Medical Radiology · Diagnostic Imaging
Series Editors: Hans-Ulrich Kauczor · Paul M. Parizel · Wilfred C. G. Peh

Douglas P. Beall · Peter L. Munk ·
Michael J. DePalma · Timothy Davis ·
Kasra Amirdelfan · Corey W. Hunter *Editors*

Intrathecal Pump Drug Delivery

Springer

Medical Radiology

Diagnostic Imaging

The book series *Medical Radiology – Diagnostic Imaging* provides accurate and up-to-date overviews about the latest advances in the rapidly evolving field of diagnostic imaging and interventional radiology. Each volume is conceived as a practical and clinically useful reference book and is developed under the direction of an experienced editor, who is a world-renowned specialist in the field. Book chapters are written by expert authors in the field and are richly illustrated with high quality figures, tables and graphs. Editors and authors are committed to provide detailed and coherent information in a readily accessible and easy-to-understand format, directly applicable to daily practice.

Medical Radiology – Diagnostic Imaging covers all organ systems and addresses all modern imaging techniques and image-guided treatment modalities, as well as hot topics in management, workflow, and quality and safety issues in radiology and imaging. The judicious choice of relevant topics, the careful selection of expert editors and authors, and the emphasis on providing practically useful information, contribute to the wide appeal and ongoing success of the series. The series is indexed in Scopus.

More information about this series at https://link.springer.com/bookseries/174

Douglas P. Beall • Peter L. Munk
Michael J. DePalma
Timothy Davis • Kasra Amirdelfan
Corey W. Hunter
Editors

Intrathecal Pump Drug Delivery

Springer

Editors
Douglas P. Beall
Comprehensive Specialty Care
Edmond, OK
USA

Michael J. DePalma
Virginia iSpine Physicians, PC
Richmond, VA
USA

Kasra Amirdelfan
IPM Medical Group, Inc.
Walnut Creek, CA
USA

Peter L. Munk
Department of Radiology
Vancouver General Hospital
Vancouver, BC
Canada

Timothy Davis
Source Healthcare
Santa Monica, CA
USA

Corey W. Hunter
Ainsworth Institute of Pain Management
New York, NY
USA

ISSN 0942-5373 ISSN 2197-4187 (electronic)
Medical Radiology
ISSN 2731-4677 ISSN 2731-4685 (electronic)
Diagnostic Imaging
ISBN 978-3-030-86243-5 ISBN 978-3-030-86244-2 (eBook)
https://doi.org/10.1007/978-3-030-86244-2

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Douglas P. Beall, MD, FIPP, FSIR, DAAPM
Director Interventional Spine Care, Comprehensive Specialty Care,
Chief of Radiology Services and Director of Fellowship Programs,
Oklahoma City, OK, USA

This book is dedicated to all the practitioners who are willing to tackle complex therapies in order to ease their patient's pain and improve their lives. My hope is that a comprehensive single source of information will help to optimize IDD therapy and improve your patient's outcomes.

Preface

Intrathecal drug delivery (IDD) has been one of my very favorite treatments since I saw my first case performed in fellowship in the early 2000s and saw the incredibly good and immediate results. After transitioning from academia and into private practice I found myself inheriting 67 intrathecal baclofen patients from two physicians who were transitioning from managing this patient population to being employed hospitalists. As an Interventional Radiologist, my staff was unfamiliar and somewhat hesitant to accept this service line but did so anyway without hesitation and this patient population quickly became their favorite group.

Intrathecal medication delivery has since become an essential part of our medical and interventional practice. In patients who have certain conditions this therapy is absolutely essential including patients who have severe spasticity, multi-site pain, severe degenerative conditions without a surgical solution, patients with chronic pain on high-dose systemic narcotics, and metastatic cancer pain especially from a pancreatic source or those with bony metastases. I have found that IDD is often the only solution for some of the most complex patients and without it they simply do not receive optimal care.

As useful and essential as this therapy is it is, in my opinion, tremendously underutilized. I think there are two primary reasons for this. The first is that IDD has had its reputation tarnished in the early days of therapy where it was commonplace to provide oral opioid medication along with intrathecal opioids. As we now know, providing oral or systemic medication is a self-defeating strategy as it causes an upregulation of the cytochrome P-450 system to the point that there is no amount of intrathecal opioid that can be provided that can overcome the patient's upregulated metabolic activity that eliminates the opioid very quickly and results in a very high tolerance to these medications. During the peak of the opioid epidemic, we were seeing patients with chronic pain that were on 500–1000 MME of morphine or more for IDD trials. One of these patients was on an incredible 1200 MME of morphine daily and refused to taper his medication dose before the trial. We typically use a 1:100 ratio of intrathecal to oral MME of opioids for a bolus trial and keep the patients overnight with continuous monitoring of the pulse oximetry and cardiac activity and multiple vital signs measurements. In this patient, however I was very reluctant to give that amount of intrathecal morphine and settled on 8 mg of morphine injected as a bolus into the lumbar spine cerebrospinal fluid. We were prepared for treatment of an overdose of intrathecal medication but what happened was exactly the opposite with the patient receiving

2–3 h of excellent pain relief followed by a return of his pain to the point where he was unhappy, wanted to take his oral medication and checked out of the hospital against medical advice. This scenario permanently etched in my mind the absolute requirement not to use a combination of systemic and intrathecal medication as there is no amount of opioid that can be given intrathecally to overcome the hypermetabolism that results from systemic opioid administration.

The second reason for underutilization of TDD relates to the perceived complicated nature of this therapy. In my opinion this is nothing more than a perception and confusion of what is complicated verses what is complex. The term complicated refers to a high level of difficulty and the pragmatic application of TDD is certainly not that. It is, however, complex which means that it utilization of this therapy has many components but it is not necessarily difficult and can be learned in a manner that is logical and straightforward. There are some useful guides to the delivery of TDD including the comprehensive consensus-based guidelines on IDD systems in the treatment of pain caused by cancer and the Polyanalgesic Consensus Guidelines but, surprisingly, there is no book that provides a comprehensive guide to the wide variety of clinical applications of IDD…that is until now.

This book was designed to be a comprehensive guide, and it has certainly accomplished that discussing all aspects of IDD including the various applications in cancer pain, nonmalignant pain, acute and chronic pain, and in severe spasticity. The information provided expands on the typical patient histories, the diagnostic processes, the surgical techniques and approaches, IDD system troubleshooting, preoperative and postoperative assessments, electronic analysis and reprogramming, different on and off-label intrathecal medications, and the management of pain or baclofen pumps. We have even included conditions and concepts that are frequently encountered clinically but never before described in the medical literature. It has certainly been a pleasure and a privilege to be involved in the writing of this book. I would like to thank all of my editors, authors, coauthors, and all others who have made this work possible. From an early observational start to a sudden immersion in intrathecal baclofen therapy to an ongoing comprehensive and diversified program, IDD just keeps getting better and just like any other tool that is have found to be optimal; it first becomes useful and then becomes essential.

Oklahoma City, OK Douglas P. Beall

Acknowledgements

Bradley Philips for his tireless and continuing contribution to Intrathecal Drug Delivery

Contents

Introduction and Background for Intrathecal Pumps Used for Pain and Spasticity

Brent Earls, Matt Sullivan, and Paul J. Christo

Contents

B. Earls · P. J. Christo (✉)
Division of Pain Medicine, Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA
e-mail: pchristo@jhmi.edu

M. Sullivan
Division of Pain Medicine, Department of Anesthesiology and Critical Care Medicine and Emergency Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Abstract

Intrathecal drug delivery has expanded since the inception of this technology in the 1980s and is utilized for a number of different conditions for the purposes of pain control and the management of spasticity. The use of intrathecal pumps is less common than many other techniques for interventional pain management but is essential in such conditions as

D. P. Beall et al. (eds.), *Intrathecal Pump Drug Delivery*, Medical Radiology Diagnostic Imaging,
https://doi.org/10.1007/978-3-030-86244-2_1

refractory pain, cancer pain, multifocal pain, severe spasticity, and in patients who are not candidates for surgical correction of their underlying condition. Intrathecal drug delivery is usually considered when analgesics or antispasmodics administered via the oral, transdermal, or intravenous routes are ineffective or are associated with unacceptable side effects. The intrathecal delivery of medications bypasses the blood-brain barrier, which produces much higher concentrations of medication within the cerebrospinal fluid. This higher concentration can serve to dramatically reduce the effective dose of the medication and can be associated with higher rates of pain and spasm reduction as compared to other routes of medication delivery. Although intrathecal drug delivery has been shown to be clinically effective and cost-effective, this pain and spasticity management tool is less well understood regarding its implantation and management than other implantable technologies. This chapter will serve to highlight the proper clinical use and appropriate management of intrathecal pumps for the management of spasticity and pain.

Abbreviations

BBB	Blood-brain barrier
CMM	Conventional medical management
CP	Cerebral palsy
CSF	Cerebrospinal fluid
CT	Computed tomography
CVA	Cerebrovascular accident
FDA	Food and drug administration
ITB	Intrathecal baclofen
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
PSS	Poststroke spasticity
ROM	Range of movement
SCI	Spinal cord injury
SCS	Spinal cord stimulator
TBI	Traumatic brain injury
TDD	Targeted drug delivery

1 Introduction and Background for Intrathecal Pumps Used for Pain and Spasticity

Chronic pain is exceedingly common with prevalence estimates ranging from 13 to 51% and is more common than other chronic conditions such as diabetes or chronic obstructive pulmonary disease, and more common than diabetes, cancer, and heart disease combined (Breivik et al. 2006; Craig et al. 2011; Fayaz et al. 2016; Gupta et al. 2010; Manchikanti et al. 2009; Tsang et al. 2008). There are more than 100 million Americans suffering from chronic pain and estimates from the Institute of Medicine place the annual healthcare cost of treating this pain at nearly $635 billion annually (Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education 2011).

In addition to the economic costs, chronic pain is a significant burden causing substantial reduction in patients' quality of life. A national pain audit found that the average quality of life score in people suffering from chronic pain was lower than that reported by people suffering from progressive neurological disorders such as Parkinson's disease (Price et al. 2019). Common chronic pain disorders such as migraine headaches and neck pain cause significant disruptions in quality of life, and low back pain causes more disability worldwide than any other single condition (Hoy et al. 2014). Patients suffering from chronic pain are also less productive in their work and are seven times more likely to quit their jobs due to ill health than the general population (Donaldson 2009).

2 Historical Background and Perspectives of Intrathecal Drug Delivery

Understanding and treating pain has been a challenge to humanity as far back as 5000 BC when the first records of using opium for analgesia were etched on clay tablets. For over 6000 years,

humankind continued this practice with similar treatments while making relatively little advancement in understanding. Even the earliest theories of anatomy by Hippocrates, who although he recognized the brain as the place of the mind and the seat of thought, sensation, emotion, and cognition still believed that the heart was responsible for pain's sensation (Linton 2005). During the Roman Empire, the Greek anatomist Galen dissected a variety of mammalian brains and posited that the cerebrum processed sensations and that certain spinal nerves control muscles. Despite anatomic advancements, the perception of pain prior to the Renaissance remained vague and largely spiritual or mystical, with the majority of theories arguing for the appeasement of God as the best treatment. With the publication of Descartes' *Treatise of Man* in 1664, the French philosopher provided the first physical and mechanical descriptions of pain pathways and laid a foundation for modern neuroanatomy (Hadjistavropoulos and Craig 2004). Descartes proposed his theory through illustrations of a hand being struck with a hammer and a foot being held near a flame, both of which resulted in pain traveling up "a fine thread" to the brain, where it would cause a variety of responses such as flinching away from or turning toward the stimulus (Hadjistavropoulos and Craig 2004).

It was not until the nineteenth century that pain as a "specific sensation" emerged and with this notion came a cascade of discoveries to characterize pain at a fundamental level. In 1811, Scottish anatomist Charles Bell published his findings from human cadaveric dissections. He discovered the existence and discrete function of the spinocerebellar tracts by demonstrating motor functions via nerve fibers exiting the ventral roots from the spine. Eleven years later, while performing his notorious public experiments on dogs, French Physiologist Francois Magendie verified the sensory function of dorsal root ganglia by exciting the anterior nerve roots of the spinal cord to cause pain. Brown-Sequard furthered this research with his findings on the decussation of pain fibers in 1880 (Laporte 2006), which was succeeded in 1889 by Edinger's discovery of the spinothalamic tracts. Edinger's implication that superficial long tracts in the lateral spinal cord were the carriers of afferent pain signal helped to complete the basic understandings of neuroanatomy enough for successful interventions and treatments.

With the invention of the hollow needle and the glass syringe by Scottish surgeon (and soon-to-be the Royal College of Physicians' President) Alexander Wood in 1853, the medical community had the tools it needed to conduct more targeted analgesic interventions. Nonetheless, the targets themselves were as of yet unknown. A contemporary and rival of Wood, fellow-surgeon Charles Hunter proved that pain relief could be achieved by injecting narcotics anywhere in the body and not just at the area of pain, as Wood had argued (Brunton 2000). Despite these advancements in neuroanatomy and medical technology, little progress had been made in the field of pharmacology, and morphine remained the primary, if not the only, analgesic available to most physicians until the late nineteenth century. Though South American Indians had been chewing coca leaves for over 5000 years, it was not until 1859 that German pharmacists isolated and characterized cocaine as the active compound. This revolutionary discovery added cocaine to a growing list of natural alkaloids that were starting to be used as empiric treatments for a variety of diseases (Holmstedt and Fredga 1981). This was occurring throughout the latter half of the nineteenth century, but the chemical structure of alkaloids would not be revealed until 1898 by the work of Nobel Laureate Richard Willstatter (Willstätter 1898). This all changed in 1884 when a young Viennese neurologist, Sigmund Freud, learned of cocaine's impressive ability to suppress fatigue and ultimately decided to try the drug himself. Inspired by what he called a "magical drug," Freud shared his experience and small samples of cocaine to his scientific contemporaries (Freud and Freud 1992). One of these was Viennese ophthalmologist, Carl Koller, who was disappointed by the failures of general anesthesia for ocular procedures, when he happened to sample the drug himself and noted a surprising

numbing effect to his tongue. In late 1884, he applied a cocaine solution to a patient's cornea with excellent anesthetic effect (Koller 1928). Halstead and Hall found that this could be directed even more precisely, at the level of the inferior alveolar and dental nerves, and subsequently pioneered the first peripheral nerve block in 1885 (López-Valverde et al. 2011).

James Leonard Corning, a surgeon in New York City, read of Koller's discovery and decided to translate this to his own neurosurgical studies. In 1885, Corning was the first to discover that cocaine delivered to the epidural space of dogs resulted in "hind limb weakness and ataxia." In 1891, Heinrich Quincke developed a uniquely fine, hollow cutting needle that would allow him to access the subarachnoid space in attempts to relieve the hydrocephalus resulting from tubercular meningitis (Dugacki 1992). Just 14 years after the first clinical application of local anesthetic, on August 16, 1898, German surgeon August Bier, and his assistant, August Hildebrand, performed the first successful intrathecal anesthesia (Pravaz and Gabriel 1853). Despite successful anesthesia after spinal cocainization in just six patients, Bier criticized his own work, stating, "so many complaints had arisen in association with this method (back and leg pain, vomiting, prolonged headache) that they equalled the complaints usually occurring after general anesthesia" (Bier 1899). Naturally, Bier and Hildebrand volunteered to perform similar experiments on each other. While the experiment on Bier resulted in CSF loss after Hildebrand struggled to connect a Prvaz syringe to the Quincke needle, he characterized the first dural puncture headache. The intrathecal anesthesia Bier delivered to Hildebrand was much more successful, as he demonstrated no sensual perception to needle sticks of the thigh, tickling of his feet, pushing a helved needle to the femur, incising his thigh, tamping out a burning cigar, pulling pubic hairs, striking his shins with an iron hammer, and even applying pressure to his testicles. Bier later wrote, "After these experiments on our own bodies, we both went to dinner without any physical complaints," though "Hildebrandt felt very poor the next morning" (Bier 1899).

3 Intrathecal Drug Delivery for Pain Indications

Intrathecal treatment of chronic pain and spasticity has been approved for those patients who experience severe symptoms from their condition and who have proven unresponsiveness to less invasive medical therapy (National Coverage Determination 2004). With such a broad indication, the role of intrathecal drug delivery continues to evolve within the pain treatment continuum. Intrathecal drug delivery had previously been seen as a salvage therapy or last resort measure. New consensus guidelines, however, suggest this modality should be considered in the same line of management as neurostimulation, with important caveats (Deer et al. 2017). These important considerations would include having a clear diagnosis, an appropriate physical examination, and a complete psychosocial evaluation (which may be optional for cancer pain) before undergoing either a trial or an implant (Deer et al. 2017).

In an article by Deer et al., an effort is made to clearly define refractory pain that may then help clinicians better assess patient suitability for neuromodulatory techniques, including intrathecal drug therapy (Deer et al. 2014). This approach helps with three important issues when beginning to consider this line of therapy, first, by preventing unnecessary device implants in inappropriate patients; second, by identifying appropriate patients early in the process, we may improve the therapeutic efficacy of treatment with implanted devices; and third, by early identification of psychosocial comorbidities, there is an opportunity to improve the treatment response by optimizing these factors prior to any device implantation.

4 Goals of Therapy

Evidence for intrathecal drug delivery (ITDD) is strong for short-term and moderate for the long-term management of neuropathic and mixed pain conditions (Smith et al. 2008). De Lissovoy et al. previously demonstrated that ITDD appears cost-effective when compared with alternative (medical) management for selected patients with pain

associated with failed back surgery (FBSS) when the duration of therapy exceeds 12–22 months (de Lissovoy et al. 1997). Kumar and colleagues modeled the comparative cost-effectiveness of the ITDD continuum, in which they explicitly addressed costs related to polyanalgesia versus conventional medical management for chronic non-cancer pain. Over 10 years, a patient receiving ITDD would stand to accrue an additional 1.15 quality-adjusted life years (QALY) compared with a patient receiving conventional medical management. Despite the increased price of the device and medication to fill it, the authors concluded that ITDD remains a highly cost-effective treatment strategy with costs of therapy falling well below commonly accepted societal willingness to pay thresholds (Kumar et al. 2013). When making management decisions for patients in chronic pain, it is important to consider factors such as cost, long-term quality of life, and duration of efficacy as they pertain to the chosen therapy.

5 Long-Term Effectiveness

Utilization of intrathecal drug delivery systems (IDDS) in patients with malignancy-related pain has significant support in the literature. Pain is a frequent symptom in patients with cancer, and it often results in substantial detrimental impact. Despite the availability of opioids and updated guidelines from reliable leading societies, undertreatment is still frequent (Greco et al. 2014). Additionally, multiple high-quality studies have shown IDDS to be more efficacious than medical management alone (Baker et al. 2004; Bruel and Burton 2016; Rauck et al. 2003; Zech et al. 1995). The Cancer Pain Trial showed that IDDS could relieve pain more effectively with less toxicity and possibly improve survival in patients with intractable cancer pain after appropriate therapy that followed approved guidelines (Smith et al. 2005). Perhaps more importantly, the patients receiving IDDS in this trial showed substantial reduction in medication side effects with the IDDS group having a 66% decrease versus a 37% decrease in the medical management group as determined using a baseline adjusted regression model ($p < 0.01$) (Smith et al. 2005).

Intrathecal drug delivery has also been shown to be very efficacious in chronic nonmalignant pain. Ziconotide has presented some challenges in clinical use due to a narrow therapeutic window and a relatively high incidence of adverse events (Hayek et al. 2015; Rauck et al. 2006). There are reports of flexible dosing strategies that may be used to mitigate unwanted adverse effects (Zech et al. 1995). This has been shown to improve the response to the therapy and decrease the need for systemic opioid medications (Pope and Deer 2015). In a study by Duarte and colleagues, they showed that participants receiving intrathecal opioids maintained a significant reduction in pain intensity and an improved quality of life up to 13 years after the initiation of treatment (Duarte et al. 2012). At a follow-up averaging 13 years after the initiation of IDDS therapy, 90% of patients continued to be very satisfied with the treatment. Other reports have shown patients followed even up to 20 years still had significantly reduced pain from their baseline (Sommer et al. 2020).

6 Types of Intrathecal Systems (Pumps)

Broadly speaking, ITDD systems are available in four different configurations and are distinguished by which parts may or may not be implanted under the skin along with their programming capabilities. The least invasive option for the intrathecal system is a percutaneous catheter (tunneled or not tunneled) connected to an external pump. A slightly more invasive option is a totally implanted catheter with a subcutaneous injection port connected to an external pump. These two abovementioned systems are usually used in patients with limited life expectancy. Next is a fully implanted fixed rate ITDD system, which is generally less expensive than programmable systems. The notable drawback is that dosage alteration requires that the pump be emptied and refilled with a new drug formulation or a different drug concentration. Finally, there are the

fully implanted and programmable ITDD systems (Duarte et al. 2016). Details about these systems, including a more robust discussion of benefits and drawbacks, will be discussed further in chapter "The Components of Intrathecal Drug Delivery".

7 Initial Drug Therapy

Several factors have been shown to contribute to the distribution of any given medication within the CSF following intrathecal administration. The five main factors include lipid solubility, baricity, regional CSF mixing, flow rate, and residence time within the intrathecal space (Table 1) (Bernards 2002). Compared to hydrophilic medications, lipophilic medications have shorter half-lives, largely due to faster redistribution into fatty tissues and higher volumes of distribution (Jose et al. 2013; Waara-Wolleat et al. 2006). Despite the hydrophilic nature of some medications, like morphine, animal and human models have shown relatively limited distribution in the CSF following continuous infusion (Wallace and Yaksh 2012). In a study by Flack et al., concentrations of morphine beyond 5 cm from the catheter, above or below the origin of infusion, were shown to be about 20% of the concentration at the infusion point itself and drop to about 5% when sampling at 10 cm (Flack et al. 2011). Studies have shown manipulation of the drug concentration or volume delivered can increase the drug spread. Some of these techniques have also shown higher rates of adverse events as well as reduction in quality of life in patients being treated with continuous intrathecal therapy. In a study by Perruchoud and colleagues, higher pump flow rates consistently demonstrated no change in pain VAS (visual analog scale) but worsening of pain and anxiety dimensions on questionnaires. This led the researchers to conclude higher flow rates may increase drug dilution thereby reducing the receptor site effect of the medication (Perruchoud et al. 2011)

Table 1 The five main factors contributing to the intrathecal distribution of medication within the cerebrospinal fluid

1.	Lipid solubility
2.	Baricity
3.	Regional CSF mixing
4.	Pump flow rate
5.	Residence time within the intrathecal space

8 Choice of Medication

Two medications have been approved by the Food and Drug Administration (FDA) for intrathecal use in treating chronic pain, morphine sulfate (Infumorph® Sterile Solution, Baxter Healthcare Corp., Deerfield, IL, USA and Mitigo™ Pirimal Critical Care, Inc., Mumbai, India) and ziconotide (Prialt® for intrathecal infusion; Jazz Pharmaceuticals, Inc., Dublin, Ireland). While morphine and ziconotide are the only two medications with an FDA indication for intrathecal use for pain, a number of combinations of drugs have been proposed in the literature to improve efficacy and reduce side effects. The methodical use of polyanalgesia may be more effective in addressing painful conditions through the modulation of multiple mechanisms and using multiple mechanisms of action to attenuate the development of tolerance (Kumar et al. 2013). This approach has the distinct potential to provide optimal pain control while reducing the need for opioid dose escalation (Kumar et al. 2013). In cancer pain, evidence would suggest that combination therapy might be warranted as a first-line strategy, which is a different recommendation as compared to the treatment of non-cancer pain (Veizi et al. 2011). It is, therefore, important to understand the patient's pain characteristics, including their pain type and location, expected length of therapy, and the patient's age when choosing a medication or combination of medications (Deer et al. 2017).

9 Adverse Events

Intrathecal therapy is not without its risks, although continued utilization over the years has improved the patients' treatment experience and

their safety (Hayek et al. 2011). Adverse events can be broadly categorized as related to the implantation procedure, medication effects, or related to the catheter or the pump itself. Adverse events related to surgical procedures can be many, but the most common are infection and CSF leak. Bleeding is uncommon but can be an emergency and should be monitored closely. Seroma formation in the pump pocket is usually benign but should also be monitored for the development of infection. Hygromas, associated with CSF leaking around the catheter, are usually self-limited but may persist and need either drainage or additional surgical attention (Czernicki et al. 2015).

Due to the number of medications and medication combinations that are used in targeted drug delivery, the potential for medication associated side effects is not insubstantial. Direct delivery at the spinal cord level is helpful to limit adverse effects usually seen with systemic delivery, but it is important to monitor the patient for side effect nevertheless. Intrathecally delivered opioid medications can cause sedation, lightheadedness, nausea, and urinary retention (Prager et al. 2014; Spiegel et al. 2021). Long-term administration has been shown to cause tolerance, hypogonadism, and low bone density (Duarte et al. 2012). In a study by Coffee and colleagues, intrathecal opioid therapy was associated with slightly higher mortality (3.8%) than cohorts of spinal cord stimulator patients and discectomy patients due to medication-related respiratory depression or overdose (Coffey et al. 2009). Alternatively, Smith and colleagues found that ITDD decreased pain intensity and improved survival in cancer patients (Smith and Coyne 2004). Intrathecal ziconotide has most commonly been associated with dizziness, nausea, and confusion. It is also important to note that ziconotide is contraindicated in patients with psychosis (Pope and Deer 2013).

Catheter migration and dislodgement are the most common device-related complications of ITDD and are reported to occur between 0.7 and 1.5% (Deer et al. 2004). Granuloma formation at the catheter tip has also been documented especially at high medication concentrations (Deer et al. 2012). Overt device failure is an extremely rare event, but it should be treated urgently to prevent medication withdrawal. Medication compounding for intrathecal use has been a popular technique to attempt to optimize the therapeutic response to ITDD while minimizing the side effects (Pope et al. 2017). This requires pharmacy compounding, which is not regulated by the FDA but by state boards of pharmacy, incorporating the United States Pharmacopeia (USP) chapters of pharmaceutical compounding for both sterile and non-sterile preparations (Gudeman et al. 2013). Recently, the FDA released a communication sharing information about pump failures, dosing errors, and other safety information so that patients and providers can make informed treatment decisions (Health, Center for Devices and Radiological 2018). A more comprehensive list, including postoperative care, will be discussed in more detail in later chapters.

10 Intrathecal Drug Delivery for Spasticity

Spasticity is defined as an abnormal increase in muscle tone caused by injury of upper motor neuron pathways regulating muscles and may be caused by injury or disease of the central nervous system. There is a velocity-dependent increased resistance to passive stretch, and this may be characterized by exaggerated tendon jerks and accompanied by hyperexcitability of the stretch reflex (Emos and Agarwal 2020). A more encompassing definition is from the 2005 SPASM consortium, which defines spasticity as disordered sensorimotor control resulting from an upper motor neuron lesion that presents as intermittent or sustained involuntary activation of muscles (Pandyan et al. 2005). A multitude of diseases can lead to the development of spasticity. In this chapter, we will introduce some of the more common causes and the principles behind its treatment.

Spasticity of spinal cord origin is most commonly seen in patients with spinal cord disease or traumatic injury. There are about 12,000 new cases of spinal cord injury (SCI) that occur each

year, and in the last 20 years, the majority of the injuries have resulted in incomplete tetraplegia (30.1%) and complete paraplegia (25.6%) (Anson and Shepherd 1996). Multiple sclerosis (MS) has shown to be a devastating disease for those who suffer from the condition. Movement disorders can vary greatly in patients with MS depending upon the location of the plaques within the brain and spinal cord, and spasticity is a common feature among patients, with up to 84% of the patients experiencing some degree of spasticity (Wallin et al. 2019). Poststroke syndrome (PSS) can also commonly cause spasticity and has been shown to cause permanent disability in about five million people worldwide every year, with about 38% of those individuals experiencing spasticity (Katan and Luft 2018; Watkins et al. 2002). While most strokes occur in the brain parenchyma, the resulting imbalance of inhibitory and excitatory signals at the spinal level is thought to be the cause of PSS (Trompetto et al. 2014). The functional impairments associated with severe spasticity seen in all of these disease processes include pain, difficulty sleeping, flexion contractures, and bladder and bowel dysfunction (Dvorak et al. 2011; Mandigo and Anderson 2006; Mutch et al. 1992; Rizzo et al. 2004). Patients with spasticity also have difficulty with various activities of daily life such as walking, changing positions, mobilizing from a wheelchair, and other activities (Dvorak et al. 2011; Mandigo and Anderson 2006; Mutch et al. 1992; Rizzo et al. 2004).

Baclofen is a GABA agonist that is thought to selectively bind to presynaptic GABA-B receptors, resulting in hyperpolarization of the motor horn cells and a subsequent reduction in hyperactivity of the muscle stretch reflexes, a decreased amount of clonus, and dampened cutaneous reflexes that elicit muscle spasms (Newman et al. 1982; Stien et al. 1987). Baclofen has been used in the treatment of spasticity since the 1960s but was not introduced as an intrathecal therapy in humans until 1984. In a case series of two patients, intrathecal baclofen was given in small doses (5–25 mcg) and showed improvement of spasticity for up to 8 h (Penn and Kroin 1984). The current literature supporting the use of baclofen can be difficult to evaluate because there is no single universally accepted standard on spasticity rating, and a large degree of heterogeneity in existing studies. The best available evidence suggests that baclofen offers the optimal efficacy for most clinical outcomes, including decreasing spasms, improving functional status, and scoring high for patient preference in patients with spasticity (Chou et al. 2004). The most common adverse reactions to intrathecal baclofen include hypotonia and somnolence, and both are reported at slightly greater than 5% in study subjects. Nausea, headache, and dry mouth were also noted in approximately 2% of participants at 2 months post implant (Ertzgaard et al. 2017). Overdose may present with sudden coma or in more insidious ways such as drowsiness, lightheadedness, dizziness, somnolence, respiratory depression, seizures, rostral progression of hypotonia, and loss of consciousness that progresses to coma. Sudden withdrawal of the medication is also a major concern as this can lead to severe symptomatology, including death. Signs of withdrawal include high fever, altered mental status, and rebound spasticity that, if severe, can lead to severe rhabdomyolysis. While these events are exceedingly rare, it is important to closely monitor patients at vulnerable times such as after dose adjustments and pump refills.

11 Conclusion

Intrathecal drug delivery as a therapy has increased since its inception due to the contributions of clinicians, pharmacologists, and medical device manufacturers and has been facilitated by the recommendations of various consensus panels (Deer et al. 2017; American Society of Anesthesiologists Task Force on Neuraxial Opioids 2016; Fitzgibbon et al. 2010). There have been algorithms introduced for the appropriate application of clinical therapies for patients with various types of pain and spasticity. There has also been widespread encouragement for continued research and development of new medications, devices, and treatment recommen-

Table 2 Targeted drug delivery important tips: The ten commandments of intrathecal pump placement

1.	Use as large of a pump that the patient's preference and body habitus will allow
2.	Use perioperative and wound antibiotics to reduce risk of infection
3.	Place the pump in the lower quadrant of the abdomen to facilitate patient comfort
4.	Do not place the pump at a depth that will make the refills overly challenging (don't place the pump too deep)
5.	Anchor the pump to the underlying fascia with durable permanent sutures
6.	In morbidly obese patients, place the pump 8–9 cm lateral to the normal midclavicular line location. This will allow for a more superficial placement as the adipose tissue is typically less thick in this location
7.	Remember the blood patch as a treatment for a CSF leak around the catheter
8.	Always calculate the final implanted length of the catheter
9.	Always aspirate the catheter prior to closing the abdominal wound to ensure catheter patency
10.	Use an abdominal binder or the equivalent for 6 weeks following implantation

Table 3 Targeted drug delivery important tips: The ten commandments of intrathecal pump management

1.	Do not use systemic opioids (i.e., oral or transdermal) concurrently with IT opioids
2.	Do not use benzodiazepine medications in patients receiving IT opioid therapy
3.	Start with branded and single medications first then convert to compounded and multiple medications if necessary
4.	Make sure not to exceed the maximum concentrations of the compounded intrathecal medications
5.	Try to achieve the maximum time between refills to maximize patient comfort and convenience
6.	Use as large of a pump that the patient's preference and body habitus will allow
7.	If pump or catheter malfunction is suspected, have a low threshold for conducting a catheter and rotor study
8.	Use the lowest amount of medication possible to accomplish the treatment goals
9.	Use the patient controlled intermittent bolus dosing feature when possible
10.	Reduction of systemic opioids prior to the trial or implantation improves the success of the IT therapy and allows for better control of pain at a lower dose

dations. This chapter has provided an introduction for the appropriate use of IT therapy in patients with chronic nonmalignant and malignancy-associated pain and in patients with spasticity from various origins. This chapter has also presented and explained the various components of IT drug delivery including the IT pump, the catheter, and the supplies for implanting the pump and catheter. In addition, we have given a brief introduction for goals of therapy, medication choice, and common adverse effects associated with IT baclofen. The processes of patient identification, pre-trialing management, IT trialing, preoperative patient management, surgical pump implantation, post-op management, and long-term medication management can be challenging even with the appropriate knowledge and guidelines, and optimal information is certainly necessary to guide treatment and produce the best quality outcomes. In addition to the guidelines discussed above, the authors of this chapter have put forth their best helpful hints in the form of the Ten Commandments for the placement and management of intrathecal pumps (Tables 2 and 3, respectively). These can be combined with other consensus guidelines for determination of optimal strategies for IT medication therapy and which patients are best suited for this treatment paradigm. The application of IT therapy can greatly benefit carefully selected patients, many of whom are otherwise susceptible to undertreatment of their difficult conditions.

References

American Society of Anesthesiologists Task Force on Neuraxial Opioids (2016) Practice guidelines for the prevention, detection, and management of respiratory depression associated with neuraxial opioid administration: an updated report by the American Society of Anesthesiologists Task Force on Neuraxial Opioids and the American Society of Regional Anesthesia and Pain Medicine. Anesthesiology 124:535–552