekoek BJM.* Respiratory arrest following extradural sufentanil. Anaesthesia 1993; 48: 1055–6.

71 *Jordan C.* Assessment of the effects of drugs on respiration. Br J Anaesth 1982; 54: 763–82.

72 *Ready LB, Loper KA, Nessly M, Wild L.* Postoperative epidural morphine is safe on surgical wards. Anesthesiology 1991; 75: 452–6.

73 *Whiting WC, Sandler AN, Lau LC, et al.* Analgesic and respiratory effects of epidural sufentanil in patients following thoracotomy. Anesthesiology 1988; 69: 36–43.

74 *Negre I, Gueneron J-P, Ecoffey C, et al.* Ventilatory response to carbon dioxide after intramuscular and epidural fentanyl. Anesth Analg 1987; 66: 707–10.

75 *Steinstra R, Van Poorten F.* Immediate respiratory arrest after caudal epidural sufentanil (Letter). Anesthesiology 1989; 71: 993–4.

76 *Abboud TK, Moore M, Zhu J, et al.* Epidural butorphanol or morphine for the relief of post-cesarean section pain: ventilatory responses to carbon dioxide. Anesth Analg 1987; 66: 887–93.

77 *Kafer ER, Brown JT, Scott D, et al.* Biphasic depression of ventilatory responses to CO_2 following epidural morphine. Anesthesiology 1983; 58: 418–27.

78 *Shook JE, Watkins WD, Camporesi EM.* Differential roles of opioid receptors in respiration, respiratory disease, and opiate-induced respiratory depression. Am Rev Respir Dis 1990; 142: 895–909.

79 *Mueller RA, Lundberg DBA, Breese GR, Hedner J, Hedner T, Jonason J.* The neuropharmacology of respiratory control. Pharmacol Rev 1982; 34: 255–85.

80 *Pokorski M, Grieb P, Wideman J.* Opiate system influences central respiratory chemosensors. Brain Res 1981; 211: 221–6.

81 *Gregory MA, Brock-Utne JG, Bux S, Downing JW.* Morphine concentration in brain and spinal cord after subarachnoid morphine injection in baboons. Anesth Analg 1985; 64: 929–32.

82 *Ready LB, Oden R, Chadwick HS, et al.* Development of an anesthesiology-based postoperative pain management service. Anesthesiology 1988; 68: 100–6.

83 *Chaney MA.* Pulse oximetry during conscious sedation (Letter). JAMA 1994; 271: 429.

84 *Sechzer PH, Egbert LD, Linde HW, Cooper DY, Dripps RD, Price HL.* Effect of CO_2 inhalation on arterial pressure, ECG and plasma catecholamines and 17-OH corticosteroids in normal man. J Appl Physiol 1960; 15: 454–8.

85 *McCaughey W, Graham JL.* The respiratory depression of epidural morphine. Anaesthesia 1982; 37: 990–5.

86 *Jensen FM, Madsen JB, Guldager H, Christensen AA, Eriksen HO.* Respiratory depression after epidural morphine in the postoperative period. Influence of posture. Acta Anaesthesiol Scand 1984; 28: 600–2.

87 *Skatrud JB, Dempsey JA, Kaiser DG.* Ventilatory response to medroxyprogesterone acetate in normal subjects: time course and mechanism. Journal of Applied Physiology: Respiratory, Environmental & Exercise Physiology 1978; 44: 939–44.

88 *Donadoni R, Rolly G, Noorduin H, Bussche GV.* Epidural sufentanil for postoperative pain relief. Anaesthesia 1985; 40: 634–8.

89 *Sidi A, Davidson JT, Behar M, Olshwang D.* Spinal narcotics and central nervous system depression. Anaesthesia 1981; 36: 1044–7.

90 *Wells DG, Davies G.* Profound central nervous system depression from epidural fentanyl for extracorporeal shock wave lithotripsy. Anesthesiology 1987; 67: 991–2.

91 *Paulus DA, Paul WL, Munson ES.* Neurologic depression after intrathecal morphine. Anesthesiology 1981; 54: 517–8.

92 *Christie JM, Meade WR, Markowsky S.* Paranoid psychosis after intrathecal morphine. Anesth Analg 1993; 77: 1298–9.

93 *Engquist A, Chraemmer Jørgensen B, Anderson HB.* Epidural morphine-induced catatonia (Letter). Lancet 1980; 2: 984.
94 *Shulman MS, Sandler A, Brebner J.* The reversal of epidural morphine induced somnolence with physostigmine. Can Anaesth Soc J 1984; 31: 678–81.
95 *Bloom F, Segal D, Ling N, Guillemin R.* Endorphins: profound behavioral effects in rats suggest new etiological factors in mental illness. Science 1976; 194: 630–2.
96 *Bowdle TA, Rooke GA.* Postoperative myoclonus and rigidity after anesthesia with opioids. Anesth Analg 1994; 78: 783–6.
97 *Krames ES, Gershow J, Glassberg A, et al.* Continuous infusion of spinally-administered narcotics for the relief of pain due to malignant disorders. Cancer 1985; 56: 696–702.
98 *Parkinson SK, Bailey SL, Little WL, Mueller JB.* Myoclonic seizure activity with chronic high-dose spinal opioid administration. Anesthesiology 1990; 72: 743–5.
99 *Atanassoff P, Alon E.* Accidental epidural injection of a large dose of morphine (Letter). Anaesthesia 1988; 43: 1056.
100 *Newman LM, Patel RV, Krolick T, Ivankovich AD.* Muscular spasm in the lower limbs of laboring patients after intrathecal administration of epinephrine and sufentanil. Anesthesiology 1994; 80: 468–71.
101 *Masoud PJ, Ohr JT, Green CD.* Transient neurologic changes after epidural morphine (Letter). Anesth Analg 1981; 60: 540.
102 *Yaksh TL, Noueihed R.* The physiology and pharmacology of spinal opiates. Ann Rev Pharmacol Toxicol 1985; 25: 433–62.
103 *Yaksh TL, Noueihed RY, Durant PAC.* Studies of the pharmacology and pathology of intrathecally administered 4-anilinopiperidine analogues and morphine in the rat and cat. Anesthesiology 1986; 64: 54–66.
104 *Belcher G, Ryall RW.* Differential excitatory and inhibitory effects of opiates on non-nociceptive and nociceptive neurones in the spinal cord of the cat. Brain Res 1978; 145: 303–14.
105 *Jacquet YF, Klee WA, Rice KC, Iijima I, Minamikawa J.* Stereospecific and nonstereospecific effects of (+)- and (−)- morphine: evidence for a new class of receptors? Science 1977; 198: 842–5.
106 *LaBella FS, Pinsky C, Havlicek V.* Morphine derivatives with diminished opiate receptor potency show enhanced central excitatory activity. Brain Res 1979; 174: 263–71.
107 *Woolf CJ.* Intrathecal high dose morphine produces hyperalgesia in the rat. Brain Res 1981; 209: 491–5.
108 *Yaksh TL, Harty GJ.* Pharmacology of the allodynia in rats evoked by high dose intrathecal morphine. J Pharmacol Exp Ther 1988; 244: 501–7.
109 *Yaksh TL, Harty GJ, Onofrio BM.* High doses of spinal morphine produce a nonopiate receptor-mediated hyperesthesia: clinical and theoretic implications. Anesthesiology 1986; 64: 590–7.
110 *Ali NMK.* Hyperalgesic response in a patient receiving high concentrations of spinal morphine (Letter). Anesthesiology 1986; 65: 449.
111 *Sjöberg M, Nitescu P, Appelgren L, Curelaru I.* Long-term intrathecal morphine and bupivacaine in patients with refractory cancer pain. Anesthesiology 1994; 80: 284–97.
112 *Crone L-AL, Conly JM, Clark KM, et al.* Recurrent herpes simplex virus labialis and the use of epidural morphine in obstetric patients. Anesth Analg 1988; 67: 318–23.
113 *Gieraerts R, Navalgund A, Vaes L, Soetens M, Chang J-L, Jahr J.* Increased incidence of itching and herpes simplex in patients given epidural morphine after cesarean section. Anesth Analg 1987; 66: 1321–4.
114 *Douglas MJ, McMorland GH.* Possible association of herpes simplex type I reactivation with epidural morphine administration (Letter). Can J Anaesth 1987; 34: 426–7.
115 *Acalovschi I.* Herpes simplex after spinal pethidine (Letter). Anaesthesia 1986; 41: 1271–2.
116 *Cardan E.* Herpes simplex after spinal morphine (Letter). Anaesthesia 1984; 39: 1031.
117 *Westmore MD.* Epidural opioids in obstetrics – a review. Anaesth Intensive Care 1990; 18: 292–300.
118 *Gieraerts R, Vaes L, Navalgund A, Jahr J.* Recurrent HSVL and the use of epidural morphine in obstetrics (Letter). Anesth Analg 1989; 68: 418.
119 *Bonnardot JP, Maillet M, Colau JC, Millot F, Deligne P.* Maternal and fetal concentration of morphine after intrathecal administration during labour. Br J Anaesth 1982; 54: 487–9.
120 *Nybell-Lindahl G, Carlsson C, Ingemarsson I, Westgren M, Paalzow L.* Maternal and fetal concentrations of morphine after epidural administration during labor. Am J Obstet Gynecol 1981; 139: 20–1.
121 *Carrie LES, O'Sullivan GM, Seegobin R.* Epidural fentanyl in labour. Anaesthesia 1981; 36: 965–9.
122 *Preston PG, Rosen MA, Hughes SC, et al.* Epidural anesthesia with fentanyl and lidocaine for cesarean section: maternal effects and neonatal outcome. Anesthesiology 1988; 68: 938–43.
123 *Vertommen JD, Van Aken H, Vandermeulen E, et al.* Maternal and neonatal effects of adding epidural sufentanil to 0.5% bupivacaine for cesarean delivery. J Clin Anesth 1991; 3: 371–6.
124 *Capogna G, Celleno D, Tomassetti M.* Maternal analgesia and neonatal effects of epidural sufentanil for cesarean section. Reg Anesth 1989; 14: 282–7.
125 *Abboud TK, Dror A, Mosaad P, et al.* Mini-dose intrathecal morphine for the relief of post-cesarean section pain:

safety, efficacy, and ventilatory responses to carbon dioxide. Anesth Analg 1988; 67: 137–43.

126 *Abouleish E, Rawal N, Fallon K, Hernandez D.* Combined intrathecal morphine and bupivacaine for cesarean section. Anesth Analg 1988; 67: 370–4.

127 *Benlabed M, Dreizzen E, Ecoffey C, Escourrou P, Migdal M, Gaultier C.* Neonatal patterns of breathing after cesarean section with or without epidural fentanyl. Anesthesiology 1990; 73: 1110–3.

128 *Hughes SC, Rosen MA, Shnider SM, Abboud TK, Stefani SJ, Norton M.* Maternal and neonatal effects of epidural morphine for labor and delivery. Anesth Analg 1984; 63: 319–24.

129 *Viscomi CM, Hood DD, Melone PJ, Eisenach JC.* Fetal heart rate variability after epidural fentanyl during labor. Anesth Analg 1990; 71: 679–83.

130 *Abouleish E, Rawal N, Shaw J, Lorenz T, Rashad MN.* Intrathecal morphine 0.2 mg versus epidural bupivacaine 0.125% or their combination: effects on parturients. Anesthesiology 1991; 74: 711–6.

131 *Baraka A, Noueihid R, Hajj S.* Intrathecal injection of morphine for obstetric analgesia. Anesthesiology 1981; 54: 136–40.

132 *Carton EG, McDonald N, McCarthy JR.* Intrathecal morphine in labour – efficacy and side effects. Ir J Med Sci 1987; 156: 323–7.

133 *Madej TH, Strunin L.* Comparison of epidural fentanyl with sufentanil. Anaesthesia 1987; 42: 1156–61.

134 *Torda TA, Pybus DA, Liberman H, Clark M, Crawford M.* Experimental comparison of extradural and i.m. morphine. Br J Anaesth 1980; 52: 939–43.

135 *Wiesenfeld-Hallin Z, Södersten P.* Spinal opiates affect sexual behaviour in rats. Nature 1984; 309: 257–8.

136 *Pybus A, Torda T, McQuay HJ, Moore RA.* Opiates and sexual function (Letter). Nature 1984; 310: 636.

137 *Barraclough CA, Sawyer CH.* Inhibition of the release of pituitary ovulatory hormone in the rat by morphine. Endocrinology 1955; 57: 329–37.

138 *Pescor MJ.* A statistical analysis of the clinical records of hospitalized drug addicts. United States Public Health Service, Public Health Reports 1938; 143: 1–30.

139 *Ueyama H, Nishimura M, Tashiro C.* Naloxone reversal of nystagmus associated with intrathecal morphine administration (Letter). Anesthesiology 1992; 76: 153.

140 *Fish DJ, Rosen SM.* Epidural opioids as a cause of vertical nystagmus. Anesthesiology 1990; 73: 785–6.

141 *Linder S, Borgeat A, Biollaz J.* Meniere-like syndrome following epidural morphine analgesia. Anesthesiology 1989; 71: 782–3.

142 *Goundrey J.* Vertigo after epidural morphine. Can J Anaesth 1990; 37: 804–5.

143 *Bahar M, Orr IA, Dundee JW.* Shrinking pupils as a warning of respiratory depression after spinal morphine (Letter). Lancet 1981; 1: 893.

144 *Gjessing J, Tomlin PJ.* Postoperative pain control with intrathecal morphine. Anaesthesia 1981; 36: 268–76.

145 *Thorén T, Wattwil M.* Effects on gastric emptying of thoracic epidural analgesia with morphine or bupivacaine. Anesth Analg 1988; 67: 687–94.

146 *Porreca F, Filla A, Burks TF.* Spinal cord mediated opiate effects on gastrointestinal transit in mice. Eur J Pharmacol 1983; 86: 135–6.

147 *Adler MW, Geller EB, Rosow CE, Cochin J.* The opioid system and temperature regulation. Ann Rev Pharmacol Toxicol 1988; 28: 429–49.

148 *Handler CM, Piliero TC, Geller EB, Adler MW.* Effect of ambient temperature on the ability of mu-, kappa- and delta-selective opioid agonists to modulate thermoregulatory mechanisms in the rat. J Pharmacol Exp Ther 1994; 268: 847–55.

149 *Rudy TA, Yaksh TL.* Hyperthermic effects of morphine: set point manipulation by a direct spinal action. Br J Pharmacol 1977; 61: 91–6.

150 *Banerjee U, Feldberg W, Lotti VJ.* Effect on body temperature of morphine and ergotamine injected into the cerebral ventricles of cats. Br J Pharmacol Chemother 1968; 32: 523–38.

151 *Lotti VJ, Lomax P, George R.* Temperature responses in the rat following intracerebral microinjection of morphine. J Pharmacol Exp Ther 1965; 150: 135–9.

152 *Johnson MD, Sevarino FB, Lema MJ.* Cessation of shivering and hypothermia associated with epidural sufentanil. Anesth Analg 1989; 68: 70–1.

153 *Sevarino FB, Johnson MD, Lema MJ, Datta S, Ostheimer GW, Naulty JS.* The effect of epidural sufentanil on shivering and body temperature in the parturient. Anesth Analg 1989; 68: 530–3.

154 *Wilder-Smith CH, Wilder-Smith OHG, Farschtschian M, Naji P.* Epidural droperidol reduces the side effects and duration of analgesia of epidural sufentanil. Anesth Analg 1994; 79: 98–104.

155 *Korinek AM, Langville M, Bonnet F, et al.* Effect of postoperative extradural morphine on ADH secretion. Br J Anaesth 1985; 57: 407–11.

156 *Simantov R, Snyder SH.* Opiate receptor binding in the pituitary gland. Brain Res 1977; 124: 178–84.

157 *Weitzman RE, Fisher DA, Minick S, Ling N, Guillemin R.* β-endorphin stimulates secretion of arginine vasopressin in vivo. Endocrinology 1977; 101: 1643–6.

158 *Masoud PJ, Green CD.* Effects of massive overdose of epidural morphine sulphate. Can Anaesth Soc J 1982; 29: 377–80.

159 *Anderson PT.* Alopecia areata after epidural morphine (Letter). Anesth Analg 1984; 63: 1142.

160 *Moore A, Bullingham R, McQuay H, Allen M, Baldwin*

D, Cole A. Spinal fluid kinetics of morphine and heroin. Cin Pharmacol Ther 1984; 35: 40–5.

161 *Coombs DW, Colburn RW, DeLeo JA, Hoopes PJ, Twitchell BB.* Comparative spinal neuropathology of hydromorphone and morphine after 9- and 30-day epidural administration in sheep. Anesth Analg 1994; 78: 674–81.

162 *Rawal N, Nuutinen L, Raj PP, et al.* Behavioral and histopathologic effects following intrathecal administration of butorphanol, sufentanil, and nalbuphine in sheep. Anesthesiology 1991; 75: 1025–34.

163 *Abouleish E, Barmada MA, Nemoto EM, Tung A, Winter P.* Acute and chronic effects of intrathecal morphine in monkeys. Br J Anaesth 1981; 53: 1027–32.

164 *Greenberg HS, Taren J, Ensminger WD, Doan K.* Benefit from and tolerance to continuous intrathecal infusion of morphine for intractable cancer pain. J Neurosurg 1982; 57: 360–4.

165 *Coombs DW, Fratkin JD, Meier FA, Nierenberg DW, Saunders RL.* Neuropathologic lesions and CSF morphine concentrations during chronic continuous intraspinal morphine infusion. A clinical and post-mortem study. Pain 1985; 22: 337–51.

166 *Yaksh TL, Onofrio BM.* Retrospective consideration of the doses of morphine given intrathecally by chronic infusion in 163 patients by 19 physicians. Pain 1987; 31: 211–23.

167 *Yaksh TL.* Effects of spinally administered agents on spinal cord blood flow: a need for further studies (Editorial). Anesthesiology 1983; 59: 173–4.

168 *Matsumiya N, Dohi S.* Effects of intravenous or subarachnoid morphine on cerebral and spinal cord hemodynamics and antagonism with naloxone in dogs. Anesthesiology 1983; 59: 175–81.

169 *Du Pen SL, Ramsey D, Chin S.* Chronic epidural morphine and preservative-induced injury. Anesthesiology 1987; 67: 987–8.

170 *Mathews E.* Epidural morphine (Letter). Lancet 1979; 1: 673.

171 *Saiki JH, Thompson S, Smith F, Atkinson R.* Paraplegia following intrathecal chemotherapy. Cancer 1972; 29: 370–4.

172 *Craig DB, Habib GG.* Flaccid paraparesis following obstetrical epidural anesthesia: possible role of benzyl alcohol. Anesth Analg 1977; 56: 219–21.

173 *Zucker-Pinchoff B, Ramanathan S.* Anaphylactic reaction to epidural fentanyl. Anesthesiology 1989; 71: 599–601.

174 *Johnson A, Bengtsson M, Löfström JB, Rane A, Wahlström A.* Influence of postoperative naloxone infusion on respiration and pain relief after intrathecal morphine. Reg Anesth 1988; 13: 146–51.

175 *Rawal N, Schött U, Dahlström B, et al.* Influence of naloxone infusion on analgesia and respiratory depression following epidural morphine. Anesthesiology 1986; 64: 194–201.

176 *Thind GS, Wells JCD, Wilkes RG.* The effects of continuous intravenous naloxone on epidural morphine analgesia. Anaesthesia 1986; 41: 582–5.

177 *Gowan JD, Hurtig JB, Fraser RA, Torbicki E, Kitts J.* Naloxone infusion after prophylactic epidural morphine: effects on incidence of postoperative side-effects and quality of analgesia. Can J Anaesth 1988; 35: 143–8.

178 *Gueneron JP, Ecoffey C, Carli P, Benhamov D, Gross JB.* Effect of naloxone infusion on analgesia and respiratory depression after epidural fentanyl. Anesth Analg 1988; 67: 35–8.

179 *Cohen SE, Ratner EF, Kreitzman TR, Archer JH, Mignano LR.* Nalbuphine is better than naloxone for treatment of side effects after epidural morphine. Anesth Analg 1992; 75: 747–52.

180 *Henderson SK, Cohen H.* Nalbuphine augmentation of analgesia and reversal of side effects following epidural hydromorphone. Anesthesiology 1986; 65: 216–8.

181 *Leykin Y, Niv D, Rudik V, Geller E.* Delayed respiratory depression following extradural injection of morphine. Isr J Med Sci 1985; 21: 855–7.

182 *Abboud TK, Afrasiabi A, Davidson J, et al.* Prophylactic oral naltrexone with epidural morphine: effect on adverse reactions and ventilatory responses to carbon dioxide. Anesthesiology 1990; 72: 233–7.

183 *Dailey PA, Brookshire GL, Shnider SM, et al.* The effects of naloxone associated with the intrathecal use of morphine in labor. Anesth Analg 1985; 64: 658–66.

184 *Cohen SE, Rothblatt AJ, Albright GA.* Early respiratory depression with epidural narcotic and intravenous droperidol. Anesthesiology 1983; 59: 559–60.

185 *Nelson TW, Lilly JK III, Baker JD III, Ackerly JA.* Treatment of pruritus secondary to epidural morphine. WV Med J 1988; 84: 183–5.

186 *Gambling DR, Howell P, Huber C, Kozak S.* Epidural butorphanol does not reduce side effects from epidural morphine after cesarean birth. Anesth Analg 1994; 78: 1099–1104.

187 *Kotelko DM, Rottman RL, Wright WC, Stone JJ, Yamashiro AY, Rosenblatt RM.* Transdermal scopolamine decreases nausea and vomiting following cesarean section in patients receiving epidural morphine. Anesthesiology 1989; 71: 675–8.