

January 2008

Urgent: Medical Device Correction

Updated Information - Inflammatory Mass (granuloma) At or Near the Distal Tip of Intrathecal Catheters

Dear Healthcare Professional,

This letter is an update to two previous communications¹ issued by Medtronic in 2001 and 2003, and is intended to provide the medical community with the current post-market incidence of reported inflammatory mass and **information that may facilitate patient management**.

Inflammatory mass presents as a chronic inflammatory or granulomatous mass at or near the distal tip of intrathecal catheters and has been reported with the intrathecal infusion of opioids, baclofen, pharmacy-compounded drugs, and other pharmacological admixtures. The precise etiology of inflammatory mass is unknown. Clinical evaluation with MRI or histology shows an association of inflammatory mass with morphine sulfate, other opioids, and analgesic admixtures. The highest reported rate of inflammatory mass formation has been associated with the use of opioids. The most plausible etiology for inflammatory mass formation with the use of opioids, as supported by preclinical studies, relates inflammatory mass to the administration of relatively high dose and/or high concentration morphine sulfate and/or other opioids. Current available information does not definitively exclude other possible contributing factors such as other infusates, catheter design or material.

Incidence of Opioid-Related Inflammatory Mass

One study that prospectively evaluated 208 patients reported a 3% incidence of inflammatory mass². Through September 2007, there has been an estimated 0.49% incidence of inflammatory mass reported to Medtronic for patients ever implanted with a drug infusion system for treatment of pain. The actual incidence is likely to be higher due to under reporting, but the extent of under reporting is currently unknown.

Based on current Medtronic analysis, the reported incidence of patients who have developed inflammatory mass (0.49%) is approximately five times higher than was reported in 2001 (0.1%). The rate of occurrence of inflammatory mass is expected to continue to increase. This may be at least partially due to the longer average duration of time that the product is implanted. Some reported cases occurred within six months, while others occurred as long as ten or more years after starting opioid therapy. Reported cases of inflammatory mass are from reports submitted to Medtronic by patients and/or health care providers, Medtronic personnel, or from scientific literature.

Table 1.0 presents a summary of the frequency of symptoms associated with 448 reports of inflammatory mass from October 1990 through September 2007. These reported patient symptoms are currently identified in the professional labeling (Appendix A). A patient may have reported more than one symptom. The most frequently reported symptoms associated with inflammatory mass are:

- decreased therapeutic response/inadequate pain relief (reported in 33.5% of patients),
- pain (reported in 32.6% of patients),
- neurological deficit/dysfunction (reported in 17.4% of patients).

Table 1.0 Summary of Symptoms Reported for Cases of Inflammatory Mass

Symptoms [a]	Number of Reports of Symptom	Percent of Cases with Symptom (n = 448)
Decreased therapeutic response/inadequate pain relief	150	33.5%
Pain	146	32.6%
Neurological deficit/dysfunction	78	17.4%
Unknown (reports did not provide the patient's condition)	74	16.5%
Paralysis/paraplegia/paresis	67	15.0%
Weakness/muscle weakness	62	13.8%
Numbness	43	9.6%
Incontinence	32	7.1%
Ambulation difficulties	12	2.7%
Urinary retention	8	1.8%
Tingling	8	1.8%
Headache	7	1.6%
Muscle spasm(s)	7	1.6%
Burning sensation	6	1.3%
Other [b]	68	15.2%

[a] There may be more than one symptom per report of inflammatory mass

[b] Multiple symptoms, each reported in less than 1% of cases of inflammatory mass

Inflammatory mass has been associated with a wide range of doses and concentrations of opioids. No dose and/or concentration of morphine sulfate can be considered completely free of risk from inflammatory mass³. The risk of inflammatory mass occurrence appears to be cumulative over time and increases with higher concentrations of opioids.

The following product information is an excerpt from the Infumorph[®] Drug Package Insert (Baxter)⁴.

The recommended initial lumbar intrathecal dose range in patients with no tolerance to opioids is 0.2 to 1 mg/day. The published range of doses for individuals who have some degree of opioid tolerance varies from 1 to 10 mg/day. The upper daily dosage limit for each patient must be individualized.

Doses above 20 mg/day should be employed with caution since they may be associated with a higher likelihood of serious side effects.

Preclinical^{5,6,7,8,9} and clinical^{10,11,12,13,14,15,16} studies with intrathecal infusion have suggested that high doses and/or high concentrations of opioids increase the risk of inflammatory mass. Additionally, Medtronic data analysis indicates the risk of developing inflammatory mass in the next six months increases at least through the first thirty-six months of opioid therapy. Therefore, intrathecal opioids should be administered to achieve adequate analgesia for as long as possible at the lowest effective dose and concentration.

Figures 1-3 graphically show the estimated cumulative risk and survival from inflammatory mass by length of implant time and by the registered indication for the intrathecal infusion system. These figures were developed using data from Medtronic's voluntary post-market reporting system:

- Figure 1: By indication: chronic pain, spasticity, and both indications combined
- Figure 2: Chronic pain (with 95% confidence limits)
- Figure 3: Spasticity (with 95% confidence limits)

Note that the history of the actual drugs used in these infusion systems is not known, although for spasticity patients it is highly likely that baclofen was included [either Novartis Pharmaceuticals' Lioresal[®] Intrathecal (baclofen injection) or pharmacy-compounded baclofen].

Actuarial Risk of Reported Inflammatory Mass Through Sept 2007, by Time Since Implant and by Indication (Pump Data as of 10/22/07)

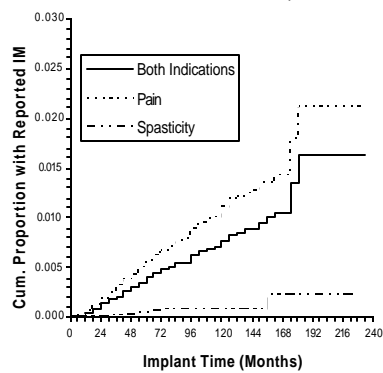


Figure 1

Actuarial Risk (with 95% Confidence Limits) of Reported Inflammatory Mass Through Sept 2007, by Time Since Implant (Pain Pump Data as of 10/22/07)

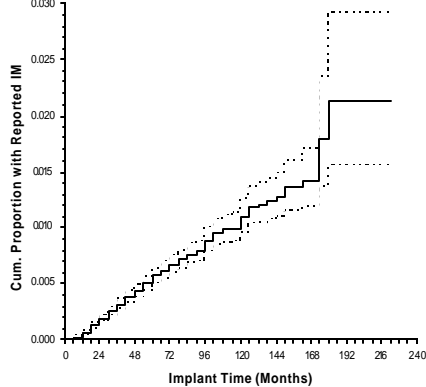
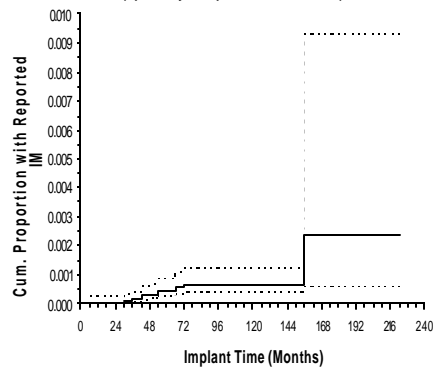


Figure 2

Actuarial Risk (with 95% Confidence Limits) of Reported Inflammatory Mass Through Sept 2007, by Time Since Implant (Spasticity Pump Data as of 10/22/07)



Note: Figure 3 Y-axis is scaled to 1/3 of Figures 1 and 2.

Figure 3

Information Regarding Intrathecal Baclofen Infusion

Medtronic has also reviewed its reports database and the medical literature to evaluate inflammatory mass in patients receiving intrathecal baclofen. There are cases of inflammatory mass reported with intrathecal baclofen as the sole agent.^{17,18,19,20} The estimated risk of developing inflammatory mass is lower for patients treated for spasticity (presumably with intrathecal baclofen) than for patients treated for pain (see Figure 1). A common symptom associated with decreased baclofen therapy is the return of spasticity in patients. Physicians managing patients on ITB TherapySM (Intrathecal Baclofen Therapy) should use their medical judgment regarding the most appropriate monitoring specific to their patients' medical needs to identify prodromal clinical signs and symptoms for inflammatory mass, especially if using pharmacy-compounded drugs or baclofen admixtures that include opioids.

Recommendations for Patient Management

Individual patient susceptibility to inflammatory mass cannot be predicted. Diligent patient management and increased awareness of inflammatory mass symptoms may reduce the incidence of inflammatory mass or its sequelae. For pain therapy, the patient management recommendations for inflammatory mass as provided in the professional labeling (see Appendix A) have not changed.

In patients with new neurological signs or symptoms, consider neurosurgical consultation and the prompt performance of an imaging procedure (for example, MRI with and without contrast or CT myelogram) to confirm or rule-out the diagnosis of an inflammatory mass.

Medtronic is aware that pharmacy-compounded drugs and other pharmacological drug mixtures may be administered to patients through drug infusion systems. Medtronic strongly advises physicians to be familiar with the approved intrathecal indications for these devices; including preservative-free morphine sulfate sterile solution; Lioresal[®] Intrathecal (baclofen injection); and preservative-free ziconotide sterile solution. The effect of administering other drugs intrathecally through these devices has not been assessed.

Summary

In summary, healthcare professionals are encouraged to consider the following recommendations:

- When administering intrathecal opioids, the lowest effective dose and concentration should be administered.
- In patients treated with Intrathecal Baclofen Therapy, physicians should closely monitor their patients in order to identify the prodromal clinical signs and symptoms of inflammatory mass, especially if using pharmacy-compounded drugs or baclofen admixtures that include opioids.
- In patients with new neurological signs or symptoms, consider neurosurgical consultation and the prompt performance of an imaging procedure to confirm or rule-out the diagnosis of an inflammatory mass.

The US Food and Drug Administration (FDA) has knowledge of this communication being sent to Healthcare Professionals.

Please report any new and/or previously unreported inflammatory mass in a patient with a Medtronic device to Medtronic Neuromodulation Product Performance at 1-800-328-0810, and to the FDA's MedWatch Program by phone at 1-800-FDA-1088, by Fax at 1-800-FDA-0178, by mail at MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20852-9787, or on the MedWatch web site at www.fda.gov/medwatch.

For Assistance

Contact Medtronic Neuromodulation Technical Services at 1-800-707-0933, Monday - Friday, 7:00 a.m. - 6:00 p.m. (Central Time), or your local Medtronic field representative. This information including links to the references or abstracts can be found on our web site at www.medtronicconnect.com.

Sincerely,

A handwritten signature in black ink, appearing to read "George Aram". The signature is fluid and cursive, with the first name "George" being more prominent than the last name "Aram".

George Aram
Vice President Quality
Medtronic Neuromodulation

Enclosure: Appendix A - Excerpts from the Approved Medtronic Professional Labeling

Appendix A

Excerpts from the Approved Medtronic Professional Labeling

Warnings

Inflammatory mass at the catheter tip (symptoms) –

An inflammatory mass that can result in serious neurological impairment, including paralysis, could occur at the tip of the implanted catheter. Patients on intraspinal opioid therapy should be monitored carefully at each visit for any new neurological signs or symptoms.

Physicians should routinely monitor patients receiving **opioids** for the following prodromal clinical signs or symptoms of inflammatory mass:

- Change in the character, quality, or intensity of pain
- Reports of new radicular pain, especially at or near the dermatomal level of the catheter tip
- Frequent or large escalations of the daily drug dose are required to maintain the analgesic effect
- Dose escalations alleviate increasing pain only temporarily

To prevent possible permanent neurological injury, physicians should immediately evaluate patients who develop the following signs or symptoms:

- New or different sensory symptoms (eg, numbness, tingling, burning, hyperesthesia, hyperalgesia)
- New, occasional, or intermittent bowel or bladder sphincter dysfunction
- New motor weakness, change in gait, or difficulty walking
- Any neurological symptoms or signs that differ from baseline (eg, reflex changes)

Physicians should routinely monitor patients receiving **intrathecal baclofen** as a sole agent for the following prodromal clinical signs or symptoms of inflammatory mass:

- Change in the character, quality, or intensity of spasticity
- Frequent or large escalations of the daily drug dose are required to maintain the antispastic effect
- Rapid dose escalations alleviate the increasing spasticity only temporarily

Refer to “Adverse events summary” for more information on recognition, treatment, and mitigation of inflammatory mass.

Intraspinal therapy –

For intraspinal therapy, use **ONLY** a preservative-free sterile solution indicated for intraspinal use. Nonindicated fluids containing preservatives or endotoxins can be neurotoxic in intraspinal applications. Using nonindicated fluids can result in adverse events including, but not limited to, extreme pain, cramps, seizures, and death.

Adverse events summary

Drug-related complications

- Local or systemic drug toxicity and related side effects
- Inflammatory mass formation at the tip of the implanted catheter particularly in patients who receive intraspinal morphine or other opioid drugs

Recognition of inflammatory mass

For patients receiving intrathecal opioids, the following **prodromal**, or **warning** signs or symptoms may occur before the onset of more severe neurological impairment:

- Change in the character, quality, or intensity of pain
- New radicular pain, especially at or near the dermatomal level of the catheter tip
- Frequent or large escalations of the daily drug dose are required to maintain the analgesic effect
- Dose escalations alleviate the increasing pain only temporarily

For patients receiving intrathecal baclofen as a sole agent, the following **prodromal**, or **warning** signs or symptoms may occur before the onset of more severe neurological impairment¹:

- Change in the character, quality, or intensity of spasticity
- Frequent or large escalations of the daily drug dose are required to maintain the antispastic effect
- Rapid dose escalations alleviate the increasing spasticity only temporarily

All patients on intraspinal opioid therapy should be monitored carefully at each visit for any new neurological signs or symptoms, including:

- New or different sensory symptoms (eg, numbness, tingling, burning, hyperesthesia, hyperalgesia)
- New, occasional, or intermittent bowel or bladder sphincter dysfunction
- New motor weakness, change in gait, or difficulty walking
- Any neurological symptom or sign that differs from baseline (eg, reflex changes)

In patients with new neurological signs or symptoms, consider neurosurgical consultation and the prompt performance of an imaging procedure (eg, MRI with and without contrast or CT myelogram) to confirm or rule-out the diagnosis of an inflammatory mass.

Treatment of inflammatory mass

Timely treatment may minimize, or help to avert permanent neurological injury.

If an inflammatory mass is detected early in its clinical course, a decrease or discontinuation of opioid delivery into the mass may cause it to shrink or disappear without the need for surgical removal.

Note: Refer to Emergency Procedures included in the technical manual packaged with the refill kit for information on emptying the pump. Stopping the pump for more than a few days can cause the rotor to stall permanently. If therapy is to be discontinued for an extended period of time, the pump should be filled with preservative-free saline and programmed to run at the minimum rate of 0.048 mL/day.

Depending upon an individual patient's clinical condition, intraspinal therapy may be continued after one of the following interventions:

- Withdraw the catheter to a level below the inflammatory mass.
- Remove the involved catheter and replace it with a new catheter positioned below the inflammatory mass.
- Disconnect the involved catheter from the connector (two-piece catheter), or transect the involved catheter above the level of the lumbo-dorsal fascia (one-piece catheter) leaving the intraspinal catheter segment undisturbed. Ligate the exposed end of involved catheter to prevent CSF loss. Implant a new catheter with its tip below the inflammatory mass, and connect the new catheter to the proximal (pump) catheter segment.

Prompt open surgical removal of the mass or decompression of the spinal canal should be considered in patients who have a significant or progressive neurological deficit.

Mitigation of inflammatory mass

Intraspinal therapy should be administered to achieve adequate clinical response for as long as possible at the lowest effective dose and concentration.

For the treatment of pain patients, whenever medically possible, the tip of the intraspinal catheter should be placed in the lumbar thecal sac, below the conus medullaris. Lumbar placement may lessen the neurological consequences if an inflammatory mass develops.

Patients who receive intraspinal opioid therapy should be monitored carefully at each visit for any new clinical and neurological signs or symptoms.

¹ Based on three case reports of patients from Murphy and Deer, respectively - Murphy PM, Skouvaklis DE, Amadeo RJJ et al. *Intrathecal Catheter Granuloma Associated with Isolated Baclofen Infusion*, *Anesthesia Analgesia* 2007; 102:848-852. Deer TR, Raso LJ, Garten TG. *Inflammatory Mass of an Intrathecal Catheter in Patients Receiving Baclofen as a Sole Agent: A Report of Two Cases and a Review of the Identification and Treatment of the Complication*. *Pain Medicine* 2007; 8(3):259-262.

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- ¹ Medtronic January 2001 letter "Important Message Regarding the Occurrence of Inflammatory Masses at the Tip of Intraspinal Catheters," and Medtronic July 2003 Educational Brief "Information about Inflammatory Mass, Intrathecal Drug Infusion"
- ² Deer, TR. A prospective analysis of intrathecal granuloma in chronic pain patients: a review of the literature and report of a surveillance study. *Pain Physician*. 2004;7:225-228.
- ³ Yaksh TL, Hassenbusch S, Burchiel K, Hildebrand KR, Page LM, Coffey RJ. Inflammatory masses associated with intrathecal drug infusion, a review of preclinical evidence and human data. *Pain Med* 2002;3:300-312.
- ⁴ Product Information Infumorph Baxter Healthcare Corp. Deerfield Illinois October 2003.
- ⁵ ibid endnote 3
- ⁶ Yaksh TL, Horais KA, Tozier NA, et al. Chronically infused intrathecal morphine in dogs. *Anesthesiology*. 2003;99:174-187.
- ⁷ Gradert TL, Baze WB, Satterfield WC, Hildebrand KR, Johansen MJ, Hassenbusch SJ. Safety of chronic intrathecal morphine infusion in a sheep model. *Anesthesiology*. 2003;99:188-198.
- ⁸ Allen JW, Horais KA, Tozier NA, et al. Time course and role of morphine dose and concentration in intrathecal granuloma formation in dogs: a combined magnetic resonance imaging and histopathology investigation. *Anesthesiology*. 2006;105:581-589.
- ⁹ Allen JW, Horais KA, Tozier NA, Yaksh TL. Opiate pharmacology of intrathecal granulomas. *Anesthesiology*. 2006;105:590-598.
- ¹⁰ McMillan MR, Doud T, Nugent W. Catheter-associated masses in patients receiving intrathecal analgesic therapy. *Anesth Analg*. 2003;96:186-190.
- ¹¹ ibid endnote 2
- ¹² ibid endnote 3
- ¹³ Hassenbusch S, Burchiel K, Coffey RJ, et al. Management of intrathecal catheter-tip inflammatory masses: a consensus statement. *Pain Med*. 2002;3:313-323.
- ¹⁴ Coffey RJ, Burchiel K. Inflammatory mass lesions associated with intrathecal drug infusion catheters: report and observations on 41 patients. *Neurosurgery*. 2002;50:78-87.
- ¹⁵ Cabbell, KL, Taren JA, Sagher O. Spinal cord compression by catheter granulomas in high-dose intrathecal morphine therapy: case report. *Neurosurgery*. 1998;42:1176-1181.
- ¹⁶ Schuchard M, Lanning R, North R, et al. Neurologic sequelae of intraspinal drug delivery systems: Results of a survey of American implanters of implantable drug delivery systems. *Neuromodulation*. 1998;1:137-148.
- ¹⁷ Murphy PM, Skouvakis DE, Amadeo RJ, Haberman C, Brazier DH, Cousins MJ. Intrathecal catheter granuloma associated with isolated baclofen infusion. *Anesth Analg*. 2006; 102:848-852.
- ¹⁸ Narouze SN, Mekhail NA. Intrathecal catheter granuloma with baclofen infusion. *Anesth Analg*. 2007; 104:209-210.
- ¹⁹ Coffey RJ, Allen JW. Not all intrathecal catheter tip MRI findings are inflammatory mass. *Anesth Analg*. 2007; 104:1600-1602.
- ²⁰ Deer TR, Raso LJ, Garten TG. Inflammatory mass of an intrathecal catheter in patients receiving baclofen as a sole agent: a report of two cases and a review of the identification and treatment of the complication. *Pain Med* 2007; 8:259-262.