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# 15 Intrathecal Drug Delivery

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## INTRODUCTION

Intrathecal drug delivery systems are a means to provide direct administration of medications into the cerebrospinal fluid (CSF). Bypassing the blood–brain barrier allows a significantly lower dose of medication to be administered to attain analgesia when compared to oral, intravenous, transdermal, or epidural routes. Within the dorsal horn of the spinal cord reside various receptors targeted in intrathecal drug delivery, including opioid receptors, alpha 2 adrenergic receptors, NMDA receptors, sodium and calcium channels, and GABA receptors.

The administration of medications directly into the intrathecal space to achieve analgesia has many benefits. The direct administration of medications allows a more rapid response at a fraction of the oral dose. The use of lower medication doses may reduce the systemic side effects. Intrathecal drug delivery systems have become a useful and effective option in the management of recalcitrant cancer and noncancer pain.

In 1898, August Bier documented the first spinal analgesia by injecting cocaine into the intrathecal space of six patients undergoing lower extremity surgery (Bier 1899). The discovery of opiate receptors in the spinal cord in 1973 provided scientific rationale for intrathecal analgesia (Pert and Snyder 1973). In 1979, Wang et al. first reported the successful use of intrathecal morphine in the treatment of intractable cancer pain (Wang, Nauss, and Thomas 1979). In 1981, the first use of an implantable intrathecal drug delivery system was reported for the management of cancer pain (Wang, Nauss, and Thomas 1979). In the 1980s, intrathecal drug delivery systems allowed a fixed continuous infusion rate of drug delivery. In 1991, externally programmable, battery-powered intrathecal drug delivery system pumps were introduced, allowing for noninvasive dose changes using an external programmer (Wallace and Yaksh 2000).

There are two general classes of patients for which intrathecal drug delivery systems are utilized in pain management: those with cancer and noncancer pain. In 1994, the

Mayo Clinic symposium on pain management extended the World Health Organization's three-step "ladder" approach to cancer pain by introducing a fourth step that included interventional pain therapies, such as spinal analgesia, nerve stimulation, and neurolytic blocks (Lamer 1994). In 2000, the Polyanalgesic Consensus Conference panel first convened to address the use of intrathecal infusion of analgesic medications to patients with chronic refractory pain. While there are no universally accepted guidelines for patient selection, those suffering from intolerable side effects of oral, intravenous, or transdermal therapies as well as those unable to obtain adequate analgesia despite high opioid doses should also be considered for intrathecal drug delivery systems.

## CSF FLOW DYNAMICS

Cerebrospinal fluid exists within the intracerebral ventricles and subarachnoid spaces as well as the central canal of the spinal cord. CSF is formed at a rate of 0.3–0.4 mL/min (approximately 500 mL/day). The total volume of CSF is 90–150 mL in adults. CSF is formed in the choroid plexus, parenchyma of the brain and spinal cord, and ependymal lining of the ventricles (Segal and Pollay 1977).

The absorption of CSF occurs primarily through the arachnoid villi and lymphatic vessels. The arachnoid villi drains cerebrospinal fluid into the great dural sinuses while the true lymphatic vessels drain CSF by means of an indirect perineural (ophthalmic, optic, and vagal nerves) course and the CNS capillary bed (Battal et al. 2011).

The classical view of cerebrospinal spinal fluid movement is termed bulk flow. CSF is created in the choroid plexus and spreads in a cranio-caudal direction propelled by hydrostatic pressure. More recent studies have shown that CSF movement is more of a pulsatile flow (Henry-Feugeas et al. 2000). Arterial pulsations and intrathoracic respiratory pressures predominantly govern pulsatile flow. At cranial and cranio-thoracic levels, arterial pulsations during diastole create a cranial flow of cerebrospinal fluid while systole creates a caudal flow (Henry-Feugeas et al. 2000). At more caudal levels, respiratory flow governs flow, causing cranial flow during deep inspiration and caudal flow during deep exhalation (Yamada et al. 2013). Cerebrospinal fluid flow is more pronounced in the cervical when compared to the lumbar region (Enzmann and Pelc 1991). CSF flow is therefore a heterogeneous, oscillatory, bidirectional, cranio-caudal movement. This movement is further influenced by the presence of venous plexuses, nerve rootlets, and epidural fat, each of which creates a barrier to flow, creating focal mixing (Stockman 2006).

## TYPES OF PUMPS: EXTERNALIZED VERSUS IMPLANTED AND RATES/MODES

Externalized and internalized pumps are two general classes of intrathecal drug delivery systems. Externalized pumps can be further classified as those with a percutaneous catheter (tunneled or not tunneled) and those with a fully implanted catheter with a subcutaneous injection port. A percutaneous catheter involves a procedure where the catheter used to infuse the intrathecal medication is introduced into the body via a needle. The catheter tip is positioned in the appropriate position using fluoroscopy. The catheter is then attached to an externalized pump, which delivers the medication. Its limitations

are the risks of infection and catheter migration. Therefore, it is usually considered a temporary solution. Externalized pumps are less invasive to place and can be useful in patients with a limited life expectancy (Bhatia et al. 2013; Cohen and Dragovich 2007).

Internalized pumps can be subdivided into those with fixed rate delivery systems and those that are programmable. Fully implanted, fixed rate intrathecal drug delivery systems deliver a constant rate of medication. They usually possess a larger reservoir, allowing for lengthier time intervals between refills. They do not require a battery to operate and are less expensive than variable rate delivery systems. Variable rate delivery systems are fully implantable devices that can either deliver an intermittent or continuous amount of intrathecal medication. Variable rate delivery systems can be programmed to administer medications at a simple continuous or variable rate. In addition, they provide the option for patient-controlled analgesia via a wireless radiofrequency transmitter. Programmable devices are battery operated and have a lifespan usually between 5 and 7 years, after which surgical revision is required to implant a new pump (Bhatia et al. 2013).

The decision to use an externalized or implanted pump is based on several factors, including life expectancy, cost, patient wishes, professional expertise, and medication requirements.

## MECHANISMS OF IMPLANTED PUMPS

There are several components to an intrathecal drug delivery system. The medication reservoir contains the solution to be infused. The Medtronic synchroMed II model 8637 reservoir is constructed using a bellows design. The reservoir expands and contracts based on the drug volume. Pressurized gas surrounding the reservoir exerts a constant pressure at normal body temperatures, propelling medication into the pump tubing. The motor and battery-powered electronics cause the roller arm in the peristaltic pump to rotate. This mechanism allows the administration of a precise, programmed amount of medication through the catheter port and into the catheter. A valve within the system prevents reservoir overfilling or overpressurization. A catheter access port located on the device allows direct access to the catheter and cerebrospinal fluid. A separate reservoir fill port allows access to the pump reservoir for medication refills. Figure 15.1 shows a labeled image of the SynchroMed II pump (Medtronic Inc. 2010).

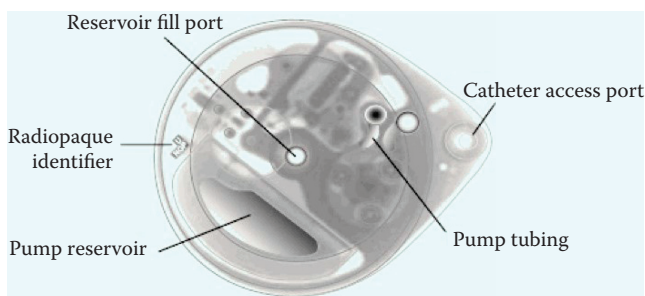


**FIGURE 15.1** SynchroMed II pump. (Image courtesy of Medtronic, Inc.)

## CHALLENGES IN INTRATHECAL DRUG DELIVERY

Once a decision to employ intrathecal therapy has been made, there are several variables that must be considered. Currently, only three medications are approved by the Federal Drug Administration for intrathecal use: morphine, ziconitide, and baclofen. Of these, morphine and ziconitide are approved for use in chronic pain. Other intrathecal medications for which extensive clinical experience and published clinical and preclinical data exist include hydromorphone, fentanyl, bupivacaine, clonidine, and sufentanyl. Medication can be dosed in a continuous or intermittent fashion using a programmable pump. Patient-controlled analgesia can be employed using a personal therapy manager in cases where patients are able to identify activities or times when their pain is exacerbated.

There are no studies defining the best rate to deliver intrathecal medications. It has been theorized that the use of lower flow rates may result in higher medication concentrations at the catheter tip, increasing the risk of granuloma formation. However, this is yet to be proven.

The physiologic properties of medications administered influence their distribution within the cerebrospinal fluid and spinal cord. Opioid medications primarily exert their effect in the gray matter of the dorsal horn (primarily lamina II or the substantia gelatinosa). The lipid solubility of an agent determines its ability to diffuse to its site of action. Lipid solubility can be expressed in terms of an agent's octanol/water partition coefficient. In order for intrathecal medications to reach their receptors, they must pass through the pia mater and white matter (containing myelinated axons) to reach their site of action within the gray matter. The myelinated fibers within the white matter make it more hydrophobic while the gray matter is more hydrophilic. As a result, hydrophilic opioids have a greater spinal bioavailability and spread more widely in the cerebrospinal fluid (Ummenhofer et al. 2000). Lipophilic agents have a more focal area of action in part due to their more rapid diffusion out of the cerebrospinal fluid (Bernards 2004).

Local anesthetic solutions can be classified as being either hypobaric, isobaric, or hyperbaric based on the solution density when compared to the density of the cerebrospinal fluid. The baricity predicts the direction of local anesthetic spread after administration into the cerebrospinal fluid based on the effects of gravity in relation to the location of medication administration, spinal curvature, and patient position. Isobaric solutions undergo limited spread in the subarachnoid space.

## CLINICAL APPLICATIONS

Several painful conditions can be treated using intrathecal drug delivery systems. Noncancer pain conditions that have been treated with intrathecal drug delivery systems include failed back surgery syndrome, compression fractures, spondylosis, spondyloisthesis, and spinal stenosis as well as spasticity following spinal cord injury, complex regional pain syndrome, chronic pancreatitis, neuropathies, and rheumatoid arthritis (Turner, Sears, and Loeser 2007; Belverud, Mogilner, and Schulder 2008). A retrospective study performed in 2010 by Atli et al. examined 55 patients with noncancer pain over a 3-year period and showed a statistically significant decrease in

visual analog pain scores between the first refill and all subsequent time periods (1, 2, and 3 years postimplant) (Atli et al. 2010). Twenty-eight patients in this study had a diagnosis of failed back surgery syndrome, 16 had neuropathic pain, five had visceral pain, and six had miscellaneous pain (lipomeningomyelocele, necrotizing fasciitis, idiopathic scoliosis, axial back pain of uncertain etiology, and osteomyelitis).

Comorbid conditions, such as depression, anxiety, and addiction, may exist in patients with chronic noncancer-related pain. Evaluation and management of these conditions should occur prior to consideration of an intrathecal drug delivery system. Personality disorders, for example, have been shown to portend poor response to long-term intrathecal therapy (Brown et al. 1999).

Intrathecal drug delivery systems can be especially useful in the management of patients with cancer-related pain. Pain is often the first sign of malignancy (Cohen and Dragovich 2007). In many cases, pain may be the most feared symptom among individuals with cancer, and it can occur at any point during the disease course. Various treatment options have been utilized in the management of cancer-related pain and include nonsteroidal anti-inflammatories, acetaminophen, opioids, neuropathic pain medications, peripheral nerve blocks, sympathetic blocks, and continuous epidural analgesia as well as intrathecal drug delivery systems. The advantage of intrathecal drug delivery is that it may reduce the systemic side effects. Furthermore, direct medication delivery to the site of action allows for more rapid and effective analgesia. Intrathecal drug delivery systems can be useful in alleviating pain in 60%–80% of patients experiencing chronic cancer-related pain (Deer et al. 2012).

In addition to pain, intrathecal drug delivery systems can be used to manage spastic hypertonia through the administration of baclofen. It has been effective in treating spastic hypertonia in spinal cord injury (Ordia et al. 1996; Coffey et al. 1993; Meythaler et al. 1992; Penn et al. 1989), cerebral palsy (Albright et al. 2003; Meythaler et al. 2001), brain injuries (Meythaler, McCary, and Hadley 1997; Becker, Alberti, and Bauer 1997), multiple sclerosis (Rizzo et al. 2004), and stroke (Ivanhoe et al. 2006). Recent studies have shown that the use of intrathecal baclofen can result in reduced impairment, improved gait, upper extremity function, and pain relief (Francisco et al. 2009; Sadiq and Wang 2006; Francisco and Boake 2003).

Intrathecal drug delivery systems may not be appropriate in all patients with clinical indications. It is contraindicated in patients with significant psychiatric comorbidities, significant emaciation preventing implantation, active infection over the catheter or pump implantation site, sepsis, cerebrospinal fluid outflow obstruction, intracranial hypertension, hemodynamic instability, and significant coagulopathy or who require continuous therapeutic anticoagulation preventing temporary discontinuation (Bottros and Christo 2014; Smith and Coyne 2003).

## COMPLICATIONS

Complications of intrathecal drug delivery systems can be classified as mechanical, pharmacologic, surgical, patient specific, and refill related. This chapter focuses on the mechanical complications. These can further be subclassified as catheter-related or pump-related complications.

Catheter-related complications have an incidence of 15%–25% (Follett et al. 2003; Follett and Naumann 2000). They can result from catheter migration, dislodgement, occlusion, kinking, leaking, puncture, or shearing. Proper catheter placement and surgical technique may decrease the incidence of shearing. For example, a paramedian approach to intrathecal catheter insertion may decrease the incidence of catheter shearing (Kamran and Wright 2001). Furthermore, several new catheters have been developed to reduce such complications (Follett and Naumann 2000). Evaluation of catheter placement and integrity can be performed by a fluoroscopic catheter dye study and should include the entire extent of the tubing, connectors, and catheter tip. Subsequently, a catheter access port aspiration may be performed to ensure free flowing CSF. Spiral computed tomography (CT) following isotonic myelogram contrast injection into the catheter access port injection can also be employed to evaluate catheter patency. Following contrast administration, the patient is immediately scanned from two vertebral segments above the catheter tip down through the pump site (Francisco et al. 2009).

Catheter tip granulomas are a rare but potentially devastating complication. A granuloma is a noninfectious collection of inflammatory cells located at the catheter tip. Over time, it can increase in size and cause spinal compression, leading to devastating neurologic complications. It has an incidence of 0.04% at 1 year and 1.16% after 6 years. The cause of these granulomas is unclear. They may arise as a result of a reaction to the infused medication, a low-grade infection, or a catheter tip reaction. Granulomas have been associated with opioids in the intrathecal space; however, they have not been reported with lipophilic opioids, such as fentanyl or sufentanil (Bottros and Christo 2014).

An intrathecal pump malfunction may result in either pump failure, underdosing, or overdosing. In addition to symptoms of medication withdrawal or overdose, an audible alarm or significant variation between the expected and actual reservoir volume may signal pump malfunction or a catheter-related problem. The most common cause of pump malfunction is the rotor (Francisco et al. 2009). Rotor failure will cause a loss of drug delivery. It can be diagnosed with a rotor test. This test involves obtaining a radiograph of the rotor, programming a specific bolus, and using repeated imaging to visualize the expected rotor rotation. The Synchromed II has a three-arm rotor, for example, and is programmed to rotate 120°. A rotor stall requires pump replacement. In some cases, a rotor stall can be seen with severely kinked catheters (Francisco et al. 2009).

## FUTURE DIRECTIONS

Future directions of intrathecal drug delivery systems include advancements in technology and medication delivery. Monitoring systems to directly measure the reservoir volume and catheter pressure can improve safety by assisting in troubleshooting and catheter occlusion detection. Material advancements may improve durability and patient outcomes.

The benefits of intrathecal drug delivery are well established; however, decreasing efficacy with prolonged treatment may limit analgesia in long-term therapy. Intrathecal microdosing has been proposed as a means to prevent opioid-induced

hyperalgesia and prolong treatment efficacy. Intrathecal microdosing involves utilizing doses as low as 25 to 50 mcg/day to produce long sustained analgesia (Deer et al. 2012). In 2012, Hamza et al. published a 3-year prospective study showing the efficacy of low-dose intrathecal opioid management in the management of chronic noncancer pain. Microdosing may be a promising alternative to traditional dosing promoting long-term efficacy and analgesia.

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