Intrathecal Drug Delivery

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History

Karl Koller, an Austrian physician, applied cocaine in 1884 as a method to provide surgical anesthesia and analgesia.[1] While subsequent local anesthetics were used frequently for perioperative anesthesia, it was the discovery of opiate receptors in the dorsal horn of the spinal cord by Yaksh in 1977 that led to the widespread interest and use of intrathecal opioids for postoperative, cancer, and non-cancer pain conditions.[2]

As scientists developed a better understanding of the physiology of the spinal cord and particularly the dorsal horn, it became apparent that pharmacologic manipulation at the spinal cord level could significantly alter the perception of pain. The first order synapse of primary nociceptive afferents in the dorsal horn is complex with multiple receptors and neurotransmitters responsible for activation or inhibition of nociception. The ability to alter nociceptive input at this level can occur with the injection of intrathecal opioid and non-opioid drugs.

Wang reported the injection of intrathecal opioids in 1979 with successful analgesia recorded in a cancer patient.[3] Since that time intrathecal opioids have been used extensively to treat chronic cancer and non-cancer pain. Similar to the oral or parenteral administration of opioids, the intrathecal delivery of opioids often leads to the development of tolerance. During the past 20+ years clinicians and investigators have been looking at opioid alternatives to intrathecal morphine and combinations of the opiate class with non-opioid analgesics.

The delivery of analgesic drugs into the intrathecal space represents neuromodulation of afferent nociception. This is distinct from neurodestructive modalities such as radiofrequency denervation or chemical neurolysis. Changes from intrathecal drug delivery are, for the most part, reversible when the infused drugs are discontinued. The ability of intrathecal drugs to alter the natural history of a variety of pain syndromes is not fully understood.

Physiology and Pharmacology of Intrathecal Drugs

The development of intrathecal drug delivery from morphine sulfate in 1979 to currently used drugs and combinations has relied, in large part, on a growing knowledge base of dorsal horn physiology and pharmacology. Research over the past 2 decades has focused investigators on several receptors and neurotransmitters.

Primary afferent nociceptors synapse in the dorsal horn of the spinal cord. This first order synapse is subject to significant modulation from supraspinal nerves descending into the spinal cord, internuncial neurons within the spinal cord, and other primary afferent neurons. Opiate receptors in the spinal cord exist primarily in the substantia gelatinosa (Rexed's laminas II and III). Spinally delivered opioids act primarily at presynaptic levels to decrease nociceptive transmission of information.

One of the most studied non-opioid, non-local anesthetic, pain modulatory systems has been the α-2 adrenergic receptor. The primary effect of α-2 drugs is activation of descending inhibitory pathways on postsynaptic afferent nociceptors in the dorsal horn.[4] Other effects of intrathecally-administered clonidine include reductions in $A\delta$- and c

fiber-mediated somatosympathetic reflexes, spontaneous sympathetic activity and increased depolarization thresholds on intrinsic spinal neurons.[5]

Intrinsic muscarinic receptors exist in laminae II and III of the dorsal horn with terminals presynaptic to primary afferent neurons. Neostigmine, a cholinesterase inhibitor, produces analgesia when injected intrathecally.[6] Recently, the interaction between this cholinergic and the adrenergic effect of clonidine has been explored. It appears that analgesia from spinally administered clonidine is mediated by spinal muscarinic and nicotinic receptors, and spinally released acetylcholine contributes to the antiallodynic effect of clonidine.[7]

Adenosine receptors are also present in the substantia gelatinosa of the dorsal horn. In animals administration of adenosine receptor agonists produces analgesia and enhance antinociception from norepinephrine and α-2 adrenergic agonists.[7] In humans, intrathecal adenosine may have limited activity as a sole drug on nociceptive processes. Adenosine does reduce the area of allodynia and/or hyperalgesia in experimental human pain models and patients with neuropathic pain. Adenosine appears to act through an adrenergic mechanism and has been shown to work synergistically with neostigmine and additively with clonidine in models of hypersensitivity.[8]

Cyclooxygenase (COX)-1 and COX-2 isoenzymes are present in glia and neurons in the spinal cord.[8] Spinal COX-2 may be upregulated in several conditions including local and peripheral inflammation. Spinally synthesized prostaglandins have been postulated to be responsible, in part, for the delayed hypersensitivity seen after chronic opioid exposure.[9] Early studies suggest that the intrathecal administration of a nonselective COX inhibitor, ketorolac, produces analgesia and may reverse the hypersensitivity/hyperalgesia seen with chronic spinal opioid delivery.[10] There is also recent evidence to show synergy between intrathecal neostigmine and ketorolac.[11]

Intrathecally administered *N*-methyl-D-aspartate (NMDA) receptor antagonists produce antinociception in patients with neuropathic pain.[12] These drugs also prevent or reduce the spinal "wind up" that appears to play a role in the development and perpetuation of some chronic pain syndromes. The hypersensitivity seen with acute or chronic opioid delivery is also favorably altered with the administration NMDA receptor antagonists. Unfortunately, many of the drugs in this class have shown neurotoxicity in animal models, thus precluding their use in human trials.

The role of intrathecal GABA-ergic drugs, gabapentin, and conotoxins are also actively reseached as potential drugs for the future.[13-14, 21]

Intrathecal Opioids

Morphine sulfate continues as the mainstay of chronic intrathecal drug delivery. The majority of implanters continue to use morphine as their number one drug in intrathecal pumps.[15] Intrathecal morphine is effective in most patients with nociceptive pain and shows some efficacy in many patients with neuropathic pain.

The dose conversion of parenteral morphine to intrathecal morphine is 100:1. A larger bolus dose may be considered for a trial injection in patients whose current opiate dose has been ineffective. Similarly, patients who experience good pain relief with systemic morphine but have intolerable side effects may achieve adequate analgesia from a smaller than calculated intrathecal dose of morphine.

The first opioid alternative to morphine is hydromorphone for most implanters.[15] Hydromorphone behaves similar to morphine in many ways with the exception that its potency is 5:1. Fentanyl, sufentanil, meperidine, and methadone have all been used intrathecally with varying results. These opioids are used primarily when morphine, hydromorphone and combinations of non-opioids and opioids have failed.

Myoclonic activity has occurred with both intrathecal morphine and hydromorphone. While there is a dose response effect for myoclonus, there is considerable interpatient variability. Some patients never experience myoclonic activity despite high doses of drug while others have severe, generalized myoclonic activity at less than expected doses. Treatment involves cessation of the drug, alternative treatment with benzodiazepines titrated to comfort, systemic opioid to prevent withdrawal, and supportive care. This authors experience has found this side effect to occur more often in cancer patients than their non-cancer counterparts.

A potentially difficult problem with either intrathecal morphine or hydromorphone involves the formation of an inflammatory mass at the tip of the catheter. In animals there was a dose response effect and the effect of intrathecal drug concentration may also be an important predictor of granuloma formation. Co-administration of intrathecal clonidine to the morphine decreases the incidence of inflammatory masses and doses of >.25 mg/day of clonidine abolished the inflammatory mass formation.[16-18]

Diagnosis of a catheter-tip inflammatory mass should be suspected if analgesia is suddenly lost or there are new, and often gradually developing neurological symptoms. If a mass is diagnosed before it has filled the thecal sac or caused severe neurological symptoms open surgery has not been required. Cessation of drug has been accompanied by disappearance or shrinking of the mass over 2-5 months.[17]

A final issue with intrathecal opioids is tolerance. Dose escalation over time seams to be a bigger problem with non-cancer pain patients although cancer patients often require a higher initial dose.[19] An expert consensus panel felt that patients requiring greater than 18-20 mg/day of intrathecal morphine should have other options explored.[20]

Intrathecal Clonidine and/or Local Anesthetics

The Food and Drug Administration (FDA) has approved the use of epidural clonidine for the management of cancer pain refractory to opioids. Most practitioners currently use clonidine intrathecally in patients with permanent indwelling pain infusion devices. For some practitioners clonidine is used second-line to opioids while others prefer to first use local anesthetics.[15] In our experience clonidine is used as a second line drug when neuropathic pain predominates. When opioids are insufficient in managing somatic pain local anesthetics (bupivicaine) may be the drug of choice. It is also reasonable to use a triple combination of opioid, clonidine and local anesthetic when a combination of 2 drugs becomes ineffective.[15]

The intrathecal dose of clonidine varies among practitioners. We commonly start at 2-4 ug/kg/hr and titrate to effect when combining with intrathecal opioid. If we are using clonidine as a sole intrathecal agent we commonly start between 4-8 ug/kg/hr and titrate to effect. We rarely exceed 30 ug/kg/hr of clonidine by intrathecal infusion. One must monitor for side effects including bradycardia, hypotension, dry mouth, and sedation. When using clonidine at low infusion doses these side effects will start gradually and allows for the initiation of the drug in an outpatient setting. Bradycardia is more significant when the catheter tip is in the upper thoracic region where sympathetic cardiac

accelerator nerves are prevalent. Two groups of patients that are more prone to the hypotensive effect of clonidine include young women with resting systolic blood pressures less than 95 mm Hg. They often do not tolerate a 10-15% drop in systolic blood pressure without developing orthostatic symptoms. Also, uncontrolled hypertensive patients are prone to exaggerated effects of clonidine as sympathetic tone is blocked.

Local anesthetics are used frequently in intrathecal drug delivery either in combination with clonidine and/or opioids. The most commonly used local anesthetic, bupivicaine, is infused between 0.5-5 mg/hr. Higher doses of bupivicaine can cause numbness, motor weakness, and possible bowel and bladder dysfunction. It is unclear if low doses (<0.5 mg/hr) provide analgesia. Tachyphylaxis can occur requiring increasing doses of local anesthetics over time. The concentration of local anesthetics in delivery systems must be considered. Many practitioners feel safe with bupivicaine concentrations at 3% (30 mg/ml). Since no commercial preparations of bupivicaine exceed 0.75% compounding of the drug is often required to prevent frequent refills. No animal toxicity data exists for high bupivicaine concentrations, and caution should be used if greater than 3% bupivicaine is anticipated.

Neostigmine and Adenosine

Intrathecal neostigmine and adenosine are considered 3rd or 4th line. They are used predominantly when opioids, local anesthetics, and clonidine have failed. Neostigmine doses for postoperative pain range from 12.5-25 ug. Infusions of 0.5-1.0 ug/hr have been tolerated in some patients. Nausea and vomiting are the predominant side effects that can preclude its use in some patients.

Adenosine is most helpful when a significant amount of hypersensitivity and/or hyperalgesia is present. This state is often seen in patients with chronic neuropathic pain conditions such as complex regional pain syndrome, mononeuropathy, or radiculopathy. The bolus dose is commonly between 1-2 mg. Experience with infusions is limited; we have started at 0.05-0.1 mg/hr. The half-life of adenosine is short, but the analgesic effect of intrathecal adenosine can last for >24 hours with single bolus injection. A side effect seen recently in patients but not human volunteers was back pain. This is transient and resolves in several hours following bolus injection. Its exact mechanism is unclear.

Ziconotide

Ziconotide represents one of the conotoxins and is classified as a specific N-type calcium channel blocker. Studies involving intrathecal infusions have demonstrated efficacy in patients with neuropathic pain.[21] The therapeutic window may be narrow as high doses can cause side effects, including nystagmus and memory loss. Current Phase III studies are examining lower doses and slower titration schedules. If the side effect profile can be minimized this drug could prove helpful in patients with refractory neuropathic pain syndromes.

Gabapentin

Possibly no drug in the past 10 years has had a greater impact in pain medicine than oral gabapentin. Early animal and human studies have demonstrated possible efficacy when gabapentin is administered intrathecally.[13] A Phase II program may start in the coming months to further evaluate this drug as an intrathecal analgesic.

Ketorolac

COX-1 and COX-2 isoenzymes are present in the spinal cord. Intrathecal ketorolac has been shown to produce analgesia in both animal and human models.[9-10] This drug may also show promise in reversing the hypersensitivity and tolerance that develops with intrathecal opioid administration. A double blind, placebo-controlled prospective trial is underway to further evaluate the efficacy of intrathecal ketorolac in patients receiving chronic, continuous infusions of opioids.

Polyanalgesia Drug Delivery

No single drug has proven effective for all patients or all disease processes. Opioids (morphine and hydromorphone) continue to be the primary class of intrathecal analgesics. Many implanters and managers of intrathecal systems recognize the need to look at alternative drugs.[15] Currently, local anesthetics and clonidine are the most commonly added drugs to opioids for intrathecal drug management. Two or three drugs are sometimes required to maximize analgesia. Long-term management of intrathecal catheter systems requires flexibility. It is unusual to manage a patient for a period of years without having to make some therapeutic changes to the pump drugs. Many implanters recognize the need for additional drugs to the currently available ones. Implanters should be aware that many of the drugs used for long-term intrathecal management are off-label uses (preservative-free morphine is the exception).

Delivery Systems

Since the early 1980's many different intrathecal delivery systems have been utilized. Exteriorized catheters, catheters attached to subcutaneous ports, constant rate infusion pumps, self-contained, fully implanted mechanical injection devices, and programmable pumps have been successfully used. In cancer patients with short life expectancies (<3-4 months) exteriorized catheters or catheters attached to subcutaneous ports and external pumps are more cost effective than internalized pumps. For patients with longer life expectancies internal, self-contained pumps are associated with fewer long-term complications including infection and catheter dislodgement.

Differences exist between implantable pump and catheter systems. It is unclear whether continuous infusion or intermittent bolus of medication provides better analgesia or less tolerance. New pump designs have the capabilities of allowing patients to administer a physician-programmed bolus for treating daily fluctuations commonly experienced by patients with chronic pain. This feature awaits FDA approval.

Characteristics of catheters include use of silastic, polyurethane, or nylon material. Catheters may have a single orifice, commonly at the tip of the catheter, or multi-orifices. Multi-orifice catheters may decrease the likelihood of occlusion. It is unclear if drug dispersion differs among the different type of catheters. Studies are underway to examine the characteristics of fluid dispersion from intrathecal catheters.

Complications of Intrathecal Drug Delivery

Complications from intrathecal drug delivery occur either around the time of implantation or during long-term management. Complications at the time of implantation are usually technically related and include infection, catheter kinking, catheter occlusion, catheter dislodgement, wound dehiscence, or pump malfunction. Many of these complications can also occur during long-term management. Additionally, intrathecal mass formation can occur during long-term administration.

Implanters should use sterile technique for catheter and pump placement. Fluoroscopy is recommended, when available, for catheter placement. For the majority of patients some sedation allows for better patient comfort and tolerability, but it is usually preferable to have patients able to respond during catheter placement in case of the catheter contacting a nerve root or being threaded into the spinal cord from the conus medullaris. Once the catheter is positioned correct placement is verified by seeing CSF dripping from the proximal end of the catheter. Small amounts of water soluble, nonionic, and iso-osmotic contrast material can be injected for further verification. Awake or sedated patients will not tolerate the injection of contrast material into the spinal cord. The implanter should investigate unusual discomfort during catheter placement or subsequent contrast injection.

Infection can occur from the procedure, from subsequent refills of drug, or from a distant hematogenous or intrathecal source. Many implanters use antibiotics in the perioperative period although it is not clear if this decreases the incidence of infection. Infected catheter systems often have to be removed. We have successfully treated some infected systems with consultation of our infectious disease colleagues, particularly in terminal patients whose end-of-life situation and analgesic requirements made the benefits of the pump more important to the patient and family.

Inflammatory masses are an unusual occurrence with intrathecal catheters systems. It is not clear what mechanism leads to their formation. Concentration and dose of morphine or hydromorphone have been shown in animals to cause intrathecal mass formation.[16] Interestingly, the addition of intrathecal clonidine ameliorates the inflammatory mass formation seen with opioids.[16]

Inflammatory masses can be either asymptomatic or produce significant neurological symptoms. Asymptomatic catheters may be treated conservatively while those producing neurological symptoms should be removed. Neurosurgical consultation should be considered if neurological symptoms persist or worsen. Conservatively treated masses should be followed with serial MRIs until it can be determined that they have resolved or are not progressive.

Summary

With the development of additional drugs and newer pump technology intrathecal drug delivery has witnessed a significant increase in utilization. No single drug or drug combination works for all patients. Complete pain relief remains elusive for many of these refractory pain syndromes. Neuropathic pain syndromes remain the most difficult to treat pain for many practitioners. Long-term success of intrathecal drug delivery starts with appropriated patient selection. Potential patients for intrathecal drug delivery should be screened and trialed prior to implantation. Patient expectations should be appropriate and efforts at functional enhancement should be maximized after pump placement, when indicated. New developments in drugs and devices should continue and make this route of analgesia very promising far into the future.

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