Intrathecal opioids in the management of acute postoperative pain

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In 1968, Melzack and Wall put forward their 'gate control theory' proposing that the spinal cord was a potential target site for modulation of pain signals. This changed our concepts about nociceptive transmission and laid the foundation for further research into dorsal horn opioid pharmacology. This led to the discovery of opioid receptors by Pert and Snyder in 1973 and the subsequent identification of dorsal horn opioid receptors by radioligand techniques in 1977. Yaksh went on to demonstrate that opioids modulate nociceptive stimuli via a direct action on the spinal cord in 1976.

Wang was the first to describe the intrathecal administration of morphine in a group of eight patients with genitourinary malignancies in 1979. Since that time, the use of intrathecal opioids has become a widely accepted technique for providing effective postoperative pain relief. The changing health economy has driven the need for greater patient throughput, rapid turnover and shorter hospital stays whilst retaining high quality medical care. The combination of intrathecal analgesia with minimally invasive surgery has led to the development of accelerated surgical care pathways.

This review will focus on the use of intrathecal opioids in the acute postoperative pain setting.

Site of action

Intrathecal opioids bind to a family of G-protein-linked pre- and postsynaptic opioid receptors in Laminae I and II of the dorsal horn. Receptor activation leads to G-protein-mediated potassium channel opening (mu and delta) and calcium channel closure (kappa), with an overall reduction in intracellular calcium. This reduces the release of excitatory transmitters (glutamate and substance P) from presynaptic C fibres, but not A fibre terminals with consequent reduction in nociceptive transmission.[1] There are significantly greater number of opioid receptors located presynaptically compared with postsynaptically. Binding of opioids to postsynaptic receptor sites in the dorsal horn results in potassium channel opening and indirect activation of descending pathways from the brainstem. Other possible target sites for intrathecal opioids have been proposed:

1. Phenylpiperidine opioids, including fentanyl and meperidine (pethidine), exhibit close structural similarities to local anaesthetics. Fentanyl has demonstrable local anaesthetic effect on sensory C primary afferent nerve fibres, which may facilitate analgesic effects.
2. An increase in lumbosacral adenosine concentrations in human cerebrospinal fluid (CSF) has followed intrathecal morphine injection in animals and humans. Adenosine is known to open potassium channels with consequent hyper polarization of nerve fibres and reduction in neuronal activity.
3. Intrathecal opioids reduce the release of gamma amino butyric acid (GABA) and glycine by a calcium-independent process from dorsal horn neurones.[2] This would appear to counter what we intuitively assume to be a damping down of neuronal activity in the context of an analgesic effect. However, it is conceivable that opioids may disinhibit inhibitory pathways, thereby reducing nociceptive transmission. This gives us new insight into the complexities of opioid mechanisms in the dorsal horn.

Physicochemical properties

The physicochemical properties of intrathecal opioids determine their onset time, duration of action, and potency. High lipid solubility and low p*K*a results in a highly potent opioid with a rapid onset of effect, but limited duration of action, whereas decreasing lipophilicity increases the

Key points

Increased lipophilicity is associated with reduced analgesic potency in the cerebrospinal fluid (CSF).

Intrathecal diamorphine becomes less lipophilic after injection as a result of metabolism in the CSF and spinal cord.

After lumbar CSF injection of a hydrophilic opioid, there is slow cephalad and circumferential spread.

There is no correlation between side-effects and dose of intrathecal opioid in the acute pain setting.

Systemic dose potency ratios of opioids are different from their intrathecal counterparts.

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duration of action. Lipid soluble opioids also resemble local anaesthetics in terms of their p*K*a, molecular weight, and partition coefficients that may explain some of the analgesic effects of CSF opioids.

At physiological pH (7.4), the tertiary amine groups of the opioids are ionized rendering them water soluble. However, it is the hydroxyl groups on the morphine molecule that are responsible for its greater water solubility compared with other opioids. Increased water solubility is responsible for slow onset of effect and long duration of action.

Potency of intrathecal opioids increases with increasing hydrophobicity. For example, fentanyl is only four times more potent than morphine when administered intrathecally but 100 times more potent after systemic administration. Systemic dose potency ratios of opioids cannot be applied to the same drugs after intrathecal administration.

Pharmacokinetics

The pharmacokinetics of intrathecal opioids are complex, follow a multi-compartmental model (Fig. 1), and are determined by the opioid physicochemical properties and the CSF dynamics. In the systemic circulation, the calculation of pharmacokinetic data such as volume of distribution assumes adequate mixing and equilibration of drug across all compartments. However, the CSF is a poorly mixed compartment with established cephalo-caudal gradients for opioids after administered into the lumbar CSF. Cephalad movement of opioids injected into the CSF is the result of:

1. Bulk flow of drug in a caudal-cephalad direction.
2. Fluctuating pressure changes within the thorax as a result of respiration, facilitating cephalad flow of CSF.
3. Expansion and relaxation of the brain, occurring as a result of the cardiac cycle. This helps to create a backward and a forward motion of CSF with a net transfer of opioid in a cephalad direction.

Opioids may also access brainstem sites as a result of uptake of opioid into the posterior radicular artery. This has been supported by autoradiographic studies in primates using radiolabelled (^{14}C) morphine that have demonstrated extensive radioactivity in the spinal cord within 15 min of injection and in the respiratory centres at 60 min post-injection in the lumbar region.

The pharmacokinetics of various lipophilic and hydrophilic intrathecal opioids have also been the source of investigation using animal models (see below). This has enabled us to make better predictions of the pharmacodynamic effects of intrathecal opioids such as potency, onset of analgesia, duration of action, and side-effects (Fig. 1)

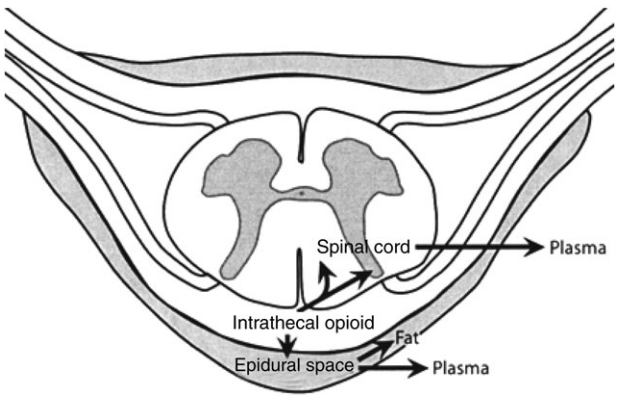

Fig 1 The fate of intrathecal opioids after injection into lumbar CSF.

Lipophilic opioids

Using a pig model, Ummenhoffer's group[3] has demonstrated that fentanyl rapidly partitions into receptor and non-receptor binding sites (epidural fat, myelin, and the white matter). This has been ascribed to its high octanol:water partition coefficient (860), resulting in a high volume of distribution in spinal cord (Fig. 1). Despite its high lipid solubility, only 8% of the unionized molecule is available for diffusion to receptor sites in the grey matter as a result of its relatively high p*K*a value (8.4). The remaining ionized portion is subject to 'ion trapping' in lipid-containing non-receptor binding sites.

After fentanyl administration: CSF concentration decreases rapidly; epidural space concentration increases; plasma concentrations increase rapidly with resultant systemic effects; and there is limited cephalad spread with segmental analgesia. Other lipophilic opioids with higher octanol:water coefficient (increased lipid solubility) and lower p*K*a values such as sufentanil and lofentanil are retained for longer periods in the spinal cord resulting in longer duration of action.

Diamorphine

Diamorphine is a lipid soluble prodrug with an octanol:water coefficient of 280 that makes it more likely to partition across the dura more readily than morphine but more slowly than fentanyl. This results in a relatively rapid clearance from the CSF, an observation supported by Moore and colleagues[4] in one of the few clinical pharmacokinetics studies to be carried out on CSF diamorphine. Diamorphine has a low p*K*a (7.6) at physiological pH producing a 34% unionized fraction (cf. fentanyl 9%) available for diffusion onto the dorsal horn opioid receptors. Diamorphine undergoes esterase metabolism within the spinal cord to water soluble metabolites (6-monoacetyl morphine and morphine) that are agonists at mu receptors with pharmacological effects. There is, therefore, a cascade of reactions whereby the physicochemical properties of the inactive parent molecule undergo significant change, resulting in active by-products with different physicochemical properties.

Hydrophilic opioids

Morphine is the most frequently used and extensively studied hydrophilic opioid administered for intrathecal use. It is 129–1737

times more hydrophilic than fentanyl with a low octanol:water coefficient (1.4), resulting in slow diffusion into the epidural space. It binds to high-affinity receptors in the dorsal horn receptor sites, but exhibits much lower capacity for binding to non-receptor sites in the myelin and white matter of the cord compared with fentanyl. This results in a small 'volume of distribution' within the spinal cord and a sustained high concentration within the CSF. This accounts for the clinically observed wide band of analgesia and propensity for cephalic spread with the potential for late onset respiratory depression. After intrathecal morphine administration, CSF concentrations are maintained with a long cord exposure time, followed by a gradual decline after 12 h (Fig. 2); there is slow diffusion into the epidural space with a consequent slow increase in plasma concentrations; cephalad spread with drug concentrations detectable as early as 30 min in cisternal CSF; poor circumferential CSF spread around the cord from the injection point; and minimal metabolism to water soluble metabolites in the CSF and spinal cord. Radiolabelled (^{14}C) morphine persists for 2 h with only 4.5% of the injected dose remaining at 3 h post-injection. The removal of drug from CSF is facilitated via a glycoprotein carrier transport system located in the choroid plexus.

Although, the above models have increased our knowledge of CSF opioid pharmacokinetics, a number of issues have yet to be addressed, including the effects of positive pressure ventilation or alterations in the baricity of opioid solutions.

Intrathecal opioids and postoperative pain

Intrathecal opioids have been demonstrated to provide effective analgesia in the postoperative period. The principal advantage of intrathecal over systemic opioid techniques is that the former produces 'segmental analgesia' resulting in localized nociception without motor, sensory, autonomic, or systemic side-effects. The latter has proved to be an unattainable goal and has been a limiting factor in the clinical use of intrathecal opioids (see below). In order to reduce the side-effect profile, the use of 'low dose' intrathecal opioids has been advocated. The term 'low dose' is a relative concept and is merely a comparison drawn between the current dosing schedules described below and the large (5 and 20 mg) doses of morphine used in earlier studies.

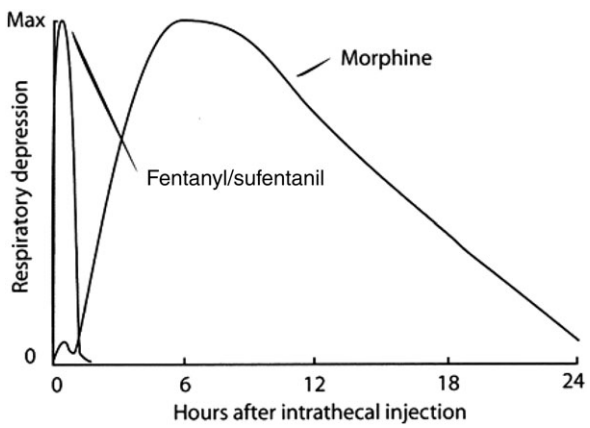

Fig 2 Time to onset of respiratory depression after fentanyl and morphine.

Day case surgery

Fentanyl is the most frequently used intrathecal lipophilic opioid and, when administered in single doses of 10–30 μg, it has a rapid onset (10–20 min) and short duration of action (4–6 h) with minimal cephalad spread making it the least likely of all the intrathecal opioids to cause delayed respiratory depression. After single administration, it can be used in day case arthroscopic surgery where it enhances analgesia without prolonging hospital stay. Morphine is unsuitable for day case surgery becasue of its slow onset time (30–60 min), dose-related duration of analgesia (13–33 h) and side-effect profile, particularly delayed onset respiratory depression.

Meperidine (pethidine) is a lipophilic opioid and has been used for analgesia after short day case procedures. The dose varies between 0.5 and 1.0 mg kg^{-1} providing short (4–6 h) duration analgesia. It is known to possess local anaesthetic (motor and sensory fibre block) and opioid agonist activity and has been used successfully for intrathecal use as a sole agent in patients with sensitivity to local anaesthetics. Meperidine is hyperbaric when injected intrathecally, so that it may be possible to influence the height of block with patient positioning. However, doses of >0.5 mg kg^{-1} can produce very high blocks. Meperidine is used infrequently because of the relative popularity of other opioids and unfavourable side-effects, and also the unknown neurotoxicity profile.

Obstetrics

The National Institute for Clinical Excellence (NICE) recommend diamorphine 0.3–0.4 mg for analgesia after elective Caesarean section in preference to morphine despite the former being unlicensed for intrathecal use. Although diamorphine has a lower lipid solubility compared with fentanyl, there is a higher proportion of unionized drug available for diffusion to receptor sites which is metabolized to active analgesic with a relatively long duration of action. This makes it ideal as an intraoperative analgesic supplement and also postoperative analgesia after Caesarean section. The dose range of diamorphine that NICE selected should be subject to some scrutiny as the maximum dose (0.4 mg) is merely sufficient to prevent intra-operative analgesic supplementation.[5] Other studies have shown that doses of up to 1 mg can provide superior postoperative analgesia with manageable side-effects.

Orthopaedic surgery

Hip and knee arthroplasty

Morphine (preservative free) is licensed for intrathecal use and can provide excellent analgesia after arthroplasty surgery. Recently, a cross-surgical specialities European collaborative (PROSPECT)

has recommended intrathecal morphine 0.1–0.2 mg after total hip arthroplasty (THA) without the need for supplementation by patient controlled analgesia (PCA) or monitoring on a High Dependency Unit.[6] Intrathecal morphine has been reported to be a superior analgesic to diamorphine for arthroplasty surgery at the comparative doses investigated. However, true comparisons on the relative effectiveness of each drug cannot be drawn precisely without first establishing the dose to produce 50% [ED_{50}] or 95% [ED_{95}] of whichever response one wishes to measure.

It is known that patients undergoing total knee arthroplasty (TKA) have generally higher postoperative analgesic demands compared with those undergoing THA. Several authors have recommended a 0.3 mg dose for TKA which has resulted in reduced PCA demands, minimal side-effects, and ward monitoring capability. However, more recently, Bowery has demonstrated that 0.5 mg was the optimum analgesic dose with no respiratory morbidity using supplemental PCA in the group studied.[7]

Spinal surgery

Intrathecal morphine is effective in alleviating pain after spinal surgery. Patients undergoing multi-level intrathecal instrumentation can be difficult to manage in terms of analgesia, respiratory function, and postoperative mobility. Urban and colleagues[8] found that a dose of 20 μg kg^{-1} morphine (0.14 mg for a 70 kg adult) reduced the need for supplemental analgesia for the first 12 h after lumbar fusion surgery. However, Boezaart and colleagues[9] recommended 0.002–0.004 mg kg^{-1} (0.15–0.3 mg for a 70 kg patient) for lumbar intrathecal surgery injected under direct vision at the end of surgery. The latter group concluded that such patients had effective analgesia with minimal side-effects and could be managed on the surgical ward.

General surgery and urology

Intrathecal morphine has been shown to provide effective analgesia for up to 24 h after laparoscopic cholecystectomy (0.075–0.1 mg) and laparoscopic colectomy (0.2 mg) without the need for high dependency care. Its role in major abdominal surgery is less clear due to the fact that the analgesic effects wear off after the first 24 h, necessitating the change in analgesia to either an epidural or PCA.[10] Ultra-low-dose intrathecal morphine (0.05 mg) has been used to control pain detrusor muscle spasm after transurethral resection of prostate (TURP).

Side-effects of intrathecal opioids

Side-effects are mediated by opioid receptors. Segmental analgesia after intrathecal opioids administration should confer a lower side-effect profile compared with systemic opioids administration. A recent prospective survey of 6000 patients reported a low incidence of side-effects and good patient satisfaction after single administration of low-dose intrathecal opioids. The side-effects of intrathecal opioids are sedation, sweating, delayed gastric emptying, urinary retention, pruritus, nausea and vomiting, and respiratory depression. The commonest side-effects are nausea vomiting, pruritus, and respiratory depression, the latter being the most feared by clinicians. Although previous studies have suggested that side-effects are dose related, recent data demonstrate that there is no clear correlation between dose and morbidity in the acute pain setting. The management of opioid-induced nausea will not be elaborated upon as this topic is extensively covered in a number of anaesthesia texts.

Respiratory depression

High-dose intrathecal opioids administered in error may result in an acute apnoeic episode requiring naloxone and supportive ventilation. However, low-dose lipophilic intrathecal opioids may cause early (0–1 h) respiratory depression, whilst the more hydrophilic opioids may cause early or late (up to 24 h) respiratory depression. Morphine-induced late onset respiratory depression occurs between 3.5 and 12 h after injection with a peak at 6 h (Fig. 2). The latter was first reported in 1979 when two patients, who were given 2 and 5 mg of morphine, were admitted to intensive care. However, in some studies, 20 mg of intrathecal hyperbaric morphine was not associated with respiratory depression. This demonstrates the unpredictable nature of this potentially serious complication.

The true incidence of respiratory depression is unknown; large retrospective studies quote an incidence of 0.03–7%. Unfortunately, there is a lack of proper definition of the term 'respiratory depression' in the literature. In a recent review of 96 articles published over 40 years, Ko and colleagues[11] found that only 46% defined respiratory depression and a further 24% went onto to define it in terms of respiratory rate alone. Respiratory rate and pulse oximetry can be poor measures of respiratory depression in the postoperative period. Levels of sedation, and ultimately blood gas analysis, are more reliable.

The risk factors for development of 'respiratory depression' include increasing age, the concomitant use of long-acting sedatives, positive pressure ventilation, and co-existing respiratory disease. Co-administration of opioid analgesics during the first 12–24 h after intrathecal administration has long been a concern regarding the development of early and late onset respiratory depression, but large scale prospective surveys have refuted this claim.

Pruritus

The incidence of pruritus is unrelated to dose and varies between 0 and 100%. Pruritus occurs most frequently in pregnant females where gestational hormones may cause alterations in the opioid receptor population. It affects the face neck and upper thorax predominantly with no correlation between itch intensity and opioid dose.

The mechanism underlying the pruritus is not fully understood. Neurophysiological studies have identified a new class of C fibres that mediate the itch response linked to centrally located receptor networks. The nature of these networks is not clear, but there is an abundance of mu opioid and 5-HT_3 receptors co-located in and

around the trigeminal nucleus. Ondansetron (5-HT_3 antagonist) has reduced the incidence of pruritus after intrathecal morphine injection in pregnant females. Furthermore, prostaglandin PGE2 and PGE1, which are known to modulate C fibre transmission, have been implicated in opioid-induced pruritus, but there has been limited therapeutic successes after the use of tenoxicam and diclofenac in patients with opioid-induced pruritus.

Although pruritus is traditionally associated with histamine release, there is no associated release of histamine in opioid-induced itching. Antihistamines are unlikely to be of any benefit at all, any relief achieved being probably because of associated sedation. Propofol inhibits posterior horn transmission and has been shown to be of benefit. Its sedative potential makes it impractical for use on the surgical ward.

Opioid receptor antagonists such as naloxone (<2 μg kg^{-1} h^{-1}) and naltrexone (6–9 mg) have been associated with the greatest success without reversal of analgesic effect. However, more data are required to establish optimum doses of antagonists in this area.

Neurotoxicity

There is no evidence that single, repeated, or continuous administration of the commonly used opioids such as morphine and fentanyl produce deleterious changes in the spinal cord of humans or monkeys. Furthermore, toxic doses of morphine have failed to demonstrate any neurological changes in primate spinal cord.

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Please see multiple choice questions 1–5