The Role of Intrathecal Drugs in the Treatment of Acute Pain

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Intrathecal opioids are widely used as useful adjuncts in the treatment of acute and chronic pain, and a number of non-opioid drugs show promise as analgesic drugs with spinal selectivity. In this review we examine the historical development and current use of intrathecal opioids and other drugs that show promise for treating pain in the perioperative period. The pharmacology and clinical use of intrathecal morphine and other opioids is reviewed in detail, including dosing guidelines for specific surgical procedures and the incidence and treatment of side effects associated with these drugs. Available data on the use of non-opioid drugs that have been tested intrathecally for use as analgesics are also reviewed. Evidence-based guidelines for dosing of intrathecal drugs for specific surgical procedures and for the treatment of the most common side effects associated with these drugs are presented.

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Opioid analgesics have long been recognized as among the most effective treatments for pain. In his treatise on gout and rheumatism (1), the 17th century English physician Thomas Sydenham wrote: "Among the remedies which it has pleased Almighty God to give man to relieve his suffering, none is so universal and so efficacious as opium."

Despite their nearly universal ability to alleviate pain, opioids have a number of unpleasant, even life-threatening, side effects: nausea and vomiting, tolerance, pruritus, urinary retention, and respiratory depression. For thousands of years, these medications were used without a known mechanism of action until 1971, when a class of highly specific opioid receptors was identified (2). Soon thereafter, opioid receptors were localized within the brain (3) and spinal cord (4). Evidence that direct application of morphine at the spinal cord level could produce spinally mediated analgesia soon followed (5). Based on this limited experimental evidence, Wang et al. (6) administered bolus intrathecal morphine and Onofrio et al. (7) reported chronic intrathecal morphine infusions, both working in patients with severe pain associated with advanced cancer; they reported the first observations of profound and prolonged pain relief with spinal opioids. Since these first, bold clinical experiments, we have witnessed a rapid transition from the laboratory to clinical practice. Intrathecal opioids are now widely used as useful adjuncts in the treatment of acute and chronic pain, and a number of non-opioid drugs show promise as analgesics with spinal selectivity. In this review, we examine the current use of intrathecal opioids and other drugs that show promise for treating pain in the perioperative period.

Search Strategy

We performed a MEDLINE search for all indexed articles published between 1966 and March 2004 using the search terms "postoperative pain," "spinal or intrathecal," "spinal analgesia," "intrathecal analgesia," "acute pain and spinal," and "postoperative pain and spinal," resulting in 1436 articles. The abstracts of all articles were reviewed to select articles on the development and use of intrathecal drugs that are representative of the current state of our knowledge. Those articles representing the best available evidence were selected (e.g., randomized, controlled trials were used in preference to observational studies when available, case reports or case series were used only when no other information was available, and retrospective analyses were generally omitted); however, there was no attempt to assign qualitative scores to each article or to combine the available data quantitatively.

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Pharmacology

Drug disposition after intrathecal administration varies depending on the lipid solubility of the individual drug, and the most closely studied drugs are the opioid analgesics. After spinal administration, typically within the cerebrospinal fluid (CSF) in the lumbar cistern, the drug is distributed within CSF. Ummenhofer et al. (8) reported a series of elegant experiments in which the concentration of morphine, fentanyl, sufentanil, and alfentanil were measured within CSF, spinal cord, epidural fat, and plasma in anesthetized pigs after lumbar intrathecal administration. From their data, they developed a multiple-compartment pharmacokinetic model that closely simulates the observed pharmacology and explains many of the clinical characteristics of the opioids used for intrathecal analgesia. The fate of opioids after intrathecal administration is complex (Fig. 1). Intrathecal opioids penetrate the spinal cord and the dura mater to enter the epidural space. Within the spinal cord, they bind to nonspecific sites within the white matter as well as to specific receptors within the dorsal horn. Drug within the spinal cord eventually reaches the plasma compartment though venous uptake. In the epidural space, the opioid is sequestered in fat and enters the plasma compartment via venous uptake. The sum of these multiple avenues for drug disposition results in the clinical characteristics observed. Any drug given intrathecally rapidly redistributes within the CSF; opioid is detectable in the cisterna magna after lumbar intrathecal administration within 30 min, even with lipophilic drugs like sufentanil (9). Indeed, all opioids move within the CSF and this rapid distribution within the CSF likely accounts for the small, but significant, incidence of respiratory depression that is observed immediately after lumbar intrathecal injection (Fig. 2) (10).

The lipophilic opioids rapidly traverse the dura where they are sequestered in the epidural fat and enter the systemic circulation; they also rapidly penetrate the spinal cord where they bind to both nonspecific sites within the white matter as well as dorsal horn receptors and eventually enter the systemic circulation as they are cleared from the spinal cord. This rapid transfer from the CSF to both spinal cord and the epidural fat accounts for the rapid onset and the prompt decline in CSF levels of opioid, accounting for the minimal rostral spread, lack of delayed respiratory depression, and relatively small dermatomal band of analgesia seen during chronic administration; vascular uptake accounts for the limited duration of analgesia of lipophilic opioids (Fig. 3).

Morphine, the prototypic hydrophilic opioid, undergoes a similar transfer to both the spinal cord and the epidural space; however, there is limited binding to fat within the epidural space and limited binding to nonspecific receptors within the spinal cord white matter. Transfer to the systemic circulation is likewise slower than the lipophilic drugs. Concentrations within the CSF decline more slowly than similar doses of lipophilic drugs, accounting for the greater degree of rostral spread, delayed respiratory depression (Fig. 2), and extensive dermatomal analgesia during chronic administration. This complex pharmacokinetic behavior explains why the location of injection for intrathecal administration remains an important determinant in the pattern of analgesia observed (11). Hydrophilic drugs result in slow onset and a wide band of analgesia surrounding the site of injection. In contrast, highly lipophilic drugs transfer rapidly from

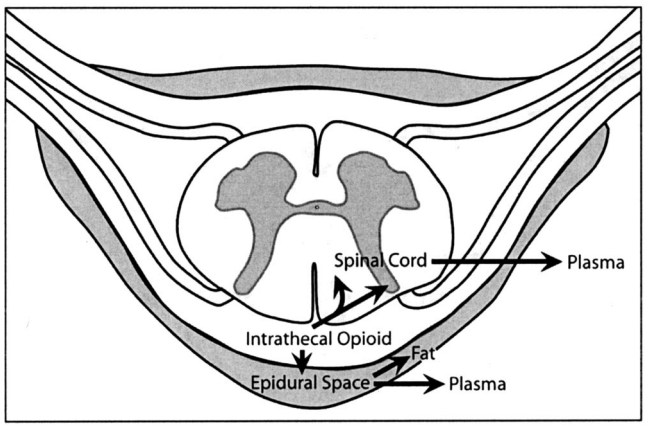

Figure 1. Disposition of opioid after intrathecal administration. After intrathecal administration, the disposition of opioids is complex and multicompartmental. Simultaneously, intrathecal opioids 1) travel cephalad within the cerebrospinal fluid (CSF), 2) enter the spinal cord, where they may bind to nonspecific sites within the white matter or specific opioid receptors within the dorsal horn, and 3) traverse the dura mater to enter the epidural space where they bind to epidural fat. From the spinal cord and epidural space, opioids enter the plasma compartment through vascular uptake. The clinical properties of each opioid (speed of onset, duration of action) and degree of rostral spread result from the sum of effects for each route. Lipophilic opioids (fentanyl/sufentanil) rapidly cross the dura, where they are sequestered in fat and gain rapid access to plasma; they also enter the spinal cord, where they may bind to nonspecific sites within the white matter as well as specific receptors within the dorsal horn and then enter the plasma. This results in rapid onset, limited and brief rostral spread resulting in early respiratory depression and a narrow band of analgesia surrounding the site of injection, and a relatively short duration of action. In contrast, the hydrophilic opioid morphine traverses the dura slowly to the epidural space where it binds little within epidural fat and only slowly enters the plasma. Morphine also enters the spinal cord and binds little to nonspecific receptors but largely to specific receptors within the dorsal horn, where uptake into the plasma occurs slowly. As a result of this limited and slow transfer from the CSF, morphine remains in relatively large concentration within the CSF; this results in slow onset, extensive and prolonged rostral spread resulting in delayed respiratory depression and a broad band of analgesia surrounding the site of injection, and a relatively long duration of action.

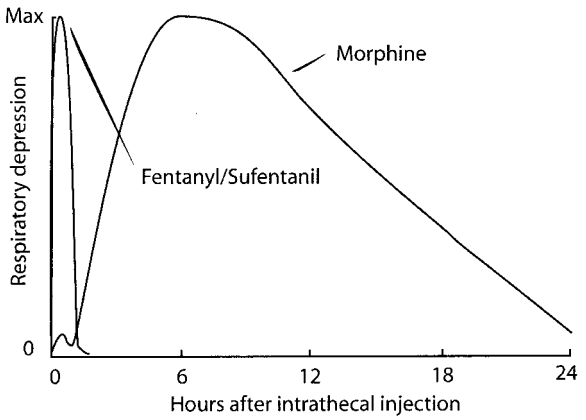

Figure 2. The average onset and duration of respiratory depression after intrathecal opioid administration. Respiratory depression after intrathecal administration of lipophilic opioids (fentanyl and sufentanil) results from rostral spread immediately after injection, occurring within the first 20–30 min after injection. In contrast, the hydrophilic opioid morphine traverses from the cerebrospinal fluid (CSF) to the spinal cord and epidural space slowly. There is a small degree of respiratory depression immediately after injection that is similar to that seen with the lipophilic drugs and a later and more prolonged respiratory depression resulting from rostral migration of morphine within the CSF that peaks at approximately 6 h after injection and can persist for 18–24 h.

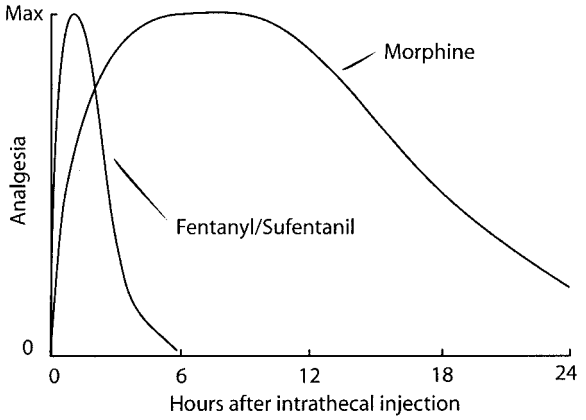

Figure 3. The average onset and duration of analgesia after intrathecal opioid administration. Lipophilic opioids (fentanyl and sufentanil) produce rapid onset of analgesia lasting from 2–4 h, whereas hydrophilic opioids (morphine) are slower in onset with a duration of analgesia extending 18–24 h.

the CSF and result in a broad band of analgesia that is much shorter in duration and the clinical observation that analgesia during prolonged infusion is limited to a narrower band of analgesia surrounding the anatomic site of administration during epidural administration (Fig. 4). The clinical dose range, onset, and duration of activity for various intrathecal opioids are shown in Table 1.

Internationally, opioids and adjuvant analgesics are supplied in varying concentrations and in preparations that include preservatives. Although the toxicity of the most common preservatives appears to be small

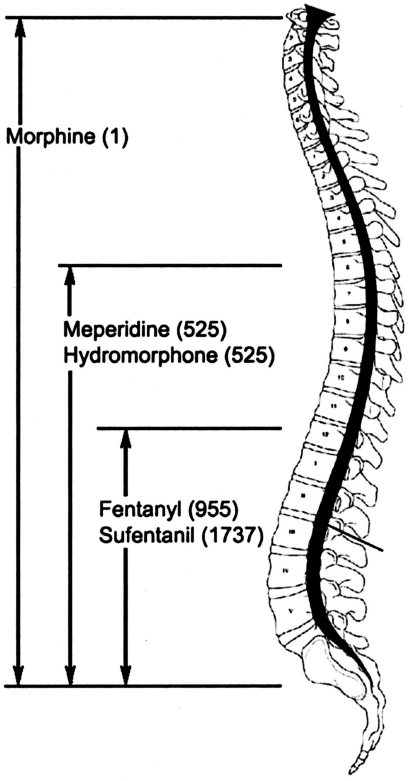

Figure 4. Spread of analgesia after intrathecal administration in the lumbar cistern. Values shown in parentheses are octanol:water partition coefficients; a larger value indicates that a drug is more lipid soluble. Lipophilic opioids result in a narrow band of analgesia whereas hydrophilic opioids produce a broader band of analgesia. In contrast, intrathecal administration of a lipophilic drug in the lumbar cistern results in a broad, but short-lived, band of analgesia limited to the lumbar dermatomes similar to that seen with chronic infusion. Despite these differing patterns of analgesia, all opioids move within the cerebrospinal fluid (CSF) and are detectable in the CSF adjacent to the brainstem soon after injection. Indeed, life-threatening respiratory depression has been reported within 20 min after intrathecal injection of fentanyl, sufentanil, and meperidine (10).

(12), benzyl alcohol and the parabens have been implicated as the cause of neurotoxicity after intrathecal administration (13).

Morphine

In early trials with intrathecal morphine, doses ranged from 500–1000 μg and profound sedation and respiratory depression were not uncommon (14). In a carefully controlled study in healthy volunteers, profound and prolonged respiratory depression was observed in all subjects who received 600 μg of intrathecal morphine (15). In more recent years, several trials have examined doses as small as 40 μg, typically, extending only as large as 300 μg. Indeed, it appears that the efficacy of doses above this range is often limited by side effects.

Table 1. Pharmacologic Properties of Common Opioids used for Intrathecal Analgesia

Opioid	Usual dose range (μg)	Onset (min)	Duration (h)	IT:IV potency ratio
Morphine	100–500	45–75	18–24	1:200
Fentanyl	5–25	5–10	1–4	1:10
Sufentanil	2.5–10	5–10	2–6	1:10

In recent years, clinical investigation surrounding use of intrathecal morphine in the perioperative period has centered on establishing the optimal dose for specific surgical procedures. Rathmell et al. (16) compared the need for supplemental IV morphine via patient-controlled analgesia after doses of intrathecal morphine ranging from 0–300 μg after total hip and knee arthroplasty. After total hip replacement, intrathecal morphine (200 μg) provided excellent analgesia. In contrast, the degree of pain experienced after total knee arthroplasty exceeded the analgesia afforded by even the largest dose of intrathecal morphine (300 μg), yet patients who received this dose nearly universally reported nausea, vomiting, and pruritus. Intrathecal morphine has been studied as an analgesic for pain after cesarean delivery (17), various orthopedic procedures (16), and a range of other surgical procedures (18) from spinal (19) to cardiac surgery (20). Two generalizations emerge. The first and most important is that the optimal dose of intrathecal morphine depends on the specific surgical procedure, with doses $<$100 μg often sufficing for pain control after cesarean delivery, whereas doses in the area of 500 μg may be required for more extensive surgery, such as thoracotomy or open abdominal aortic aneurysm repair. The best available evidence relating to optimal dosing for specific procedures is presented in Table 2. The second generalization is that the incidence of side effects increases in proportion to the dose administered, with doses in excess of 300 μg producing nausea, vomiting, pruritus, and urinary retention in most recipients. Indeed, there appears to be a ceiling analgesic effect for intrathecal morphine above which the risk of side effects outweighs the benefits of improved analgesia. Despite the excellent analgesia afforded by use of intrathecal morphine, carefully controlled studies in high-risk patients have failed to demonstrate any beneficial effects on outcome in terms of reduced perioperative renal, pulmonary, and cardiac complications or mortality (21). The prolonged duration of action along with the risk of late respiratory depression associated with intrathecal morphine point to the need for hospitalization and monitoring after administration. This drug is not suitable for ambulatory procedures. Preservative-free morphine is currently the only drug discussed in this review that is approved by the United States Food and Drug Administration for intrathecal use in the treatment of acute pain.

Other Opioids

Fentanyl and Sufentanil

Fentanyl and sufentanil are the best studied and most commonly used lipophilic drugs for intrathecal delivery. Two major trends in use of these drugs as analgesics have evolved in recent years: the first is a closer definition of their role as analgesics for labor, delivery, and postcesarean delivery; the second is the recognition that addition of small doses of lipophilic opioids during spinal anesthesia for ambulatory procedures can produce more rapid onset and better quality surgical block and lead to more rapid recovery of motor function and allow for earlier discharge after surgery. Both drugs can be summarized as having a rapid onset of analgesia (10–15 min) with a short duration of action (2–5 h).

Bucklin et al. (22) performed a meta-analysis of 7 randomized, controlled trials and concluded that intrathecal opioids (including morphine 200 μg, sufentanil 2–10 μg, and fentanyl 25 μg) provide comparable analgesia 15–20 min after injection in early labor with a more frequent incidence of pruritus compared with epidural local anesthetics. Duration of analgesia depends on the stage of labor. Viscomi et al. (23) found that 10 μg intrathecal sufentanil, combined with 2.5 mg of bupivacaine, provided analgesia that was significantly shorter in duration in advanced labor (120 $\pm$ 26 min) compared with early labor (163 $\pm$ 57 min). Intrathecal sufentanil is approximately 4.5 times more potent than intrathecal fentanyl in laboring parturients (24). Single-shot techniques provide predictable analgesia but of limited duration. In obstetrics, where prolonged labor and operative delivery often occur, many practitioners now take advantage of the best of both spinal and epidural techniques using combined spinal-epidural analgesia (CSE). In a prospective, randomized comparison of CSE versus epidural analgesia for labor, Norris et al. (25) found that progress and outcome of labor were similar in women receiving10 μg intrathecal sufentanil with 2.0 mg bupivacaine or 10 μg epidural sufentanil and 12.5–25.0 mg bupivacaine followed by continuous epidural infusion of 0.083% bupivacaine plus 0.3 μg/mL sufentanil. Intrathecal opioids also provide effective analgesia after cesarean delivery. In a review of the use of intrathecal lipophilic opioids as adjuncts for surgical

Table 2. Optimal Intrathecal (IT) Opioid Dose for Specific Surgical Procedures

Procedure	Optimal IT opioid and dose	Comments
Labor analgesia	Sufentanil 2.5–5 μg	Larger doses (>7.5 μg) are associated with an increased incidence of fetal bradycardia (129).
Cesarean delivery	Morphine 100 μg	Fentanyl (10–40 μg) and sufentanil (10–15 μg) improve intraoperative analgesia but do not produce significant postoperative analgesia (15).
Outpatient procedures under spinal anesthesia (e.g., knee arthroscopy)	Fentanyl 10–25 μg Sufentanil 5–12.5 μg	These intrathecal lipophilic opioids speed onset of block and improve both intraoperative and immediate postoperative analgesia without prolonging motor block (18).
Transurethral resection of the prostate (TURP)	Morphine 50 μg	This small dose of intrathecal morphine was equivalent to 100 μg after TURP (130).
Major orthopedic surgery (e.g., total joint arthroplasty)	Morphine 200–300 μg	Although these doses of intrathecal morphine provide excellent analgesia after total hip arthroplasty they are inadequate for pain relief after total knee arthroplasty, reflecting the greater degree of pain reported by patients undergoing knee replacement (16).
Thoracotomy	Morphine 500 μg	Lumbar intrathecal morphine improves pain relief and reduces but does not eliminate the need for supplemental IV opioid analgesics (131).
Fast-track cardiac surgery	Morphine 500–600 μg (8 μg/kg)	Lumbar intrathecal morphine administered prior to elective cardiac surgery combined with remifentanil/desflurane anesthesia provided superior analgesia when compared to a sufentanil/desflurane anesthetic (132).
Major abdominal/vascular surgery (e.g., open abdominal aortic aneurysm repair)	Morphine 500–600 μg	Lumbar intrathecal morphine provided more intense analgesia than IV patient-controlled analgesia with morphine (21).

spinal anesthesia, Hamber and Viscomi (18) recommended using 20–30 μg fentanyl or 5–7.5 μg of sufentanil to supplement bupivacaine spinal anesthesia for cesarean delivery. The addition of these doses of intrathecal opioid led to faster onset of block, improved intraoperative and postoperative analgesia that lasted 2-5 h, and decreased nausea and vomiting during cesarean delivery.

Much recent work has focused on the addition of intrathecal lipophilic opioids to local anesthetics during spinal anesthesia for brief outpatient surgery. In this setting, adding fentanyl or sufentanil to bupivacaine or lidocaine results in more rapid onset of block and improved analgesia, both intraoperatively and for the first several hours after surgery (18). In efforts to take advantage of the improved analgesia without motor blockade, a series of investigations have examined combining lipophilic opioids with small doses of local anesthetic. Ben-David et al. (26) reported that patients receiving 20 mg of 0.5% lidocaine in dextrose with 20 μg fentanyl for knee arthroscopy were ready for discharge an average of 45 min after placement of the spinal drugs (range, 28–180 min). Likewise, addition of fentanyl (10 μg) to small doses of hyperbaric bupivacaine (5 mg) enhanced the quality and duration of sensory block without prolonging the intensity or duration of motor block in patients undergoing knee arthroscopy (27). The addition of intrathecal fentanyl (10–25 μg) to surgical spinal anesthetics hastens the onset of surgical anesthesia, enhances intraoperative analgesia, and provides several hours of postoperative analgesia without prolonging motor block or delaying discharge.

Meperidine

Meperidine produces a local anesthetic effect in addition to its properties as an opioid analgesic (28). It has been reported to provide similar surgical anesthesia for perineal and lower extremity surgery as the sole anesthetic compared to bupivacaine (29). The duration of sensory block after intrathecal administration of meperidine was 112 ± 19 min in those receiving 1.5 mg/kg compared with 79 ± 27 min in those receiving 1.2 mg/kg; respiratory depression within 5–50 min of administration, hypotension (>30% decline in systolic arterial blood pressure), nausea, and vomiting were all common side effects (30). The addition of meperidine 10 mg to intrathecal bupivacaine for cesarean delivery was associated with prolonged postoperative analgesia but with more frequent intraoperative nausea and vomiting (31). Another randomized trial examining use of intrathecal meperidine (15 or 25 mg) for CSE during labor was halted because of the frequent incidence of the nausea and vomiting associated with this drug (32). Adding small doses of meperidine (0.3 mg/kg) to spinal lidocaine also prolongs postoperative analgesia after transurethral resection of the prostate (33). Despite the theoretic appeal of meperidine as a drug that can provide both opioid and local anesthetic effects, it has gained limited popularity owing to the frequent association with

nausea and vomiting. Detailed dose-response studies examining analgesic effects at smaller intrathecal doses are not available.

Hydromorphone

Long-term, continuous infusion of hydromorphone was not associated with spinal cord toxicity in an animal model (34) and has gained popularity and acceptance as an alternative to morphine as an analgesic drug for treatment of chronic pain using continuous intrathecal drug delivery systems (35). Hydromorphone has also been used effectively as a neuraxial drug for continuous epidural analgesia after thoracotomy (36), prostatectomy (37), and spinal fusion (38). Liu et al. (37) randomized 16 patients who had undergone prostatectomy to receive hydromorphone via patient-controlled analgesia either via an epidural or an IV route and measured the effectiveness and dose requirements. Patients receiving hydromorphone via the IV route required twice as much hydromorphone as those receiving the same drug via an epidural route (approximately 2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ versus 4 $\mu g \cdot kg^{-1} \cdot h^{-1}$ in the IV versus epidural groups, respectively, during hours 3–24 after surgery). There are only limited data on intrathecal dosing of hydromorphone in the acute setting. Drakeford et al. (39) randomized 60 patients undergoing total joint arthroplasty to receive either saline, morphine 500 μg, or hydromorphone 2 μg/kg intrathecally. Both morphine and hydromorphone produced significantly better postoperative pain relief with similar incidence of side effects when compared with saline. Like morphine, systemic doses of hydromorphone required to produce similar analgesia after IV administration are several hundred times the doses required after intrathecal administration (40) and produce similar duration of analgesia and side effects. The limited available data suggest that intrathecal hydromorphone 50–100 μg produces analgesia and side effects similar to 100–200 μg of intrathecal morphine with similar side effects and duration of action.

Methadone

The d-enantiomer of methadone is a weak opioid with low affinity to the *N*-methyl-D-aspartate (NMDA) receptor, a class of receptors with potential analgesic effects. However, in the antinociceptive dose range, the NMDA antagonism does not appear to contribute to the mechanism of d-methadone analgesia (41). There are only limited, uncontrolled reports of use of intrathecal methadone for intrathecal use via continuous infusion for chronic pain (42) and acute postoperative pain (43).

Non-Opioids as Adjuvants and Analgesics for Intrathecal Use

Clonidine

Clonidine is a specific α_2-receptor agonist; α_2-receptors are present within both presynaptic and postsynaptic terminals of primary afferent nociceptive neurons within the dorsal horn of the spinal cord. Spinal α_2-receptor agonists alter pain transmission by binding presynaptically to nociceptive Aδ and C fiber terminals and reducing neurotransmitter release, and postsynaptically by hyperpolarizing second order neurons within the dorsal horn (44). Clonidine produces analgesia by activating α_2-receptors; direct intrathecal administration produces selective spinally-mediated analgesia (45,46). Spinal clonidine produces dose-dependent analgesia with hypotension, bradycardia and sedation; it is not associated with respiratory depression or pruritus (47).

Clonidine has demonstrated effects on reducing both nociceptive and neuropathic pain in experimental models and in clinical use. Eisenach et al. (48) used intradermal capsaicin-induced hyperalgesia to produce central hypersensitivity and allodynia and noxious heat to produce acute pain in a series of healthy volunteers. They found that 150 μg of clonidine administered intrathecally, but not IV, relieved pain and allodynia, supporting a spinal selective mechanism for analgesia. In a placebo-controlled, randomized study, patients with severe cancer pain despite large doses of opioids received epidural clonidine (30 μg/h) or placebo (49). Epidural clonidine provided significant pain relief, particularly in patients with neuropathic pain.

Reports on the use of intrathecal clonidine in the perioperative period are numerous and collectively point toward synergistic action with spinal local anesthetics (50) with less urinary retention than spinal morphine (51). Clonidine has been demonstrated in numerous studies to prolong sensory and motor block. Eisenach et al. (47) reviewed the use of clonidine for regional anesthesia in 1996. Their summary analysis of numerous studies found that clonidine 75–225 μg (average, 146 μg) added to spinal bupivacaine 13.75–15 mg prolonged sensory block from 2.5 to 3.7 h and motor block from 2.4 to 3.3 h (47). Clonidine intensifies the degree of sensory block, reduces tourniquet pain (52), and appears to prolong and intensify the effects of spinal local anesthetic by altering systemic absorption (53). The degree of sympatholysis and hypotension after typical spinal local anesthetic doses (e.g., 15 mg bupivacaine) is near maximal; thus, adding intrathecal clonidine results in no increased hypotension (47). Hemodynamic effects of clonidine after neuraxial administration begin within 30 min, reach maximum effect within 1–2 h, and last approximately 6–8 h after a single injection (47).

There are few studies examining clonidine in combination with intrathecal opioids. Sites et al. (54) found that combining intrathecal morphine (250 μg) with intrathecal clonidine (25 or 75 μg) reduced the need for supplemental analgesics and improved pain control after total knee arthroplasty. Side effects were similar with the exception that patients receiving clonidine had more hypotension during the first 6 h after surgery.

Neostigmine

Spinal administration of neostigmine, an acetylcholinesterase inhibitor, inhibits breakdown of the endogenous neurotransmitter acetylcholine, thereby inducing analgesia (50). Eisenach et al. (55) demonstrated that acetylcholine has intrinsic analgesic properties, and that the concentration of acetylcholine in CSF is increased during painful electrical stimulation. They further suggested that enhanced amounts of acetylcholine released from preganglionic sympathetic neurons after spinal neostigmine administration may counteract the sympatholytic actions of local anesthetics or α_2-agonists (reducing the degree of hypotension) and add a synergistic antinociceptive effect to spinal α_2-agonists (55).

In preliminary dose-ranging studies in surgical patients and healthy volunteers, intrathecal neostigmine 10–50 μg provided analgesia (56). Nausea and lower extremity weakness were common in doses exceeding 100–150 μg, but sedation, pruritus, respiratory depression, and hemodynamic changes did not occur (57). Adding 6.25–25 μg neostigmine to spinal bupivacaine improves sensory and motor block (56), delays resolution of block (56), and reduces postoperative analgesic requirements (58). All doses were associated with a frequent incidence of nausea and vomiting that was resistant to pharmacologic treatment (56,58).

One study (59) demonstrated that adding 1–5-μg neostigmine to 100 μg intrathecal morphine improved analgesia without increasing side effects after gynecological surgery. The incidence of nausea and the prolongation of recovery from spinal anesthesia suggest that neostigmine is not a useful adjuvant; further examination of small dose neostigmine in combination with intrathecal opioids is warranted.

Adenosine

Adenosine produces receptor-specific analgesia via both peripheral and central mechanisms, and adenosine receptors are present in high density within the dorsal horn of the spinal cord (60). After animal toxicity testing suggested safety, a phase I dose-ranging trial of 0.25–2 mg of intrathecal adenosine in healthy volunteers showed no effect on arterial blood pressure, end-tidal carbon dioxide, or neurologic function; headache and back pain were common side effects (61). Adenosine produced no effect on acute thermal or chemical pain but reduced mechanical hyperalgesia and allodynia from intradermal capsaicin for at least 24 h (62). Adenosine concentrations in CSF increased after intrathecal, but not IV, administration of opioids, suggesting a role for adenosine in spinal opioid receptor activation and analgesia (63). A randomized study of 25 parturients who received 10 μg of intrathecal sufentanil with or without 500 μg of adenosine showed no differences in the degree or duration of pain relief (64). Further clinical trials of intrathecal adenosine are warranted; its role as an analgesic will likely be limited to injury associated with acute hyperalgesia (e.g., surgery) and treatment of neuropathic pain (62).

Epinephrine

Adding the vasoconstrictor epinephrine (0.1–0.6 mg) to spinal local anesthetics intensifies and extends the duration of sensory and motor block in a dose-dependent fashion (65,66). Epinephrine may produce both direct analgesia through α-adrenergic receptor binding as well as prolongation of local anesthetic effect by vasoconstriction and decreased clearance. Adding epinephrine to intrathecal opioid (sufentanil, fentanyl) has no effect on the intensity or duration of analgesia for labor (67,68) but may increase the incidence of nausea and vomiting (67). Using epinephrine is a safe and effective means of prolonging and intensifying spinal anesthesia, although at the expense of delayed return of motor function and micturition (69). Thus, epinephrine is an unsuitable adjunct for use in the ambulatory setting.

Ketorolac

Cyclooxygenase-2 (COX-2) activity in the spinal cord plays a key role in sensitization to sensory stimuli during acute inflammation (70), but intrathecal administration of COX-2 specific inhibitors has minimal analgesic effects in an incisional model of postoperative pain (71). Studies in experimental animals suggests that COX-1 plays an important role in spinal cord pain processing and sensitization after surgery and that spinally administered specific COX-1 inhibitors may be useful to treat postoperative pain (72). In a phase I safety assessment of intrathecal ketorolac in volunteers, a single 0.25–2 mg intrathecal dose of ketorolac did not affect sensory or motor function or deep tendon reflexes, and there were no subjective sensations, neurologic or otherwise, reported by the volunteers. Ketorolac did not reduce pain reported from heat stimuli applied to the lateral calf (73). Intrathecal ketorolac lacks efficacy in normal rats subjected to acute, noxious heat stimuli but enhances the antinociceptive effects of clonidine (74). Further study is

needed to define the role of intrathecal ketorolac in treating acute pain.

Midazolam

There has been much recent attention toward the use of the benzodiazepine midazolam as an intrathecal drug in the treatment of both acute and chronic pain. Yaksh and Allen (75) recently reviewed the existing animal and human data regarding use of intrathecal midazolam. Basic science work with γ-amino butyric acid suggests that it may play an important role in regulating primary as well as dorsal (sensory) and motor horn excitability. Preclinical studies in animal models have demonstrated significant analgesia without changes in sympathetic outflow. At larger doses (typically 3 or more times the dose required to produce analgesic effects), reversible degradation of motor strength and coordination appear. Early toxicity studies in rabbits (76) suggested that midazolam produced significant spinal cord toxicity, even after single-shot administration in clinically relevant doses. However, recent animal studies examining the effects of long-term intrathecal administration of midazolam showed no discernible toxicity (77). Yaksh and Allen (75) conclude that current data ". . .support the assertion of a degree of safety for this modality [intrathecal midazolam] within the doses and concentrations examined."

The use of intrathecal midazolam in humans has been reported in at least 18 peer-reviewed reports with an estimated 797 patients (75) since 1986. The overall clinical effects are characterized by an increased duration of sensory and motor block when administered with spinal local anesthetic, an increase in time to first request for supplemental analgesia postoperatively, and a decrease in postoperative analgesic requirements. There appears to be no increase in adverse effects, including hypotension, bradycardia, micturition, or nausea/vomiting, when midazolam is combined with another intrathecal local anesthetic and/or opioid compared with groups not receiving intrathecal midazolam. Tucker et al. (78) reported a prospective observational study of 1100 patients who underwent various surgical procedures with spinal anesthesia with or without the addition of 2 mg of intrathecal midazolam. Intrathecal midazolam was not associated with an increased risk of symptoms suggestive of neurological impairment, including motor or sensory changes and bladder or bowel dysfunction. Tucker et al. (79) randomized 30 parturients to receive intrathecal midazolam 2 mg, fentanyl 10 μg, or the combination of both drugs. Labor pain was not altered by midazolam alone, was modestly reduced by fentanyl alone, and was reduced most by the combination of the two drugs. They concluded that intrathecal midazolam enhanced the analgesic effect of fentanyl without increasing maternal or fetal adverse effects. Current reports suggest that the use of midazolam in a dose not exceeding 1–2 mg at a concentration not exceeding 1 mg/mL, delivered either alone or as an intrathecal adjuvant, has positive effects on perioperative pain and does not increase the incidence of adverse events (75). Although current formulations are preservative-free, commercially available stock solutions of midazolam hydrochloride are supplied in concentrations of 5 mg/mL at a pH 3.4–3.6 (75). The solubility rapidly declines to <1 mg/mL at pH 4.5–5, and cloudiness (precipitation) has been reported when the 5 mg/mL is diluted with higher pH saline or CSF (80).

Complications Associated with Intrathecal Opioid Use

Pruritus

Pruritus after intrathecal administration of opioids is common and occurs more often than after systemic administration. Szarvas et al. (81) reviewed the pathophysiology and treatment of neuraxial opioid-induced pruritus. The incidence of pruritus after intrathecal administration of opioid varies from 30% to 100% (82–87). The incidence among the commonly used intrathecal opioids (morphine, fentanyl, sufentanil) has been reported to be similarly frequent (88,89). The exact mechanism of neuraxial opioid-induced pruritus remains unclear (83). Naloxone's reversibility of pruritus supports the existence of an opioid receptor-mediated central mechanism. The mechanism does not appear to be histamine related (90). Pharmacological therapies include antihistamines, 5-HT_3-receptor antagonists, opiate antagonists and combination agonist-antagonists, propofol, and nonsteroidal anti-inflammatory drugs (83). Histamine is not released and does not appear to be causative (91). Antihistamines are thus unlikely to have any role in prevention. The sedative properties may be helpful in interrupting the itch-scratch cycle but without relieving itch sensation (92). Despite its widespread use, diphenhydramine has little demonstrated efficacy in the treatment of neuraxial opioid-induced pruritus (84,90). Ondansetron has demonstrated efficacy in both prevention and treatment of pruritus associated with neuraxial opioids (84,93). The opioid antagonists naloxone and naltrexone (91), as well as the agonist-antagonist nalbuphine (94), are the most effective drugs for prevention and treatment of neuraxial opioid-induced pruritus. When the pure antagonists are used in larger doses, they also reverse analgesia (94). Nalbuphine appears to be the most effective drug when compared with naloxone, diphenhydramine, and ondansetron (94,95). Propofol, in subhypnotic doses, has also proven effective in the prevention and treatment of

neuraxial opioid-induced pruritus. Propofol, 10 mg bolus followed by 30 mg/24h infusion (96) or 10 mg without infusion (97), markedly reduced the incidence of pruritus. However, studies in obstetric populations have failed to show any effect of similar doses of propofol on neuraxial opioid-induced pruritus (98,99). Treatment of opioid-induced pruritus remains a challenge. Ondansetron, propofol, and nalbuphine have proven efficacy in the treatment of neuraxial opioid-induced pruritus (Table 3).

Urinary Retention

Urinary retention after administration of intrathecal opioids is common. This side effect can be observed soon after intrathecal injection of morphine and lasts for 14–16 h, regardless of the dose used (100). The incidence of urinary retention appears to be most frequent with intrathecal morphine at ~35% (101) and is more common after neuraxial administration than after IV or IM administration (102). The incidence does not appear to be dose related but is more frequent after intrathecal morphine than after lipophilic opioids (103,27). Indeed, intrathecal sufentanil alone for lithotripsy was associated with a shorter time to voluntary micturition than spinal lidocaine (104).

Opioids affect urination *via* several mechanisms including alteration of parasympathetic tone and central analgesic action, which modify the pain threshold for the bladder and contribute to retention (100). Urinary retention secondary to neuraxial opioids is likely related to interaction with opioid receptors located in the sacral spinal cord. This interaction promotes inhibition of sacral parasympathetic nervous system outflow, which causes marked detrusor muscle relaxation and an increase in maximal bladder capacity (100). Naloxone can prevent or reverse urodynamic changes after neuraxial morphine; however the dose required may partially or completely reverse analgesia (100). Nalbuphine may also reverse the urinary effects of neuraxial morphine (105). If patients are unable to void for ≥6 h, urinary catheterization should be performed to prevent myogenic bladder damage resulting from prolonged distention. Because urinary retention is infrequent with use of lipophilic intrathecal opioids, they are the preferred adjuvants for outpatient surgery with spinal anesthesia (18).

Nausea and Vomiting

All opioids, regardless of route of administration, can produce nausea and vomiting. The incidence after neuraxial administration is approximately 30% (106), but the incidence varies with the particular opioid used and, in some settings, also varies with the dose administered. Intrathecal morphine led to a dose-dependent increase in vomiting in volunteers (15) but caused no increase in nausea and vomiting when added to spinal bupivacaine (107,108). Others have demonstrated a dose-dependent increase in nausea and vomiting with intrathecal morphine (109,110). Together, these data suggest that intrathecal morphine does not increase the incidence of nausea and vomiting after major surgery when compared with systemic administration of morphine, particularly if the dose is <100 μg (111). In contrast, fentanyl and sufentanil have been associated with little or no nausea or vomiting after intrathecal administration of a single dose (103,112,113).

Nausea and vomiting induced by neuraxial opioids may be a systemic effect, particularly with lipophilic opioids, or may be the result of cephalad migration of drug in the CSF and subsequent interaction with opioid receptors located in the area postrema (111). Sensitization of the vestibular system to motion and decreased gastric emptying produced by opioids may also play a role.

For shorter or less painful procedures, use of lipophilic opioids will minimize the risk of nausea and vomiting. Both fentanyl and sufentanil were shown to decrease the rate of intraoperative nausea and vomiting during cesarean delivery when compared with local anesthetic alone for spinal anesthesia (18). Dexamethasone and droperidol have been shown to be effective for prevention of nausea and vomiting after epidural morphine (114). Combinations of scopolamine and promethazine used as preventative measures decreased the incidence of nausea and vomiting (111).

Respiratory Depression

The most feared complication of opioid administration is respiratory depression. The pharmacology and time course of opioid-induced respiratory depression have been discussed previously in this review (Fig. 2). The true incidence of clinically significant respiratory depression is not known, but evidence from smaller controlled trials and large observational studies confirm that it is infrequent (115). The majority of prospective studies of epidural morphine have not detected clinically significant respiratory depression, but they are hindered by relatively small sample sizes and are markedly underpowered to detect such a rare event (116). Ko et al. (117) reviewed the use of the term "respiratory depression" and found that there is no clear definition, leading to difficulty and confusion when comparing available studies. The incidence is infrequent for doses commonly used clinically but the incidence is dose-dependent for both hydrophilic and lipophilic opioids (118). The incidence of respiratory depression associated with continuous epidural infusions containing opioids has been estimated from large observational studies, with estimates ranging from 0.09% to 0.4% (119–125). The risk of respiratory

Table 3. Incidence, Proposed Mechanisms, and Treatment for Intrathecal Opioid-Related Side Effects

Complication	Incidence	Proposed mechanism	Treatment	Commentary
Pruritus	• Varies from 30%–100% • Increased in parturients • Varies with opioid used • Likely dose dependent • Increased with epinephrine	Exact mechanism unclear. Postulates include "itch center" in the central nervous system, medullary dorsal horn activation, antagonism of inhibitory transmitters. Modulation of the serotonergic pathway and involvement of prostaglandins may be important as well	• Ondansetron 4–8 mg IV • Nalbuphine 4 mg IV • Propofol 10 mg IV bolus + small dose infusion • Infusion of naloxone • Oral naltrexone	• Propofol may be less effective for the parturient • Histamine release does not appear to be causative
Urinary retention	• As frequent as 35% with morphine • More common than with IV/IM administration • Morphine > fentanyl/sufentanil • Not dose related	Likely related to interaction with opioid receptors in the sacral spinal cord, promoting inhibition of sacral parasympathetic nervous system outflow. This causes detrusor muscle relaxation and an increase in maximal bladder capacity.	• Opioid antagonist and agonist-antagonist including naloxone, naltrexone and nalbuphine	• Inability to void postoperatively is a multifactorial problem—risk factors include surgery type (especially hernia) preexisting obstructive problems, volume status, spinal anesthesia with epinephrine. • This is μ- and δ-receptor mediated
Nausea and vomiting	• Different rates for different opioids (morphine > fentanyl = sufentanil) • Likely dose dependent • Frequent incidence with IV/IM	May be a systemic effect vs. cephalad migration in the cerebrospinal fluid (CSF) and interaction with opioid receptors in the area postrema. Sensitization of the vestibular system to motion and decreased gastric emptying produced by opioids may play a role.	• Use smallest effective dose • For ambulatory procedures use lipophilic opioid instead of morphine. Dexamethasone and droperidol have shown efficacy as well as combinations of scopolamine and promethazine.	• Intrathecal opioids appear to have a protective effect against intraoperative nausea and vomiting during cesarean delivery
Respiratory depression	• Overall estimates: 0.07%–0.49%. • Dose dependent • All opioids can cause • Typically lipophilic early onset (<2 h) and morphine both early and late onset (6–12 h)	Secondary to rostral spread in CSF	• Prevention: Establish a monitoring protocol for your institution and train personnel; a dedicated acute pain service can establish appropriate protocols and monitor adverse events • Opioid antagonists including naloxone, naltrexone, nalmefene	• Risk factors include large dose; concomitant use of additional opioid and or sedatives, age >65 yr, opioid naïve patient • Late onset depression more apparent with morphine • There is not an opioid free from risk

depression after epidural or intrathecal opioid is less than 1%, and limited data suggest that the risk is similar to that of opioids delivered via the parenteral route (116). In a double-blind study of healthy volunteers randomly assigned to receive placebo, IV morphine (0.14 mg/kg), or intrathecal morphine (300 μg), depression of the ventilatory response to hypoxia was similar in magnitude after either IV or intrathecal morphine but longer lasting after intrathecal administration (126).

Risk factors for the development of respiratory depression include large doses, concomitant use of additional opioids and/or sedatives, administration in opioid-naïve patients, and age >65 yr (116,122,123). Detection of respiratory depression after intrathecal administration of opioid may be difficult. Respiratory rate may or may not decrease (124), and significant hypercapnia can occur despite a normal respiratory rate (124). Pulse oximetry may be valuable (15), but the most reliable clinical sign of significant respiratory depression appears to be a depressed level of consciousness (116,124). Protocols for monitoring vary, but typical duration of monitoring is 18 to 24 h after intrathecal morphine and 4 to 6 h after intrathecal fentanyl or sufentanil (124). Lipophilic opioids are now used more frequently in the ambulatory setting, where patients are discharged shortly after surgery; respiratory depression more than 2 h after intrathecal injection of fentanyl or sufentanil has never been described. Patients can be safely managed on regular wards when personnel are trained, emergency guidelines are available, patient dosing and selection are appropriate, and respiratory rate and patient level of consciousness are checked hourly (124). The efficacy and safety of spinal opioids in surgical wards are best assured when these analgesic techniques are used under the supervision of organized acute pain services (127,128).

Conclusions

Intrathecal administration of opioids can provide excellent pain relief after a wide range of operative procedures, including procedures performed in the ambulatory setting. Understanding of optimal doses for specific procedures has improved, but side effects remain common. Knowledge of spinally mediated analgesia is evolving rapidly and a number of non-opioid compounds may prove useful as analgesics that will reduce side effects and improve treatment for both nociceptive and neuropathic pain.

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