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Mechanisms of action of intrathecal medications

Richard K. Simpson, Jr, MD, PhD

Departments of Neurosurgery, Anesthesiology, and Physical Medicine and Rehabilitation, Baylor College of Medicine, 6550 Fannin Street, Suite 900, Houston, TX 77030–2725, USA

Background and history

Many methods of pain management are currently available and are discussed in detail in other articles in this issue. Intrathecal delivery of analgesics as part of this pain management spectrum is generally believed to be a therapeutic consideration only when other methods have failed to control pain adequately, produce serious unwanted side effects, or cause unacceptable neurologic deficits. This latter concern is of particular significance regarding the management of pain with neuroablative procedures. Until recently, neuroablation has been viewed as the last step in pain management after all other methods have been exhausted and have failed.

Neuroaugmentation was born out of the recognized limitations of neuroablative procedures. Neuroaugmentation consists primarily of neurostimulation, such as epidural spinal cord stimulation, and continuous drug delivery devices, such as intrathecal administration of opiates. Neurostimulation has a unique role in the management of pain and is discussed in another article in this issue. When neurostimulation is not a consideration and other methods of pain management are unsuccessful, continuous drug delivery via an intrathecal route should be considered. Targeted drug delivery, or the administration of analgesics directly to areas in the central nervous system involved in generating the pain signal, can adequately manage pain with limited side effects.

Original studies of intrathecal medication for the management of pain began with a series of animal studies by Yaksh and Rudy in 1976 [1]. Morphine, when delivered to the neuraxis, produced dramatic analgesia in either rats or primates. Such laboratory evidence quickly led to clinical trials and case by case observations in patients suffering from a variety of painful states. The speedy application to human beings was promoted by the recognized reversible nature of the drug, the minimal invasiveness of the procedure to administer the drug, and the lack of serious side effects if the drug was administered in a controlled manner with the patient under careful observation.

These early clinical studies reported a great deal of success in battling refractory pain states produced by cancer. Milam Leavens and his colleagues from M.D. Anderson Hospital in Houston, Texas were among these pioneers of intrathecal delivery of opiates for cancer pain. In an 1982 report by Leavens et al [2], four patients had approximately 80% pain relief without reported significant side effects. Since that early report, many contemporary studies have supported the observations regarding the effectiveness of intrathecal morphine for pain management. Recently, Gilmer-Hill et al [3] reported a similar range of pain relief in nine patients with pancreatic cancer pain.

Pain produced by mechanisms other than cancer can also be managed with intrathecal morphine. Reports by Penn and Paice [4] nearly 15 years ago revealed successful management of eight patients with failed back surgery. Good to excellent pain relief was observed in this patient series, with no reported significant side effects. In a recent study by Angel et al [5] of eight patients with failed back surgery and other injuries, approximately three quarters had excellent pain relief. Pain produced by mechanisms other than cancer has also been successfully managed with intrathecal opiates. These mechanisms include postherpetic neuralgia, arachnoiditis, peripheral nerve injury, and reflex sympathetic dystrophy.

E-mail address: rsimpson@bcm.tmc.edu

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During the early 1980s, partly in response to the success of intrathecal delivery of morphine for pain management, fully implantable infusion pumps were developed. Before the development of these implantable devices, intrathecal infusions were accomplished by single bolus injection via a lumbar puncture or an intrathecal catheter connected to an external pump. These methods of application had many inherent limitations, including the potential for a cerebrospinal fluid leak from multiple punctures, respiratory depression from a bolus injection, and meningitis from an exteriorized catheter.

Although the focus of this article is on the intrathecal delivery of analgesics for pain control, the primary analgesics used are opiates, specifically morphine. Other opiates are used intrathecally for pain management, and other type of anesthetics and analgesics are occasionally delivered by this route. In addition, many laboratory studies are reporting that several different families of pharmacologic compounds can favorably influence the pain response as a single compound or as a mixture of compounds. These include excitatory amino acid analogues, antispasmodic compounds, α_2 agents, and many others. The development of continuous infusion drug delivery devices for intrathecal administration of drugs and the use of novel compounds in these devices have greatly improved pain management. Nevertheless, considerable attention must be devoted to issues of the chosen delivery site, patient selection, type of device used, surgical technique, complication avoidance, and vigilant patient follow-up before the true success of this pain management technique can be fully realized.

Delivery site

Continuous rather than or in addition to bolus delivery is considered to be a more effective method of analgesic delivery because it tends to produce a constant level of pain relief rather than an on-off or see-saw type of experience. Several studies in the 1980s studied this concept and examined whether or not intraventricular versus intraspinal access to the cerebrospinal fluid space was superior. The overall effectiveness between these two routes of intrathecal delivery is relatively comparable. A recent study by Karavelis and colleagues [6] provides some general guidelines for the use of intraventricular administration of morphine. The intraventricular method is more invasive and is generally reserved for refractory cancer pain of cephalic origin or diffuse cancer pain that does not respond to intraspinal delivery methods.

Epidural versus intrathecal delivery of drug for pain management has also been a point of debate. Although delivery to either site can produce analgesia, there are several reasons why intrathecal delivery is considered to be superior. As with parenteral or enteral delivery, epidural delivery requires higher doses than does intrathecal drug delivery. These higher doses can produce undesirable systemic side effects and produce pain relief over a more limited topographic area. In addition, the reservoir in the pump device is depleted more rapidly and requires more frequent refills if drug delivery is via the epidural route. Catheter fibrosis and obstruction of the catheter tip as well as migration out of the needed delivery area reduce the drug's effectiveness. A more serious problem is an epidural-to-intrathecal migration of the catheter, which can result in an accidental and potentially fatal overdose. The converse is not true. Serious consideration must be given to the possibility of systemic reactions to withdrawal if an intrathecal-to-epidural migration is of concern.

Patient selection

A multidisciplinary approach to each patient is highly desirable to determine if a patient is a reasonable candidate for intrathecal drug delivery. An assessment of the impact of many factors that pertain to a particular discipline on the outcome of this method of pain management can be undertaken more accurately. Such factors as psychologic influences, family support, and others can be ascertained and used to determine the likelihood of a successful outcome from this therapy. There are two stages of patient selection for intrathecal delivery of morphine for pain management. The initial stage is to determine if a patient is a candidate or not for this particular method. To provide the best chance for a good outcome, patients should have a clearly identifiable physiologic generator of their pain. Pain that has no clear physiologic basis is not likely to respond favorably to intrathecal medication. Again, psychologic issues need to be thoroughly addressed. Serious depression, secondary gain issues, drug-seeking behavior, and intrafamily issues, such as codependence, can all impede the successful outcome of this therapy.

Practical issues, such as known allergy to the compound to be infused, can limit the use of

intrathecal drug delivery for pain. Restricted cerebrospinal fluid flow from an epidural mass or leptomeningeal disease or spinal canal compromise from bony compression can render this technique unsuccessful. Coexisting disease, such as systemic infection, coagulopathic states, and general debilitation, necessarily obviate the use of this method. Any medical issue that would seriously affect patient survival after a small surgical procedure would exclude such a patient from receiving this method of pain management. Acute renal failure, unstable angina, evolving stroke, severe pulmonary disease, active internal hemorrhage, and many other medical problems that often accompany patients with cancer pain in particular would preclude such a patient from an intrathecal drug delivery device. In addition, a limited life expectancy, generally less than 4 months, challenges the cost-effectiveness of these devices.

Each patient should have completed a course of therapy that would eliminate other medical or reasonable surgical options for satisfactory pain management. Short of ablative surgical procedures, all other pain management approaches should be explored before a patient is considered a candidate for continuous intrathecal drug delivery. This is especially important for intrathecal therapy applied to pain that is not from cancer. Not only is the issue of psychologic influences on pain more problematic in noncancer pain, but doses tend to be higher, patients' life expectancies are generally longer, correction of certain structural conditions may be helpful, and a clearly defined generator of pain can be somewhat elusive. Maximum medical management must be fully considered in these highly complex patients.

Another potential source of patient exclusion from candidacy for intrathecal drug delivery is the amount of medication taken at the time of assessment. High doses of narcotics taken orally or parenterally can produce a degree of tolerance that limits the effectiveness of intrathecal morphine. This can be true for either cancer or noncancer pain. The volume and rate of delivery of intrathecal narcotics may render such a drug delivery system impractical. Other practical issues from a surgical standpoint include patient size, body habitus, degree of inanition, and logistic issues (eg, a patient's ability to travel for follow-up evaluations, device management), and all have an impact on the determination of whether a patient is a candidate for an intrathecal drug delivery system.

The second and extremely important stage in the patient selection process is the response to a trial of intrathecal opiates. This is accomplished via lumbar puncture with or without catheter placement. If a catheter is used, it can be secured to an external pump. Intrathecal delivery can be done using a simple bolusing technique or with constant infusion with periodic changes in the rate to determine optimal benefits. Bolusing can be done once or many times (generally separated by 24 hours for each bolus) until the optimal response is achieved. Constant infusion for several days can provide a more reliable picture of how the intrathecal drug delivery device will perform, at least for the short-term application. Several guidelines exist for intrathecal trials of morphine [7]. The trials are generally done in the intensive care unit (ICU) setting. Depending on the level of narcotics already used by the patient, intrathecal delivery can begin as a 0.5- to 1.0-mg bolus of a morphine preparation that is compatible with cerebrospinal fluid administration. Higher doses on successive days may be necessary to produce the desired effect. If constant infusion is undertaken, infusion rates of 2 to 8 mg/d may be required. Even higher doses may be necessary under special circumstances. Patient selection issues may develop, however, and the limitations of the output volume of these devices may become of concern.

Throughout the trial, it is occasionally difficult to ascertain the effectiveness of the medication and whether or not it is truly beneficial. Concerns that may have been borderline issues regarding the decision to proceed to stage 2 and that were not clear during stage 1 of patient selection may be assessed at stage 2. Psychologic issues, secondary gain, subtle drug-seeking efforts, and other medical problems might be discovered during stage 2. Periodic assessment at set intervals with visual analogue scales or other instruments for pain measurement is worthwhile. Evaluation of the patient by a nurse or by other personnel who do not have knowledge of the dose or the results from previous visual analogue scales reported by the patient is an optimal method to assess the benefit of intrathecal delivery of drugs. Once it becomes clear that the patient is having a satisfactory degree of pain relief from the trial without significant side effects, it may be decided whether that individual is a reasonable candidate for an implantable device.

Device selection

Several intrathecal drug delivery systems are available. Several of these systems can be employed to deliver intraspinal or intraventricular

medication. The discussion in this section concentrates on the intraspinal method of intrathecal drug delivery.

There exist two basic families of intrathecal drug delivery systems. These include a catheter secured to an externalized method of infusion, such as a pump, or a catheter secured to an internal reservoir or pump. The internalized system can be subclassified into four groups: the simple injection port style, the patient-activated pump, the continuous flow pump, and the complex programmable pump system. The externalized system has a limited utility because of concerns about infection and cerebrospinal fluid leakage. Patients with limited life expectancies, generally less than 4 months, or patients who require short-term analgesia often readily respond to this type of intrathecal drug delivery.

For the external pump system, a lumbar puncture is done, a catheter is threaded intrathecally, and the catheter tip is placed at a predetermined site based on pain location. The catheter is externalized and is secured to an adjustable outflow pump that can deliver medication at slow rates. Another method is to secure the intrathecal catheter to a bubble-shaped reservoir, which is, in turn, secured in a subcutaneous fashion. The chamber can be accessed via a needle and external catheter system, which is, in turn, secured to a pump. The same, although rarely done, can be accomplished for intraventricular delivery, which uses either a twist drill or burr hole opening for catheter access of the ventricular system. For short-term use of a intrathecal catheter–external pump system, the catheter can be exteriorized at the point of insertion. For longer use, the catheter can be tunneled subcutaneously for a short distance before being exteriorized, which may reduce the rate of infection.

In contrast, the internal system requires securing the intrathecal catheter to one of the four types of devices mentioned previously, which is, in turn, placed into a subcutaneous pocket for access. The simple port system, similar to that described previously, is secured to the catheter and placed into a small subcutaneous pocket for access. Generally, these ports are percutaneously accessed for bolus injections at specified time intervals. As mentioned, these ports can be percutaneously accessed by an external pump–catheter system for short-term continuous infusions.

The patient-activated pump is a device that is secured to an intrathecal catheter and then placed into a subcutaneous pocket. The unique feature of this type of pump is that a patient can press on a specific area of the subcutaneous device to change the rate of infusion or provide a bolus infusion if necessary at preset limits. As with all implanted reservoirs, refilling is done in a percutaneous manner once the chamber becomes depleted. The continuous flow pumps are, again, secured to the intrathecal catheter and deliver the medication at one rate. Constant flow pumps require that if a change in the concentration to the patient is necessary to maintain satisfactory pain relief, the reservoir be emptied and a new concentration be infused to provide the new level of medication. The constant continuous flow pumps use a bellows method and compressed gas to deliver the medication. There are no batteries in this system; hence, the pump does not need to be periodically replaced.

Programmable adjustable rate pumps provide greater versatility for intrathecal drug delivery. Some pumps can be programmed to deliver two or more rates. No other features are available with this type of device. The most versatile implanted intrathecal drug delivery device is the fully programmable variable rate pump. These devices, again, are secured to an intrathecal catheter and placed into subcutaneous pocket. They can deliver at a constant rate in a continuous fashion but can also be programmed to deliver at different rates and to deliver boluses. They can also be programmed to provide a routine of different rates throughout the course of the day. As with other reservoirs, these pumps require periodic percutaneous refills of medication. Unlike the constant rate devices, these pumps use battery power and the pump itself requires periodic revision, generally every 3 to 7 years.

As the delivery system becomes more complex, the cost increases considerably. Cost-effective issues must be addressed on a patient by patient basis. If a patient has a limited life expectancy or only requires short-term therapy from time to time, an external system with a port style device may suffice. If a patient has episodic pain that requires intrathecal drug delivery, a patient-activated device may be of value. If a patient's pain and medication needs are relatively stable, a constant rate pump may suffice. For patients with life expectancies that are likely not to exceed a few years, a constant infusion pump with limited programmability may be worthwhile. Several devices are available to meet the wide range of needs of patients requiring intrathecal drug delivery. The more complex programmable pumps may be

necessary for patients with long life expectancies or those with complex pain patterns.

Implantation technique

Surgical methods for implanting the devices used for intrathecal drug delivery are relatively simple and common to each of the devices described previously. Despite the relatively simple procedure for implanting these devices, great care must be taken to minimize complications as well as additional suffering and cost to patients who are often already overwhelmed by these issues. The generalized description for implantation of these devices discussed below reflects the author's experience with more than 500 such implants and is an attempt to provide the clinician with some reasonable guidelines.

For implanting an intrathecal catheter via an intraspinal approach, a lumbar puncture is done using an extremely vigilant sterile technique. The traditional entry points of L2 to L3 or L3 to L4 are most commonly used. Use of lower entry points is more difficult to perform and limits the upper limit of catheter tip placement. Use of entry points above the L1 level risks injury to the conus medullaris or other areas of the spinal cord and is avoided unless absolutely necessary. To avoid damage to these structures if higher catheter placement is necessary or if previous surgery prevents percutaneous access, an open placement of the catheter via a small laminotomy and intradural approach may need to be considered.

Once the intrathecal space has been entered and successful entry is verified by free-flowing cerebrospinal fluid, an intraoperative myelogram should be done using a C-arm and contrast. Infusion of contrast assures optimal placement of the catheter and free flow of cerebrospinal fluid, the catheter tip location, and if any leaks are present in the epidural or subcutaneous spaces. An unsuspected laceration of the catheter can occur at or around the needle entry point. Coils or kinks in the catheter system can be easily visualized and managed using this technique. Once the catheter is in the optimal position, it can be secured to any of the many devices mentioned previously. Catheter tip location has been traditionally described to be optimal at T10. Higher level placement risks a higher likelihood of respiratory embarrassment because of suppression of the brain stem or general cerebral activity. Suppression of intercostal activity or, if the catheter is placed higher yet, phrenic nerve activity may also contribute to respiratory compromise and should be considered. Higher placement, even into the cervical canal, has been done with safety and efficacy, however.

Once a catheter has been placed, it may be left in place for several days and externalized to a drug pump for a trial of intrathecal opiates. If placement is for long-term treatment, the catheter is secured to one of the four internalized devices mentioned previously. The design of the subcutaneous pocket must take into consideration the ease of access for programming and refills, patient comfort and mobility, and the size of the device. In general, the easiest location for pocket creation is in the abdominal area between the costal margin and superior iliac crest, lateral to the midline. This offers a large area of potential sites along with avoidance of having the device rest on bony structures, which can cause pain and produce skin breakdown. Access is relatively easy; patients can monitor and protect the device; and even in obese patients, refill is rarely a problem.

The pocket, again, can be quite large, particularly for the programmable devices. This requires the elevation of a large flap with a relatively tenuous blood supply. Great care must be undertaken to create the pocket so as to prevent the potential for infection, skin breakdown, or seroma formation. Careful sterile surgical technique and hemostasis minimize complications, the potential for the removal of an expensive device, and the likelihood of reimplantation of another device. Likewise, great care must be undertaken at the needle insertion site to address these same issues but also to avoid damaging the catheter. A subcutaneous tunnel is created between the two incisions, and the catheter is led through the tunnel either as a single unit or with an extension catheter and is attached to the drug delivery device. The connections are secured in such a manner so as to prevent separation after installation. A variety of anchoring methods are available to secure the catheter in position as well as the pump. Anchoring of the components of the device minimizes catheter migration and pump rotation or flipping.

Surgical complications can occur despite the relatively simple nature of this procedure. Infection is the most common complication. Although long-term antibiotics can be given in an attempt to salvage the device, the device generally needs to be removed, at least in part, to eradicate the infection effectively. Meningitis can occur and must be recognized and treated quickly to minimize additional neurologic injury in these already seriously impaired patients. Hematoma

formation at the device site can often be addressed with a pressure dressing rather than by reopening the incision. Seroma formation rarely presents a serious problem. Intraspinal bleeding may cause spinal cord compression, however, and requires an emergency decompression to treat it adequately. Cerebrospinal fluid leakage can produce a postural headache and even fill up the device pocket if it persists. Although lying flat in bed with sufficient hydration generally resolves the leakage, an epidural blood patch at the catheter entry site can be used effectively. Persistent cerebrospinal leakage, if untreated, can even produce chronic subdural hematomas in patients who have significant cerebral atrophy.

Potential complications

Neurologic injury other than from meningitis or cord/cauda equina compression is rare. The catheters and stylets used in most systems are soft and malleable. Temporary radicular symptoms can occur and require repositioning of the catheter. These symptoms can occur soon after the procedure or in a delayed fashion. Intraspinal cord placement of the catheter can also occur, producing myelopathic signs or signs of conus medullaris compression. Removal of the catheter is necessary, and decompression may be advisable. If imaging studies are required, the catheter can present some artifact but generally not enough to limit a clinical decision. The pump device can create significant artifact and obstruction of the view of certain areas, and this must be taken into consideration as the evaluation proceeds. MRI scanning can be done safely if the pump is off. Additional safety measures include the removal of drug from the reservoir with saline replacement and aspiration of the catheter, although these latter measures are not always done on a routine basis.

Other complications are related to the device and system components. The catheters can migrate out of optimal position or can obstruct, kink, fracture, and separate. The drug pump or chamber can fail mechanically or, in the case of programmable devices, fail to respond. The motors can stall, the internal electric mechanisms can fail, and the telemetry devices can become nonfunctional. If a suspected device failure has occurred, plain films are helpful. If the plain films are not useful tests, testing of device function can be undertaken and is outlined in the user manuals. For example, with regard to the programmable pump system, the catheter can be accessed and tested by a percutaneous approach via a side port that bypasses the pump itself. Contrast can be infused if the catheter can be aspirated to check for fractures or migration with standard radiographic technique. Infusion of contrast without aspirating the catheter first can lead to an overdose and must be considered during this maneuver.

The pump device itself can be evaluated by several means. The volume in the reservoir should match the anticipated or calculated volume since the last refill if the system is functioning optimally, depending on the type of device used. If these figures do not match, additional studies must be done. These can include infusion of an isotope into the reservoir for a nuclear medicine study. With regard to the programmable pump, the pump is programmed at a high rate to deliver the isotope through the system and to the cerebrospinal fluid. The pump/reservoir, catheter, and intrathecal space can be assessed to some degree. Radiographic evaluation of the pump motor can be done by programming a measured bolus into the pump. The motor rotates a certain number of degrees if functioning properly. Unfortunately, none of these techniques reveals if the pump is functioning at a suboptimal level or in an intermittent manner. Clinical suspicion supplemented by these limited diagnostic tools remains the best method of intrathecal drug delivery device evaluation. To provide the patient with optimal management, one or more components of the system may need to be revised or replaced.

Medical complications can occur with the use of these devices. Although other drugs can be infused intrathecally by these delivery devices, opiates (primarily preservative-free morphine) are the most common drugs used. The most serious complication is respiratory depression to the point of arrest. To limit these concerns, intrathecal trials in the immediate period after implantation should be performed in an ICU-like setting. Other complications are similar to those found with the enterally or parenterally administered opiates. These include drowsiness, confusion, itching, hypotension, and possibly arrhythmias. If intrathecal doses are at higher concentrations, systemic side effects similar to those observed with peripheral administration can occur. These may include constipation, urinary retention, gastrointestinal disturbances, edema, fatigue, and weakness. Withdrawal can also be a serious medical complication. This generally occurs when the pump reservoir becomes depleted before a refill can be undertaken or when the pump device malfunctions in some manner. Battery

depletion before the device can be replaced can result in the patient experiencing a withdrawal reaction. These symptoms reflect those found with peripheral administration of opiates and include sweating, nausea, vomiting, hypo- or hypertension, delirium, and possibly seizures. Patients can be maintained on oral opiates until the device can be replaced or revised.

Device management

Management of the intrathecal drug delivery devices involves revising or replacing malfunctioning or depleted components, refilling the reservoir, dose adjustment if necessary, and, most importantly, evaluation of the patient for other sources of pain. A reasonable but strict follow-up plan should be instituted for each patient, because changes in the type and dose of other coexisting medications are likely to mitigate undesired drug interactions.

Revising and replacing the components that have failed was addressed in the previous section. All these devices require periodic maintenance, even if it is simply the refill of a reservoir. Based on the output needs of the patient for satisfactory pain control, a refill time can be calculated. Patients are brought to the clinic before their reservoir depletion date for a refill not only for pain management but to avoid withdrawal reactions as well. Refill of ports and reservoirs is generally done with a syringe and a noncoring needle. The reservoir is filled to within the limits of the system under strict aseptic conditions. Before refilling the system, the chamber is aspirated to determine if the delivery rate reflects the residual volume. The refilling technique must be performed with great diligence; otherwise, there exists the potential for subcutaneous delivery of the medication or even direct intrathecal delivery of the refill volume with potentially fatal consequences.

From time to time, adjustments in the delivered dose are necessary. For the constant rate pumps or the simple port style systems, this would require changing the concentration of the medication delivered to the reservoir. For external systems, changing the concentration or flow rate from the external pump would be necessary. For the programmable pump, this would require changing the output characteristics of the device within the limits of the system. The reason for adjustments in the output of the system must be addressed on a patient by patient basis. Occasionally, failure of a component of the system is the reason. Escalation of pain is common, particularly in patients with cancer. Another source of pain must be suspected if a sudden change in intrathecal delivery is required, however.

Patients with progressive metastatic cancer or, in the case of noncancer pain, progressive reflex sympathetic dystrophy may have serious underlying pathologic findings apart from their primary pain generator. These could include abdominal disease, such as cholecystitis, urinary tract infection, kidney stone, angina, diffuse metastasis, decubitus formation, unrecognized trauma, or a possible psychologic issue manifested as a need for increasing medication. The intrathecally administered doses can be increased, theoretically, to the limits of the output features of the device or based on the pharmacologic characteristics of the infused medication. When extremely high doses become necessary and other reasons for pain dose escalation have been addressed, this may reflect tolerance to the medication, and other methods of pain management may need to be considered once high-output requirements are placed on the device. Other intrathecally administered compounds may need to be considered, singularly or in combination with morphine or another opiate. Peripherally administered medication may supplement the role of the intrathecal drug delivery system. Lastly, neuroablative procedures may be considered. Nevertheless, intrathecal drug delivery under conditions of good patient selection provides a valuable method to treat cancer-related and noncancer-related pain in many patients.

Treatment outcomes

Outcomes from treatment of chronic pain produced by cancer are outlined in Table 1. This table clearly reflects the wide range of doses delivered on a daily basis from implantable devices. Despite the doses delivered, these patients had significant pain relief as defined by the table. Patient series that did not report a distinct percentage of good to excellent outcomes were found to have "significant" pain relief, which has been defined as greater than 50%. It is clear from these myriad results over the past two decades that intrathecal opiates offer a reasonable therapeutic modality for the treatment of chronic pain produced by cancer.

Outcomes from the treatment of chronic pain produced by noncancer mechanisms are outlined in Table 2. Again, although somewhat more controversial, patient reports provided in this table

Table 1
Outcomes from treatment of chronic pain produced by cancer

Name	Number of patients	Average follow-up (days)	Dose range (mg/day)	Relief of pain
Meynadier, et al, 1985 [40]	25	162	1.0	96%
Lazorthes, et al, 1985 [39]	48	120	1.0–10.0	100%
Laugner, et al, 1985 [38]	41	60	1.5–7.5	75%
Krames, et al, 1985 [37]	16	12	4–32	75%
Gestin, et al, 1986 [35]	121	68	1–21	> 50%
Shetter, et al, 1986 [45]	8	90	28.0	75%
Penn, et al, 1987 [4]	8	unknown	1–26	80%
Penn, et al, 1987 [4]	35	unknown	unknown	61%
Zriksen, et al, 1989 [51]	7	40	2–16	> 50%
Onofrio, et al, 1990 [41]	53	15	1–5	65%
Sjoberg, et al, 1991 [46]	52	23	10–25	> 50%
Plummer, et al, 1991 [43]	17	147	1–5	> 50%
Follett, et al, 1992 [34]	35	231	0.65–15	77%
Wagemans, et al, 1997 [49]	40	37	20	> 50%
Van Dongen, et al, 1993 [48]	51	unknown	8	> 50%
Sjoberg, et al, 1994 [47]	53	29	6	> 50%
Andersen, et al, 1996 [32]	27	unknown	unknown	85%
Paice, et al, 1996 [42]	133	365	14.2	95%
Gestin, et al, 1997 [35]	50	154	0.4–94	> 50%
Sallerin-Caute, et al, 1998 [44]	159	90	1–80	80%
Gilmer-Hill, et al, 1999 [3]	9	137	3–73	100%

suggest intrathecal opiates should be considered as a therapeutic option for chronic pain from non-cancer etiologies. Chronic neuropathic pain can be refractory to aggressive medical management and may respond quite well to intrathecal opiates if patient selection is done in a careful manner. The studies outlined in the table suggest that greater than 50% success in the treatment of neuropathic pain can be obtained.

The future

There are two directions for the future of chronic pain management by the technique of intrathecal opiate delivery. This does not include the potential for the development of currently used technologies for even more targeted delivery of medication. Such technologies as are currently used in the laboratory include reverse microdialysis or ionophoretic delivery of therapeutic agents. It also does not include genetic engineering, whereby precise cellular delivery of therapeutic agents may be accomplished via viral vectors or other means to the cell nucleus so that the cellular machinery can produce compounds that are directed against the generators of chronic pain. The two practical directions at this time include the use of current medications singularly or in a cocktail for intrathecal delivery that are not normally delivered in that manner and the development of new medications or more complex compounds that are explicitly engineered for the method of intrathecal delivery.

Table 2
Outcomes from the treatment of chronic pain produced by noncancer mechanisms

Name	Number of patients	Average follow-up (years)	Dose range (mg/day)	Relief of pain
Auld, et al, 1985 [33]	32	2	Unknown	65%
Penn, et al, 1987 [4]	8	unknown	1–26	61%
Hassenbusch, et al, 1991 [36]	11	unknown	unknown	75%
Plummer, et al, 1991 [43]	12	0.5	unknown	83%
Winkelmuller, et al, 1996 [50]	129	3.4	0.5–5.7	77%
Paice, et al, 1996 [42]	296	1.0	1.0	95%
Angel, et al, 1998 [5]	15	3.0	unknown	73%

Currently, the US Food and Drug Administration has approved only morphine and baclofen for intrathecal use. Other opiates are used for intrathecal delivery in a variety of clinical settings for pain management, including meperidine, hydromorphone, fentanyl, and sufentanil. Many practitioners use or mix local anesthetics, most commonly bupivacaine or the antispasmodic baclofen. Several ongoing clinical studies as well as studies conducted in the laboratory are investigating the utility of many other families of compounds for use as intrathecally delivered agents for chronic pain management [8,9]. These new families of compounds include NMDA receptor antagonists, inhibitory amino acid analogues, α_2-adrenergic agonists, GABA-ergic agents, calcium channel blockers, acetylcholinesterase inhibitors, and somatostatin analogues. Several other families of compounds are likely to be explored in depth once preservative-free, cerebrospinal fluid–compatible, nonneurotoxic derivatives can be developed. These include tricyclic antidepressants, anticonvulsants, and nitric acid–oriented compounds among others.

The popularity of NMDA agents as instruments to modify central nervous system activity soared in the mid-1980s. Only recently have these compounds attracted the interest of the pain management community. The basis for their activity is through the influence of calcium conduction through the cell membrane. A highly recognized member of this family of compounds is ketamine. The primary feature of these compounds is reflected by their ability to treat neuropathic pain and possibly reduce opiate tolerance. Yang [10] has shown that intrathecally delivered ketamine is not only effective in the management of pain in cancer patients but that it can reduce the coexisting morphine requirements of these patients.

Other compounds associated with the NMDA family of agents include MK-801 and 4-AP. Several studies have shown that the NMDA receptor acts independent from the opioid family of receptors with regard to neuropathic pain [11]. When dynorphin A was administered to laboratory animals, the pain response was blocked by MK-801 but not by naloxone. Simpson and associates [12,13] found a similar response in a peripheral nerve injury model of neuropathic pain. Similarly, Hansebout and associates [14] found that 4-AP was reasonably effective in the management of neuropathic pain and that further studies need to be instituted to explore possibilities of this family of compounds being used to combat chronic pain in general.

Inhibitory amino acid compounds have also shown great promise as therapeutic agents for neuropathic pain [15]. Glycine is the most prominent postsynaptic inhibitory amino acid in the central nervous system and occurs in high concentration within the spinal cord. It also carries properties that potentially make it a highly desirable compound for spasticity and other movement disorders. Simpson and colleagues [12,13] demonstrated that intrathecal infusion of glycine in experimental animals reduces both mechanonociception and thermal nociception. These properties are likely to be independent of the NMDA receptor as mentioned previously. The strychnine-sensitive receptor for glycine may influence neuropathic pain rather than the nonstrychnine or NMDA-associated glycine receptors.

Clonidine is the premier α_2-adrenergic agonist thought to have promising pain management features. Clonidine, generally regarded as an excellent compound for treating patients with more difficult expressions of hypertension, has been intensively studied for its analgesic properties. As an example, Middleton and associates [16] found that intrathecally administered clonidine is particularly effective in the management of pain caused by a spinal cord injury. This type of pain is particularly refractory to a variety of medical and surgical regimens and therefore often requires innovative approaches for effective management, such as intrathecal clonidine.

Spasticity produced by spinal cord injury, brain injury, or a variety of diseases affecting the central nervous system can respond favorably to intrathecal baclofen. Recently, intrathecal baclofen has been found to have analgesic properties as well. Loubser and colleagues [17] found that baclofen delivered intrathecally was particularly effective in treating the burning type of dysesthesias associated with spinal cord injury. Intrathecal baclofen has been used singularly or in combination with other compounds for the management of chronic pain. Intrathecal baclofen may be effective in the simultaneous treatment of spasticity and the symptoms of neuropathic pain associated with a spinal cord injury. Other compounds modulating gamma-aminobutyric acid (GABA) activity are also being studied for their utility as intrathecally delivered agents for treating chronic pain [18].

Pain signal transmission is likely to involve the conductance of calcium through the neuronal cell membrane or axonal membrane. Hence, calcium

channel blockers, particularly those that are neuronal specific, may influence the pain response in a favorable manner. This was the logic in pursuing a study of the properties of zaconotide or SNX-111. A study by Malmberg and Yaksh [19] has revealed the antinociceptive properties of these complex neuronal-specific calcium channel blockers when delivered intrathecally. These compounds derived from the giant cone snail, which uses these compounds to paralyze its prey, are being explored in patients for their efficacy and toxicity in the management of neuropathic pain. Results from these studies are forthcoming.

Acetylcholine is one of the best-defined neurotransmitters in the body. Commonly associated with the neuromuscular junction, acetylcholine is also found in the dorsal horn and may serve as an inhibitory neurotransmitter at that locale, thereby influencing surrounding interneurons involved in the pain response. Modulation of acetylcholine in this milieu may influence pain. This concept has led to the study of intrathecal infusion of acetylcholinesterase inhibitors, such as neostigmine [20]. Recently, Smith [21] has shown that constant intraspinal cholinergic stimulation via infusion of compounds interfering with the breakdown of acetylcholine can inhibit the pain response produced by substance P.

Several years ago, Penn and colleagues [22] introduced the concept that somatostatin and its analogues may favorably influence the pain response. According to this study, interneurons in the dorsal horn use somatostatin and its analogues as neurotransmitters. These neurotransmitters act in an inhibitory fashion and suppress activity in the presynaptic and postsynaptic junctions, particularly in the substantia gelatinosa and the periaqueductal gray areas. Intrathecal infusion in human beings produced a reduction in the pain response and was believed to be a reasonable alternative or supplement to opioids in the treatment of chronic pain from cancer. Octreotide, the most prominent member of this family of compounds, represents a significant alternative to morphine and morphine-like drugs and possesses manageable side effects [23].

Not only are these compounds and others being explored for their safety and efficacy as drugs for chronic pain management, but other and completely new approaches to the successful treatment of chronic pain are being explored. Lazorthes and colleagues [24] are exploring the potential for adrenal chromaffin cell delivery, a direct cellular transplant concept that has demonstrated great promise for the treatment of cancer pain. In addition, drug dispensing systems, such as the intrathecal drug delivery device, can be modified for improved targeted drug delivery. Encapsulated cell implants show great promise as another weapon in the armamentarium for pain management. Again, as shown by Sagen et al [25], catheters and a drug pump can deliver immunologically protected encapsulated cells to the central nervous system as a form of tissue transplantation. Another mechanism of drug delivery recently explored has been through the use of liposomes. Delivery by this method into the intrathecal environment may slow the rate of metabolism of analgesic agents, thus improving on their efficacy [26].

Another dimension of pain management may be the creation of compounds that are based on DNA/RNA interaction rather than on peptide or polypeptide formation. Huang and Simpson [27–31] have shown that compounds that interfere with the translation of mRNA can then alter the production of the normal protein product. Antisense compounds, altered mRNA sequences that resemble the natural mRNA, delivered to cells can compete with the native mRNA and thus reduce, alter, or interfere with the natural protein product that would normally be derived. Theoretically, antisense compounds can be developed to interfere with the production of intrinsic compounds that would normally produce some feature or characteristic of chronic pain. Such a compound may also be delivered via a catheter and drug pump system for a more precise targeted approach to the pain generator tissue sites in the central nervous system.

Summary

Intrathecal delivery of medications for the management of chronic pain syndromes reflects a modern targeted delivery system with the potential for even greater efficacy than is outlined in Tables 1 and 2. The twentieth century ushered in the development of parenteral approaches of medical therapy for chronic pain and other diseases that were superior to the traditional oral delivery methods known in the preceding century. Targeted drug delivery represents a significant advancement in the treatment of patients with chronic pain and is likely be the method of choice for the twenty-first century. This method of delivery is best represented by current drug delivery systems, such as the intrathecal drug pump. Traditional pharmacologic agents will still be used in the twenty-first century; however, the

development of novel compounds, transplanted tissues, and genetic engineering will likely usher in a new era of pain management, including their use as analgesics for intraspinal infusion.

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