Intrathecal Distal End Catheter Occlusions as a Result of pH & Salt Concentration Gradients Between Delivery Solution & Cerebrospinal Fluid (CSF)

SYNCHROMED® EL & SYNCHROMED II INFUSION SYSTEMS

BY MEDTRONIC NEUROMODULATION

Intrathecal Distal End Catheter Occlusions as a Result of pH & Salt Concentration Gradients Between Delivery Solution & Cerebrospinal Fluid (CSF)

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Summary

Medtronic has confirmed through engineering analyses that the use of indicated and nonindicated drug formulations can result in collection of protein in the catheter lumen, distal end. Although this may occur with any drug, nonindicated drug formulations can result in significant collection of material in the catheter lumen resulting in complete occlusion of the catheter, loss of patency, and therapy cessation. CSF proteins have been identified in returned catheters with occlusion at the distal end.

Nonindicated formulations are not approved for use with the infusion systems. Use of nonindicated drugs or fluids may result in increased risks to the patient due to permanent damage to the catheter requiring surgical replacement and a loss or change in therapy, which may lead to a return of underlying symptoms, drug withdrawal symptoms, or a clinically significant or fatal drug underdose.

Nonindicated drug formulations include drugs not listed in the Indications labeling, admixtures, compounded drugs, and unapproved drug concentrations. Indications labeling is provided with the pump and catheter systems; additional copies of the labeling can be requested from Medtronic.

How Does Distal Catheter Occlusion Occur?

Mixing of the drug and cerebrospinal fluid (CSF) normally occurs in and around the distal end of the intrathecal catheter. High salt concentration gradients and pH gradients between the drug and CSF in this mixing area can result in an environment that promotes more precipitation and aggregation of available proteins within the distal portion of the catheter, ultimately leading to complete occlusion of the distal catheter lumen and ports.

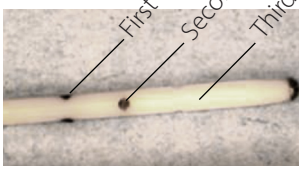
Protein aggregation within the distal end of the catheter can lead to complete occlusion of the catheter, and therapy cessation.

- Nonindicated drug formulations may have pH different than that of indicated drug formulations, resulting in higher pH gradients relative to CSF pH that result in more aggregation of protein than with indicated drug formulations.
- Nonindicated drug formulations can introduce a higher concentration of inorganic salt ions than are present in lumbar CSF, which can result in more aggregation of protein than with indicated drug formulations.
- CSF Proteins have been identified in returned catheters with occlusion at the distal end.

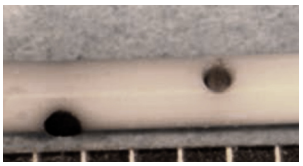
The pH of lumbar CSF is 7.3,* and all drugs indicated for intrathecal infusion have a pH greater than pH 4.0.**

Images Collected During Medtronic Returned-Product Analysis of Two Different Catheters Returned for Distal Catheter Occlusion

Catheter A

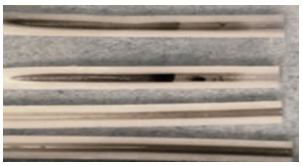


Distal End, Overview



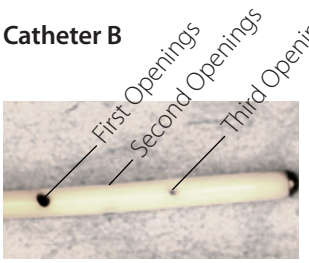
Occlusion, Close-up, First and Second Openings

Distal End Lumen, No Occlusion Material Noted, Third Openings

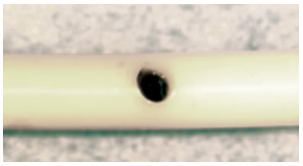


Distal End Lumen, Partially Occluded Lumen, First and Second Openings

Catheter B

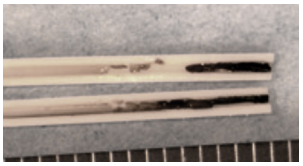


Distal End, Overview



Partially Occluded Hole, Close-up, First Openings

Distal End Lumen, No Occlusion Material Noted, Second and Third Openings



Distal End, Partially Occluded Lumen, First Openings

Confirmed Nonindicated Drugs That Have Resulted in Distal Catheter Occlusion

The in-pump stability of labeled drugs has been studied for specific chemical conditions. When pH changes as a result of compounding or admixing the drug, it may degrade to generate drug impurities resulting in altered stability of the drug product. Through returned product analysis and in vitro testing, Medtronic has confirmed nonindicated drugs that result in intrathecal catheter occlusion at the distal end include:

- Compounded drugs, including some formulations of baclofen and morphine
- Admixtures for severe spasticity therapy containing baclofen with clonidine, and baclofen mixed with other drugs
- Admixtures for chonic pain therapy containing morphine, baclofen, hydromorphone, clonidine, bupivacaine, fentanyl, and/or sufentanil.

Other nonindicated drug formulations may also result in intrathecal catheter occlusion at the distal end.

Clinical Significance

Intrathecal catheter occlusion at the distal end results in therapy cessation.

Conclusion & Recommendations

Use only those drugs that are indicated for use in the SynchroMed® EL & SynchroMed II infusion systems to minimize the potential for occlusion at the distal end of the intrathecal catheter. Using nonindicated drugs increases the likelihood of occlusion at the distal end of the catheter. If nonindicated drug formulations have been used with the SynchroMed EL or SynchroMed II infusion systems, product reliability may be impacted; therefore, more frequent patient follow-up may be required to evaluate ongoing system performance.

References

* Artru A., Yaksh TL(ed.) Spinal cerebrospinal fluid chemistry and physiology. *Spinal Drug Delivery.* Elsevier Science B.V. (8)177-185.1999.

** See Prialt® disclosure for more information.

SynchroMed® II Drug Infusion System Brief Summary:
Product technical manuals and the appropriate drug labeling must be reviewed prior to use for detailed disclosure.
Indications: US: Chronic intraspinal (epidural and intrathecal) infusion of preservative-free morphine sulfate sterile solution in the treatment of chronic intractable pain, chronic intrathecal infusion of preservative-free ziconotide sterile solution for the management of severe chronic pain, and chronic intrathecal infusion of Lioresal® Intrathecal (baclofen injection) for the management of severe spasticity; chronic intravascular infusion of floxuridine (FUDR) or methotrexate for the treatment of primary or metastatic cancer. Outside of US: Chronic infusion of drugs or fluids tested as compatible and listed in the product labeling. **Contraindications:** When infection is present; when the pump cannot be implanted 2.5 cm or less from the surface of the skin; when body size is not sufficient to accept pump bulk and weight; when contraindications exist relating to the drug; drugs with preservatives. Do not use the Personal Therapy Manager accessory to administer opioid to opioid-naïve patients or to administer ziconotide. **Warnings: Comply with all product instructions for initial preparation and filling, implantation, programming, refilling, and injecting into the catheter access port (CAP) of the pump. Failure to comply with all instructions can lead to technical errors or improper use of implanted infusion pumps and result in additional surgical procedures, a return of underlying symptoms, or a clinically significant or fatal drug under- or overdose.** Refer to the appropriate drug labeling for specific under- or overdose symptoms and methods of management. Avoid using short wave (RF) diathermy within 30 cm of the pump or catheter. Diathermy may produce significant temperature rises in the area of the pump and continue to heat the tissue in a localized area. If overheated, the pump may over infuse the drug, potentially causing a drug overdose. Effects of other types of diathermy (microwave, ultrasonic, etc.) on the pump are unknown. An inflammatory mass that can result in serious neurological impairment, including paralysis, may occur at the tip of the implanted catheter. Clinicians should monitor patients on intraspinal therapy carefully for any new neurological signs or symptoms. For intraspinal therapy, use only preservative-free sterile solution indicated for intraspinal use. Use only Medtronic components indicated for use with this system. Failure to firmly secure connections can allow drug or cerebrospinal fluid (CSF) leakage into tissue and result in tissue damage or inadequate therapy. A postoperative priming bolus should not be programmed if the pump is a replacement and the catheter has not been aspirated. Refer to appropriate drug labeling for indications, contraindications, warnings, precautions, dosage and administration information, and screening procedures. Physicians must be familiar with the drug stability information in the technical manual and must understand the dose relationship to drug concentration and pump flow rate before prescribing pump infusion. Implantation and ongoing system management must be performed by individuals trained in the operation and handling of the infusion system. Inform patients of the signs and symptoms of drug under- or overdose, appropriate drug warnings and precautions regarding drug interactions, potential side effects, and signs and symptoms that require medical attention. Instruct patients to notify their clinician of travel plans, to return for refills at prescribed times, avoid activities such as strenuous exercise or contact sports that jar, impact, twist, or stretch the body, to always carry their Medtronic device identification card, to avoid manipulating the pump through the skin, and to notify healthcare professionals of the implanted pump before medical tests/procedures. Patients must consult their physician before engaging in activities involving pressure or temperature changes (e.g., scuba diving, saunas, hot tubs, hyperbaric chambers, flights, skydiving, etc.) Inform patients that pump has an Elective Replacement Indicator (ERI) that sounds when the pump is nearing its end of service. When the alarm sounds, patients must contact their doctor to schedule pump replacement. **Precautions:** The pump is ethylene oxide sterilized. Do not use if the product or package is damaged, the sterile seal is broken, or the "Use By" date has expired. Do not reuse or resterilize the pump; it is intended for "single use only." Do not expose the pump to temperatures above 43°C or below 5°C. Consider use of peri- and post-operative antibiotics for pump implantation, for any subsequent surgical procedure, or if infection is present. For patients prone to CSF leaks, clinicians should consider special procedures, such as a blood patch. Follow instructions for emptying and filling the pump during a replacement or revisions that require removal of the pump from the pocket. Explant the pump postmortem if incineration is planned (to avoid explosion), or if local environmental regulations mandate removal. Return explanted devices to Medtronic for analysis and safe disposal. Do not implant a pump dropped onto a hard surface or showing signs of damage. Implant the pump less than 2.5 cm from the surface of the skin. Ensure pump ports will be easy to access after implant, that the catheter is not kinked and secured well away from pump ports before suturing. Keep the implant site clean, dry, and protected from pressure or irritation. If therapy is discontinued for an extended period of time, fill the reservoir with preservative-free saline in intraspinal applications or appropriate heparinized solution (if not contraindicated) in vascular applications.
The magnetic field or telemetry signals produced by the programmer may cause sensing problems and inappropriate device responses with an implantable pacemaker and/or defibrillator. Electromagnetic interference (EMI) is an energy field generated by equipment found in the home, work, medical, or public environments. Most EMI normally encountered will not affect the operation of the pump. Exceptions include: injury resulting from heating of the pump which can damage surrounding tissue (diathermy, MRI), system damage which can require surgical replacement or result in loss/change in symptom control (defibrillation, electrocautery, high-output ultrasonics, radiation therapy), and operational changes to the pump causing the motor to stop, loss of therapy, return of underlying symptoms, and require confirmation of pump function (diathermy, high magnetic field devices, hyperbaric/hypobaric conditions, magnetic resonance imaging (MRI)). MRI will temporarily stop the pump motor's rotor due to the magnetic field of the MRI scanner and suspend drug infusion during MRI exposure which will cause the pump alarm to sound. The pump should resume normal operation upon termination of MRI exposure. Prior to MRI, the physician should determine if the patient can safely be deprived of drug delivery. If not, alternative delivery methods for the drug can be utilized during the MRI scan. Prior to scheduling an MRI scan and upon its completion, pump status should be confirmed. **Adverse Events:** Include, but are not limited to, cessation of therapy due to end of device service life or component failure, change in flow performance due to component failure, inability to program the device due to programmer failure, CAP component failure; inaccessible refill port due to inverted pump, pocket seroma, hematoma, erosion, infection, post-lumbar puncture (spinal headache), CSF leak, radiculitis, arachnoiditis, bleeding, spinal cord damage, meningitis (intrathecal applications), anesthesia complications, damage to the pump, catheter and catheter access system due to improper handling and filling before, during, or after implantation; change in catheter performance due to catheter kinking, disconnection, leakage, breakage, occlusion, dislodgement, migration, or catheter fibrosis; body rejection phenomena, surgical replacement of pump or catheter due to complications; local and systemic drug toxicity and related side effects, complications due to use of unapproved drugs and/or not using drugs in accordance with drug labeling, or inflammatory mass at the tip of the catheter. USA Rx Only Rev 0209

Lioresal® Intrathecal (baclofen injection)
Package Insert

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