

Focused Review

Drug-Related Side Effects of Long-term Intrathecal Morphine Therapy

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Background: The introduction of intrathecal opioid administration for intractable chronic non-malignant pain and cancer pain is considered as one of the most important breakthroughs in pain management. Morphine, the only opioid approved by FDA for intrathecal administration, has been increasingly utilized for this purpose. For over 3 decades, there have been numerous reports on the non-nociceptive side effects associated with ever increasing long-term intrathecal morphine usage.

Objectives: To review the literature on side effects due to long-term intrathecal morphine therapy with discussions of alternate treatment options.

Design: English-language publications were identified through MEDLINE search and the bibliographies of identified articles were reviewed.

Results: Most side effects of intrathecal morphine therapy are dose dependent and mediated by opioid receptors. Common ones include nausea, vomiting, pruritus, urinary retention, constipation, sexual dysfunction, and edema. Less common ones include respiratory depression, and hyperalgesia. Catheter tip inflammatory mass formation is a less common complication that may not be mediated by opioid receptors.

Conclusion: The utilization of intrathecal morphine administration for cancer and intractable non-malignant chronic pain represents an important leap forward in pain management. Yet, a wide variety of non-nociceptive side effects may also occur in susceptible patients. The side effects due to intrathecal morphine administration are mostly mediated by opioid receptors. Treatment usually involves the utilization of opioid receptor antagonist, such as naloxone. Patients considering intrathecal opioid pump therapy should be informed and advised about the possible side effects associated with long-term intrathecal morphine administration prior to placement of a permanent morphine infusion pump.

Key words: side effects, intrathecal morphine, opioid receptors

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The discovery of specific opioid receptors in the central nervous system in the 1970s marked a milestone for spinally mediated analgesia (1-4). In 1976, Yaksh and Rudy demonstrated the efficacy of intrathecal opioids in abolishing pain in animal models (4), and in 1979, Wang et al reported the first case of intrathecal administration of morphine used effectively for pain relief in humans (5). Since the 1980s, intraspinal drug delivery therapy has been increasingly utilized, first in cancer patients, later on in patients with non-malignant intractable pain who failed to respond to conventional treatment or could not tolerate systemic opioid therapy due to side effects. By infusing a small amount of analgesic directly into the cerebrospinal fluid in close proximity to the receptor sites in the spinal cord, one is able to achieve profound anti-nociception by the spinally mediated analgesia, sparing some of the side effects caused by systemic opioids (6-10). There are at least 3 distinct types of opioid receptors: mu, kappa, and delta. These are widely distributed in the brain, spinal cord, and around peripheral nociceptors (11). Mu receptors modulate responses to mechanical, chemical and thermal nociception at the supraspinal level. Kappa receptors appear to modulate spinally mediated thermal nociception and chemical visceral nociception. Delta receptors may modulate mechanical and inflammatory nociception (11).

Morphine, the only FDA approved opioid for intrathecal administration, is effective, inexpensive, and well tolerated by majority of patients (12). However, with the ever-increasing application of intrathecal morphine for intractable painful conditions, more and more clinically relevant side effects become evident.

PHARMACOKINETICS OF INTRATHECAL MORPHINE

The side effects of intrathecal opioids are caused by the presence of an opioids either in the cerebral spinal fluid (CSF) or in the blood (13). Vascular uptake of opioids following intrathecal administration does occur to some degree, but it is clinically insignificant (14-16). Almost all intrathecal opioid-related side effects are mediated by opioid receptors (13). However, the pharmacokinetics of intrathecally administered opioids varies significantly depending on its lipophilicity. Fentanyl, e.g., with high lipophilicity, penetrates the spinal cord rapidly, leaving little to ascend cephalic in the cerebral spinal fluid (CSF). In contrast, morphine, with high hydrophilicity, penetrates the spinal cord

slowly, allowing a considerable amount of the drug to ascend cephalad in the CSF (13). The mechanism of cephalad migration of morphine is thought to be due to bulk flow of CSF (17), which ascends from the lumbar region, reaching the cisterna magna by 1-2 hours and the fourth and lateral ventricles by 3-6 hours (17). Intrathecally administered morphine produces slower onset and longer duration of anti-nociception, but a higher incidence of certain side effects (13). The majority of the commonly seen pharmacological side effects while receiving intrathecal morphine therapy, such as pruritus, nausea/vomiting, urinary retention, constipation, mental status change, and respiratory depression, can be easily antagonized by the mu antagonist, naloxone (13). However, the analgesic effect may (18) or may not (19) be maintained. Side effects of intrathecal morphine therapy are usually common at the initiation phase of the treatment and generally resolve with standard medical management during the first 3 months (10). The incidence of drug-related side effects with long-term intrathecal morphine therapy decreases with medical management and dose reduction as therapy continues (10).

SIDE EFFECTS OF INTRATHECAL MORPHINE

Pruritus

Pruritus is one of the most common side effects associated with intrathecal morphine administration. Its incidence varies from 0 to 100% (13). It is mostly localized in the face, neck or upper thorax although it may also be generalized (20,21). It is usually mild; severe pruritus only occurs in 1% of patients. It usually occurs within a few hours of drug administration and may even precede the onset of analgesia (22). The incidence of pruritus due to long-term intrathecal morphine administration is about 14% (10). Pruritus, induced by intrathecal morphine administration, is thought to be caused by cephalad migration of the drug in the CSF to interact with the trigeminal nucleus located in the superficial medulla (23). The trigeminal nucleus descends into the cervical spinal cord and connects with the substantia gelatinosa of the dorsal horn. The interaction of opioids in the substantia gelatinosa may initiate the "itch reflex" (24,25). Altered CNS pain perception may also play a part in pruritus induced by intrathecal morphine (25). Rapid development of tolerance to itching usually occurs in 1-2 weeks after initiation of intrathecal morphine therapy (26). Pruritus can be readily treated with the mu antagonist, nal-

oxone, IV drip at 5mcg/kg/hour without losing analgesia (26). Although opioids may enhance the release of histamine from mast cell by activating H1 receptor on itch-specific C fibers (11), it is unlikely for this to be the mechanism that causes pruritus in patients on intrathecal morphine therapy (13). Interestingly, antihistamines can be useful in treating pruritus caused by intrathecal morphine, likely due to its sedative effects (13). The proposed mechanism of opioid induced itching includes involvement of serotonergic receptors and/or mu and kappa receptors (11). The 5HT3-receptor antagonist, ondansetron (4-8mg PO Q8H prn), was found to decrease itching caused by intrathecal morphine (27,28). Nalbuphine (10mg IV/IM/SC Q3-6H prn), a mu antagonist and kappa agonist, was found to lessen itching in patients on intrathecal morphine without causing reversal of analgesia (29,30).

Nausea and Vomiting

Nausea and vomiting are commonly seen with intrathecal morphine administration. Chaney noted the incidence of nausea and vomiting following acute intrathecal opioid administration to be 30% (13), although the incidence following long-term intrathecal morphine delivery is unknown. This incidence was found to be related to the intrathecal morphine dosage by Bailey et al (22), while Raffaelli et al found no clear correlation between the dose and the incidence of nausea and vomiting in opioid-naïve patients following intrathecal opioid administration (31). However, both of the above studies were done in patients following acute intrathecal morphine administration. Anderson et al reported the incidence of nausea as 21% in patients on long-term intrathecal morphine therapy, but was improved by dose reduction (10). Nausea and vomiting induced by intrathecal morphine are likely the result of cephalad migration of drug in the CSF and subsequent interaction with opioid receptors located in the chemoreceptor trigger zone (area postrema) (32-34). Sensitization of the vestibular system (35) and decreased gastric emptying (36) by opioids may also contribute to the development of nausea and vomiting. Positional changes may exacerbate these symptoms (31). Based on etiologies, different pharmacological regimens can be used to treat them, e.g., those secondary to vestibular stimulation (worsened by movement, position change) respond to meclizine (25mg PO Q6H prn), promethazine (25mg PO Q6H prn) and scopolamine (0.1mg Patch Q 72 H); those secondary to constipation respond to metoclo-

pramide (10mg PO Q6H prn), stool softeners/or bowel stimulants; those secondary to chemoreceptor trigger zone stimulation respond to droperidol (0.625-2.5mg IV/IM), hydroxyzine (25mg PO Q6H prn), and prochlorperazine (10mg PO Q6H prn) (11,26). Some patients may require more than 2 different types of antiemetics simultaneously to achieve efficacy (37).

Urinary Retention

Urinary retention following intrathecal morphine administration has an estimated incidence between 42% and 80% (12,22) and is more common in elderly men with enlarged prostates (12,22). It is much more common than following the administration of equivalent doses of morphine given intramuscularly or intravenously (38). The incidence of urinary retention with long-term intrathecal morphine therapy is only at 3 % (10). It is believed to be dose independent (39). The interaction with opioid receptors in the sacral cord, resulting in the inhibition of sacral parasympathetic outflow and subsequent detrusor relaxation, is felt to be responsible for inducing urinary retention (40). This effect appears to be mediated by mu and delta, but not kappa receptors (41). Urinary retention has never been reported following intraventricular morphine administration, suggesting a spinally mediated mechanism (42). Endogenous opioids are suspected to play a role in bladder function control through modulation of parasympathetic outflow at the sacral cord level (43). The detrusor relaxation caused by epidural morphine in humans is readily reversed with naloxone (0.1-0.2mg Q 3 min prn IV/IM/SC) (40), although reversal of analgesia is also likely (44). Cholinomimetic agents such as bethanecol (10-30mg PO TID) may be helpful to treat urinary retention induced by opioids (45).

Constipation

Anderson et al found that 30% of the patients in their study experienced constipation at least once over a 2-year follow-up period (10). Intrathecal morphine may prolong the intestinal transit time (46,47). The decreased gastrointestinal motility caused by intrathecal morphine is due to the interaction with opioid receptors in the spinal cord, rather than from systemic absorption (47,48), even though systemic opioid is well known to cause constipation by a direct action on opioid receptors present in the gastrointestinal smooth muscle (49). Patients on intrathecal morphine therapy may present with signs and symp-

toms of ileus, which, in turn, may cause nausea and vomiting (46-48). Some authors have recommended a prophylactic approach with cathartics (42,49,50). The recommended guidelines include starting with a stool softener (e.g. docusate, 100 mg PO bid) and a bowel stimulant (e.g. senna, 2 Tabs PO BID, bisacodyl, 10mg PO/PR prn), increasing dosages as needed before adding laxatives (e.g. mineral oil, glycerine suppositories) (49). Prokinetic agents such as metoclopramide (10mg PO TID) or domperidone (10-20mg PO TID) can be added if the constipation has not responded to the above conventional treatments (49). Naloxone can readily reverse opioid-induced constipation, either induced centrally or peripherally, even though only 2% of the orally administered naloxone will reach the CNS due to extensive first-pass metabolism (51). Because of the very narrow therapeutic window of naloxone, which is prone to precipitating analgesic withdrawal, it is reasonable to start low (0.6–1 mg PO TID), titrate up as needed to 5mg PO TID (49).

Fluid Retention

Water retention and peripheral edema caused by intrathecal opioids can be quite problematic (52). Although the incidence of long-term intrathecal opioid induced edema ranges from 6.1% (12) to 21.7% (53), edema due to intrathecal morphine occurred in only 3% (10), 11.7% (54), and 16% (52), respectively in 3 different studies. Pharmacokinetic studies suggest the cephalad migration of morphine in the CSF, and subsequent interaction with opioid receptors in the posterior pituitary gland, stimulates vasopressin release by the posterior pituitary (13). Anderson et al noted only transient improvement of edema after changing intrathecal morphine to hydromorphone and recurrent edema following prolonged exposure to intrathecal hydromorphone (52). Aldrete et al observed leg/foot edema in 5/23 patients on intrathecal opioids (21.7%), compared to 2 of 5 on morphine; and 3 of 5 on oxymorphone (53). They also noted cases with severe pedal edema, seeping lesions that minimally responded to treatment with diuretics, compression stockings and pumps, only to lessen with opioid dose reduction, and in 2 severe cases, almost complete resolution of edema after infusion cessation. Treatment of intrathecal opioid-induced edema starts with simple measures such leg raising, elastic stockings, compressive air pumps, and salt and fluid restriction (49). Diuretics may also be used with benefit (49). Aldrete et al recommended that pre-existing leg venous insufficiency and edema

be considered relative contraindication for intrathecal opioid therapy (53).

Mental Status Change

Mental status change, presented as sedation and lethargy, occurred in 10–14% of patients receiving long-term intrathecal morphine infusion therapy (10). The degree of sedation appears to be dose related (22). Profound CNS depression, i.e., coma, has been reported (55). Respiratory depression must be suspected whenever sedation occurs following intrathecal opioid administration (56). Mental status changes, apart from sedation, may also present as paranoid psychosis, catatonia, euphoria, anxiety, delirium and hallucination (57,58). Cephalad drug migration in the CSF and subsequent interactions with opioid receptors in the brain such as the thalamus, limbic system and cerebral cortex is suggested (13). When these side effects are evident, opioid dose reduction should be tried first. Sedation can be treated with “traditional” psychostimulants such as methylphenidate (5–10mg PO QD-BID prn) (59) or the “new” psychostimulants such as modafinil (200–400mg PO QD prn) (60). Delirium and hallucination are treated with neuroleptics such as haloperidol (1–5mg PO BID prn) or benzodiazepines such as lorazepam (0.5–1mg TID PO prn) (49).

Sexual Dysfunction

Impotency or decreased libido may occur more frequently than previously recognized by physicians (54). Abs et al studied 73 patients (29 male and 44 female) on intrathecal opioid therapy (68 with morphine; 5 with hydromorphone) for non-malignant pain. They noted decreased libido or impotency in 23 of 24 men receiving long-term intrathecal opioids (61). The serum testosterone levels in 23 males in the treatment group were significantly lower than the control group; decreased libido was reported in 22 of 32 women on intrathecal opioid therapy. Significantly lowered serum LH, FSH were found in all 18 postmenopausal females. All 21 premenopausal females developed either amenorrhea or irregular menstrual cycles with lowered serum LH, estradiol and progesterone. They concluded that the majority of men and all women receiving intrathecal opioids developed hypogonadotropic hypogonadism and recommended substitutive sex steroids in such patients (61). Currently, there are increasing concerns about intrathecal opioid induced hypogonadism. The mechanism of this action is by alteration of the hypothalamic-pituitary-gonadal axis

(49). Opioid dosage reduction, opioid rotation, and hormone replacement therapy have all been recommended (62), although to date, there are no established standards for managing this complication.

Respiratory Depression

Respiratory depression is the most feared complication of intrathecal morphine therapy. Clinically important respiratory depression has been reported following intrathecal morphine (63,64). Respiratory depression due to intraspinal opioids is divided into 2 types; early respiratory depression occurs within 2 hours of drug administration; delayed respiratory depression occurs after 2 hours of drug administration. Early respiratory depression due to intrathecal morphine administration has never been reported. Delayed respiratory depression results from the cephalad migration of the opioid in the CSF and subsequent interaction with the opioid receptors located in the ventral medulla (65,66). There was paucity of reports in the literature on delayed respiratory depression caused by long-term intrathecal morphine therapy. Scherens et al reported one case of respiratory depression while on long-term intrathecal morphine in a 41-year-old male with severe neuropathic upper extremity pain due to brachial plexopathy (64). The patient developed progressive deterioration of his pulmonary status, i.e., respiratory acidosis and bradypnea with gradual escalation of his intrathecal morphine dosage over one year period of time. Respiratory compromise improved with dose reduction. Ruan et al encountered a case of respiratory failure following delayed intrathecal morphine pump refill in a 65-year-old lady with intractable chronic low back pain. After being on intrathecal morphine therapy for over 6 months, the patient missed her pump refill appointment due to a family emergency. Following her pump refill 12 days later, she developed respiratory failure, presumably caused by an abolished opioid tolerance due to the empty pump (unpublished data, in preparation). Reversal of respiratory depression can be readily accomplished with the administration of mu antagonist i.e. naloxone or a kappa agonist/mu antagonist i.e. nalbuphine (67-69). Kaiser and Brinton reported an interesting approach of treating intrathecal morphine overdose by aspiration of CSF and replacement with normal saline (70).

Hyperalgesia

Hyperalgesia induced by intrathecal morphine ad-

ministration has been studied in animals (71-75) and humans (76-79). High dose intrathecal morphine administration may produce hyperalgesia and allodynia on rare occasions (80). These are not opioid receptor mediated events (81). Early reports suggested causality by intrathecal high dose morphine to block glycine or gamma-aminobutyric acid (GABA)-mediated inhibition (82,83). Mao et al, and Dunbar and Pulai independently demonstrated that N-methyl-D-aspartate (NMDA) receptor antagonists reduced thermal hyperalgesia caused by intrathecal morphine administration (84,85). Ibuki et al demonstrated the increased content of excitatory amino acid (EAA) neurotransmitter in spinal cord tissue with intrathecal morphine administration (86). Intrathecal morphine induced hyperalgesia has been linked to the increased EAA availability and receptor sensitivity in spinal cord tissue, although other neurotransmitter systems may also play a role (80). Morphine-3-glucuronide, the major metabolite of morphine, has been suggested to induce nociception following intrathecal high dose morphine administration (81). More and more evidence suggests that the development of tolerance and hyperalgesia share common mechanisms (49).

Management approaches include

1. opioid dose reduction
2. opioid rotation to methadone to employ the NMDA antagonist properties of methadone (87,88)
3. IV ketamine at subanesthetic doses for NMDA antagonist action (0.5mg/kg bolus and 0.25mg/kg/h) (89,90)
4. addition of alpha-2-adrenergic agonist, i.e. Clonidine epidurally (4ug/kg in 10 ml NS X 20 minutes followed by 2ug/kg/h for 12 hours) (91)
5. IV lidocaine (1-3mg/kg over 20-30 minutes followed by SC or IV infusion at 0.5-2 mg/kg/h) (92)
6. low dose infusion of naloxone (0.05mg/h) to selectively block excitatory activity mediated by mu receptor (93-95).

Catheter Tip Granuloma

Inflammatory mass lesions at the tip of intrathecal catheters or catheter tip granulomas have been increasingly recognized over the past 2 decades. Since the first case report by North et al in 1991, on intrathecal catheter tip mass causing spinal cord compression (96), more case studies (97-103) and systemic review (104) have been published. The incidence of intrathecal catheter tip inflammatory mass has been reported to be 0.4 after 2 years of therapy, increasing to 1.16%

after 6 years of therapy (105). The incidence of asymptomatic lesions may be much higher (103). It was hypothesized that the high morphine concentration, duration of high concentration infusion, catheter tip location, and poor CSF flow patterns contributed together to the development of catheter tip granulomas (104-106). Allen et al demonstrated that catheter tip granuloma formation depends on the concentration, not the dose of infused morphine (107). The FDA approves preservative free intrathecal morphine in concentrations of 10–25mg/ml (108). However, in practice, some clinicians use compounded preservative free morphine at concentrations of 50mg/ml so as to prolong the duration for pump refill, which may increase the risk of granuloma formation (108). Nevertheless, Yaksh et al noted 30% of granulomas developed in patients receiving less than 10mg/day; 40% were using morphine concentrations of less than 25mg/ml (109). Allen et al also demonstrated that the catheter tip granuloma formation does not depend on opioid receptor activation (110). Yaksh et al found the addition of Clonidine at greater than 250mcg/day to intrathecal morphine could prevent granuloma development in a canine model (105). Based on this finding, some physicians including author routinely use Clonidine as an adjunct with morphine to inhibit granuloma formation (personal observation, J. Patrick Couch, MD, Physicians' Pain Specialists of Alabama, Mobile, AL). In view of the concentration dependent effect of intrathecal morphine on granuloma formation, Peng and Massucitte recommended that the intrathecal opioid daily dosage and concentrations be kept as low

as possible (111). Because catheter-associated masses can cause devastating neurological injury, McMillan suggested initial and periodic radiographic screening such as computed tomography with myelography and high-resolution magnetic resonance scanning (112). In contrast, a consensus panel in 2002 did not believe existing data support routine radiographic surveillance of all patients, instead, the panel emphasized the need for vigilance, regular assessment and a high index of suspicion for granulomas to detect them before the onset of neurological deficit (106). In asymptomatic and minimally symptomatic patients, initiation of saline infusion and/or termination of drug infusion usually result in spontaneous regression of mass lesions (112). In patients with progressive myelopathy or cauda equina syndrome, surgical decompression and removal of the mass lesion are usually required to restore neurological function (113).

SUMMARY

With the increasing utilization of intrathecal morphine administration for cancer and non-malignant chronic pain, it is important to be aware of the wide variety of non-nociceptive side effects which may also occur in susceptible patients. Physicians utilizing intrathecal morphine therapy should be well aware of the non-nociceptive side effects. It will also be of benefit for eligible spinal pump candidates to be informed and advised about the possible side effects associated with long-term intrathecal morphine administration prior to the placement of permanent morphine infusion pumps.

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