NEUROMODULATION: TECHNOLOGY AT THE NEURAL INTERFACE

Volume 11 • Number 2 • 2008
http://www.blackwell-synergy.com/loi/ner

ORIGINAL ARTICLE

Management of Intrathecal Catheter-Tip Inflammatory Masses: An Updated 2007 Consensus Statement From An Expert Panel

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ABSTRACT

Background. Expert panel of physicians and nonphysicians, all expert in intrathecal (IT) therapies, convened in the years 2000 and 2003 to make recommendations for the rational use of IT analgesics based on the preclinical and clinical literature known up to those times, presentations of the expert panel, discussions on current practice and standards, and the result of surveys of physicians using IT agents. An expert panel of physicians and convened in 2007 to review previous recommendations and to form recommendations for the rational use of IT agents as they pertain to new scientific and clinical information regarding the etiology, prevention and treatment for IT granuloma. **Method.** A review of preclinical and clinical literature from 2000 to 2006 was undertaken and disseminated to an expert panel of physicians. Focused discussions concerning the rational use of IT agents and its relationship to the etiology of, prevention of, and treatment of IT granuloma were held. **Results.** This report presents here new knowledge of the etiology of catheter tip granuloma and guidelines for its prevention and treatment.

KEY WORDS: *Complications, etiology, granuloma formation, intrathecal, nonopioids, opioids, prevention, treatment.*

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Introduction

Inflammatory mass is a serious complication associated with the tip of catheters implanted with drug delivery systems delivering intrathecal (IT) opioids and nonopioids. An undiagnosed inflammatory mass, also termed a granuloma, can compress the spinal cord, thereby inducing neurologic injury that may produce permanent damage to the spinal cord (1). Neurologic deficits associated with granulomas include paralysis, sensory loss, and impaired bowel and bladder function (2). The first case report of a granuloma identified at the tip of a catheter in an IT analgesic infusion system for the treatment of chronic intractable pain was published in 1991 (3). Schuchard et al. published the results of their survey on neurologic sequelae of implantable drug delivery systems from implanters in the United States and Europe (4). The authors mailed to 3269 implanters of intraspinal infusion systems to identify new cases of neurologic sequelae of pump implantation. Five hundred and nineteen out of 3264 surveys mailed out responded. Of the 519 responders, there were 488 "no" respondents and 31 "yes" respondents to the question: "did any patient of yours develop neurologic sequelae or granulomatous catheter mass formation after implant of their intraspinal catheters?" Six new cases of granulomatous mass formations at catheter tips were reported, 27 cases of neurologic sequelae due to other etiologies also were noted. The authors concluded that "the problem of postimplant neurologic sequelae is potentially devastating. Increased vigilance for early diagnosis may prevent the development of permanent paralysis. Gadolinium enhanced MRI scanning at the catheter tip is the imaging study of choice for diagnosis. Any patient developing a new area of pain, weakness or rapid escalation in intrathecal drug dose should be thoroughly assessed." By November 2000, a total of 41 case reports of catheter-related inflammatory masses in patients receiving IT analgesics for pain had been published in the medical literature, reported to Medtronic Inc. (Minneapolis, MN, USA), or reported to the U.S. Food and Drug Administration. By 2001, the increased frequency of cases identified in such patients could be attributed to several factors, including more long-term usage of intrathecal therapy and more acceptance of the therapy and, therefore, more implants. In addition, the dissemination of scientific knowledge pertaining to the risk of granuloma associated with IT drug delivery and increased voluntary surveillance and reporting by physicians has contributed to the increased incidence.

In response to a growing concern about catheter-tip masses, an expert panel of clinicians experienced in the field of IT analgesics for chronic pain management convened in 2000 and then again in 2003. The panelists reviewed and summarized published preclinical and clinical data on the etiology, pathophysiology, toxicity, and incidence of catheter-tip inflammatory masses, unpublished case reports and their own clinical experience. The major outcome of this conference was a published consensus statement for the management of IT catheter-tip inflammatory masses (5). The report summarized evidence for a possible causal relationship between IT opioids and nonopioids, particularly morphine sulfate infusion, and catheter-tip inflammatory masses. The publication contained consensus recommendations to potentially prevent, diagnose, and treat catheter-tip inflammatory masses in a manner thereby mitigating adverse neurologic adverse. The panelists evaluated inferential data and hypotheses in order to formulate rational, evidence-based hypotheses on the identification of granulomas during prodromal growth stages, on the reversal of mass formation through appropriate intervention, and on the preventing the development of inflammatory masses. They proposed recommendations for specific algorithmic steps to guide physicians in screening for and treatment of catheter-tip granulomas in their patients. Finally, the consensus panel established directives for future research that could further the prevention, early detection and mitigation of inflammatory masses.

The 2002 consensus panel on granuloma concluded that catheter-tip granulomas only develop in patients with implanted pumps for chronic pain undergoing treatment with IT opioid medications, alone or combined with other nonopioid analgesics, or with analgesic medications not labeled for long-term IT use (5). The majority of these patients had nonmalignant pain and when compared to patients with cancer pain received higher cumulative doses of IT analgesics because of their longer life expectancy and subsequently longer exposure to IT medications. As stated in this published report, one key diagnostic clue to the presence of an IT mass in a patient is diminished analgesia accompanied by new, gradually progressive neurologic symptoms and signs.

Anecdotal reports from both the literature and the panelists' experiences indicated that, if a granuloma were detected before the onset of severe neurologic symptoms or before the mass filled the spinal canal, open surgery was not necessarily required to remove the mass. Instead, the panel, at that time, felt that discontinuing IT delivery of the drug through the affected catheter often resulted in either a shrinkage or disappearance of the mass within two to five months. The 2002 consensus panel advised physicians to routinely conduct vigilant follow-up of any suspicious clinical indicators that might signal the presence of a catheter-tip inflammatory mass, thereby mitigating the risk for neurologic sequelae. The most important 2002 guidelines issues in this regard called for placement of the catheter in the lumbar thecal sac, when possible, and administration of a low daily IT dose of opioid medication, particularly morphine sulfate to minimize severity from granuloma and/or the incidence of granuloma (5).

TABLE 1. 2002 Recommendations: Diagnosis, Treatment, and Prevention of Catheter-Tip Granuloma Formation

Screening, detection, and diagnosis
1. Document a thorough baseline evaluation.
2. Document three-dimensional location of the IT catheter tip at implantation.
3. Provide attentive follow-up and remain alert to diminishing analgesic effects, loss of previously satisfactory pain relief, remarkable or unusual increases in the patients underlying pain, sleep or frequent dose escalations, or neurologic symptoms suggestive of an inflammatory mass.
4. If granuloma is suspect, conduct a low threshold for performing contrast-enhanced T1-weighted magnetic resonance imaging or computed tomography myelogram.
5. Conduct microbiological culture analysis and stains of pertinent specimens (eg, cerebrospinal fluid [CSF], port CSF aspirates, the catheter tip aliquots, pump reservoir contents, samples of abnormal intraspinal tissue) whenever a catheter-tip mass is detected, even though infection is an unlikely cause.

Treatment of the mass and management of the drug infusion system
1. Mildly symptomatic patients can be treated conservatively by drug cessation through the catheter into the mass.
2. Patients with severe neurologic symptoms should have a neurosurgical consult and possible neurosurgical removal of the mass.

Prevention of the mass and mitigation of neurologic sequelae
1. Consider placement of the catheter tip in the lumbar thecal sac.
2. Keep the drug dose and concentration as low as possible for as long as possible while still achieving adequate analgesia.

Conclusions of the First and Second Polyanalgesic Consensus

Etiology of Inflammatory Masses

The 2000 Granuloma Consensus Panel (5) and the Second Polyanalgesic Consensus (6) did not identify a precise pathophysiologic mechanism resulting in the formation of catheter-tip inflammatory masses. However, the existing data from animal models suggested that the administration of certain medications, typically opioid medications delivered into the IT space, could provoke an inflammatory response in tissues of the brain or spinal cord. The panel proposed several hypothetical causes of an inflammatory cell response that included a lack of "tight junctions" between the endothelial cells of the granuloma. Under normal circumstances, "tight junctions" of endothelial cells in blood vessels, brain, or spinal cord tissue inhibit large molecular weight compounds from passing between endothelial cells and extravasate in the surrounding interstitial space. Porous spaces in the vascular supply of the granuloma might allow inflammatory cells of extra-axial tissues to migrate through the walls of small dural or meningeal vessels outside the blood–central nervous system barrier and into areas such as the IT space. This hypothesis also would explain why inflammatory masses do not cause direct neurotoxicity of the spinal cord or alter spinal morphology, even though they exert extrinsic mechanical compression on the spinal cord.

Evidence presented at the 2002 conference suggested that it is the size and mass effect of granulomas that cause damage to the spinal cord or nerve rootlets and not a direct neurotoxic effect of the agents infused. The current state of research at the time was not adequate to determine whether catheter material (silicone elastomer [silastic] or polyurethane material), pump material, device characteristics, or flow of agents from the catheter tip contributed to the formation of granuloma. Infectious agents also were considered an unlikely cause of catheter-tip mass based on the available evidence at the time.

TABLE 2. Concentrations and Doses of IT Agents Recommended by the Polyanalgesic Consensus Panelists 2003

Drug	Maximum concentration	Maximum dose/day
Morphine	30 mg/mL	15 mg
Hydromorphone	30 mg/mL	10 mg
Bupivacaine	38 mg/mL	30 mg
Clonidine	2 mg/mL	1.0 mg

2002 Consensus Recommendations

The 2002 Consensus Recommendations for the diagnosis, treatment, and prevention of catheter-tip granuloma formation are summarized in Table 1 below. To further prevent catheter-tip granuloma, the Polyanalgesic Consensus Conference 2003, published in 2004 (6), suggested the maximum concentrations and doses of intrathecal agents perfused (Table 2).

2007 Consensus Conference

The objectives of the 2007 Polyanalgesic Consensus Conference were to synthesize current clinical and preclinical data, both published and anecdotal, for the purpose of reevaluating and reformulating hypotheses concerning the etiology of IT catheter-tip inflammatory masses associated with polyanalgesic therapy; and to update recommendations for the prevention, detection, treatment, and mitigation of such masses in a manner that minimizes adverse neurologic sequelae.

The Consensus Panel

The 2007 consensus recommendations were developed by a panel of experts in the field of IT therapy. All of the

practitioners on the panel have had extensive clinical experience in the use of IT polyanalgesic therapy to treat patients with chronic intractable pain of malignant or nonmalignant origins. Some of the panelists had gained their knowledge exclusively from private practice, some from their combined private and academic practices, and several from their academic medical research. This report reflects their consensus opinion.

Methods

The methods used by the 2007 consensus panel members to develop this report consisted of the following activities:

- conductance of a literature review of preclinical and clinical material published between the years 2000 and 2006;
- presentation of oral and graphic presentations of updated literature and case studies compiled from both published and unpublished reports and the panelists' own clinical experience;
- interactive group discussion among all panelists during the conference for the purpose of formulating and updating recommendations for the diagnose and treatment of catheter-tip inflammatory masses in a manner that minimizes adverse neurologic events from such masses; and
- postconference participation in a written survey questionnaire in order to obtain direct feedback from the panelists on issues relating to IT granuloma.

Results

Building on the recommendations of the 2000 Polyanalgesia Consensus Conference Panel (7–10), the 2002 Intrathecal Granuloma Consensus Panel (5), and the 2003 Polyanalgesia Consensus Conference Panel (6), the 2007 Polyanalgesic Consensus Conference panelists generated the following work that is presented in this article:

- review of pertinent preclinical research and human studies published from 2000 to 2006 integrated with a review of unpublished case reports and expert anecdotal experience on IT catheter-tip inflammatory mass;
- discussion of evidence-based trends that provide an integrated summary of current expert consensus based on published and unpublished case reports;
- panelists' responses to a survey questionnaire on key clinical issues;
- a revised and updated algorithm for the prevention, screening and diagnosis, treatment and mitigation of IT catheter-tip inflammatory masses; and
- a list of considerations for future research that can better elucidate causal mechanisms, strategies for prevention, and efficacious treatment for masses and reversal of neurologic complications.

The Published Literature

Since the 2002 consensus statement was issued (5), numerous articles have been published that elucidate a causal association between IT opioid medication and catheter-tip granuloma in animal models and under clinical conditions. Several studies and editorial opinions offer new data on the etiology, pathophysiology, signs and symptoms, screening, treatment, and mitigation of catheter-related granulomatous masses.

Preclinical Data, Pathology, and Pathophysiologic Mechanisms

Preclinical data suggest that the majority of inflammatory masses typically contain acute and chronic reactive inflammatory cells derived from the arachnoid layer and/or fibrosis that does not directly impact the neural parenchyma (11). Using histomicroscopic analyses, an IT granuloma appears as an extraparenchymal mass localized at the tip of the catheter delivering IT morphine, hydromorphone, and other IT agents via implantable pumps (4). Recent evidence from serial magnetic resonance images in dogs indicates that while such masses are a buildup of granulation tissue, they do not fit the classic histopathologic definition of an authentic granuloma (12). Histologic assessment of granuloma in humans typically shows both acute and chronic inflammatory processes, as evidenced by the presence of macrophages, neutrophils, and monocytes, often with a necrotic center, but without an infectious process (4,7).

Preclinical Studies in Dogs

Preclinical investigations in sheep and dogs with IT morphine infusions predictably lead to catheter-tip inflammatory masses (2). Catheter granulomas have been causally associated with increasing IT morphine doses and concentrations in beagle dogs (1,11). Masses were observed after 28 days in one beagle dog at 1.5 mg/day (the lowest morphine dose tested); in two beagle dogs at 3 and 9 mg/day; and in all three animals at 12 mg/day. Mass formation did not occur when varying amounts of clonidine (> 0.25 mg/day) was added in an amount of up to 1.5 mg/day of morphine. Groups of adult dogs administered chronic IT infusions of a highly selective, partial, differential, opioid agonist, [D-Pen(2),D-Pen(5)]-enkephalin (DPDPE), displayed prominent hind limb dysfunction that progressed in animals receiving 6 mg/mL of drug over a 28-day interval (13). Minimal neurologic changes were observed in the saline or 3 mg/mL, DPDPE dogs. Granulomas were detected in the IT space proximal to the catheter tip in three of four animals receiving 6 mg/mL and one of four given 3 mg/mL, DPDPE. These large masses showed necrosis and fibrosis combined with chronic inflammatory changes due to infiltration of macrophages, granulocytes, and monocytes. The granulomas contained

mouse, antihuman, macrophages-positive, inflammatory cells that expressed tumor necrosis factor-α. In another animal study, steady-state cerebrospinal fluid (CSF), DPDPE levels were sampled at specified time points following IT bolus (3 mg/mL) and 24 h, DPDPE infusion (3 and 6 mg/mL) with dual IT catheters. CSF DPDPE levels were 18.6 ± 1.0 and 22.6 ± 4.0 μg/mL for 3 and 6 mg/mL infusions, respectively. The authors found that DPDPE appears to produce a concentration, time-dependent IT inflammatory mass (13).

Serial magnetic resonance imaging (MRI) revealed that IT morphine infusions initiated a rapid formation and regression of granuloma formation in dogs receiving morphine infusions (12.5 mg/mL at 40 μL/hour for 10 or 31 days) that was dependent on local concentration (12). The dogs administered morphine displayed MRI enhancement in tissues in the pericatheter region as early as three days with a more pronounced and prominent signal evident by 10 days. Removal of morphine from the infusate decreased the mass volume within seven days. In a separate study, dose vs. concentration as the etiology for IT granuloma formation was evaluated in dogs administered 28-day continuous, fixed-rate, IT infusions (vehicle, 12 mg morphine/day as 12.5 mg/mL at 40 μL/hour, or 1.5 mg/mL at 334 μL/hour [12 mg/day]) (12). The fixed rate infusion of different concentrations produced a dose-dependent increase in granuloma formation. Formation of granuloma was associated with lumbar CSF morphine concentrations of about 40 μg/mL. The incidence of granuloma formation was 100% for dogs receiving 12.5 mg/mL at 40 μL/hour (12 mg/day), 25% (one of four dogs) for animals treated with 12 mg/day at 1.5 mg/mL (334 μL/hour), and zero for the vehicle-treated dogs.

In a safety study to determine the effects of a chronic IT morphine and clonidine infusion in dogs, six groups ($N = 3$ each) of beagle dogs received infusions (40 μL/hour) of saline or 1.5, 3, 6, 9, or 12 mg/day of morphine for 28 days. Four additional groups received morphine at 40 μL/hour (1.5 mg/day) plus clonidine (0.25–1.0 mg/day), or clonidine alone at 100 μg/hour (4.8 mg/day) (1,13). Allodynia was reported shortly after infusion began in dogs given 9 or 12 mg/day of morphine. A concentration-dependent increase in hind limb dysfunction was reported during the course of the infusion. Necropsy showed minimal reactions in saline dogs. A local aseptic IT inflammatory mass formed at the catheter tip in all animals receiving 12 mg/day morphine. All animals exhibiting motor dysfunction had masses, but not all animals with masses showed motor dysfunction. The masses, formed from the dura-arachnoid layer, resulting in significant local tissue compression at the spinal cord. Multifocal collections of neutrophils, monocytes, macrophages, and plasma cells were found in the masses. In other animals, clonidine alone did not cause inflammatory masses, and clonidine combined with morphine decreased the morphine inflammatory reaction. These findings confirm earlier studies suggesting that high levels of IT morphine may cause aseptic IT inflammatory masses (1,11,13). Results in dogs suggest that IT therapy of morphine combined with doses of clonidine infusions greater than 0.25–1.0 mg/day may prevent the formation of granuloma (14) by suppressing the local inflammatory effects of morphine (13).

Preclinical Studies in Sheep

In an early study, three groups of sheep implanted with silicone epidural catheters for 9 or 30 days within the epidural space received morphine ($N = 6$, 100 mg/day, 25 mg/cc), hydromorphine ($N = 6$, 30 mg/day, 10 mg/cc), or saline ($N = 3$) (15). Large granulomatous inflammatory masses compressed the spinal cord with motor deficits. High doses of IT hydromorphone (12 mg/day) for 28–31 days in sheep ($N = 3$) resulted in gaiting deficits and biting behavior, but no inflammatory masses in a sheep model (16). Mild-to-moderate inflammation occurred 5 cm cranial to the catheter tip with doses of 6–9 mg/day. A low dose of 3 mg/day produced no neurotoxicity; spinal histopathologic changes were consistent with those reported in the saline-treated sheep.

From these preclinical studies the panel concludes that high concentrations and high doses of IT morphine delivered via a catheter may cause inflammatory masses in at least two species (dog and sheep). Some studies show that the addition of IT clonidine may suppress or prevent the formulation of granuloma in dogs (11,13,14).

Etiology

Medications Implicated in Inflammatory Masses

Most of the evidence discussed in the 2002 Granuloma Consensus and the 2003 Polyanalgesic Consensus Update pertains to chronic IT morphine sulfate infusion. Recent evidence indicates that certain other opioid infusions also have varying effects on the formation of granulomatous masses (17). Two sets of experiments were performed in dogs to evaluate the analgesic activity (analgesic dose and the maximum tolerated dose) and toxicity of different IT opioid infusions: morphine sulfate, hydromorphone, D/L-methadone, L-methadone, D-methadone, fentanyl, [d-Ala2,N-Me-Phe4,Gly5-ol]-enkephalin (DAMGO), naloxone, or saline (12). Six-hour IT infusions produced a time-dependent increase in thermal escape latency, a test for nociception in rats and mice. Dose-limiting motor dysfunction and sedation, and hypersensitivity were observed at higher concentrations. Full analgesic dose/maximum tolerated dose was achieved as follows: morphine, 0.9/12.0; hydromorphone, 1.0/3.0; D/L-methadone, 2.8/3; L-methadone, 1.0/> 1.0; fentanyl, 0.3/2.0; DAMGO, 0.1/> 2.0; D-methadone,

> 1/> 1; naloxone, > 10/> 10. Continuous IT infusion of the maximum tolerated dose was administered for up to 28 days to determine toxicity and spinal pathology. Analysis showed that 100% intradural granuloma formation occurring after infusion with morphine, hydromorphone, L-methadone, and naloxone. Parenchymal necrosis resulting from D/L- and D-methadone was associated with the N-methyl-D-aspartate antagonist action of the D-isomer. DAMGO produced a mass in only one of three animals. Animals receiving IT saline and IT fentanyl exhibited no granulomas. These results suggest that the formation of IT opioid-induced masses does not depend exclusively on opioid receptor activation. Rather, opioids administered IT at equianalgesic doses pose varying risks for granuloma formation.

Concentration vs. Dose

There is compelling evidence to support the contention that the development of inflammatory masses is associated with both morphine concentration and total daily dosage (17). More than 90 cases of inflammatory masses located at the tips of IT drug administration catheters, primarily associated with morphine sulfate infusion, have been reported since 1992 (2). The incidence of these inflammatory masses reportedly increases with the length of time of IT drug treatment, ranging between 0.4% after two years of treatment and 1.16% after six years of treatment. A morphine sulfate study conducted in sheep resulted in catheter-tip masses in two of three animals that received the highest doses (12 or 18 mg/day). Despite the association between higher doses and concentrations of morphine and granulomas in dogs, these infusions in these animal models are of short duration. The formation of granulomas in humans is less predictable than in sheep and dog models. The data from animal models fail to clarify whether there is a safe (ie, non-granuloma-inciting) IT dosage in humans of any IT analgesics (2). However, these data do support the notion that concentration and dose of all opioids, except fentanyl, are important in the etiology of inflammatory masses at the tip of catheters of implantable drug delivery systems.

The Clinical Data

Etiology

As stated above, the administration of high-dose IT opioid medications into the IT space can lead to the formation of granulomatous mass, resulting in decreased pain relief and neurologic sequelae (18,19). Masses may be either asymptomatic or symptomatic resulting in varying levels of neurologic injury, including severe neurologic sequelae such as paralysis, paresis, and spasticity. Although several medications have been associated with granulomatous masses, morphine and increasingly hydromorphone infusions are implicated in the majority of cases.

Patients typically experience a delay in the onset of symptoms following implantation. Subtle sensory changes precede neurologic changes. Patient breakthrough pain (ie, increased and altered chronic pain) has been clinically interpreted as "tolerance" to the medications infused and subsequently treated by caregivers by increasing pump rates (20); however, it is now known that this breakthrough pain to the infusion of analgesics may be a sign of impending granuloma formation.

Medications Implicated in Inflammatory Masses

Catheter-tip inflammatory masses have been reported in human patients receiving IT opioid medications, alone or combined with other agents. As noted previously, although intraspinal medications were used originally to treat patients with limited life expectancies, these therapies increasingly are being used to treat nonmalignant pain. Longer-term treatment has resulted in new complications that occur as a result of the relatively longer life expectancy of patients with benign sources of pain (5,21).

As previously stated, morphine infusion is causally related to the development of IT granuloma. While morphine is implicated in most catheter-associated IT granulomas, IT baclofen, administered alone, has been associated with the formation of granulomatous masses in one reported case (22). A 57-year-old woman who developed quadriplegia was unresponsive to oral doses of baclofen that were titrated to 80 mg/day to manage severe spasms. Her response improved after undergoing implantation of an IT pump delivering baclofen at an initial dose of 200 µg/day. The patient's spasms were controlled and remained stable for a duration of 38 months, while the dosage was gradually increased to a level of 400 µg/day. After 38 months, her spasms started to increase and remained poorly managed, in spite of repeated dose escalations. Contrast dye, injected via the pump's side port into the IT space, and postmyelographic computerized tomography revealed that catheter displacement and/or fracture were not responsible for the increase in the patient's baclofen dose requirements. These studies did reveal the presence of a catheter tip-associated granuloma. This case is rare but noteworthy because it is the first time that a catheter-tip granuloma, in a patient receiving IT baclofen only, has been reported in the literature.

Catheter Position and Granuloma

Several data-driven reports and editorial opinion, including the published guidelines of the 2002 Polyanalgesia Consensus Conference (5), have called for IT catheter placement to be below the conus medullaris to prevent the severe and sometimes permanent neurologic sequelae associated with catheter-tip inflammatory masses (23). However, evidence from case reports suggests that implantation of IT catheters

tips located at or below the conus medullaris does not necessarily remove all risk of neurologic injury that can result from inflammatory granulomas. Shields et al. presented a unique case of an extramedullary IT granuloma that formed and was adherent to the conus medullaris in a patient with an IT catheter below the conus (24). The patient was a 47-year-old man with a history of traumatic L1 compression fracture who had had five lumbar and thoracic surgeries with instrumentation over a period of 15 years. The patient subsequently received implantation of an IT drug deliver system (SynchroMed®, Medtronic Inc.) that provided adequate pain control for five years (IT dose of 5 mg of morphine per day for 12–18 months prior to presentation). The patient was admitted to the hospital for severe, unremitting neuropathic pain and subsequently underwent a neurologic examination. The patient was diagnosed with hypesthesia (without allodynia) from L2-S1 in the left lower extremity. A diagnosis of cauda equina syndrome was entertained. A T2-weighted hyperintense, T1-weighted hypointense, IT, 7-mm ovoid, extramedullary lesion, consistent with a catheter-tip granuloma, was confirmed by lumbar spine MRI. The mass was located to the left of and lateral to the conus medullaris with the conus displaced to the right. The conus appeared as a central abnormal T2 hyperintensity signal, radiating craniocaudally for one vertebral level and suggestive of cord edema. The patient eventually recovered following surgical explantation and implantation of an IT drug delivery system in which the catheter penetrated the dura at L3 with a caudal course to the level of L5.

In another unique case study, an intradural extra-axial mass was detected in the sacral region in a 71-year-old white male patient implanted with an IT pump for opioid treatment of failed back surgery syndrome (23). The patient experienced some postoperative pain relief but presented with progressive saddle anesthesia and bowel/bladder incontinence three years after undergoing implantation. He had achieved adequate pain control with hydromorphone being administered at a rate of 110 mg/day at a concentration of 400 mg/cc. A space occupying lesion associated with the catheter tip was confirmed by MRI. The patient received an emergent second level complete sacral laminectomy with partial resection of an intradural, extra-axial mass that was identified as a sterile inflammatory mass on histologic examination. The IT catheter was removed, but neurologic function was not restored after the patient's discharge. These examples reinforce the need for physicians to be vigilant in diagnosing potential catheter-tip granulomas in patients implanted with IT drug pumps for pain therapy in the lumbar and sacral regions.

Clinical Sequelae: Signs and Symptoms

One of the clinical clues to the presence of a mass includes increased pain with a corresponding increased requirement for more IT analgesic medication (12). Patients may present with a motor or sensory dysfunction prior to being diagnosed with a mass. In an intergroup analysis of two study cohorts, patients with catheter-associated granulomas were younger and were receiving a higher morphine dose than patients without masses. The differences in the demographic and treatment variables between these two patient populations were statistically significant ($p = 0.05$) (25).

In one series of case reports, the average catheter infusion time associated with formation of a mass was 27 days (19). In another clinical investigation, patients with catheter-associated granulomas developed symptoms several months after the initiation of IT therapy, and complained of increased pain prior to the presentation of signs and symptoms of neurologic injury (21).

Differential Diagnosis of Granulomas

The differential diagnosis of IT granulomatous masses must include other neurologic sequellae of intraspinal delivery of medications including direct trauma to the spinal cord of the catheter itself, direct toxicity of the agent infused and other spinal tissue masses, including metastatic disease. However, IT masses can occur from rather rare sources. In a rare case study, a 67-year-old female patient with a totally implanted drug delivery system for IT delivery for failed back syndrome presented with sensory complaints and back pain suggestive of a spinal cord tumor (26). An MRI scan showed a mass impinging on the thoracic spinal cord that, on surgical operation and chemical analysis, proved to be a mass containing bupivacaine precipitate situated at the tip of the catheter.

Screening and Detection

Diagnostic clues to the presence of a mass, as stated previously, include reduced analgesic effects of opioid medications concomitant with evolving neurologic signs and symptoms. A mass that is detected before it compresses the spinal cord, or before it evokes serious neurologic deficits sometimes can be treated using minimally invasive procedures rather than open surgery to remove the mass. Discontinuing the opioid/nonopioid therapy administered through the affected catheter may lead to a shrinkage or disappearance of the mass within a period of two to five months. This consensus panel, as previous panels have, recommends that prompt attention and follow-up measures be performed to detect masses in patients requiring high-dose intraspinal opioid therapy and those who receive medications or admixtures that are not approved for IT use (5,27). The severity and possibly incidence of inflammatory masses may be prevented or mitigated through the use of minimally invasive practices. The preventive practices advocated in the 2002 Consensus Report include administering the lowest daily IT opioid dose as possible for as long a time

as possible before going to higher doses; placing the catheter in the lumbar thecal sac; and closely monitoring patients for an extra-axial mass or catheter malfunction (5).

These recommendations are supported by the findings of an earlier review of 41 cases of patients reported to have IT drug catheter-related inflammatory mass lesions (27). The purpose of the review was to evaluate hypotheses regarding the etiology of the lesions. The masses were found to be located in the thoracic region of most patients in the study. The case studies, including 16 from the published literature and 25 from unpublished reports, were compiled through November 30, 2000. The patients all had chronic pain. In 39 of 41 cases, patients had received IT morphine or hydromorphone, either alone or mixed with other medications, for a mean duration of 24.5 months. Surgical specimens of the masses revealed noninfectious chronic inflammation, granuloma formation, and fibrosis or necrosis. These results provide further evidence for a causal association between relatively high-concentration or high-dose IT opioid medications and IT catheter-tip mass lesions (27).

Evidence from a comparative case study suggests that patients receiving long-term IT opioid therapy should undergo periodic radiographic surveillance to detect for the formation of catheter-associated IT masses, thereby avoiding or minimizing the risk for subsequent neurologic damage (25). Radiocontrast myelography and computed tomography (CT) scanning were performed to screen for catheter-associated masses in seven patients receiving IT analgesic medications for chronic intractable pain. IT masses associated with the tip of the drug infusion catheter were observed in three of seven patients following 118 months of treatment. One patient reported exacerbation of neuropathic pain, and two patients were asymptomatic at the time the masses were observed. The mean duration of treatment prior to diagnosis of the catheter-associated mass was 19.6 month, with a range of 16–25 months. The IT mass shrunk in one asymptomatic patient after treatment was discontinued. In the second asymptomatic patient, the mass remained stable for more than one year of ongoing therapy after hydromorphone was substituted for morphine. No further neurologic dysfunction or injury was observed in either asymptomatic patient after therapy was modified (25).

While the majority of granulomatous masses are sterile, bacterial infection from both aerobic and anaerobic organisms may also be a cause of inflammatory masses. Masses should be routinely evaluated for the existence of organisms even years after placement of the catheter (21). In one case study, a patient presented with neurologic symptoms of pain and dysaesthesiae in the lower back and thigh (28). Paresis of the iliopsoas muscle also was evident. MRI detected an intradural, extramedullary mass at the IT catheter tip. The mass that enhanced with gadolinium was located at the level of L1. The patient had undergone implantation of an IT catheter 11 years earlier for analgesic infusion to treat phantom pain following amputation of the right arm. Following removal of the catheter, the patient's pain disappeared and his neurologic function was completely restored. Analysis of cultures of lumbar CSF and the catheter tip showed coagulase-negative staphylococcus. The patient was treated with an antibiotic regimen of cephalosporins for six weeks. Miele suggests that the risk of bacterial infection is a potentially serious complication of IT catheter-associated granulomas (21).

Patient Risk Management

Inflammatory masses reportedly occur in approximately 0.1% in a population of IT pump patients, but this statistic may be an underestimation and the true incidence may actually be higher (12). Risk management for IT granuloma should include written informed consent of its risk occurring at any time during infusion therapy. Patients not only carry a risk of granuloma, but if a granuloma is found and therapy is suddenly withdrawn, patients do have the risk of developing serious opioid withdrawal syndrome when opioids have been infused, and if they are receiving clonidine and/or baclofen, the sudden withdrawal of these agents can lead to serious complications, including death. Physician hypervigilism when monitoring patients after initiation of therapy, dose change, or drug change is a critical component of risk management.

Screening and Diagnosis

T1- and T2-weighted MRI scans, with and without gadolinium, that are taken at the level of the catheter tip are considered safe and the recommended method of choice for diagnosing granulomas in most patients. MRI scans of patients with granuloma reveal inflammatory mass lesions that seem relatively isointense in relation to the spinal cord on T1-weighted images (20). Scans that are hyperintense with a hypointense rim (or ring enhancement) appearing on T2-weighted images may be indicative of spinal cord compression or combined compression and local inflammation from the granuloma. Another valuable method that can be used to detect IT granulomas is CT myelogram after an injection of nonionic radio contrast material through the pump side port to reveal granulomas and/or obstructions at the catheter tip. Additionally, serial neurologic examinations should be undertaken during pump refill visits to identify new neurologic deficits raising the suspicion of masses during early stages of development. MRI scans are then warranted in cases where abnormalities are observed (19,21).

While MRI to screen for granulomas remains the preferred procedure for detecting intraspinal masses, MRI is not cost-effective or readily available for routine use due to the overall low incidence of catheter tip-associated granulomas (21). However, in a surveillance study published in 2004,

MRI or CT imaging was used to screen for IT granulomas in 208 patients receiving IT infusions for a duration of 34 weeks (19). While 80% of all patients were asymptomatic, a significant mass was observed in six patients (3%). Five of these six patients were asymptomatic. The patients with masses underwent percutaneous catheter revisions by pulling the catheter tip out of the mass without complications. No significant difference in average catheter infusion time was found between patients with or without granulomas. No specific medications or concentrations were associated with the presence of granulomas in this study (19). Yet, as noted, other evidence suggests that the formation of granulomatous masses are related to the use of higher doses of morphine, the most commonly used IT opioid therapy (21).

If masses are found, physicians should be attentive to factors such as the precise location of the mass in relation to the catheter tip (with or without tracking along the catheter), type of implant used, length of time of the implant, daily dose in milligrams and in volume (as an indicator of particle or volume effect), concentration of medication used, histopathologic analyses, if any (eg, giant cells, eosinophils, inflammatory processes), cultures (fungal, aerobic, anaerobic), and complications (eg, infection, tumors) (20).

Treatment/intervention

Because of preclinical evidence of the granuloma sparing effect of clonidine (14), some physicians advise routinely combining clonidine as an adjunct with morphine or other opioid analgesics in IT infusion systems to inhibit granuloma formation. However, preliminary evidence suggests that clonidine may not provide the same granuloma-inhibiting effect in humans as reported in large animal models. In a case report of a woman receiving an IT infusion for complex regional pain syndrome, type I, of her left lower extremity, chronic infusion of IT clonidine with morphine failed to prevent granuloma development (2). The results of this study, based on this one patient, suggest that clonidine may not clinically protect against morphine-induced granuloma. The authors point out that the rate of increase in morphine (reaching a maximum of 15 mg/day, 17.5 mg/mL for 35 months) was not atypically large for either a dose or concentration (2,29). In another case study (18), a 47-year-old male patient who had received a stable IT morphine infusion, 8 mg, and clonidine, 40 μg/day, suddenly required escalating doses of morphine for greater pain control in 2001. In May 2002, the patient was switched to hydromorphone and clonidine, 12.5 mg/mL and 150 μg/mL, respectively, infusing at 0.3 mL/day. When the patient presented with progressive T9 paraparesis in October 2003, a CT scan with myelogram revealed total blockage of contrast flow at T8–T9. An extramedullary mass compressing the spinal cord was discovered through surgical exploration. The mass was surgically removed four weeks later, leading to an improvement in neurologic function. The granuloma that developed in this case also challenges the notion that IT clonidine has a sparing effect on the formation of granuloma in patients receiving high-dose IT opioids. The authors warn that anesthesiologists in particular should be aware of the potentially serious complications associated with IT pump therapy, because anesthesiologists implant the majority of IT pumps and catheters.

Data on causal associations between either sufentanil and fentanyl and inflammatory masses are limited, but granulomas have not been reported in patients receiving IT sufentanil. In a study of 92 patients undergoing opioid treatment for pain, one patient was diagnosed with an inflammatory mass while receiving IT fentanyl. However, in this report, no information was disclosed regarding the patient's exposure to other IT analgesics such as morphine prior to receiving IT fentanyl (11). As stated above, fentanyl and sufentanil are not associated with IT granuloma formation in preclinical studies and hypothetically may pose a decreased clinical risk of developing inflammatory masses because of the higher lipophilic characteristics of these two agents. Compared to morphine, fentanyl and sufentanil have a higher potency that permits patients to receive lower doses over time. Safety studies on chronic and continuous IT delivery of opioid medications other than morphine need to be undertaken in large animal models (eg, beagle or sheep) before their increased safety is proven (11).

2007 Panel Consensus Recommendations for IT Granuloma Diagnosis, Treatment, and Prevention Algorithm

The evidence for effective treatment of granuloma has remained fairly consistent since the publication of the Expert Consensus Statement on the management of IT catheter-tip inflammatory masses in 2002 (5). The first line of treatment for patients with minimal symptoms is to discontinue intraspinal infusion, usually an opioid medication, change to saline, and/or empty the drug reservoir. In several reported cases, the mass either shrunk or disappeared within two to five months following this intervention. The present panel recommends withdrawing the catheter tip from the mass by about 2 cm is effective in preventing growth of the mass. In fact, many of these masses do disappear once the catheter tip is removed from them. To prevent formation of a new mass at the new location of the catheter tip, the panel recommends decreasing both concentration and dose of the infused analgesics or changing to fentanyl or sufentanil. In the presence of significant or worsening neurologic signs and symptoms associated with the mass, the panel recommends that if these signs and symptoms worsen, neurosurgical excision/removal of the mass may be necessary.

Empirical and Theoretical Considerations Regarding Causation of Granuloma

Role of Catheters

All of the survey respondents agreed that there is no evidence to establish an association between any particular catheter type or material and granuloma formation. Granulomas have not been described in association with other catheter types made of silastic material such as shunts, leaving flow characteristics, concentration of the agent, the agent, and dose of the agent as the likely culprits for granuloma formation. Characteristics of the catheter that are typically observed when granulomas occur are not always consistent, but include stiffness of the tip, difficulty of aspiration of CSF, flow restriction, and obstruction (occlusion) of flow. The pathology at the catheter tip may account for some of these characteristics and does involve a gradual accumulation of granulocytes, macrophages, and neutrophils. This collection of inflammatory cells grows over time to create a space-occupying lesion adjacent to the pia/arachnoid layer. A combination of high concentration and/or dose of the agent infused and supposed patient susceptibility may also affect catheter functioning.

Most panelists agreed that granulomas do not necessarily develop slowly following catheter insertion. In animal models, at least, granulomas develop quite rapidly at high concentrations of drug. Most panelists expressed that they had not experienced a predictable time course for granuloma formation in relation to each drug involved in this complication. Deer et al. published data showing that granulomas do develop 24 months on average in susceptible patients receiving either IT morphine or hydromorphone (19). The panelists, in general felt that, at this juncture, it is not possible to determine when a particular granuloma will develop in a particular patient because of the temporal variation. This variability was attributed to several factors, including type of drug (ie, opioid medication), flow rate of the drug, CSF flow rate of the patient, amount of CSF that any one patient has, position of the catheter, etc.

While no quantifiable data exist on the issue of time course to granuloma formation, clinical experience reveals that some patients implanted with catheters for more than 15 years never develop a granuloma. Because of this, it is supposed that only "susceptible" patients develop granulomas. In other patients, however, granulomas do form within the first year of initiating therapy or even more rapidly following a dose increase to a high concentration of opioid in a previously, seemingly disease free patient and well-functioning pump.

Flow Rate vs. Concentration

The consensus of the panelists and based on the most robust etiological evidence was that granulomas are most likely a function of drug dose, drug concentration, a combination of the two, the way the drug is delivered, and/or CSF flow rate. However, the panelists were nearly evenly split in their positions on whether granuloma formation is related to dose, concentration, and/or flow rate. Concentration and dose, generally, was viewed as more critical than flow by the panelists, although the concentration of any agent at the catheter tip where granulomas form may be a function of both drug concentration and flow rate; specifically, granuloma formation is associated specifically with a higher concentration of drug at a low infusion rate and a low cerebral spinal fluid flow rate (30,31).

Most panelists thought that there does exist a difference, theoretically at least, in the rate of granuloma formation caused by bolus infusions vs. continuous infusions through the catheter. Although there are no studies to prove this and the evidence is more intuitive than not, the panelists felt that specific area of the spinal cord receives more drug at lower infusion rates (continuous) and low CSF flow rates than is the case seen with bolus injections, hence the resumed granuloma sparing effect of bolus injections. However, the panel did also feel that frequent *repeated* boluses of high-concentration opioid medications might potentially lead to a similar proinflammatory effect as continuous infusions. In one anecdotal case reported among the panel, turbulent flow induced by a patient controlled bolus dose of 0.5 mg up to four times daily in a cancer patient failed to stop granuloma formation at six months.

Compounding

Based on evidence in the literature, the panelists did not think that compounding plays a role in the development of granulomas. As stated above, the preponderance of information is that granuloma formation is a concentration-dose flow-rate-dependent phenomenon, not a compounding pharmacy-dependent phenomenon. However, having all agreed on this, the panelists did acknowledge that, because quality control is extremely important when manufacturing or compounding medications, especially IT medications, standardized compounding, following U.S. Pharmacopeia (32) and/or American Society of Health Care Pharmacists guidelines (33) should be used to prevent other untoward complications. The panelists who were surveyed obtained their compounded medications primarily from independent pharmacies, including a dedicated outsourced compounding pharmacy. It was proposed that physicians review the published drug queries from each compounding company prior to administering a drug. The panelists felt that in the future, retrospective evaluation of granuloma data collected from individual practices and compiled for input into a registry may serve to identify any factors that do link compounding pharmacies to granuloma occurrence and/or other neurologic sequellae such as direct drug toxicities.

Detection and Diagnosis

Clinical Assessment/Patient History/Surveillance

If a granuloma is suspected, the panel's consensus recommendation is to complete a careful patient history, conduct a careful neurologic physical examination, and perform an MRI (T1-weighted image with gadolinium) and/or CT myelogram to rule in or rule out granuloma. The panelists felt that myelography could be performed through the side port of the pump as previously stated, when feasible. The following questions that should be asked during neurologic assessment of patients include:

1. Are you experiencing any "new" neurologic complaints . . . *such as new segmental complaints* (segmental to the catheter tip)? Segmental complaints may include numbness/allodynia/hyperalgesia over the trunk or extremity.
2. Are you experiencing any "new" bowel or bladder complaints such as urinary hesitancy/frequency or inability to defecate?
3. Are you having new sexual dysfunction such as inability to achieve organism in females, inability to have or sustain an erection and/or ejaculate in males?
4. Are you having frequent new falls?
5. Are your legs or arms/hands weak?

Neurologic examination must include a careful examination for the following:

- segmental allodynia/hyperalgesia/numbness at the receptive field of the spinal cord area that the catheter tip lies
- DTR's of the extremities
- muscle examination for strength/paresis and fasciculations
- examination for clonus
- examination for cremasteric reflex/anal reflex in patients that granuloma is highly expected

The panelists differed in their opinions on how frequent surveillance should be conducted. Most respondents thought that surveillance was warranted only with the presentation of symptoms such as neurologic status changes and/or analgesic changes. Others felt that patients should be image screened at least every six months for granuloma if they are at high risk for its formation (high-dose/high-concentration/low-infusion rates). Finally, the panelists agreed that because the rate of granuloma formation is low at one out of every 200 patients (0.5%), patients should receive clinical surveillance with granuloma focused questions and focused neurologic examinations, at least annually, but preferably every three to four months. Asymptomatic low risk patients (low-dose/low-concentration/higher-flow rates) may undergo surveillance, at the very least, during a routine diagnostic work-up prior to a battery replacement (ie, every six to seven years) and every 3.5 years during mid-cycle.

Markers for Granuloma

Possible markers proposed for identifying granuloma formation include pain, neurologic change, and CSF analysis. Periodic assays for CSF protein elevation are possible by aspirating CSF from the pump's catheter side port or directly, though not often feasible, by spinal tap. The panelists felt that each lumbar puncture performed for this purpose does create a risk for the introduction of bacteria into the CSF where the implanted system is located.

Some of the panelists have identified an occasional "black colored precipitate" from the tip of implanted IT catheters when aspirating catheter contents and felt that this material presaged granuloma formation. The panelists felt that this black colored material should be looked for when aspirating CSF and catheter contents from the side port of the pump and advised that, if found, the infusate should be changed to lower dose/concentration or the use of different drug such as fentanyl. Analytical studies performed by one of the panelists, though not published, indicate that this blackish precipitate may be a collection of neutrophils, granulocytes, and macrophages (R. Levy, unpublished data).

Prevention and Treatment of the Mass and Management of the Drug Infusion System

Prevention of Catheter-Tip Masses and Mitigation of Neurologic Sequelae

The panelists felt that there are several prophylactic measures that might be taken to prevent granulomas. These prophylactic measures include using bolus dosing instead of slow continuous infusion, minimizing concentration/dose of the agent infused (eg, especially of morphine sulfate and hydromorphone) to the daily dose limits proposed by the Consensus Panel, avoiding ultra slow flow rates and/or delivering the drug into a larger CSF space over the spinal cord such as T7–T10. The panelists recommend that agents infused via the pump into the thecal space should be within the recommendations stated in the Polyanalgesic Conference 2007 recommendations. All of the panelists agreed that limiting concentration and dose was far more important to safety than strategies that might be used to decrease refill times by increasing concentrations (Table 3). In addition, use of the nonopioid agent clonidine and the opioid, fentanyl, based on animal data, might be helpful in preventing tip granuloma with the caveat that there are known reports of patients developing granulomas with IT clonidine and fentanyl.

Several of the panelists expressed the view that there was insufficient information concerning the spacial location of the catheter tip, because there is evidence in the literature that suggests neurologically significant tip granulomas grow wherever the catheter tip is placed. Some panelists, citing their own clinical experience, suggested

TABLE 3. Concentrations and Doses of IT Agents Recommended by the Polyanalgesic Consensus Panelists 2007

Drug	Maximum concentration	Maximum dose/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	1.0 mg
Ziconotide	100 μg/mL	19.2 μg (Elan recommendations)

that dorsally placed catheters were associated with less granuloma formation when compared to ventrally placed catheters and that when these granulomas did form in the dorsal CSF space they were easier to manage with less side-effects. These panelists who felt that dorsally placed catheters would lie in larger CSF spaces than when place in ventral spaces, thereby creating a situation where drug infused into the space, would have a greater chance of being diluted. This experience was not shared universally by all of the panelists. It was noted by all that catheter-tip granulomas have been known to form at all levels of the IT space; however, those that do form at catheter-tip locations that are placed either away from the spinal cord or in spaces that have greater CSF area than others are usually less neurologically significant than those near or on the spinal cord. Specific IT locations that were suggested for catheter-tip placement included the dorsal CSF space, at L1–L2, or at T7–T10.

It also was agreed by all that the catheter tip could be positioned below the cord in the lumbar IT space as recommended by the Consensus Conference 2002, but, most likely, efficacy will be lost, especially if lipophilic agents are used. When lipophilic agents are used very little medication diffuses far from the catheter tip therefore when contemplating use of lipohilic agents, the catheter tip should be placed as close to the spinal cord segment processing the patient's pain as possible.

Conclusions and Recommendations

The 2007 Expert Consensus has developed a set of recommendations regarding diagnosis and management of tip granuloma on the basis of 1) evidence-based trends gleaned primarily from the published literature data (from physiochemical, animal, and clinical studies); and 2) expert consensus opinion that emerged during the conference through clinically informed discussion and survey responses of interdisciplinary practitioners who perform IT analgesic pain medicine. The recommendations, presented above and summarized in Table 4, are an integrated summary of the most clinically relevant findings drawn from these two distinct, but overlapping, sources. It should be emphasized that the recommendations published here were derived from consensus based on expert clinical experience and a complete review of relevant literature. Consensus in no way implies complete agreement of all of the panelists and there was dissent. As an example, the panelists, after much discussion, recommended a 60% reduction from previous recommendations for the maximum allowable dose of intrathecal hydromorphone. There was much discussion and debate over this recommended reduction in maximum allowable dose, however, by consensus of opinion, the majority of the panelists felt that this reduction was necessary based on preclinical and clinical experience with the agent as it pertains to the development of IT granuloma.

The recommendations are intended to serve as suggestions to clinic practice rather than finalized rules of clinical behavior. Due to the rapid changes occurring in this field, physicians and other clinicians providing administration of IT analgesic medications are advised to use their own clinical judgment, experience, and expertise in accepting, declining, or modifying any of these recommendations.

Etiology

Intrathecal granulomas are not associated with known infectious agents or catheter material or type but are causally associated with:

- high dose/concentration (particularly concentration) of IT agents infused
- local concentration effect of the infusate delivered over a long period of time
- a combination of high drug concentration and slow CSF flow rate
- all analgesic medications used intrathecally, except for sufentanil and ziconotide. Fentanyl appears to be somewhat safer than the more hydrophilic agents (particularly morphine, hydromorphone)
- baclofen infusion

Pathophysiology and Clinical Sequelae

General Characteristics

1. Early granulomas are not always recognizable but may be associated with increased pain, new pain, or some segmental neurologic change.

TABLE 4. 2007 Recommendations: Diagnosis, Treatment, and Prevention of Catheter-Tip Granuloma Formation

Prevention
1. Minimize concentrations and doses of intrathecal (IT) agents, especially of morphine sulfate and hydromorphone.
2. Avoid ultra-slow flow rates.
3. Refill pumps more often (eg, every one to two months) to keep concentration low.
4. Add clonidine to single opioid or nonopioid analgesic combination.
5. Switch to fentanyl or sufentanil alone or combined with nonopioid medications if concerned about granuloma formation.

Screening/detection clinical assessment/patient history/surveillance
1. Take patient history and perform physical examinations on patients with IT therapy often. Patients of low risk should receive surveillance, at least annually, but preferably every three to four months. Patients at high risk (patients with high doses/high concentrations of IT analgesics/antispasmodics) should have examinations and even screening imaging more often.
2. If patient complains of insufficient analgesia, sudden loss of analgesia, onset of new pain, or if neurologic signs and symptoms including decrease in DTR's or clonus have appeared, perform a magnetic resonance imaging (MRI) (T1-weighted MRI with gadolinium) or computed tomography myelogram.
3. If imaging is negative and symptoms persist, change clinical direction by increasing the dose, changing the agent infused, adding another synergistic analgesic, or moving the catheter.
4. If a mass is confirmed move the catheter out of the granuloma (continue IT therapy at lower doses/concentrations or change the drug) or replace the catheter, and resume systemic analgesics.

Treatment
1. If no neurologic impairment, try moving the catheter down 2–3 cm. Change drug concentration/dose down and or change to safer medication such as fentanyl/ziconotide.
2. If symptoms persist, in spite of moving catheter, quickly wean patient off of IT opiates, remove drug from pump, and fill pump with saline. Be careful of withdrawal signs and symptoms and treat, especially in patients with baclofen and/or clonidine.
3. If symptoms decrease after pulling catheter out of mass, perform scan again within six months.
4. If a small granuloma is detected by MRI at follow-up after pulling catheter back, weigh advantages of catheter adjustment vs. a catheter explantation.
5. If granuloma causes spinal cord compression and/or neurologic signs or symptoms persist, removal is recommended.

2. Tip granulomas have been reported within most locations within the thecal sac, including the cervical, thoracic, lumbar, and sacral spaces.
3. Because most catheter tips are place within the thoracic thecal sac, most granulomas have been reported to exist between T7 and T12.
4. Gradual accumulation of inflammatory cells (granulocytes, macrophages, monocytes, neutrophils, plasma cells) grows to form inflammatory masses.
5. Aerobic/anaerobic bacterial infection rare, but may be present.
6. Significant increase in cisternal CSF protein and white blood cell count present.
7. Black colored precipitous material at the tip some catheters may be medication precipitate and/or neutrophils, granulocytes, and macrophages, presaging the existence of a granuloma.

Characteristics of the Catheters With Granulomas

- stiffness of the tip
- difficulty aspirating CSF
- obstruction (occlusion) to flow may be noted
- there is flow restriction

Timeline to Development of Tip Granulomas

- months or years to develop
- shorter periods of only 27 days of catheter infusion time have been reported

Appendices

Appendix I: IT Granuloma Survey Questions

1. What is the "black stuff" that is found at tip of catheters?
2. What is the maximum concentration of morphine that should be used intraspinally?
3. Is there any particular catheter type associated with granuloma formation?
4. Can pathology and myelogram results be correlated?
5. At what point do you intervene when patient is losing analgesic effect, you cannot aspirate but myelogram study is clean?
6. Should we critically look at morphine and consider moving it from first line agent?
7. What are the characteristics of catheter when granulomas occur?
8. Is there a predictable time course for granuloma formation associated with each drug that is reported to cause this problem?
9. How often should we do surveillance CTs? Two month? Three month?
10. Do you think granuloma formation is related more to flow rate or drug concentration?
11. Is there a difference in granuloma formation when you give bolus infusions vs. continuous infusions through the catheter?
12. Is it a continuity issue—that is, granulomas very slowly develop after catheters are put in?

13. Is there a marker we can identify for granuloma formation?
14. Should we refill pumps more often to decrease risk for granuloma (eg, every two months)?
15. Are granulomas more or less common with dorsal placement?
16. Where have you seen granuloma formation in your patients (what area of spinal cord)?
17. What is the optimal screening protocol and treatment protocol for granulomas?
18. What is the trip point to get a myelogram to look for a granuloma?
19. When you suspect a granuloma, what do you do?
20. Is there anything prophylactic that we can do to prevent granulomas?
21. Where should we put the tip of the catheter to reduce risk for granuloma formation?
22. Who is compounding the medications when granulomas occur?
23. What is best why to do surveillance—CT, MRI, myelogram, nuclear medicine study?
24. How frequently should surveillance be done?

Appendix II: Sample Informed Consent Form: Informed Consent for Intrathecal Drug Therapy

1. I understand that the administration of intrathecal drug therapy may be associated with certain side-effects and/or adverse effects. The most serious side-effects include, but are not limited to: respiratory depression, myoclonus, meningitis, coma, withdrawal syndrome from my intrathecally administered medications should the pump not work properly or if there is an error in programming my intrathecal drug delivery system, hospitalization and even death. Other side-effects include, but are not limited to: itching, urinary retention, constipation, nausea, vomiting, dizziness, anxiety, depression, edema, and alterations in hormone levels and bone density.
2. It is my responsibility to refrain from driving or participate in any other possibly hazardous activity if I am experiencing any side-effects such as drowsiness or decreased ability to concentrate.
3. I understand that there is a risk of developing a granuloma at the tip of my intrathecal catheter, a noninfectious or infectious mass at the tip of the implanted catheter. Granuloma formation is associated with the delivery of intraspinal medications, especially at higher doses and higher concentrations of the opioid medication used. Complications of an intrathecal granuloma include, but are not limited to: new neurologic symptoms such as pain, weakness, bladder or bowel dysfunction, paresis, paralysis, sexual dysfunctions and may require surgical removal of the granuloma, equipment or both.
4. I have been informed that the following medications are not Food and Drug Administration approved for administration by intrathecal therapy: hydromorphone (Dilaudid), fentanyl, methadone, bupivicaine, and clonidine. However, there is data to support their intrathecal uses in the treatment of severe intractable pain that has not responded to conventional measures, and might be used by your doctor as part of your intrathecal therapy.
5. I understand that the following risks that may result from a pump refill procedure: failure to refill the pump for whatever reason, infection of skin over the pump, pump pocket, or implanted pump system, meningitis, inadvertent withdrawal or overdose of medication due to either injection of the medication into the pump pocket, error in programming the pump, or failure of the pump itself. I understand that these complications are serious and that I might require resuscitation or hospitalization, be seriously ill, or that I might have permanent neurologic damage or die from any and all of these complications.

My signature below indicates that I have read and understand the above. I have had an opportunity to ask questions and feel satisfied with the explanation received.

Patient name (Print)	Signature	Date
Witness (Print)	Signature	Date

Acknowledgments

The authors wish to thank Elan Pharmaceuticals for their financial support of the 2007 Polyanalgesia Conference, MedXcel for their provision of logistics for the meeting and Continuing Medical Education Interface Associates for their assistance in medical writing of this document.

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