Management of Intrathecal Catheter-Tip Inflammatory Masses: A Consensus Statement

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ABSTRACT

Objectives. In a companion article, we synthesized current clinical and preclinical data to formulate hypotheses about the etiology of drug administration catheter-tip inflammatory masses. In this article, we communicate our recommendations for the detection, treatment, mitigation, and prevention of such masses.

Methods. We reviewed published and unpublished case reports and our own experiences to find methods to diagnose and treat catheter-tip inflammatory masses in a manner that minimized adverse neurological sequelae. We also formulated hypotheses about theoretical ways to mitigate, and possibly, prevent the formation of such masses.

Results. Human cases have occurred only in patients with chronic pain who received intrathecal opioid drugs, alone or mixed with other drugs, or in patients who received agents that were not labeled for long-term intrathecal use. Most patients had noncancer pain owing to their large representation among the population with implanted pumps. Such patients also had a longer life expectancy and exposure to intrathecal drugs, and they received higher daily doses than patients with cancer pain. Clues to diagnosis included the loss of analgesic drug effects accompanied by new, gradually progressive neurological symptoms and signs. When a mass was diagnosed before it filled the spinal canal or before it caused severe neurological symptoms, open surgery to remove the mass often was not required. Anecdotal reports and the authors’ experiences suggest that cessation of drug administration through the affected catheter was followed by shrinkage or disappearance of the mass over a period of 2-5 months.

Conclusions. Attentive follow-up and maintenance of an index of suspicion should permit timely diagnosis, minimally invasive treatment, and avoidance of neurological injury from catheter-tip inflammatory masses. Whenever it is feasible, positioning the catheter in the lumbar thecal sac and/or keeping the daily intrathecal opioid dose as low as possible for as long possible may mitigate the seriousness, and perhaps, reduce the incidence of such inflammatory masses.

Key Words. Complications; Granuloma; Inflammatory Mass; Intraspinal Catheter; Intrathecal Drugs; Morphine; Pain

Introduction

The first case of an inflammatory mass at the tip of an intrathecal morphine infusion catheter to treat
chronic intractable pain was reported by North et al. in 1991 [1]. More recently, Coffey and Burchiel analyzed 41 cases compiled from the medical literature (as of November 2000) and from reports to Medtronic, Inc. (Minneapolis, MN) or to the U.S. Food and Drug Administration (FDA) [2]. All of the cases to date involved patients treated for pain. None of the reports involved patients who received baclofen (Lioresal® Intrathecal, Medtronic, Inc., Minneapolis, MN) as their only intrathecal drug. A more recent compilation of clinical cases appears in the companion article by Yaksh et al. [3] that appears elsewhere in this issue. Physician community interest in the inflammatory mass phenomenon increased during 2001 along with the number of reported cases (Figure 1). Figure 1 illustrates each case only once, under the year in which the mass was diagnosed, or under the earliest date that the event was reported and includes the five cases previously reported in an article by Schuchard et al. in 1998 [27]. The apparent increase in cases most likely reflects heightened awareness in the medical community and increased reporting by physicians after a January 2001 “Dear Doctor” mailing [3] and after the publication of abstracts and presentations at scientific meetings [4].

A preliminary life-table estimate of risk for occurrence of an inflammatory mass revealed that the risk increased over time [3]. Owing to the voluntary nature of case reports and uncertainties regarding the denominator, the life-table calculations probably underestimate the risk of developing a catheter-tip mass. Thus, the long-term usage and efficacy of intrathecal drug therapy was another factor that contributed to the apparent increase in cases. A growing number of patients were at risk because they were exposed to intrathecal analgesic drugs for greater periods of time.

The recent convergence of physician and scientific interest, the apparent increase in the number of cases, and the availability of new preclinical (animal) data motivated the authors to form a consensus panel to address the following issues: First, to summarize the pertinent preclinical (animal) and human data and to evaluate hypotheses regarding etiology of catheter-tip inflammatory masses in the companion article [3]; Second, to provide recommendations for clinicians about the detection and imaging diagnosis of such masses; Third, to provide guidance for physicians in the treatment of patients with catheter-tip masses; and Finally, to present information that may guide future studies that may help physicians prevent the occurrence or mitigate the consequences of these masses.

The Consensus Panel

Fourteen panel members contributed to this article: nine anesthesiology-pain specialists (MC, TD, SDuP, MH, EK, JR, PS, KDW, and MW) and five neurosurgeons (KB, RJC, KF, SH, and OS). All of the physicians are experienced in the use of intrathecal drug therapy to treat patients with chronic intractable pain caused by cancer or noncancer-related conditions. Their diverse backgrounds spanned private and academic practices in the United States and Australia, and included implanters of devices marketed by different manufacturers. This report includes laboratory

Figure 1 Reports of inflammatory mass cases by year of occurrence, 1990–2001.
and clinical data, where available, as well as the collective assessments and recommendations of these experienced intrathecal analgesia therapists.

Etiology of the Inflammatory Masses

The etiology and precise pathophysiologic mechanism(s) that leads to the formation of catheter-tip inflammatory masses remains to be defined. Evidence that supports or refutes various etiologic hypotheses is examined in more detail in the companion article [3]. The preponderance of animal experimental data to date suggests that an inflammatory response occurs after certain drugs, most commonly opioids, are administered into the intrathecal space [2,3].

While there is evidence that opioids can incite an inflammatory response in brain/spinal cord tissue, the mechanism(s) remains unclear. Morphine can act as a mitogen and activate a mitogen-activated protein kinase cascade, thus activating lymphocyte activity [5,6]. Alternatively, opioids cause human endothelial cells, granulocytes, and monocytes to release nitric oxide, which in turn might, in the presence of mesangial cells, lead to monocyte migration [7–9]. Finally, morphine has been shown to enhance cytokine formation, leading to an inflammatory cell response [10]. Whether the phenomenon is µ-opioid-receptor mediated or naloxone reversible remains to be determined [11].

Endothelial cells in blood vessels, brain, or spinal cord tissue have “tight junctions,” meaning that the cell membrane of each endothelial cell is tightly adherent to the cell membranes of the adjacent endothelial cells. Thus, under normal circumstances, large molecular weight molecules cannot pass between endothelial cells and extravasate in the surrounding interstitial space. This is the reason that intravenous contrast for radiologic procedures does not “enhance” or accumulate in the normal brain or spinal cord tissue. Enhancement of the masses on magnetic resonance imaging (MRI) scans, after intravenous injection of contrast, in the situation of a granuloma thus indicates a lack of tight junctions in the masses’ vascular supply [2,12–14].

This observation is consistent with the blood-borne origin of inflammatory cells that composed the human surgical specimens and all of the inflammatory masses that were examined histologically during the course of animal studies ([3], Hassenbusch S and Yaksh T, personal observations). The ability of inflammatory cells to migrate through the walls of small dural or meningeal vessels outside the blood–central nervous system (CNS) barrier also is consistent with the lack of CNS toxicity, apart from extrinsic compression. Preservation of an arachnoid plane between the granuloma and the spinal cord also suggests an origin from extra-axial tissues. Literature and anecdotal reports also have described masses that arise after chronic opioid administration in other non-CNS locations that include the epidural space and the subcutaneous tunnel at the site of a catheter break or disconnection ([15–18], Coffey RJ and Follett K, personal observations).

Human clinical reports and animal studies strongly support the hypothesis that injury to the spinal cord or nerve roots was produced by the size and mass effect of the inflammatory masses and not by a direct neurotoxic effect of preservative-free opioids and other drugs ([3], Hassenbusch S, and Yaksh T, personal observations). The intraspinal masses that arose after the intrathecal administration of chemically contaminated drugs or drugs that were compounded in bulk from erroneously labeled containers appear to have been a different, very rare problem [19]. Catheter material might be a contributing factor, since most granuloma reports are associated with the most common material for catheters, silicone elastomer (silastic). However, the much lower frequency of polyurethane-material catheter implantation, especially in combination with constant-rate infusion pumps rather than the more common variable-rate pumps, makes it very difficult to assess catheter material and/or pump flow characteristics as etiologic agents. The preponderance of negative cultures and the absence of acute inflammatory cells in surgical specimens made infection an unlikely cause in most cases. The three positive cultures reported in the literature may have been surgical or environmental contaminants [1,13]. So far, a catheter-tip mass caused by an infectious agent has not been found among the other cases that we reviewed. Even though infection is an unlikely cause, we recommend that physicians continue to perform microbiological cultures and stains of pertinent specimens (e.g., cerebrospinal fluid [CSF], access port CSF aspirates, the catheter tip, pump reservoir contents, samples of abnormal intraspinal tissue) whenever they encounter a catheter-tip mass.

Detection and Diagnosis

Clinical Assessment

A relevant neurological history and examination should be documented in the patient’s medical record before implantation of an intraspinal drug administration system. This forms a baseline for comparison in the event that new symptoms or signs appear that raise the possibility of a catheter-
tip mass. At the time of implantation, the three-dimensional location of the intrathecal catheter tip, based upon the results of biplane radiographic imaging, should be documented in the medical record. Routine postimplantation office visits and refill sessions provide an opportunity, when appropriate to the patient’s care, to record a brief interval history and perform a neurological examination of the patient’s lower extremity motor, sensory, and reflex functions, as appropriate. The patient interview should include specific questions about any changes in bowel and bladder function.

Subtle prodromal symptoms and signs during early growth of catheter-tip masses described in previous reports have included diminishing analgesic effects (loss of previously satisfactory pain relief) and remarkable or unusual increases in the patient’s underlying pain. Another feature of many cases was that patients required unusually steep or frequent dose escalations to recapture analgesic effects. In some cases, dose escalations and sizable drug boluses reduced the patient’s pain only temporarily or to a lesser degree than previous experience predicted. When the catheter tip was located in the thoracic spinal canal, early symptoms of an extraxial inflammatory mass sometimes included thoracic radicular pain that simulated intercostal neuralgia or cholecystitis. Catheter-tip masses in the lumbar region sometimes simulated nerve root compression from a herniated intervertebral disc or spinal stenosis.

Although fluctuations in patients’ subjective symptoms and underlying pain levels are common after the implantation of drug delivery systems, the occurrence of new or extraordinary complaints that require unexpected analgesic dose changes should alert physicians to consider a catheter-tip mass among other possibilities in the differential diagnosis. Gradual, insidious neurological deterioration weeks or months after the appearance of subjective symptoms was the most common clinical course before the onset of myelopathy or cauda equina syndrome in cases reported to date [2]. Awareness of the phenomenon and maintenance of an index of suspicion are important factors to help physicians detect such inflammatory masses early in the clinical course.

Overt symptoms and findings that warrant prompt investigation to rule out the presence of a catheter-tip mass include changes in the patient’s baseline neurological condition, such as: Motor weakness, including gait difficulties; Sensory loss, including proprioceptive lower extremity reflexes; Any evidence of bowel or bladder sphincter dysfunction. Suspicious subjective symptoms include new or different reports of numbness, tingling, burning, hyperesthesia, hyperalgesia, or the occurrence of pain (especially radicular pain that corresponds to the level of the catheter tip) during catheter access port injections or programmed pump boluses. Pain upon injection into the catheter, which may be encountered during system troubleshooting procedures, should alert the physician to discontinue the procedure and perform a diagnostic imaging study as soon as possible.

The authors recommend that physicians consider the following actions if they detect symptoms and signs suggestive of a catheter-tip mass. First, review the patient’s current complaints, history, and neurological examination thoroughly. Second, nonsurgical pain specialists should consider a consultation that includes a review of imaging studies with a neurosurgeon. And third, the physician should arrange the timely performance of a definitive diagnostic imaging procedure to confirm or rule out the suspected diagnosis. Treatment, likewise, should be started in a timely manner. Laboratory tests and electromyography or nerve conduction studies are apparently not useful in this setting.

**Imaging Diagnosis**

Physicians should have a low threshold for performing an imaging study to confirm or rule out the presence of a catheter-tip mass in patients with suspicious symptoms or physical findings. Illustrations of catheter-tip inflammatory masses identified on MRI and/or computed tomographic (CT)-myelogram images appear in the case reports by Bejjani, Blount, Cabbell, North, and their respective colleagues [1,3,12–14]. Unless medically contraindicated, MRI with and without intravenous gadolinium contrast enhancement or CT-myelogram is the imaging procedure of choice. Physicians should follow their customary safe procedures to assure that the MRI procedure does not turn off the pump or otherwise alter its programming. Catheter-tip masses are visualized best on intravenous contrast-enhanced T₁-weighted images. The mass appears as an enhancing lesion having the tip of the drug administration catheter embedded within it. The catheter may be difficult to see on some MRI scans, depending upon the pulse sequence, imaging plane, and slice thickness. Correlation between MRI scans and biplane radiographs is strongly recommended to identify the location of the catheter tip. Readers are cautioned not to overinterpret MRI artifacts caused by the radio-opaque metal marker (e.g., titanium) that is embedded in the tip of some closed-
end catheters. The helical titanium wire embedded within the wall of other catheter models also might cause imaging artifacts. Metallic artifacts on MRI scans are especially prominent on conventional T_{1}-weighted images. Absolute or relative contraindications to MRI include the presence of a cardiac pacemaker, certain prosthetic heart valves, certain neurostimulation devices, gadolinium contrast allergy, and claustrophobia.

In patients who have MRI contraindications, such as implanted cardiac pacemakers, spinal cord stimulation systems, or spinal instrumentation that obscures the MRI scan, high resolution CT-myelography provides an excellent means of detecting catheter-tip masses. CT-myelography using approved, nonionic, water-soluble contrast material injected via a lumbar puncture has identified catheter-tip masses successfully in all cases in which the technique was used. Physicians who plan to image the spinal canal and evaluate the infusion system’s continuity by injecting contrast material through a catheter access port should consider the following factors beforehand. One concern is to avoid intrathecal drug overdose, depending upon the amount of drug in the catheter and access-port dead space. This factor is important if a preliminary attempt to aspirate CSF through the access port was unsuccessful. Another consideration involves the possibility of injecting fluid and contrast material directly into the mass. Theoretically, that action could inflate the mass and further compress the spinal cord or nerve roots if a large mass already had compromised the spinal canal. Finally, physicians should remember that access port procedures can leave the catheter dead space and the access port devoid of drug unless deliberate steps are taken to refill the catheter at the end of the procedure. The importance of such steps depend upon the patient’s condition, the flow rate of the pump (hence, the time lapse until drug infusion resumes), and the specific drug(s) and dose(s) being infused.

Other imaging-based system troubleshooting methods are not recommended. These include pump cisternograms, which consist of filling the pump reservoir with dilute, water-soluble myelographic contrast material or indium-DTPA, a radionuclide tracer, and allowing the pump to infuse the reservoir contents for a number of hours or days. Pump cisternograms utilize an imaging modality (CT or nuclear medicine scan) to provide information about the condition of the spinal canal and flow through the pump and catheter system. Given the time-consuming nature of such studies, their uncertain interpretation, and the urgency of establishing the presence of a catheter-tip mass once that diagnosis is suspected, the authors recommend use of conventional MRI or CT-myelography to promptly confirm or rule out the diagnosis.

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

Optimal patient treatment and infusion system management should take into account the patient’s clinical condition, the physician’s experience and judgment, and the dictum, primum non nocere (first, do no harm). Once an imaging study confirms the presence of a catheter-tip mass, the physician must decide whether to remove the mass and whether or not to remove part or all of the drug infusion system (Figure 2). If the decision is made to leave the infusion system in place, the responsible physician eventually must decide whether to continue intrathecal therapy and whether to change the dose, concentration, or even the drug(s) being infused.

Some patients may require the substitution of oral, transdermal, or parenteral opioid medications. Depending upon the drug(s) and dose(s) that they received previously, the management or prevention of drug withdrawal may require hospitalization, regardless of whether surgery is planned to remove the mass, or to remove or revise the infusion system.

### Treatment of Catheter-Tip Inflammatory Masses

Deliberate planning can minimize the interval between the diagnosis of a catheter-tip inflammatory mass and its definitive treatment. Timely treatment, in turn, may help to avert permanent neurological injury. A history of progressive neurological symptoms or deficits and an imaging diagnosis of a large inflammatory mass that compromises the spinal canal should alert the physician to hospitalize the patient emergently, stop the drug infusion, and/or empty the drug reservoir, depending on the model of pump. Stopping certain programmable pumps for longer than a few days can cause the rotor to stall, making it impossible to restart the device. If resumption of therapy is anticipated, such pumps may be filled with preservative-free saline and allowed to run at an extremely slow rate (≤0.1 mL/day). Whenever necessary, physicians who are not neurosurgeons should request a neurosurgical evaluation of the patient and review of the pertinent imaging studies as appropriate.

### Surgical Removal of the Mass

The most commonly reported treatment for masses that caused significant or rapidly evolving neurologi-
Surgical intervention to remove the mass and/or decompress the spinal canal has restored neurological function or prevented further neurological deterioration in several reported cases [2]. The extent of resection was limited in some cases owing to adhesions to the spinal cord or nerve roots or because of the ventral location of a mass beneath the thoracic spinal cord. Because the masses were not neoplastic, in several cases the postoperative residual mass gradually shrank or disappeared over time [2,3].

Treatment of the Mass Without Surgical Removal

In contrast to the cases that presented with paraplegia or progressive myelopathy, a number of minimally or mildly symptomatic patients had small masses that were diagnosed during investigation of diminished analgesic efficacy or other subjective complaints. The masses did not significantly compress neural structures, nor compromise neurological function, and were managed safely and successfully without open surgical decompression or removal of the mass. However, the treatment of such patients did include the prompt discontinuation of intrathecal drug administration into the mass through the affected catheter. We have personally treated patients and have reviewed cases that verify the success of this mode of therapy in appropriately selected patients. Shrinkage or disappearance of the mass was documented on follow-up imaging studies after an interval of 2–5 months [2]. Consequently, catheter-tip inflammatory masses that are detected early in the clinical course can be treated safely and effectively by maneuvers directed at the drug infusion system.

Management of the Drug Infusion System

Permanent removal of the pump and/or intrathecal catheter was the most common method to deal with the infusion system in previous reports (36 of 92 cases) [2,3]. However, removal of infusion system components often accompanied surgical resection of the mass (32 of 92 cases) [2,3]. Our experiences and review of cases reported to date strongly suggest that the presence of a catheter-tip inflamma-

Figure 2 Management algorithm for intrathecal inflammatory masses.
Intrathecal inflammatory mass should not automatically lead to pump or catheter removal and permanent cessation of intrathecal therapy. Management strategies that permit therapy to continue after only a brief interruption are consistent with reports that masses have disappeared or decreased dramatically in size after a variety of interventions directed at the involved catheter. These include: 1) Removal of the involved catheter and placement of a new one during the same operation or at a later date; 2) Disconnection of the involved catheter from the pump, leaving the intraspinal segment undisturbed, and placement of a new intraspinal catheter segment at the same operation or at a later date; and 3) Withdrawal of the involved catheter to position its tip below the mass. Each of the treatments options listed here causes cessation of drug infusion into the mass. Continued drug infusion into a progressively symptomatic, but unrecognized, catheter-tip mass was associated with progressive neurological injury in several reported cases [2,20]. Bearing in mind the relatively short periods of postoperative observation to date, one case has been reported that described a new mass that arose on a replacement catheter [14].

The article by Cabbell et al. [14] is especially illuminating in this regard. A long-term spinal infusion patient who developed right leg weakness/numbness was found to have a T10 catheter-tip mass that eventually required resection, because the symptoms/findings did not resolve despite removal of the catheter. At the patient’s request, intrathecal morphine was started again for pain control, but, three years later, the patient developed right leg pain and clumsiness and was found to have an intradural mass at T12–L1. This time, however, close clinical observation and MRI corroborated regression of this mass over 2 months of saline infusion via the spinal infusion pump. After regression of this mass, the pump was filled with hydromorphone and no additional granuloma issues were observed, at least up until the time that the paper was submitted. One theoretical treatment that is not recommended by the authors would be to attempt to aspirate the contents of the mass through the catheter or pump access port. Although several case reports described masses having liquid or necrotic contents, no data suggest that the material can be aspirated through a hypodermic needle or even through the catheter lumen. A single patient reportedly was treated by infusion of hypertonic saline and Wydase® solution (Wyeth–Ayerst, Philadelphia, PA), a bovine testicular hyaluronidase enzyme, into the mass via the pump [2]. Neither of these agents is approved for intrathecal use, the patient’s outcome was not reported, and the authors advise against that mode of therapy.

Operations on the infusion system in patients who harbor an intraspinal mass, especially procedures that involve manipulation of the affected catheter or implantation of a new one, should be performed under fluoroscopic monitoring with the patient under local anesthesia and minimal sedation. Lower extremity motor and sensory function should be assessed periodically during the procedure. Because catheters labeled for chronic intrathecal use are radio-opaque, the level of the tip can be monitored fluoroscopically. Removal or partial withdrawal of the involved catheter in 12 reported cases and in the authors’ experience did not cause spinal cord or nerve root injury or intraspinal hemorrhage when only gentle traction was applied [2]. The consensus panel recommends abandonment of efforts to withdraw the catheter if force beyond gentle traction is required and/or if the patient reports intraoperative symptoms that indicate displacement of the mass. When that occurs, and if the patient’s neurological condition permits, we recommend ligation of the affected catheter and anchoring it to the lumbodorsal fascia. An alternative, if warranted, is to remove the catheter during open surgical exposure of the mass.

Selection of Drugs and Doses

The decision whether to revise or replace the involved catheter soon after diagnosis and the decision whether and when to resume intrathecal drug infusion depend upon the patient’s neurological status and how well he/she tolerates suspension or cessation of intrathecal therapy. The shortest interval on record before documented shrinkage of a catheter-tip mass was almost 2 months (7 weeks). Intervals of 6 months or longer were reported in other cases, but the time between imaging studies was not stated. Still, waiting for follow-up imaging to confirm shrinkage of the mass before resuming intrathecal therapy would commit the patient to a drug holiday lasting a minimum of almost 2 months.

Regardless of the timing of catheter replacement or revision, most physicians positioned the catheter or more vertebral segments away from the level of the mass. Often they elected to place the catheter near or below the conus medullaris (L–1 or L–2), although it should be noted that this might decrease the efficacy of the treatment, particularly with the use of lipophilic drugs. Reports also indicate that most patients experienced improved pain control at lower drug doses after replacement or revision of the affected catheter. We believe that re-
establishment of drug infusion directly into the subarachnoid space, as opposed to within the inflammatory mass, explains the recapture of analgesic effects in these patients. A related explanation may be that the mass had physically blocked CSF and drug flow. Removal of the affected catheter from within the mass may decompress the spinal canal just enough to permit CSF and drug to circulate more effectively.

Published reports and anecdotal reports have described a variety of intrathecal drug management strategies in patients who had been treated for a catheter-tip mass. Each of the authors who has personally treated such patients either changed the drug being infused or decreased the concentration of the original drug upon resuming therapy. Though several opioid drugs, local anesthetic agents, and clonidine are currently administrated through intrathecal infusion systems and in various combinations to treat patients with intractable pain, only one analgesic formulation, preservative-free morphine sulfate (Infumorph-500®, Elkins–Sinn, Cherry Hill, NJ), is labeled for chronic intrathecal use. When considering a change from one opioid drug to another, physicians should take analgesic potency into account, as well as the available safety data and prescribing information and the expected effects of a different catheter position on the distribution of hydrophilic versus lipophilic agents [23].

Prevention of Catheter-Tip Masses and Mitigation of Neurologic Sequelae

Intrathecal Drugs

Physicians should consider the interplay of pharmacological and anatomic factors in the placement of intrathecal catheters. Chronic infusion of the labeled formulation of morphine sulfate, a hydrophilic compound, into the lumbar thecal sac should achieve satisfactory drug levels and analgesic efficacy regardless of the dermatomal level of the patient’s pain. Second-line agents commonly used to recapture efficacy in difficult cases include hydromorphone, which is unlabeled for chronic intrathecal use, is slightly less hydrophilic than morphine, and has a potency-adjusted efficacy profile similar to morphine [23]. In contrast, fentanyl, sufentanil, and local anesthetic drugs are more lipophilic than morphine and would not be expected to produce worthwhile analgesia if infused several segments away from the spinal segment(s) that mediates the patient’s pain.

The clustering of cases in some practices and the absence of cases in others has raised the issue of whether different levels of vigilance (e.g., asymptomatic patient screening, ascertainment bias) versus intrathecal drug prescribing practices influenced the detection and/or occurrence of a catheter-tip masses. Conversely, the clustering in some geographic areas or groups might overestimate the true incidence because of radiologists who are sensitized to observe any catheter-tip abnormalities, regardless of whether the abnormalities represent true granulomata or simply radiologic abnormalities from the catheter-tip material. At present, none of the available evidence suggests that different opioid drugs are associated with different levels of risk for the formation of catheter-tip inflammatory masses. Only three reported patients exclusively received opioid drugs other than morphine sulfate or hydromorphone throughout their clinical course [2–4]. The influence of opioid–clonidine, opioid–bupivacaine, or other unlabeled admixtures on mass formation in humans also is unclear. Nineteen of 92 patients (20%) received an opioid–clonidine or –bupivacaine admixture, either at the time a mass was diagnosed or earlier in their clinical course [3]. Although data from two pain management centers (Cousins M, personal observation, Buchser E, personal communication) and one series of experiments (Yakshe T, personal observation) suggest that clonidine- or bupivacaine-containing admixtures may diminish the risk of inflammatory mass formation, the authors believe that it is premature to draw firm conclusions or make recommendations at this time.

Drug Concentration and Dose

A broad consensus exists within the pain management medical community that intrathecal opioids should be prescribed and maintained at the lowest effective dose for as long as possible. [24] Opioid–clonidine and/or –bupivacaine admixtures eventually may be approved as safe and effective for long-term intrathecal use. If such admixtures also are found to have morphine- or opioid-sparing effects (long-term analgesia at lower opioid-equivalent doses), combination therapy may provide part of the solution to prevent or forestall inflammatory mass formation.

Intrathecal drug dose escalation during the prodromal period before the diagnosis of many catheter-tip mass cases has confounded attempts to determine whether the administration of high-dose, high-concentration opioid medications contributed to the formation of the inflammatory mass or merely reflected the clinicians’ response to waning efficacy. The results of animal studies in two mammalian species that we reviewed in our companion article provide a partial answer [3]. Those studies revealed an apparent dose or concentration response with respect to the formation of inflamma-
tory masses in both dogs and sheep, although the experimental design could not discriminate an absolute dose effect from the effects of concentration. In light of the human and animal data, it still appears prudent to keep the intrathecal morphine concentration as low as possible and/or practical.

At least part of the impetus to employ high concentration opioid drugs in intrathecal drug pumps has been the limited volume of the reservoir in some programmable pumps and the relatively high daily infusion rate in some constant flow systems. Those limitations cause patients whose intrathecal opioid requirements have escalated over time to require unacceptable frequent pump refill appointments unless the physician employs relatively high-concentration morphine or more potent agents (such as hydromorphone). As a consequence, patient risk factors may be interdependent. The longer a patient remains on intrathecal therapy (an apparent risk factor), the more likely that patient is to require a higher opioid dose that is prescribed as a high-concentration formulation (another apparent risk factor) in order to maintain acceptable refill intervals.

Formulations of preservative-free morphine for intrathecal administration having a concentration >25 mg/mL commonly are compounded at hospital or contract pharmacies from nonsterile morphine sulfate powder to create a solution that is sterilized by passage through a 0.22-μm filter. Advances in pump design may provide a partial solution to the compounding dilemma. Recently approved constant-flow-rate pumps are available with a large drug reservoir (up to 60 mL) and a slow infusion rate (<0.5 mL/day). The next generation of programmable infusion pumps also will have larger drug reservoirs (40 mL) and will support infusion rates <0.1 mL/day. Thus, larger pump reservoir volumes allow physicians a variety of means to treat patients using lower morphine concentrations while maintaining acceptable refill intervals. Still, the issue remains unsettled whether the absolute opioid dose, the infused opioid concentration, or both (or neither) influence a patient’s risk for formation of a catheter-tip inflammatory mass. Follow-up animal studies beyond those described in our companion article [3] may help to answer this question. For example, one could determine whether the same daily dose of intrathecal opioid medication that reliably caused catheter tip mass formation in an experimental model had the same effect when administered in a 5 to 10 times larger volume (0.2–0.1 times concentration). In addition, a cross-sectional population study that included neuroimaging findings on 300 to 500 asymptomatic patients treated with long-term intrathecal opioid therapy might yield complementary data on the influence of drug dose, concentration, and other factors on humans.

**Screening Asymptomatic Patients**

MRI or CT-myelographic screening of patients on intrathecal therapy for chronic pain who are otherwise asymptomatic is not supported by present literature, but physicians can individualize this to their practice. However, as mentioned earlier, physicians should maintain a low threshold for ordering such studies in patients perceived to be at risk. Even subjective or relatively minor symptoms in a patient on long-term intrathecal opioid therapy may justify an imaging study, especially if recent dose escalations, loss of pain relief, or new radicular pain raise the possibility of a catheter-tip mass as part of the physician’s differential diagnosis.

**Implant Technique and Catheter-Tip Location**

Individual patient considerations, such as neoplastic involvement of the spine or extensive previous surgery, sometimes require the placement of drug infusion catheters within the thoracic, or even the cervical, spinal canal. If a lipophilic drug is to be infused, it may be necessary to position the catheter tip near the spinal cord dermatomal level corresponding to the location of the pain in the body. However, purely anatomic considerations reveal that a catheter tip positioned above the conus medullaris can place the spinal cord at risk for injury in the event that a mass develops. In contrast, a lumbar-level catheter tip, placed below the conus medullaris, should not cause a spinal cord injury, even if a mass were to develop. In addition, the nerve roots of the cauda equina are invested with Schwann cell myelin, are part of the peripheral nervous system, and are more resistant to injury than the central axons within the spinal cord. In previous reports, lumbar catheter-tip masses that affected the cauda equina caused less severe neurological deficits that were more likely to improve after surgery or other treatments than higher catheter-tip masses that injured the spinal cord. Despite all these theoretical considerations, it is not clear whether there is a greater risk with a thoracic catheter tip. In some situations, a thoracic catheter is needed for the infusion of a lipid-soluble drug or a local anesthetic agent. The physician should always consider all these factors in the determination of the final location of the permanent catheter’s tip.

The surgical techniques used during catheter implantation and the dorsal–ventral location of the catheter within the spinal canal did not appear to influence the formation of inflammatory masses.
However, two of the authors have hypothesized that catheter tips located in the thoracic region may indirectly cause higher local drug concentrations around the catheter tip than one would expect [2,25,26]. High local drug concentrations may set the stage for a localized inflammatory response and eventual mass formation within the meninges (Yaksh T, personal observation).

Conclusions and Recommendations

Despite the lack of controlled trials or large epidemiological studies, the panel has reviewed a significant amount of clinical and preclinical data that support the following conclusions and recommendations regarding the detection and treatment of catheter-tip inflammatory masses, as summarized in Table 1. Our analysis of the various hypotheses regarding etiology also leads to recommendations on prevention, mitigation of neurological sequelae, and areas of future research.

Inadequately treated chronic pain is a serious condition that carries its own risks and morbidity. In that context, the risk of developing a catheter-tip mass as a consequence of long-term intrathecal drug administration should remain acceptable, provided that the treatment is effective. Physicians should select and screen patients carefully to maximize the likelihood of therapeutic efficacy. Physicians also should consider the catheter-tip mass phenomenon in the risks of the procedure and the long-term therapy.

Thorough baseline evaluation and attentive follow-up form the foundation for early diagnosis in the event that a catheter-tip mass develops. Physicians should remain alert to the signs and symptoms described in this article and others and should maintain an index of suspicion when they encounter otherwise unexplained patient symptoms or complaints. Noninvasive diagnosis is possible using contrast-enhanced $T_1$-weighted MRI. CT-myelography is just as effective in confirming the diagnosis in individuals for whom MRI is contraindicated (e.g., patients with cardiac pacemakers and certain other prosthetic devices).

A number of acceptable treatment options are available. The selection predominantly depends upon the patient’s clinical condition. Surgical removal or decompression is not mandatory in all patients, especially those who have few or mild symptoms. When a patient presents with a profound or progressive neurological deficit, the authors recommend surgical consultation and participation in the decision-making process.

While catheter placement in the lumbar versus the thoracic spinal canal cannot be relied upon to prevent the development of an inflammatory mass, lumbar placement theoretically might mitigate the neurological consequences if a mass occurs. This is because the spinal cord, which is more susceptible than the cauda equina to permanent injury from extrinsic compression, ends in the upper lumbar region.

Given the unsettled nature of the evidence regarding the etiology of catheter-tip inflammatory masses, recommendations about prevention also are speculative. Still, such masses have not been reported in patients with lumboperitoneal shunts, nor in those who have received intrathecal baclofen. This leaves opioid-drug-related phenomena as a significant component of the most plausible hypothesis. With that in mind, the authors repeat the same recommendation regarding intrathecal opioid prescribing practices that has been made for decades: Keep the dose and concentration as low as possible for as long as possible while still achieving adequate analgesia.

References


