

IMPORTANT PATIENT SAFETY MANAGEMENT INFORMATION EDUCATIONAL BRIEF



Medtronic

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Patient Mortality after Implant and Initiation of Intrathecal Infusion Therapy for Pain

Model 8637 SynchroMed[®] II Implantable Pump
Model 8626/8627 SynchroMed[®] EL Implantable Pump
Model 8616/8617 SynchroMed[®] Implantable Pump
Model 8472 IsoMed[®] Implantable Pump

Tools for Safe Patient Management

Purpose

This Educational Brief provides important pain therapy information for physicians who implant and/or manage patients with Medtronic SynchroMed[®] or IsoMed[®] infusion systems. This education brief is intended to remind clinicians of the appropriate drug administration and monitoring procedures. Adherence to these procedures will reduce the risk of death or serious injury during initiation of intrathecal opioid therapy for pain – or during re-initiation of intrathecal opioid drug administration after temporary interruption or discontinuation of therapy.

PLEASE NOTE:

Preservative-free morphine sulfate sterile solution (Infumorph) is the only opioid drug currently approved by the US FDA for chronic intrathecal administration using the SynchroMed infusion system. The recommendations in this education brief are based upon the Infumorph package insert. Clinicians who elect to use off label drugs in the Medtronic SynchroMed infusion system must be aware of the prescribing information for those medications.

Explanation of the Issue

Between December, 2005 and March, 2006 Medtronic received reports of nine patient deaths within three days after the initiation – or re-initiation following interrupted use – of intrathecal opioid therapy for pain. The cases involved new system implants, catheter revisions, and system replacements. Medtronic has concluded the patient deaths were most likely caused by opioid and/or sedative drug overdose.

Investigation Findings

Medtronic interviewed the implanting physicians and analyzed returned infusion pumps, programming records and medical examiner reports. **Available evidence indicates that the infusion systems operated normally, and that device malfunction was not the cause of these adverse events.**

The investigation identified multiple factors that contributed to the patients deaths:

- **Relatively high initial doses:** Seven deaths occurred after the initiation – or re-initiation after interrupted use – of intrathecal opioid therapy at relatively high morphine or morphine-equivalent daily doses compared to the range of starting doses recommended in the Infumorph¹ drug labeling/package insert.
- **Respiratory depressant effects of intrathecal opioids:** Profound respiratory depression can occur after initiating intrathecal opioid therapy – even in patients exposed to long-term systemic opioids. All nine deaths involved patients who were just started on intrathecal opioid therapy, or for whom the therapy was restarted after weeks of interruption.
- **Insufficient patient monitoring:** Seven of the patients were released from the hospital within 24 hours after *initiation* of intrathecal opioid therapy for pain or after *re-initiation* of intrathecal therapy following interrupted use.
- **Concomitant medications:** Seven patients were prescribed, administered in-hospital, or self-administered systemic opioid and/or sedative drugs. Those concomitant medications may have amplified the respiratory depressant effects of the intrathecal opioids.
- **Co-morbid risk factors:** Several patients had risk factors for respiratory depression that included pulmonary disease, severe obesity, and/or advanced age.
- **Intrathecal Catheter and Pump Tube Volume:** In two cases, the internal pump tubing and intrathecal catheter volumes were not accounted for correctly. These errors increased the intended dose of the intrathecal drug.

In summary, it appears that the etiology of these patient deaths was multi-factorial and not due to device malfunction. However, Medtronic believes that analysis of these cases has revealed important information for implanters and managing physicians.

Recommendations for Patient Management

Patient Population

The patient population potentially at risk includes all patients receiving intrathecal opiate therapy, especially those who are: intrathecal opiate-naive; those with labeled risk factors (e.g., advanced age, underlying pulmonary disease, severe obesity, kyphoscoliosis, paralysis of the phrenic nerve, or hepatic or renal disease); and those patients having their therapy initiated at a high dose (morphine or morphine-equivalent daily dosage >1 mg/day). Exposure to systemic opioids does not necessarily provide an individual patient with an increased threshold for the profound respiratory depressant effects that can be induced by intrathecal opioids. Patients who have had their intrathecal opioids interrupted for any reason (e.g., because of catheter, pump, or system malfunctions) may be effectively opioid naive at the time of system revision. Such patients should be treated as if they were newly implanted.

Initiate Therapy according to the Infumorph Package Insert

The Infumorph package insert recommends an initial dose for continuous intrathecal infusion of morphine of ≤ 1.0 mg/day.¹ The same considerations that apply to initial intrathecal opioid dose selection also apply to therapy re-initiation after interrupted use for pain. For each patient titrate to a therapeutic dose, allowing adequate time between dosing changes for detection and management of any side-effects. Comorbid risk factors and concomitant systemic opioid and or

¹Product Information. Infumorph Baxter Healthcare Corp. Deerfield Illinois October 2003.

sedative drugs can potentiate the respiratory depressant effects of intrathecal opioids. A reduced intrathecal opioid starting dose can be prescribed when such factors are present. Physicians also should be aware of the complexity and uncertainty involved in converting a systemic opioid dose to an equianalgesic intrathecal dose.²

Choose a drug concentration only after first selecting the patient's starting intrathecal dose, and with the following considerations in mind: The starting dose may need to be decreased, and the lowest intrathecal drug dose deliverable by SynchroMed EL and SynchroMed II is approximately 1/20 of the drug concentration.

Co-administration of medications that have respiratory depressant effects (e.g. opioids, anxiolytics, sedatives, and others) heighten the need for adequate supervision and monitoring during the immediate postoperative period.

Closely monitor patients after the initiation – or re-initiation after interrupted use – of continuous intrathecal opioid therapy. Patients should be monitored in an adequately equipped facility for sufficient time to assure that they do not experience serious or life-threatening side effects, especially respiratory depression. The Infumorph package insert states, “*The facility must be equipped with resuscitative equipment, oxygen, naloxone injection, and other resuscitative drugs.*” Post-operative monitoring is especially important in patients with comorbid risk factors and/or who are administered concomitant medications. Refer to the attached Infumorph package insert for complete prescribing information.

Programming

Ensure that device programming is performed correctly. When performing a pump or catheter replacement, be sure to account for the entire drug volume in the system – including the inner pump tubing and the intrathecal catheter. For programming assistance, contact Medtronic Neurological Technical Services (1-800-707-0933).

Education

Educate patients, accompanying individuals, and caregivers about the signs and symptoms of opioid and sedative drug overdose. Instruct them to seek emergency medical assistance when signs or symptoms first appear.

For Assistance

In the United States, contact Medtronic Technical Services: 1-800-707-0933. Outside of the United States, contact your Medtronic Representative.

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² Anderson R, Saiers JH, Abram S, Schlicht CS. Accuracy in equianalgesic dosing: conversion dilemmas. *J Pain Symptom Management*. 2001; 21:397-406.