

Case Scenario: Self-extraction of Intrathecal Pump Medication with a Concomitant Intrathecal Granulomatous Mass

Bryan S. Williams, M.D., M.P.H.,* David Wong, M.D.,† Sandeep Amin, M.D.*

INTRATHECAL drug delivery systems are frequently used to treat chronic pain and spasticity conditions. One of the first clinical uses of an implantable intrathecal opioid delivery device occurred in 1981 for the management of chronic malignant pain,¹ although trials of opioids for intractable cancer pain began with Wang in 1979.² Initially utilized as a means of pain amelioration in cancer patients, intrathecal therapy now has indications that have expanded to include nonmalignant chronic pain conditions.^{3–6} Opioids are often utilized as an infusion agent, with the principal advantage of intrathecal delivery near the site of action within the central nervous system, increasing the therapeutic efficacy, and thus reducing the likelihood of side effects associated with other delivery modalities. The implementation of intrathecal drug delivery systems has shown efficacy in many pain states,^{7,8} but complications or adverse effects may arise. Aprili *et al.*, in a recent systematic review and meta-analysis, examined the potential risks of intrathecal catheters in cancer patients and reported rates of 2.3% (95% CI, 0.8–6.1) and 1.4% (95% CI, 0.5–3.8) for superficial and deep infections, respectively; bleeding was found to be 0.9% (95% CI, 0–2.0) and neurologic injury 0.4% (95% CI, 0–1.0).⁹ The most significant adverse event of mortality can be associated with intrathecal opioids, and mortality rates have been reported of 0.088% at 3 days after implantation, 0.39% at 1

month, and 3.89% at 1 yr, a higher mortality rate than after spinal cord stimulation implants or after lumbar discectomy in community hospitals.¹⁰ The purpose of presenting this case is to highlight key points essential for the diagnosis and treatment of intrathecal granulomatous masses and the vigilance required by physicians managing patients with intrathecal drug delivery systems.

Case Report

A 38-yr-old female registered nurse presented to the pain medicine clinic for continued management of her chronic thoracic spine pain and possible malfunction of her intrathecal drug delivery system. The patient's past medical history was significant for depression, anterior cervical discectomy with fusion, and a SynchroMed EL Infusion Pump® (Medtronic Neurologic, Minneapolis, MN) placement for chronic pain related to T4 and T5 vertebral hemangiomas. The intrathecal pump was placed 9 months before her initial visit in our clinic. She was previously evaluated by multiple pain medicine specialists, with failure to attenuate her pain complaint. Upon initial evaluation she was receiving 40 mg/day of intrathecal morphine at a concentration of 50 mg/ml. At implantation she began therapy at 10 mg/day (20 mg/ml) but escalated to 40 mg/day. The high concentration, daily dose, and lack of analgesia prompted further evaluation of the system, which included cannulation of the catheter access port to evaluate patency of the intrathecal catheter. A lack of cerebral spinal fluid back-flow necessitated further evaluation, which included a catheter-access-port myelogram showing an intact catheter. Upon further inspection and injection of contrast medium, extreme back pain and the appearance at thoracic level 12 of a flame-shaped pooling of contrast at the tip of the catheter (fig. 1A) led to a diagnostic magnetic resonance imaging (MRI) scan, which confirmed the suspicion of an intrathecal catheter-tip mass (figs. 1B and C). After the diagnosis of the catheter-tip mass, further interrogation of the intrathecal pump revealed discrepancies between the aspirated residual volume and the calculated residual volume. The expected residual volume from telem-

* Assistant Professor of Anesthesiology, Division of Pain Medicine, † Resident Physician, Department of Anesthesiology, Rush Medical College, Rush University Medical Center, Chicago, Illinois.

Received from Rush Medical College, Rush University Medical Center, Chicago, Illinois. Submitted for publication March 28, 2010. Accepted for publication August 4, 2010. Support was provided solely from institutional and/or departmental sources.

Address correspondence to Dr. Williams: Division of Pain Medicine, Department of Anesthesiology and Critical Care Medicine, Rush University Medical Center, 1653 West Congress Parkway, Chicago, Illinois 60612-3833. bryan.williams@yahoo.com. Information on purchasing reprints may be found at www.anesthesiology.org, or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

Copyright © 2011, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins. Anesthesiology 2011; 114: 424–30

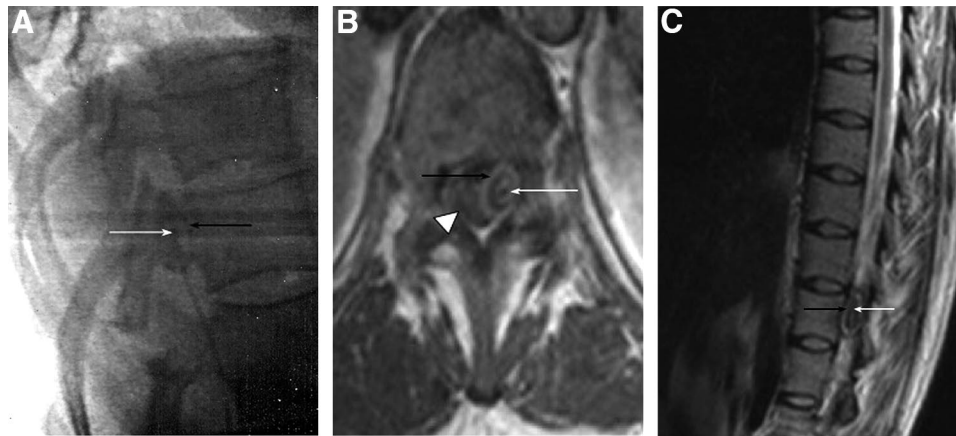


Fig. 1. (A) Lateral radiographic view of catheter access-port myelogram. Flame tip mass (*black arrow*) in spinal canal representing a granulomatous inflammatory mass at the tip of the intrathecal catheter (*white arrow*). (B) Axial view of T2-weighted magnetic resonance image. Granulomatous mass (*black arrow*) demonstrated around the tip of the catheter (*white arrow*) and lateral displacement of the spinal cord (*arrow head*). (C) Sagittal view of T2 weighted magnetic resonance image. Granulomatous mass (*black arrow*) demonstrated at thoracic level 12 around the tip of the catheter (*white arrow*) within spinal canal space.

etry was 7.6 ml, and the actual (aspirated) residual volume was 1.0 ml. In addition, evidence of multiple needle sticks at the reservoir fill port prompted further questioning, after which the patient admitted to accessing the pump and self-administering morphine intramuscularly. The patient was extracting 1 ml intrathecal morphine (50 mg/ml) with a standard bevel needle (nondeflected) and delivering (5 mg) diluents intramuscularly and replacing the withdrawn reservoir volume with saline. Subsequent to this admission, intrathecal medication delivery was discontinued, and the intrathecal pump was explanted, with surgical removal of the granulomatous mass without complications. The patient was administered transdermal clonidine for withdrawal prophylaxis and referred for substance abuse rehabilitation. Alternative treatment of her chronic pain included vertebroplasty at T4 and T5, transdermal fentanyl, hydrocodone/acetaminophen, and clonazepam, which provided satisfactory analgesia.

Discussion

Important issues to consider in this case include the following:

What Are Intrathecal Inflammatory Masses?

Inflammatory masses can develop at the tip of an indwelling intrathecal catheter; they are typically associated with intrathecal delivery of opioids (*e.g.*, morphine) but also have been described with the delivery of nonopioid medications (*e.g.*, baclofen).¹¹ These mass lesions have often been described as granulomas, granulomatous masses, or granulomatous inflammatory masses. A granuloma is a focus of chronic inflammation consisting of a microscopic aggregation of macrophages that are transformed into epithelium-like cells, surrounded by a collar of mononuclear leukocytes, principally lymphocytes and occasionally plasma cells.¹²

Granulomatous inflammation is a distinctive pattern of chronic inflammation that is formed to contain an offending agent.¹² In histopathological examinations of the inflammatory reaction in intrathecal masses, the inflammatory mass is devoid of the epithelium-like macrophages¹³ constituting granulomatous inflammation; it is thus not a true “granuloma,” even though this term is commonly used to describe these inflammatory masses. The reaction contains signs of both acute and chronic inflammatory processes but lacks the essential elements that define granulomas.¹⁴

Epidemiology of Granulomatous Inflammatory Masses

The first intrathecal catheter-tip mass was reported by North *et al.* in 1991,¹⁵ but since then there have been numerous case studies reporting occurrences, management, and treatment outcomes of this phenomenon. Although the incidence of catheter-related granulomatous mass formation is uncertain, reports range from fewer than 1%¹⁶ to 3%,¹⁷ with incidence increasing with the length of therapy.^{18,19} The incidence of self-extraction from intrathecal drug delivery systems is unknown, but these authors are aware of one other case published in the literature,²⁰ and one case of administering illicit substances *via* an intrathecal pump has been reported.²¹

How Is an Intrathecal Catheter Tip Granulomatous Mass Diagnosed?

Table 1 presents diagnostic characteristics of intrathecal catheter-tip masses. Most lesions develop slowly. Therefore, subtle but progressive neurologic decline or new onset motor weakness, including gait difficulties, sensory loss, proprioceptive loss, hyperactive or hypoactive lower extremity reflexes, and any evidence of bowel or bladder sphincter dysfunction, may be an indication of mass effect related to an intrathecal mass.²²

Table 1. Diagnostic Characteristics of Intrathecal Catheter-Tip Mass

- Discordant reservoir volumes at refill
- Increase or change in underlying pain characteristics after prolonged periods of stability
- Generalized pain or radicular pain on injection or aspiration of the catheter access port
- Diminishing analgesic efficacy despite frequent increases in medication dose
- Marked increases in medication dose titrations
- New or unusual complaints that require unexpected analgesic dose changes

The imaging modality of choice is MRI if no contraindication is present.^{16,23} Ring enhancement has been observed with the administration of contrast medium (gadolinium) but does not appear to be critical in diagnosis.¹⁷ On MRI, contrast-enhanced T1-weighted imaging typically reveals enhancement of the lesion.^{22,23} On unenhanced T1-weighted images, the masses vary in appearance and have intermediate to mildly low signal intensity.²³ Variable signal intensity characteristics on T2-weighted images have been reported but peripheral ring enhancement with central hypointensity is often observed^{16,24} (figs. 1B and C). Concern arises with respect to the magnetic field imposed during the exam; the patient may experience a slight tugging sensation at the pump implant site, but the effect is less than that due to gravity. The magnetic field of the MRI scanner will temporarily stop the rotor of the SynchroMed II pump motor and suspend drug infusion for the duration of the MRI exposure. The pump should resume normal operation upon termination of MRI exposure. Presence of the pump can potentially cause an increase of the local temperature in tissues near the pump (approximately 1°C at 1.5 T). After imaging, the clinician programmer should be used to interrogate the pump to ensure that no changes in programming occurred. § An alternative modality is a computed tomography-myelogram using nonionic, water-soluble contrast to assist in differentiating between the granulomatous mass and the spinal cord.^{16,22,24} At initial presentation of suspected catheter malfunction or occlusion, an intraspinal catheter-accessed myelogram (dye study) may be undertaken. The injectant (non-ionic, water-soluble radiographic contrast medium) may produce a “flame-tipped lesion” (fig. 1A). Upon injection, mass effect may cause the patient to experience increased pain in a radicular pattern that corresponds to the level of the catheter tip.

What Are the Predisposing Factors?

Risk factors associated with the development of intrathecal masses have been examined in multiple studies^{16,25} and recommendations made for prevention of intrathecal masses.²⁶ Data from animal studies with extrapolation to human subjects have borne out that medication concentration and

not dose predispose to mass formation.^{13,18} In addition, the location, either lumbar or thoracic, plays a role in the potential for neurologic compromise. The majority of intrathecal catheters are placed in the thoracic area, near the innervating spinal segment of abdominal pain origins. In the thoracic area, the ventral subarachnoid space may have a region of low cerebral spinal fluid flow.^{18,27} Placement of a catheter by a Tuohy needle, in a conventional manner, may cause the catheter trajectory to turn rostrally only after the catheter deflects off the ventral dura mater at the level of insertion; it will then reside within the ventral thoracic subarachnoid space. Consequently, the local concentration of infused drugs in the subarachnoid space may be higher than anticipated.¹⁸ A propagating mass in this area has the potential to impinge the spinal cord and cause neurologic deficits or compromise. A lumbar catheter, placed caudal to the conus medullaris, would reside in an area of greater cerebral spinal fluid flow, but placement in the lumbar area would be caudal to the spinal cord, which may confer a greater margin of safety if a mass propagates at the catheter tip. In a study of 41 patients with intrathecal masses Coffey and Burchiel²⁷ described chronic noncancer pain conditions as an additional predisposing factor for intrathecal mass formation, presumably because of the life expectancy difference between chronic cancer and noncancer patients. In this study the mean duration of therapy was 24.5 months before either symptoms or discovery of an intrathecal mass.²⁷

What Are the Clinical Features?

Inflammatory masses have been reported with intrathecal administration of all medications except sufentanil and rarely with fentanyl.^{26,28} Through returned product analysis and *in vitro* testing, Medtronic Neuromodulation has confirmed “nonindicated drugs” that result in intrathecal catheter occlusion include compounded medication of baclofen and morphine, admixtures of baclofen with clonidine, baclofen mixed with other drugs, and admixtures for chronic pain therapy containing morphine, baclofen, hydromorphone, clonidine, bupivacaine, fentanyl, and/or sufentanil. § The propagation of the inflammation with mast cell degranulation, histamine release, and other inflammatory mediators results in the mass formation. As the mass increases in size, medication outflow may be impeded, and a “mass effect” may impinge on neural structures. Although the patient in our report was not experiencing neurologic symptoms or deficits, the continued propagation of the lesion could have led to increased mass effect and subsequent neurologic compromise. In fact, occult granulomatous masses may be present without neurologic deficits.¹⁷ As stated earlier, sudden increases in intrathecal dose requirements for pain attenuation are common in patients with intrathecal catheter-tip masses. In addition, new onset neurologic symptoms, particularly at the level of the catheter tip, changes in pain quality, and higher than predicted residual volume remaining in the reservoir at pump refills should raise suspicion for catheter-

§ www.medtronic.com. Accessed January 23, 2010.

related complications. Although increasing dose requirements and new neurologic deficits are suspicious for inflammatory masses, these changes may be related to disease progression, new disease processes, catheter malfunction, and pump malfunction.¹⁷ The symptoms usually develop gradually,¹⁶ but acute presentations have been reported.²⁷

What Is the Pathogenesis of Intrathecal Mass Lesions?

Microscopic pathology of intrathecal morphine-related granulomas often reveals necrotic tissue surrounded by macrophages, plasma cells, eosinophils, or lymphocytes.¹⁶ In this patient the surgical pathology was consistent with fibrous tissue with old hemorrhage, necrotic tissue, and chronic inflammation. No neoplastic cells were seen, and all cultures were negative. Speculation regarding the etiology of the masses at various times has included the chemical characteristics, concentration, or immunologic effects of the infused medications; impurities in, or contamination of, medication sources; bacterial infection, pyrogens, or endotoxins; silicone allergy; catheter design features; and/or delayed effects of traumatic catheter implantation.¹⁸ The risk of infection during medication refills has been examined; under sterile conditions, refills of intrathecal implanted pumps do not seem to be a risk.²⁹ In a study utilizing MRI in dogs, substitution of saline for morphine subsequent to the development of a granuloma led to a regression of the granuloma and the conclusion that mass formation was dependent on the local concentration, not the dose, of morphine.¹⁴ Alternatively, studies in large-animal models have shown that these masses reflect either a dose- or concentration-dependent effect, and the effects of dose *versus* concentration cannot be clearly distinguished.^{18,30}

How Can Intrathecal Granulomatous Masses Be Treated and Prevented?

New onset neurologic deficits at the time of mass discovery necessitate a neurologic exam and may require neurosurgical consultation. Prompt surgical intervention to excise the mass and/or the catheter may result in rapid clinical improvement and restoration of neurologic function or prevent further neurologic deterioration.^{22,27} If signs of spinal cord atrophy or necrosis are observed, residual deficits are likely.¹⁶ The masses are not neoplastic, and several cases have reported that the postoperative residual mass gradually contracted or disappeared over time.^{18,22,27} If no acute neurologic deficits are present at mass discovery, conservative measures may be employed. Case records and anecdotal reports suggest that patients with a mass that does not fill the spinal canal or cause neurologic impairment sometimes can be treated by discontinuing/emptying the drug infusion pump or by refilling it with preservative-free normal saline to infuse at a minimal rate.²⁷ Contraction, reduction, or disappearance of masses has been described on follow-up imaging studies after an interval of 2–5 months.^{22,27,31} Substantial decrement of the intrathecal mass seen on imaging studies is necessary before

resumption of intrathecal treatment should be considered. In addition, treatment options include removal of the catheter and placement of a new catheter under monitored anesthesia care at the time of removal or at a later date. Another viable option is disconnecting the catheter from the pump, obliterating the lumen of the catheter, leaving the intraspinal catheter segment undisturbed, and placing a new intraspinal catheter segment at the same operation or at a later date.^{17,22} In all management options, the infused medication is discontinued. Catheter revision with medication rotation allows intrathecal treatment to continue with minimal interruption in medication delivery. Many physicians may opt for this approach because there is cessation of the offending agent and the mass is removed. The medication rotation should include medications at doses recognized as less likely to precipitate intrathecal masses. The placement of the catheter can be caudal to the conus medullaris, which may decrease the “mass effect” of an intrathecal mass if formation occurs. The catheters should not be placed preferentially such that they reside in the ventral intrathecal space, where the greatest area of low-cerebral spinal fluid flow occurs.^{18,26} Theoretically, a dorsally placed catheter may avoid this low-flow segment, but it has been reported that dorsal or ventral placement of catheters does not appear to influence the formation of inflammatory masses.²²

Prevention

Multiple features are involved in the development of intrathecal catheter-tip masses. The medication delivered to the intrathecal space, medication concentration, and dose appear to be the most important factors associated with mass

Table 2. Recommended Concentration and Doses of Intrathecal Medications

Medication	Maximum Concentration	Maximum Dose per Day
Morphine*†	20 mg/ml	15 mg
Hydromorphone†	10 mg/ml	4 mg
Fentanyl†	2 mg/ml	No known upper limit
Sufentanil	50 µg/ml (not available for compounding)	No known upper limit
Bupivacaine†	40 mg/ml	30 mg
Clonidine†	2 mg/ml	1 mg
Ziconitide*	10 µg/ml	19.2 µg (manufacturer recommendation)
Baclofen*†	2,000 µg/ml (commercially available)	1,000 µg (limited experience with daily doses greater than 1,000 µg/day)

* Food and Drug Administration approved for intrathecal therapy.
† Associated with granulomatous inflammatory masses.

Table 3. Recommendations for Prevention and Treatment of Catheter-tip Inflammatory Mass and Self-extraction of an Intrathecal Pump

Issue	Recommendation
● New Patient (with IT pump)	<ul style="list-style-type: none"> ● Complete history and physical (neurological) ● Review concentration and dose of IT medications through course of prior treatment
● Implantation	<ul style="list-style-type: none"> ● Consider screening imaging ● Place catheter tip in dorsal intrathecal space ● Place catheter tip caudal to conus medullaris ● Lowest effective dose of single opioid medication or addition of nonopioid (e.g., clonidine)
● Ineffective analgesia with escalating dose titration (after prolonged period of stability)	<ul style="list-style-type: none"> ● Ensure that pump is functioning properly (e.g., pump stalls, catheter malfunction) ● Review refill interval ● Maintain concentration and dose recommendations and add second nonopioid medication (clonidine or bupivacaine) <ul style="list-style-type: none"> ● Opioid rotation
● Suspected inflammatory mass	<ul style="list-style-type: none"> ● Review refill residuals ● Aspiration from catheter ● Review patient history for new-onset neurologic complaints ● Catheter access port myelogram (dye study) ● MRI (if no contraindication) ● CT myelogram (if MRI contraindicated)
● Confirmed catheter-tip inflammatory mass	<p>No neurologic symptoms:</p> <ul style="list-style-type: none"> ● Discontinue IT medication infusion (supplement with enteral/transdermal medications) ● Neurosurgical consultation ● Continued monitoring of neurologic symptoms ● Consider removal and/or replacement of intrathecal catheter ● Imaging study for resolution of mass ● Reinitiate IT therapy with alternate medication(s) <p>Neurologic symptoms (e.g., sensory change, progressive myelopathy/paraplegia):</p> <ul style="list-style-type: none"> ● Neurosurgical consultation ● Discontinue IT medication infusion (supplement with enteral/transdermal medications) ● Removal and/or replacement of intrathecal catheter under monitored anesthesia care or evoked potential monitoring
● Suspected self-extraction	<ul style="list-style-type: none"> ● Evaluated reservoir fill port (site) for evidence of puncture sites ● Review refill residuals ● Signs and symptoms of drug addiction
● Confirmed self-extraction	<ul style="list-style-type: none"> ● Discontinue intrathecal therapy ● Referral to addiction medicine ● Alternative treatment regimen

CT = computed tomography; IT = intrathecal; MRI = magnetic resonance imaging.

formation. Morphine is the most commonly implicated medication in the development of intrathecal granulomatous masses, especially at higher concentrations.^{16,18} As treatment duration increases, many patients develop tolerance, requiring dose escalations to maintain analgesic efficacy. The concentration of the medication is increased to maintain refill intervals. The maximum concentration and dose recommended by the Polyanalgesic Consensus Panelists are represented in table 2. In many reported cases of catheter-tip masses, the concentration of morphine has been at or above 40 mg/ml. If the concentration requirements reach this level, alternative strategies should be utilized. In surveys of implanting physicians, up to 35% of patients using morphine alone fail the therapy.¹⁷ Clonidine has been described as having protective properties with respect to inflammatory

mass formation,^{18,22} but it has also been reported to fail in protection against inflammatory mass events.³¹ Nevertheless, if morphine is the agent of choice, clonidine may present synergistic analgesic effects, thus allowing a lower dose of morphine through the course of treatment. Alternatively, hydromorphone can be delivered to the intrathecal space and may have advantages over morphine because it is a significantly more potent analgesic than morphine. It has been reported that equivalent pain control can be achieved with much lower intrathecal doses of hydromorphone than morphine (approximately 20% of morphine doses), with a lower potential for undesirable side effects.^{32,33} Medication rotation and a polyanalgesic approach of adding a second or third medication before the concentration or daily dose of any one medication reaches the upper limit of recommendations may

prove prudent in reducing the incidence of intrathecal mass propagation.

The potential for significant neurologic compromise that may occur with an intrathecal catheter-tip inflammatory mass and the adverse consequences of self-extraction from an intrathecal pump necessitate aggressive assessment and management. The goals of intrathecal therapy are analgesia, functional restoration, and minimizing morbidity from the therapy. Achieving these goals begins with patient evaluations for potential psychosocial issues that may preclude implantation. When initiating intrathecal therapy or assuming care of an intrathecal pump, an initial neurologic assessment is paramount. A screening imaging study is not essential, but when assuming care for a previously implanted pump this should be considered. Medication concentration and dose recommendations serve as a reference for titration of intrathecal medications. In addition, neurologic assessment should be performed at each refill interval, along with assessment of treatment goals and adverse effects of the medications. Furthermore, assessment of expected and actual residual volumes should be assessed at every refill visit. The flow rate should be within $\pm 14.5\%$ of the programmed rate; a flow rate error of $\pm 25\%$ is a marker of significant discrepancy between expected and actual residual volumes.[§]

Patients with chronic nonmalignant pain may benefit from psychologic evaluation before intrathecal therapy. Although not an absolute contraindication to intrathecal therapy, risk factors such as untreated substance abuse and unrealistic expectations of intrathecal therapy may preclude intrathecal trial/implantation. If self-extraction is suspected or confirmed, intrathecal therapy should be discontinued and alternative treatment along with addiction therapy should be initiated. Optimal outcome requires well-coordinated multidisciplinary care. Table 3 summarizes common diagnostic and treatment issues and provides recommendations to avoid their potentially serious sequelae.

Knowledge Gap

Intrathecal granulomatous masses and self-extraction from an intrathecal pump have both been reported in the literature, but not concomitantly. It is unclear whether the high morphine dose and concentration were solely causative in the propagation of the mass or whether repeated entrance to the pump by the patient under nonsterile conditions introduced nonsterile, potentially inflammatory material. Although the inciting event that precipitated the granulomatous mass formation is unclear, the cause is most likely multifactorial. Several studies demonstrate the hazards of high-dose intrathecal opioids, but additional studies and recommendations are needed to clarify predisposing factors and device safety measures to prevent intrathecal medication substance abuse. The use of intrathecal opioids should, theoretically, confer less abuse potential than enteral or parenteral opioids. Through this case scenario, noteworthy findings are that the potential for substance abuse remains in patients with intra-

thecal pumps and that although consensus recommendations are readily available, based on the best available evidence, responsible medication prescribing is still lacking. Continued investigations will be necessary to determine the best practice (*i.e.*, polyanalgesia, nonopioid medications) for the management of intrathecal medication delivery in chronic nonmalignant pain patients. Finally, specific attention should be paid to patients who exhibit characteristics of substance abuse before intrathecal trial/implantation.

References

1. Onofrio BM, Yaksh TL, Arnold PG: Continuous low-dose intrathecal morphine administration in the treatment of chronic pain of malignant origin. *Mayo Clin Proc* 1981; 56:516-20
2. Wang JK, Nauss LA, Thomas JE: Pain relief by intrathecally applied morphine in man. *ANESTHESIOLOGY* 1979; 50:149-51
3. Kumar K, Kelly M, Pirlot T: Continuous intrathecal morphine treatment for chronic pain of nonmalignant etiology: Long-term benefits and efficacy. *Surg Neurol* 2001; 55:79-86
4. Kongkam P, Wagner DL, Sherman S, Fogel EL, Whittaker SC, Watkins JL, McHenry L, Lehman GA: Intrathecal narcotic infusion pumps for intractable pain of chronic pancreatitis: A pilot series. *Am J Gastroenterol* 2009; 104:1249-55
5. Kumar K, Bodani V, Bishop S, Tracey S: Use of intrathecal bupivacaine in refractory chronic nonmalignant pain. *Pain Med* 2009; 10:819-28
6. Angel IF, Gould HJ Jr., Carey ME: Intrathecal morphine pump as a treatment option in chronic pain of nonmalignant origin. *Surg Neurol* 1998; 49:92-8
7. Anderson VC, Burchiel KJ: A prospective study of long-term intrathecal morphine in the management of chronic nonmalignant pain. *Neurosurgery* 1999; 44:289-300
8. Smith TJ, Staats PS, Deer T, Stearns LJ, Rauck RL, Boortz-Marx RL, Buchser E, Català E, Bryce DA, Coyne PJ, Pool GE, Implantable Drug Delivery Systems Study Group: Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: Impact on pain, drug-related toxicity, and survival. *J Clin Oncol* 2002; 20:4040-9
9. April D, Bandschapp O, Rochlitz C, Urwyler A, Ruppen W: Serious complications associated with external intrathecal catheters used in cancer pain patients: A systematic review and meta-analysis. *ANESTHESIOLOGY* 2009; 111:1346-55
10. Coffey RJ, Owens ML, Broste SK, Dubois MY, Ferrante FM, Schultz DM, Stearns LJ, Turner MS: Mortality associated with implantation and management of intrathecal opioid drug infusion systems to treat noncancer pain. *ANESTHESIOLOGY* 2009; 111:881-91
11. Deer TR, Raso LJ, Garten TG: Inflammatory mass of an intrathecal catheter in patients receiving baclofen as a sole agent: A report of two cases and a review of the identification and treatment of the complication. *Pain Med* 2007; 8:259-62
12. Kumar V, Abbas AK, Fausto N, Aster J: Acute and chronic inflammation, Robbins and Cotran Pathologic Basis of Disease, 8th Ed. Saunders Elsevier, Philadelphia, 2010; pp 73-4
13. Yaksh TL, Horais KA, Tozier NA, Allen JW, Rathbun M, Rossi SS, Sommer C, Meschter C, Richter PJ, Hildebrand KR: Chronically infused intrathecal morphine in dogs. *ANESTHESIOLOGY* 2003; 99:174-87
14. Allen JW, Horais KA, Tozier NA, Wegner K, Corbeil JA, Mattrey RF, Rossi SS, Yaksh TL: Time course and role of morphine dose and concentration in intrathecal granuloma formation in dogs: A combined magnetic resonance imaging and histopathology investigation. *ANESTHESIOLOGY* 2006; 105: 581-9

15. North RB, Cutchis PN, Epstein JA, Long DM: Spinal cord compression complicating subarachnoid infusion of morphine: Case report and laboratory experience. *Neurosurgery* 1991; 29:778-84
16. Miele VJ, Price KO, Bloomfield S, Hogg J, Bailes JE: A review of intrathecal morphine therapy related granulomas. *Eur J Pain* 2006; 10:251-61
17. Deer TR: A prospective analysis of intrathecal granuloma in chronic pain patients: A review of the literature and report of a surveillance study. *Pain Physician* 2004; 7:225-8
18. Yaksh TL, Hassenbusch S, Burchiel K, Hildebrand KR, Page LM, Coffey RJ: Inflammatory masses associated with intrathecal drug infusion: A review of preclinical evidence and human data. *Pain Med* 2002; 3:300-12
19. Follett KA: Intrathecal analgesia and catheter-tip inflammatory masses. *ANESTHESIOLOGY* 2003; 99:5-6
20. Kittelberger KP, Buchheit TE, Rice SF: Self-extraction of intrathecal pump opioid (letter). *ANESTHESIOLOGY* 2004; 101:807
21. Burton AW, Conroy B, Garcia E, Solanki D, Williams CG: Illicit substance abuse *via* an implanted intrathecal pump. *ANESTHESIOLOGY* 1998; 89:1264-7
22. Hassenbusch S, Burchiel K, Coffey RJ, Cousins MJ, Deer T, Hahn MB, Pen SD, Follett KA, Krames E, Rogers JN, Sagher O, Staats PS, Wallace M, Willis KD: Management of intrathecal catheter-tip inflammatory masses: A consensus statement. *Pain Med* 2002; 3:313-23
23. Phillips J, Escott E, Moossy J, Kellermier H: Imaging appearance of intrathecal catheter tip granulomas: Report of three cases and review of the literature. *AJR* 2007; 189:W375-81
24. Blount JP, Remley KB, Yue SK, Erickson DL: Intrathecal granuloma complicating chronic spinal infusion of morphine. Report of three cases. *J Neurosurg* 1996; 84:272-6
25. Deer TR, Raso LJ, Coffey RJ, Allen JW: Intrathecal baclofen and catheter tip inflammatory mass lesions (granulomas): A reevaluation of case reports and imaging findings in light of experimental, clinicopathological, and radiological evidence. *Pain Med* 2008; 9:391-5
26. Deer T, Krames ES, Hassenbusch SJ, Burton A, Caraway D, Dupen S, Eisenach J, Erdek M, Grigsby E, Kim P, Levy R, McDowell G, Mekhail N, Panchal S, Prager J, Rauck R, Saulino M, Sitzman T, Staats P, Stanton-Hicks M, Stearns L, Willis KD, Witt W, Follett K, Huntoon M, Liem L, Rathmell J, Wallace M, Buchser E, Cousins M, Ver Donck A: Polyanalgesic Consensus Conference 2007: Recommendations for the management of pain by intrathecal (intraspinal) drug delivery: Report of an Interdisciplinary Expert Panel. *Neuromodulation* 2007; 10:300-8
27. Coffey RJ, Burchiel K: Inflammatory mass lesions associated with intrathecal drug infusion catheters: Report and observations on 41 patients. *Neurosurgery* 2002; 50:78-86
28. Waara-Wolleat KL, Hildebrand KR, Stewart GR: A review of intrathecal fentanyl and sufentanil for the treatment of chronic pain. *Pain Med* 2006; 7:251-9
29. Dario A, Scamoni C, Picano M, Fortini G, Cuffari S, Tomei G: The infection risk of intrathecal drug infusion pumps after multiple refill procedures. *Neuromodulation* 2005; 8:36-9
30. Gradert TL, Baze WB, Satterfield WC, Hildebrand KR, Johansen MJ, Hassenbusch SJ: Safety of chronic intrathecal morphine infusion in a sheep model. *ANESTHESIOLOGY* 2003; 99:188-98
31. Toombs JD, Follett KA, Rosenquist RW, Benton LM: Intrathecal catheter tip inflammatory mass: A failure of clonidine to protect. *ANESTHESIOLOGY* 2005; 102:687-90
32. Johansen MJ, Satterfield WC, Baze WB, Hildebrand KR, Gradert TL, Hassenbusch SJ: Continuous intrathecal infusion of hydromorphone: Safety in the sheep model and clinical implications. *Pain Med* 2004; 5:14-25
33. Anderson VC, Cooke B, Burchiel KJ: Intrathecal hydromorphone for chronic nonmalignant pain: A retrospective study. *Pain Med* 2001; 2:287-97