

RESEARCH PAPERS

Inflammatory Masses Associated with Intrathecal Drug Infusion: A Review of Preclinical Evidence and Human Data

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ABSTRACT

Objectives. The phenomenon of inflammatory masses at the tips of intrathecal drug administration catheters was the subject of a recent case-compilation report and a number of animal studies. We sought to synthesize current clinical and preclinical data to formulate hypotheses about the etiology of catheter-tip masses.

Methods. We reviewed the published human clinical data, new unpublished clinical data, and the results of preclinical studies in two mammalian species, beagle dogs and sheep.

Results. Intrathecal morphine sulfate studies in beagle dogs suggested that the observed inflammatory reaction was dose or concentration dependent. Masses occurred after 28 days in one of three animals at 1.5 mg/day (the lowest morphine dose tested); in two of three animals at 3 and 9 mg/day; and in three of three animals at 12 mg/day. The addition of various amounts of clonidine to 1.5 mg/day of morphine revealed no mass formation when the clonidine dose was >0.25 mg/day. A morphine sulfate study that was performed in sheep using a commercially marketed drug administration system found catheter tip masses in two of three animals that received 12 or 18 mg/day of morphine, the highest doses tested. Human cases have occurred only in pain patients who received intrathecal opioids, alone or mixed with other drugs, or in patients who received investigational agents (such as superoxide dismutase or the partial μ -opioid-receptor agonist, tramadol) that were not labeled for long-term intrathecal use.

Discussion/Conclusions. The evidence suggests that the long-term administration of opioids, especially morphine, caused the masses that were observed in humans and in two species of animals. A relationship probably exists between mass formation and intrathecal morphine doses or concentration. Other factors remain to be investigated.

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

Introduction

The phenomenon of intradural-extramedullary masses at the tips of intrathecal drug infusion cath-

eters recently was reviewed by Coffey and Burchiel [1]. They compiled 41 cases: 16 from the medical literature and 25 from reports to Medtronic, Inc. (Minneapolis, MN) and the U.S. Food and Drug Administration (FDA) as of November 2000. Another 51 cases were identified as a consequence of increased reporting after scientific meeting presentations and an informational "Dear Doctor" letter

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to physicians in 2001. Recently reported cases were similar to previously reported ones. These reports typically described chronic inflammatory masses that were not infectious in origin and that surrounded the tip of intrathecal drug administration catheters in patients treated for chronic intractable pain [1–7]. Previous investigators described a variety of clinical scenarios that appeared to be associated with growth of the masses and that differed from the fibrotic reaction that occurs around the tip of chronically implanted epidural catheters [8–14]. Speculation regarding the etiology of the masses at various times has included the chemical characteristics, concentration, or immunologic effects of the infused drugs; impurities in, or contamination of, drug sources; bacterial infection, pyrogens, or endotoxins; silicone allergy; catheter design features; and/or delayed effects of traumatic catheter implantation procedures. The large number of patients currently implanted with intraspinal drug delivery devices and the potential severity of neurological injuries that can be associated with catheter-tip masses dictate further investigation of this phenomenon.

A converging line of evidence became apparent during preclinical investigations of the potential toxicity of clonidine plus morphine mixtures administered chronically to the intrathecal space of beagle dogs (Yaksh T, personal observation). The finding of inflammatory masses associated with motor and behavioral effects in dogs led to additional studies in the beagle dog model that subsequently were confirmed in another mammalian species, sheep.

Intrathecal Morphine and Clonidine plus Morphine Studies in Beagle Dogs

A study was conducted in beagle dogs to determine the effects of a 28-day continuous lumbar intrathecal

infusion of morphine (Table 1) or clonidine and morphine admixtures (Table 2). The initial pilot study in beagles (not reviewed here) attempted to assess the safety of clonidine and clonidine–morphine admixtures in order to develop an intrathecal clonidine formulation for human use. Some animals exposed to morphine-containing admixtures, but not clonidine alone, developed catheter-tip inflammatory masses. The following summarized data were obtained and analyzed in the chronically catheterized beagle dog model [15]. A full analysis of these and additional data are presented in detail elsewhere [16]. The model involved retrograde cannulation of the dog's spinal canal with a polyethylene (PE-10) catheter from the atlanto–occipital interspace to the lower thoracic or upper lumbar region. The catheter was tunneled subcutaneously and connected to an adjustable external pump located in a specially fitted vest, which the animal wore for the duration of the experiment. Drug infusion began after complete recovery from anesthesia and surgery 3 days after catheter implantation and persisted for 28 days. Treatment groups are summarized in Tables 1 and 2. Each group consisted of three dogs, each treated with the same drug(s) and daily dosages, administered at a constant infusion rate of 40 μ L/hour (0.96 mL/day). Thus, higher daily doses were achieved in each successive treatment group by increasing the morphine concentration. Morphine solutions were prepared from Infumorph® 500 (25 mg/mL morphine sulfate; Elkins–Sinn, Cherry Hill, NJ) diluted with 0.9% sodium chloride for injection, USP to provide the desired concentration. The clonidine hydrochloride test article was a sterile solution suitable for intrathecal infusion. The clonidine test article was manufactured under Good Manufacturing Guidelines and supplied at a concentration of 2 mg/mL. At the time of sacrifice, dogs were deeply anesthetized and underwent perfusion fixation. Spinal cord blocks from

Table 1 Summary of spinal histopathology: Intrathecal morphine infusion in beagle dogs

Morphine sulfate dose, mg/day	Anatomic regions examined				Number of catheter-tip masses per group
	Cervical region	Thoracic region	Lumbar, adjacent to catheter tip	Lumbar, caudal to catheter tip	
0 (saline)	1/1/1	1/1/1	2/1/2+	1/1/2	0/3
1.5	1/1/1	1/1/1	2+/2+/4	2/1/2	1/3
3	1/1/1	1/2/1	2+/4/4	0/2/3	2/3
6	1/1/1	1/1/1	2–/4+/+3–	1/3/2	1/3
9	1/1+/1	0/1+/1	3/4/4	3/3/3	2/3
12	1/1/0	2/1/1	4/4/3	4/3/1	3/3

Each row presents the results for a group of three beagle dogs treated with the same drugs and daily dose; the results for individual dogs are separated by slash (/) marks. All intrathecal drug doses were administered at a flow rate of 40 μ L/hour (0.96 mL/day). Histopathologic quantification of inflammatory response: 0 = normal; 1 = minimal-to-mild inflammation; 2 = mild; 3 = moderate; 4 = severe inflammation; + or – indicates slightly more or less severe inflammation, respectively.

Table 2 Summary of spinal histopathology: Intrathecal morphine plus clonidine infusion in beagle dogs

Morphine and clonidine doses, mg/day	Anatomic regions examined				Number of catheter tip masses per group
	Cervical region	Thoracic region	Lumbar, adjacent to catheter tip	Lumbar, caudal to catheter tip	
0.25 clonidine plus 1.5 morphine	1/1/0	2/1/0	4/3/3–	2/1/1	1/3
0.50 clonidine plus 1.5 morphine	1/1/1	1/2/1	3/3/3	1/3/1	0/3
1.0 clonidine plus 1.5 morphine	0/1/0	0/1/0	1/2/0	0/0/1	0/3

Each row presents the results for a group of three beagle dogs treated with the same drugs and daily dose; the results for individual dogs are separated by slash (/) marks. All intrathecal drug doses were administered at a flow rate of 40 μ L/hour (0.96 mL/day).

Histopathologic quantification of inflammatory response: 0 = normal; 1 = minimal-to-mild inflammation; 2 = mild; 3 = moderate; 4 = severe inflammation; + or – indicates slightly more or less severe inflammation, respectively.

each dog were taken for sectioning, staining, and analysis by a pathologist not informed as to treatment.

Behavioral and Neurological Results

None of the treatment groups (morphine alone or clonidine plus morphine in various doses) displayed sedation over the infusion interval. In the morphine-alone portion of the study, there was a dose-dependent increase in observations of hind-limb motor dysfunction as assessed by cumulative scores for coordination and muscle tone over 28 days in animals that received >3 mg/day of morphine. Changes in motor function occurred earlier in animals that received higher intrathecal morphine doses. The earliest motor signs were increased hind-limb tone that progressed to weakness and were consistent with an upper motor neuron lesion (e.g., removal of descending motor inhibition, leaving local motor neurons intact). Saline-treated and 1.5-mg/day-morphine-treated animals displayed no neurological abnormalities.

In the clonidine plus morphine portion of the study, animals that received clonidine (0.25–1.0 mg/day) plus morphine (1.5 mg/day) showed mild changes in motor tone that began immediately after the initiation of the infusion. Unlike the effects observed after higher morphine doses in the morphine-alone groups, the effects of clonidine plus morphine were observed immediately after the drug infusion began and did not progress over time. Specifically, no disabling motor signs or paralysis were observed. Clonidine plus morphine animals displayed only minimal neurological effects during the drug infusion period (mild hind-limb stiffness and/or incoordination and mild hypersensitivity in the dorsal region).

Spinal Histopathology

In the morphine-alone portion of the study (Table 1), histopathological examination revealed mild inflammatory reactions in control (saline) animals

consistent with a local foreign body reaction, presumably to the intrathecal catheter. However, at the higher morphine doses, local inflammatory masses developed in the vicinity of the catheter tips, which most often were located between T12 and L2. In some cases, the masses were large enough to cause spinal cord compression. Because all animals were sacrificed at approximately 28 days after the start of drug infusion, the time course and origin of the catheter-tip masses could not be defined by this study. These masses were composed of lymphocytes and macrophages. Evidence of increased vascularity of these masses was also apparent. Importantly, serial section examination emphasized that granulomatous masses arose from dura-arachnoid layer and not the pia or spinal cord. Systematic histochemistry showed no specific neuronal loss within the parenchyma, demyelination, or evidence of reactive astrogliosis (as indicated by staining for glial fibrillary acidic protein). Staining for bacteria and fungi were negative. Histological staining revealed significant immune reactivity for TNF α and IL-1 β in the inflammatory mass. In dogs displaying inflammatory masses, cisternal cerebrospinal fluid (CSF) sampled at sacrifice indicated that there was a significant increase in cisternal CSF protein and white-blood-cell count but not glucose, as compared with other treatment dogs that did not develop granulomas.

In the clonidine plus morphine portion of the study (Table 2), the treatment groups exhibited diminishing inflammatory findings as the dose of clonidine was increased. Dogs that received the highest dose of clonidine (1.0 mg/day) showed minimal toxicity. A single animal in the 0.25-mg/day-clonidine plus 1.5-mg/day-morphine group was the only one that developed a small inflammatory mass.

In summary, intrathecal morphine sulfate infusion produced a dose-dependent local inflammatory reaction at the catheter tip in the beagle model. A safe dose of morphine sulfate was less than 1.5 mg/day in

this model. A dose of 12 mg/day consistently produced catheter-tip inflammatory masses, whereas doses less than 12 mg/day produced masses in one to two individuals of each three-animal treatment group. In contrast, intrathecal clonidine hydrochloride appeared to diminish the local inflammatory reaction produced by low-dose morphine (1.5 mg/day). These findings are consistent with the results obtained in the pilot study (not reviewed here), wherein clonidine alone (2 mg/mL, 4.8 mg/day for 28 days) caused no toxicity and resulted in an inflammatory profile that appeared more benign than the mild reaction found after saline infusion in the control groups.

Intrathecal Morphine Infusion in Sheep

Another study was conducted to determine the maximum safe dose (with respect to inflammatory mass formation) of intrathecal morphine sulfate infusion in sheep, a larger species with spinal canal dimensions that approximate the human clinical situation more closely than the beagle model. Animals were implanted with a SynchroMed® Infusion System (Medtronic, Inc., Minneapolis, MN) using a Tuohy needle technique to implant the lumbar silicone catheters. Animals were allowed to recover from the implant surgery for approximately 7 days before drug infusion was initiated. All morphine solutions were prepared from Infumorph® 500 (25 mg/mL morphine sulfate; Elkins-Sinn, Cherry Hill, NJ) diluted with 0.9% sodium chloride, USP, as necessary, to provide the concentration required to administer the desired daily dose at the constant infusion rate of 80 μ L/hour (1.92 mL/day). Six dose groups of three animals per group were evaluated—0 (saline control), 3, 6, 9, 12, and 18 mg/day. All animals were infused for 28 days, at which time, animals were euthanized, a necropsy was performed, and tissues were collected for microscopic examination.

During the course of the study, animals were observed daily for behavior and motor function.

Behavioral and Neurological Results

The results are summarized in Table 3. Two of three sheep in each of the highest dose groups (12 and 18 mg/day) developed significant lameness in one hind leg. In affected sheep, signs of lameness were apparent as early as 1 week after the initiation of morphine infusion. All of the sheep in the two highest dose groups exhibited frank pain behavior (biting and wool pulling of the caudal lumbar area), which is similar to the allodynic behavior previously described in rats [17] and also reported in beagles infused with intrathecal morphine.

With the exception of one sheep, none of the other animals in this study exhibited any significant clinical signs. The single exceptional animal received 18 mg/day of intrathecal morphine and exhibited seizure-like activity on two separate occasions. This was the only animal in the high-dose group that did not develop a catheter-tip inflammatory mass.

Spinal Histopathology

Gross pathological examination revealed that all four lame animals also had large inflammatory masses that appeared to arise at the catheter tip and to extend caudally along the shaft of the catheter. Microscopic examination revealed that the masses consisted of acute and chronic inflammatory cells (eosinophils, prominent large and vacuolated histiocytes, lymphocytes, plasma cells, fibroblasts, and maturing fibrous connective tissue). The inflammatory masses produced severe compression of the spinal cord. Animals treated with <12 mg/day of morphine and those treated with saline displayed mild chronic inflammation and cord compression that was most likely due to the presence of the silicone catheter. Another histological change observed in animals treated with

Table 3 Summary of spinal histopathology and motor observations: Intrathecal morphine infusion in sheep

Morphine sulfate dose, mg/day	Anatomic regions examined				Unilateral hind limb lameness, N per group
	Region of catheter tip	Mid-catheter, caudal to catheter tip	5 cm cranial to catheter tip	Number of catheter-tip masses per group	
0 (saline)	C+/C+/0	C+/C+/C+	0/0/0	0/3	0/3
3	C+/C+/0	C+/C+/0	0/0/0	0/3	0/3
6	C+/0/C+	C+/C+/C+	C+/0/0	0/3	0/3
9	C+/C+/C+	C+/C+/C+	0/C+/C++	0/3	0/3
12	AC+++/AC+++/C+	AC++/AC++/C+	0/C+/0	2/3	2/3
18	C+/AC+++/AC+++	C+/AC++/AC++	0/C+/0	2/3	2/3

Each row presents the results for a group of three sheep treated with the same drugs and daily dose of morphine; the results for individual sheep are separated by slash (/) marks. All intrathecal drug doses were administered at a flow rate of 80 μ L/hour (1.92 mL/day). Histopathologic quantification of inflammatory response: 0 = normal findings; A = acute inflammation; C = chronic inflammation; AC = acute and chronic inflammation; + / + + / + + + indicate mild, moderate, or severe findings, respectively.

morphine at doses ≥ 6 mg/day was the presence of mild ($N = 4$) or moderate ($N = 1$) chronic inflammation in the region 5 cm cranial to the catheter tip. Because this finding was not present in the saline- or 3-mg/day-morphine-treated animals, the changes were most likely related to morphine infusion.

In summary, intrathecal morphine sulfate infusion produced a dose-dependent inflammatory reaction at the catheter tip in the sheep model. Doses ≥ 12 mg/day produced inflammatory masses that were large enough to cause severe spinal cord compression and motor deficits. A dose of 3 mg/day appeared to be a safe dose in this species. Histological changes after the 3-mg/day-morphine infusion were equivalent to those produced by saline. Although doses of 6 and 9 mg/day produced no clinical signs or catheter-tip masses, pathological analysis of some animals did reveal mild-to-moderate chronic inflammation that was located cranial to the catheter tip and that was not seen in saline-treated animals.

Review of Human Clinical Data

The phenomenon of an intradural-extramedullary mass at the tip of a drug infusion catheter was reported first by North et al. in 1991 [6]. More recently, Coffey and Burchiel reviewed the cumulative clinical data as of November 30, 2000 [1]. They hypothesized that the etiology involved interplay between the physical or chemical characteristics or the concentration of the infused drugs (predominantly opioids) and location of the drug administration catheter, especially within the ventral thoracic subarachnoid space—a region of low CSF flow and volume. Table 13 summarizes our review of previ-

Table 4 Clinical features of 92 patients with catheter-tip inflammatory masses

Number of cases	N = 92
Age	mean: 53.6, range: 34–84 (age not reported N = 16)
Sex	female: 45, male: 35 (sex not reported N = 12)
Duration of therapy	median: 25 months mean: 29 months range: 0.5–120 months
Etiology of pain	cancer pain: 7 noncancer pain: 74 (failed spinal surgery: 47) not reported: 11
Level of catheter tip and mass	thoracic: 56* lumbar: 8 not reported: 28

The aggregate number of cases equals 92; N = 18 cases reported in the literature; N = 74 cases from postmarketing surveillance reports by physicians. *The exact vertebral level was not reported in three cases with thoracic-level myelopathy.

ous and current hypotheses regarding the etiology of catheter-tip inflammatory masses.

Fifty-one additional cases, defined using the same criteria as previously reported, have been reported either in the medical literature ($N = 2$) or from postmarketing surveillance reports ($N = 49$) since the cut-off date for the last published review. Each involved the direct or radiographic observation of an intradural-extramedullary mass at the tip of an intrathecal drug infusion catheter, regardless of whether or not the mass caused neurological symptoms. Masses or fibrosis associated with drug delivery catheters in the epidural space or outside the spinal canal were excluded. Owing to confidentiality regulations and voluntary reporting practices, data were not audited or compared with original medical records. Undoubtedly, an unknown num-

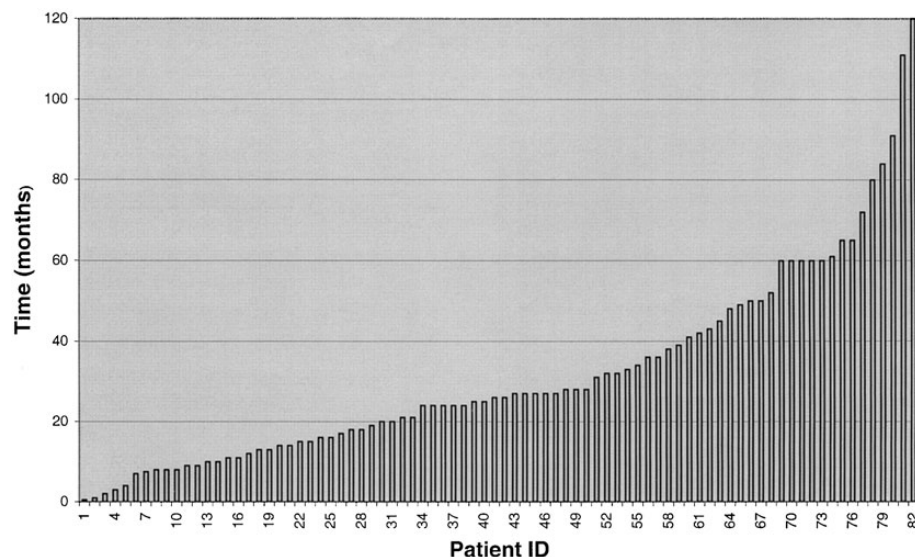


Figure 1 Histogram showing the duration of intrathecal drug therapy (treatment time) before diagnosis of an intraspinal catheter-tip mass (median: 25 months, range: 0.5–120 months). The case identification numbers (x axis) are arbitrary. Data reported on 82 cases only.

Table 5 Summary of intrathecal drugs at diagnosis of catheter-tip mass*

Drug or drugs	Number of cases
Morphine alone	46
Morphine in combination	11
Hydromorphone alone	7
Hydromorphone in combination	8
Tramadol N = 1, fentanyl N = 1	2
No drug information reported	18
Total	92

*Other intrathecal drugs administered *before* diagnosis of mass include superoxide dismutase and sufentanil.

ber of additional cases have gone unreported. Most likely, this has caused us to underestimate the incidence and prevalence of catheter-tip masses.

Clinical Features of Inflammatory Mass Cases and Results of Therapy

The demographic and presenting clinical features of the patients, the drugs that were being administered at the time a mass was diagnosed, the imaging findings, treatment, and follow-up are summarized in Tables 4–12. We identified a total of 92 cases over the 12 years since 1990: 41 that were reported in 2002 (16 from the literature and 25 from post-marketing surveillance reports by physicians) and 51 new reports (two from the literature and 49 from postmarketing surveillance reports). The mean duration of therapy was 29 months (Figure 1, median: 25 months, range: 0.5–120 months). The majority of patients, 74 of 92, had noncancer pain. Drugs administered at the time a mass was diagnosed included morphine alone (N = 46) or mixed with other drugs (N = 11) (Table 5). The daily intrathecal morphine dose was ≥ 10 mg/day in 28 of 40 cases where dosage information data were reported, and the morphine concentration was ≥ 25 mg/mL in 28 of 33 cases where that information was reported (Table 6). Morphine concentrations > 25 mg/mL most likely indicated pharmacy compounding. Fifteen patients received hydromorphone (Table 7), and

Table 6 Intrathecal morphine dose or concentration in 47 patients with data reported

	Number of patients
Intrathecal morphine dose	
Number with daily dose reported	40
Morphine dose < 10 mg/day	12
Morphine dose 10–14 mg/day	14
Morphine dose ≥ 15 mg/day	14
Intrathecal morphine concentration	
Number with concentration reported	33
Morphine concentration ≤ 25 mg/mL	13
Morphine concentration 26–49 mg/mL	2
Morphine concentration ≥ 50 mg/mL	18

three patients received other drugs or drug mixtures. No catheter-tip masses were reported in patients who received baclofen as the only intrathecal drug. To date, every reported case of inflammatory mass for which information about the drugs administered was available involved chronic intrathecal infusion of an opioid alone or in combination with other agents. Opioids included morphine, hydromorphone, fentanyl, sufentanil, or the partial μ -opioid-receptor agonist, tramadol.

The neurological symptoms and/or signs that led to the diagnosis of an intraspinal mass varied in severity from loss of analgesic drug effects to complete paraplegia. In most cases, the diagnosis of an inflammatory mass was confirmed by magnetic resonance imaging (MRI) or computerized tomography (CT) myelography (Table 8). Most patients experienced the gradual, progressive onset of neurological symptoms and signs. Ten patients experienced a sudden neurological deficit, either with (N = 3) or without (N = 7) prodromal symptoms (Table 9). Fifty-four patients underwent surgery to relieve spinal cord or cauda equina compression, and 36 patients had one or more components of their drug administration systems removed (Table 10).

A few patients who had minimal neurological findings were managed successfully without surgery to remove or debulk their masses or to decompress their spinal canals. Anecdotal reports described patients with masses that did not fill the spinal canal or cause neurological impairment who were treated by stopping or emptying the drug infusion pump or by refilling it with preservative-free normal saline to run at a minimal infusion rate. In those cases, the masses either stabilized or became smaller spontaneously over a period of months. However, when patients with impending paraplegia from a mass that filled the spinal canal were not operated promptly, permanent neurological impairment occurred. Twenty-eight patients recovered fully after treatment, another 27 recovered ambulatory status, and 15 became nonambulatory, one of whom died from a pulmonary embolus (Table 11). Examination of 46 surgical specimens most often revealed findings of chronic inflammation and/or fibrosis (Table 12). Three cultures were positive for organisms believed to be contaminants [5,6].

Estimation of Incidence and Risk

The number of reported human cases in the United States and contemporaneous pump implantation, explantation, and patient mortality data were used to perform a life-table analysis and to calculate the risk of developing a catheter-tip mass in patients treated

Table 7 Hydromorphone (HM) dose and concentration in 15 patients with data reported

HM dose (mg/day)	HM concentration (mg/mL)	Other intrathecal drugs at diagnosis	Previous intrathecal drugs before diagnosis
64.8	100	bupivacaine	sufentanil
50	100	clonidine	unknown
14	54	unknown	unknown
30	50	unknown	unknown
24	50	bupivacaine	morphine + bupivacaine
unknown	50	unknown	unknown
11.5	unknown	clonidine	unknown
11	40	unknown	unknown
unknown	30	clonidine	unknown
7.3	20	tetracaine	unknown
4–5	10	unknown	unknown
1	unknown	baclofen	morphine + baclofen
unknown	unknown	unknown	unknown
unknown	unknown	unknown	unknown
unknown	unknown	bupivacaine	morphine + bupivacaine

Each line in the table contains data for a single patient.

for chronic pain (Figure 2). Because no cases were reported that involved patients treated with intrathecal baclofen for spasticity, incidence rates were calculated only for patients treated using intrathecal drug pumps for chronic pain. A comparison of inflammatory mass patients with cancer pain and non-cancer pain did not indicate any differences in risk. However, the relatively small number of cancer pain cases combined with their higher annual mortality yielded a much smaller population at risk during the later years of intrathecal drug exposure, when the risk appears to increase. Consequently, all pain patients were pooled together. Assumptions regarding the mortality of cancer pain patients and noncancer pain patients and assumptions regarding the discontinuation of intrathecal drug therapy over time were all used to reduce the population assumed to be at risk over time. An unknown degree of underreporting of cases used in the life-table analysis likely resulted in this analysis underestimating the risk of developing a catheter-tip mass. Errors in these assumptions could

also increase or decrease the risk estimates. Another important point is that a substantial increase in reported cases occurred after a “Dear Doctor” letter and report forms were sent to physicians in January 2001.

For all pain patients, the estimated cumulative risk of developing an inflammatory mass was 0.04% over 1 year, 0.12% over 2 years, 0.22% over 3 years, 0.31% over 4 years, 0.52% over 5 years, and 1.15% over 6 years. Estimates of the risk of developing a mass in the next year appear to increase somewhat the longer the patient has the implanted system. For example, the risk of developing a mass in the next year was estimated to be 0.08% at year 1, but 0.21% at year 4.

Discussion

Proposed Etiologic Hypotheses

Before the 2002 review by Coffey and Burchiel, etiologic hypotheses included drug-related mechanisms, infection, pyrogens, silicone hypersensitivity, surgical trauma, catheter-tip design, and predisposing patient conditions, such as arachnoiditis [1–8, 16,17]. Other possible hypotheses include catheter tip location, impure or contaminated drugs, and the

Table 8 Neurological and imaging diagnosis

Signs and/or symptoms	Number of cases
Loss of drug effect only	12
New-onset radicular pain or paresthesias	12
Complete spinal cord injury	15
Incomplete spinal cord injury	29
Para- or monoparesis, level not stated	9
Cauda equina or nerve root syndrome	8
Neurological signs not specified	7
Total	92
Diagnostic Imaging	
MRI	45
Myelogram or myelogram plus CT	17
MRI and myelogram plus CT	4
Imaging modality not specified	26
Total	92

Table 9 Tempo of onset of neurological signs and symptoms

Tempo of onset	Number of cases
Sudden deficit without prodromal symptoms	7
Sudden deficit after prodromal symptoms	3
Slowly progressive neurologic deficit	34
Total cases with known timing of symptom onset	44
Number of cases without symptom-onset data	48

Table 10 Treatment of the mass and drug administration system

	Number of cases
Treatment of Mass	
Complete resection	32
Partial resection	10
Resection, extent not reported	12
No surgical treatment of mass	22
Treatment of mass not reported	16
Total	92
Treatment of drug administration system	
Pump and/or catheter removed	36
Pump and/or catheter revised	12
Pump and catheter not operated	17
Operation on system not reported	27
Total	92

effects of opioid drugs on the immune system and/or the blood–central nervous system (CNS) barrier (Table 13).

The rarity of positive cultures and the absence of positive tissue stains for microbes in human and animal specimens eliminated chronic infection as a likely cause for the mass lesions [1,5,6]. None of the patient histories or experimental animal observations were consistent with an endotoxin or pyrogen insult, which would have caused manifestations that resembled aseptic meningitis [20]. Testing of commercially available intrathecal morphine sulfate was negative for endotoxins [21].

Silicone allergy also was unlikely given the masses location exclusively at the tips of active drug infusion catheters and their absence on silicone lumbar shunts [22,23]. The role of genuine, IgE-mediated silicone allergy in other disorders also has been discredited [24]. The documented disappearance of masses from inactive or disconnected silicone-elastomer catheters also has discredited the silicone allergy hypothesis. Moreover, the inflammatory masses observed in dogs after chronic morphine infusion occurred in an experimental model that employed polyethylene infusion catheters. Importantly, the canine model as employed in these studies has been used extensively for preclinical safety evaluation, and the granulomatous reaction

Table 11 Neurological outcome

Status at last follow-up	Number of cases
Complete recovery	28*
Partial recovery, ambulatory	27
Minimal or no recovery, non-ambulatory	15**
No clinical follow-up, or condition not reported	22
Total	92

*One patient was paraplegic before system implantation.

**One patient died of a pulmonary embolus 1 month after becoming paraplegic.

was not observed with low morphine concentrations [25] or with certain other agents, including 28-day infusions of baclofen, clonidine, adenosine, neostigmine, or ketorolac ([26–28], Yaksh T, unpublished observations).

Early case reports involved patients who were implanted with catheters that had a single end-hole design. Until recently, such catheters were the only devices labeled for chronic intrathecal implantation. Cases now have occurred in association with closed-end, multi-hole catheters, a finding that makes catheter-tip design a less likely cause for the formation of mass lesions.

North et al. raised the issue of spinal arachnoiditis as a predisposing patient factor in their sentinel case report [6]. The subsequent occurrence of inflammatory masses in cancer-pain patients and other individuals who had no previous history of spinal surgery argues against arachnoiditis as the cause for those masses. However, previous spinal surgery and normal variations in the anatomy of arachnoidal membranes can cause blind pockets or loculations within the subarachnoid space. Those anatomic variants may, in turn, influence the local concentration of infused drugs.

An outbreak of intraspinal masses associated with the administration of chemically contaminated drugs or drugs that were compounded in bulk from erroneously labeled containers appears to have been an isolated phenomenon [29]. Finally, the latency of months to years before the appearance of symptoms, in most cases, argues against implant trauma as an etiology [1,7,10].

The inability of previous hypotheses to explain most reported cases and the results of chronic dose-ranging studies of intrathecal morphine (and morphine plus clonidine mixtures) in two animal species prompted us to evaluate additional hypotheses regarding the etiology of catheter-tip inflammatory

Table 12 Histopathology of catheter-tip inflammatory masses

Pathological findings	Number of cases
Inflammation and/or granuloma formation	18
Inflammation/granuloma plus fibrosis	11
Inflammation/granuloma plus necrosis	7
Inflammation plus necrosis and fibrosis	3
Inflammation/granuloma plus calcification	1
Inflammation, fibrosis, and hematoma	1
Fibrosis only	4
Scarring and gliosis	1
Mass operated and/or no pathology reported	21
Mass not operated	25
Total	92

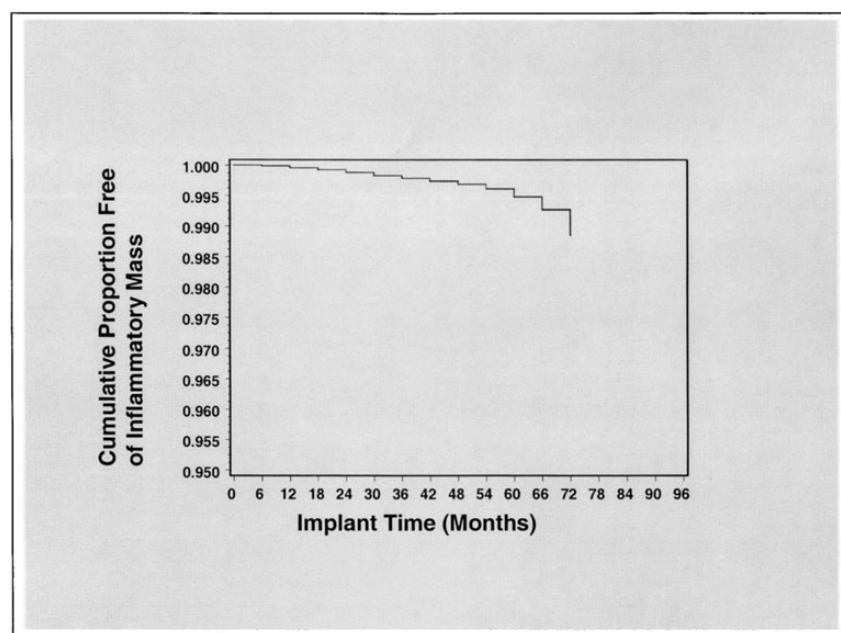


Figure 2 Life-table estimate of the risk for development of a catheter-tip mass during up to 6 years of intrathecal drug therapy. The risk increases over time from approximately 0.0004 (0.04%) after 1 year to approximately 0.0115 (1.15%) after 6 years.

masses. The most plausible explanations for the human and animal data implicate the properties of intrathecal drugs, especially morphine, in combination with intraspinal CSF flow dynamics, and possibly, catheter tip location. At present, specific formulations of two drugs—morphine sulfate (Duramorph® and Infumorph, Elkins-Sinn, Inc., Cherry Hill, NJ) and baclofen (Lioresal® Intrathecal, Medtronic, Inc., Minneapolis, MN)—are labeled for chronic intrathecal administration using implantable infusion pumps. Other formulations of preservative-free morphine compounded by pharmacies from powdered morphine sulfate are not, strictly speaking, labeled for intrathecal use. A variety of other commonly administered drugs or drug mixtures, including but not limited to hydromorphone, bupivacaine, and clonidine, also are not specifically labeled for long-term intrathecal administration. With the exception of a single small study that evaluated the safety of continuous intrathecal bupivacaine infusion for 16 weeks in dogs [30], no preclinical animal data have been published regarding the long-term neuropathological effects of continuous intrathecal infusion of these agents.

Drug Properties, Dosage, and Concentration

Intrathecal drug delivery creates a relatively high drug concentration, compared with systemic administration, within and around the spinal cord. This feature of the therapy may contribute to the phenomenon of catheter-tip mass formation. The apparent dose response for mass formation observed in the beagle dog and sheep studies actually

may have been a drug-concentration response. One species, the sheep, has a spinal canal diameter comparable with that of humans. All of the animal studies employed blinded pathologic analyses, preservative-free saline control groups, and commercially available preservative-free morphine sulfate that was labeled for chronic intrathecal administration. Daily doses were scaled to simulate those employed in human clinical practice. The studies in each animal species employed a constant infusion rate: 40 and 80 $\mu\text{L}/\text{hour}$, which equals 0.96 and 1.92 mL/day , respectively, in the dog and sheep studies. Different daily doses were delivered by filling the pump reservoirs with different drug concentrations. A separate series of experiments would be necessary to determine whether the absolute daily drug dose, or the drug concentration, was responsible for the masses that were observed. Such studies are currently in progress in the dog model. Despite these limitations, the available experimental evidence implicates one or more properties of opioid drugs (especially morphine) as an important cause for inflammatory mass formation. Furthermore, the tip of an active drug infusion catheter, where one would encounter the highest local CSF drug concentration, formed the epicenter of all of the masses that were described in human case reports and animal experiments.

The preponderance of thoracic-level catheter tips in human case reports is intriguing, but does not necessarily indicate causation. Data on the vertebral levels of inflammatory masses and catheter

Table 13 Summary of hypotheses regarding the etiology of catheter-tip masses

Proposed etiology (pertinent references)	Evaluation of plausibility	Data pros and cons
Silicone or other catheter materials [9,15,22–24]	Unlikely	Genuine IgE-mediated silicone allergy is unlikely and has been discredited as a mechanism for other disorders (e.g., after breast implants). Inflammatory mass lesions have not been reported on silicone or polyurethane lumboperitoneal shunts or in patients treated with intrathecal baclofen for spasticity. An interaction among catheter materials and other factors is possible, in theory, but has not been investigated thoroughly.
Catheter-tip design	Unlikely	Early cases involved single end-hole catheters because of market predominance. Later reports involved closed-end, multi-hole catheters.
Infection [1,5,6]	Unlikely	Tissue stains and cultures overwhelmingly have been negative. Three positive culture reports involved subcultures and/or commensal skin organisms that may have been contaminants. Animal studies ruled out infection, and human and animal specimens contained few or no polymorphonuclear cells.
Endotoxin (pyrogens) [20,21]	Unlikely	The presence of bacterial endotoxins was not sought in human or animal cases because the characteristic syndrome, aseptic meningitis, was not observed.
Surgical trauma or implant technique [7,37]	Unlikely	Surgical trauma causes early postoperative deficits, inconsistent with the months-to-years latency for catheter-tip mass lesions. Cases have occurred in association with every variation in implant technique.
Catheter tip location [1,31,32]	Possible contributing factor	The thoracic region has the narrowest relative intrathecal space and slow CSF flow. But the fact that most implanters have positioned the catheter tip in the thoracic spinal canal confounds analysis of this factor.
Intrathecal opioids and other drugs [1–7,18,19,29]	Most likely	All of the reported human cases received intrathecal opioid drugs (counting tramadol as a partial μ -opioid-receptor agonist). Animal studies suggest that mass formation occurs with a morphine dose or concentration response.

tip locations, preponderantly in the thoracic region (Figure 3 and Table 4), may reflect the distribution of implanted catheters rather than increased risk. Despite the long duration of analgesia and wide neuraxial distribution of morphine delivered to the lumbar subarachnoid space, many physicians position the tip of intrathecal catheters within the thoracic spinal canal. Reasons include a perceived need to deliver analgesic drugs close to the spinal cord segment that corresponds to the distribution of the patient's pain. Lipid-soluble opioids and local anesthetic agents are most effective when delivered close to the painful segment(s) acutely, during spinal anesthesia, or subacutely, during short-term epidural infusions. However, no data exist to support the notion that intrathecal morphine is more effective when delivered at, or near, the painful segment. One limitation of intrathecal drug delivery studies in nonprimate animals (including dogs and sheep) is that the spinal cord occupies the entire length of the lumbar spinal canal. This made the animal studies summarized in this article similar to

the situation for human patients with thoracic-level drug administration catheters.

Catheter Tip Location, Spinal Anatomy, and CSF Dynamics

Investigations during the early 1990s that employed MRI to model pulsatile CSF flow along the craniospinal axis found maximal flow velocities “approaching the convexities of the spinal canal, i.e., located anteriorly in the cervical, posteriorly in the thoracic, and anteriorly in the lumbar canal” [30, 31]. The ventral thoracic subarachnoid space was the longest region of low-CSF flow within the intrathecal compartment. To date, other investigators have not attempted to replicate those findings. Although no systematic data were recorded on the dorsal–ventral location of patients’ catheter tips and inflammatory masses, observations have revealed that most thoracic-level intrathecal drug administration catheters reside in the ventral subarachnoid space. One explanation for this anecdotal observation is that implantation using the conventional in-

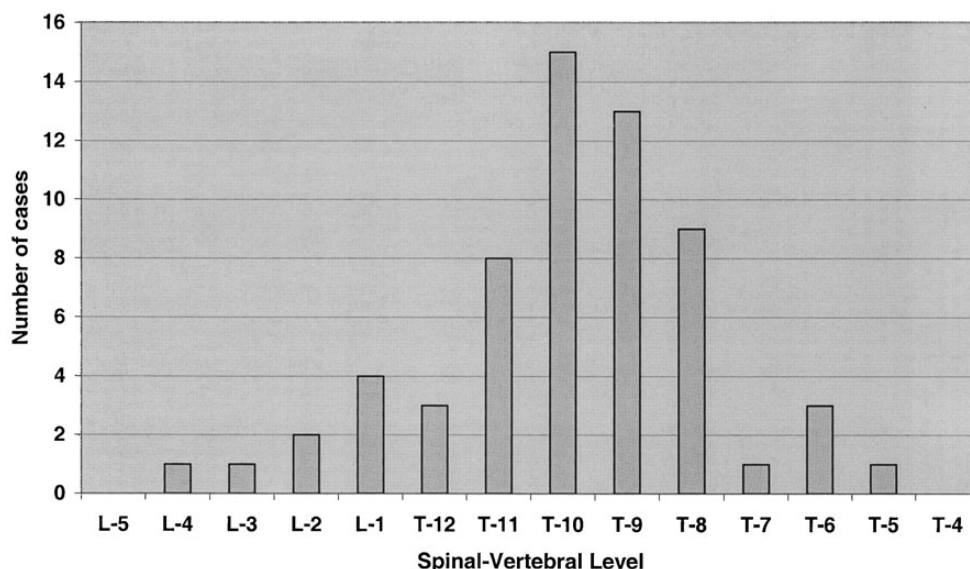


Figure 3 Histogram showing the number of catheter-tip masses that were diagnosed (number), and by implication, catheter tips that were located at each level of the spinal canal (spinal level) in 61 cases where the level was reported precisely. The low thoracic region is the most common location for the tip of intrathecal catheters. In light of that fact, the available data do not implicate thoracic catheter location as the principal risk factor for development of a catheter-tip inflammatory mass.

terspinous approach with a Tuohy needle causes the catheter trajectory to turn rostrally only after the catheter deflects off the ventral dura mater at the level of insertion. The combination of a steep insertion trajectory and catheter tip placement several segments rostral to the insertion site causes many intrathecal catheter tips to reside within the ventral thoracic subarachnoid space, a narrow region with low CSF flow and mixing. Consequently, the local concentration of infused drugs in the subarachnoid space may be even higher than anticipated. Theoretically, the drug concentration near the catheter tip may approach the concentration of drug in the pump reservoir. This hypothetical situation may be exacerbated even further by the use of high concentration drugs at low flow rates in order to lengthen the interval between pump refill appointments.

Another consequence of thoracic catheter tip placement is proximity to the spinal cord. A mass that develops on a thoracic-level catheter tip potentially can cause spinal cord compression. Catheter placement below the conus medullaris precludes spinal cord involvement. The few reported cases of masses that involved the peripheral, Schwann cell-invested roots of the cauda equina were associated with less severe neurological deficits and more complete recovery.

An important question relates to whether this effect is mediated by an opioid receptor or relates to some component of morphine's structure in a metabolite.

Interestingly, previous work with hydromorphone reported granulomas following epithelial delivery [34]. More recently, intrathecal hydromorphone infusions were also shown to have the ability to initiate inflammatory masses in the dog and sheep models (personal observation, TL Yaksh and S Hassenbusch). Such observations are consistent with but do not prove that this pathology is μ opioid receptor mediated. Accordingly, we hypothesize that a localized inflammatory reaction may cause disruption of local CSF flow and drug-distribution patterns. Systemic opioids can suppress natural leukocyte killer activity, mitogenic activity, and lymphocyte counts. Under other experimental conditions, an opioid-induced increase in lymphocyte activity may involve μ -opioid receptors [33]. However, the *in vivo* role of those receptors has not been established, and the naloxone-reversibility of the inflammatory mass phenomenon has not yet been investigated. The precise mechanism and portal by which blood-borne lymphocytes and other chronic inflammatory cells enter the subarachnoid space in response to intrathecal opioid infusions also remain to be determined. Although the chain of causality is speculative, morphine releases nitric oxide (NO) from endothelial cells. NO is a chemoattractant for inflammatory cells from the meningeal vasculature. So, high local concentrations of continuously administered morphine might generate sustained concentrations of NO. In turn, that could stimulate the diapedesis of inflam-

matory cells through meningeal vessels as the initial event in formation of a catheter-tip inflammatory mass.

Enhancement of the lesions on MRI scans [1,4,5,18] is consistent with the expected lack of a blood–CNS barrier in masses having a blood-borne inflammatory cell origin (Hassenbusch S and Yaksh T, personal observations). As noted above, systematic examination of serial sections in the dog provides strong certainty that these cells arise from the meningeal vasculature. The lack of CNS toxicity, apart from extrinsic compression, also supports the non-CNS-tissue origin of the mass lesions. Other literature and anecdotal reports have described masses that arose after opioid drug administration within non-neural tissues that include the epidural space and the subcutaneous tunnel at the site of a catheter break or disconnection ([8,11,33,37], Coffey RJ, personal observation, Follett K, personal communication). It should be emphasized that the epidural reaction is additionally complicated because of the foreign body response in this space, which is characterized by the significant presence of fibroblasts forming a well-organized encapsulating sheath [35,36].

Eventually, local CSF flow would become more erratic as an inflammatory mass increased in size. Decreased CSF and drug flows may have contributed to the poor pain control that was reported in so many cases. The increased pain, in turn, often was treated by increasing the morphine dose, changing to a more potent opioid, or adding a drug not labeled for chronic intrathecal use. The data cannot distinguish poor drug delivery followed by dose escalation as a consequence of a catheter-tip mass versus commonplace drug tolerance. However, extraordinary increases in some patients' intrathecal drug requirements occurred shortly before a catheter-tip mass was diagnosed.

The growing mass may cause a vicious cycle that consists of a cascading cellular immune stimulus, higher drug dosages, and a reactive response around the catheter tip, followed by further disruption of CSF flow and drug distribution as the mass increases. This scenario could explain the prodromal loss of pain control reported by many patients, the escalations of intrathecal drug dosage, concentration, and potency before a mass was diagnosed, and the apparent rapid onset of myelopathy that was observed in a number of cases. Mechanical compression by a growing extra-axial mass and local accumulation of morphine metabolites that cause increased nociceptive responses also may have contributed to some patients' complaints of radicular pain and loss of analgesia [17].

Conclusions

We hypothesize that the properties of intrathecal morphine and some drugs, especially other opioids that are not labeled for chronic intrathecal use, may be responsible for the growth of inflammatory masses at the tip of intrathecal drug delivery catheters. CSF flow dynamics within the spinal canal may contribute to the accumulation of local intrathecal drug concentrations that approach the drug concentrations in the pump reservoir. Previous spinal surgery or normal variations in the anatomy of arachnoid membranes also may influence the local concentration of intraspinal drugs. Positioning the tip of drug administration catheters below the conus medullaris may not eliminate the risk of developing a mass, but would preclude injury to the spinal cord. The drug labeling information for Infumorph® brand of preservative-free morphine sulfate sterile solution (Elkins-Sinn, Inc., Cherry Hill, NJ) does not address the issue of intrathecal catheter-tip inflammatory masses. However, the drug package insert states: "The published range of doses for individuals who have some degree of tolerance varies from 1 to 10 mg/day. . . . Doses above 20 mg/day should be employed with caution since they may be associated with a higher likelihood of serious effects . . ." We believe that the risk of developing a catheter-tip mass is another reason to limit the dose of intrathecal morphine.

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