Intrathecal Therapy
For the Management of
Cancer and Noncancer Pain

Part I:
Cancer Pain
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Noncancer Pain
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Cancer pain results from the growth of cancer in human tissues, or the pain is produced by any of the therapies implemented to treat a malignancy. Adequate pain control can be achieved in the great majority of patients by implementing an aggressive pharmacologic treatment strategy with the use of opioids and adjuvants.\(^1,2\) The implementation of such a strategy may achieve adequate pain control in 90% to 95% of patients.\(^3\) Consequently, 5% to 10% of patients will require some form of invasive therapy.

**Introduction**

To implement optimal analgesic therapy, a thorough history and physical examination are essential, as is the judicious use of diagnostic testing to try to define the pathophysiologic components involved in the expression of pain. Intrathecal (IT) opioids are very effective for the treatment of somatic and visceral pain, but IT bupivacaine and/or clonidine is necessary for the treatment of neuropathic pain. Thus, a definition of the specific pathophysiologic components is critical for successful management.

When specific guidelines are followed, the great majority of patients with cancer-related pain may expect adequate pain control. Control of pain and its related symptoms is a cornerstone of cancer treatment because it enhances quality of life by improving function and promoting compliance with treatment. Control of pain allows patients to focus on the joys of life.\(^4\) In addition to its salutary effects on quality of life, mounting evidence suggests that good pain control may positively influence survival.\(^5,6\)

**Intraspinal Analgesia**

Neuraxial analgesia is achieved by the epidural or
IT administration of an opioid alone—very rarely—or in combination with another agent, such as bupivacaine, clonidine, or ziconotide (Prialt, Elan). When neuraxial analgesia is used, pain relief is obtained in a highly selective fashion, without motor and sympathetic blockade, so that these modalities are highly adaptable to the home care environment.

When it was first introduced, the rationale behind neuraxial opioid therapy was that the administration of small quantities of opioids in close proximity to their receptors in the substantia gelatinosa of the spinal cord would achieve high concentrations at these sites. As a result, this type of analgesia is superior to that obtained with opioids administered by other routes because the total amount of drug is reduced and side effects are minimized. Currently, the biggest advantage is the ability to use multiple agents to target multiple receptors, resulting in better control of neuropathic, somatic, and visceral pain while minimizing side effects.

In general, patients with an expected survival time of longer than 3 months are candidates for IT therapy with a permanent intraspinal catheter and an implanted subcutaneous pump. Conversely, patients whose expected survival is less than 3 months require epidural therapy with an implanted system, such as the DuPen (Bard Access Systems) epidural catheter or the Port-a-Cath (Smiths Medical), which are connected to an external pump with the capability of allowing patient-controlled analgesia.

**Clinical Studies**

A recently published multicenter prospective randomized clinical trial compared IT therapy with comprehensive medical management after 1 month in 202 patients with refractory pain due to cancer. The primary outcome measure was a 20% improvement in analgesia, as measured on a visual analog scale (VAS) of 0 to 10. Additionally, changes in side effects based on the National Cancer Institute common toxicity criteria were monitored. Patients in the IT group showed a slight trend toward better analgesia, but the difference did not achieve statistical significance. However, a statistically significant improvement in the side-effect profile of patients randomized to the IT group was observed. The 2 side effects that were most noticeably less severe with IT therapy were constipation and impaired consciousness. After 6 months, a trend toward increased survival was also noted in the IT group (54% vs 37%). Although the total number of patients alive at the end of the analysis was small, approximately 25% more patients randomized to the IT group had survived.

A prospective longitudinal analysis of 30 crossover

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### Table 1. Methods of Assessing Performance Status

<table>
<thead>
<tr>
<th>ECOG</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all predisease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out light or sedentary work (eg, light housework, office work)</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to work; up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled, cannot carry on any self-care. Totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Karnofsky</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>100</td>
<td>Normal; no complaints, no evidence of disease</td>
</tr>
<tr>
<td>90</td>
<td>Able to carry on normal activity; minor signs or symptoms of disease</td>
</tr>
<tr>
<td>80</td>
<td>Normal activity with effort; some signs or symptoms of disease</td>
</tr>
<tr>
<td>70</td>
<td>Cares for self; unable to carry on normal activity or to do active work</td>
</tr>
<tr>
<td>60</td>
<td>Requires occasional assistance but is able to care for most needs</td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance and frequent medical care</td>
</tr>
<tr>
<td>40</td>
<td>Disabled, requires special care and assistance</td>
</tr>
<tr>
<td>30</td>
<td>Severely disabled, hospitalization indicated; death not imminent</td>
</tr>
<tr>
<td>20</td>
<td>Very sick; hospitalization necessary; active supportive treatment necessary</td>
</tr>
<tr>
<td>10</td>
<td>Moribund; fatal processes; progressing rapidly</td>
</tr>
<tr>
<td>0</td>
<td>Dead</td>
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ECOG, Eastern Cooperative Oncology Group
patients who received IT therapy found significant decreases in pain scores and drug toxicity (27% and 51%, respectively).11 Median survival was 103 days after crossover to an implantable drug delivery system, which was similar to that of patients in the randomized controlled trial.11

The implementation of IT therapy is initially expensive because of the cost of equipment. In contrast, the cost of implementing long-term epidural therapy is low. Two studies evaluated the cost of implementing therapy with these 2 modalities. The analyses showed a “break-even” point at approximately 3 months.12,13 Epidural therapy therefore becomes expensive after 3 months, one reason to limit its use to patients whose anticipated survival is shorter.

Clinical Guidelines

A consensus panel recently published updated recommendations for the use of IT medications in patients with chronic noncancer pain.14 Although the consensus conclusions are limited to the noncancer population, 4 issues are important to discuss in this review:

- equianalgesic doses of hydromorphone;
- maximum doses of hydromorphone;
- spinal cord lesions associated with bupivacaine; and
- ziconotide as a first-line agent.

Equianalgesic Doses of Hydromorphone

One study quoted in the consensus did not examine equianalgesic doses of morphine and hydromorphone15; the researchers administered hydromorphone at “a dose equivalent to the minimum intrathecal morphine dose shown to produce inflammatory masses in our sheep model (12 mg/d).” Thus, there is no basis for the authors of the consensus to conclude that “intrathecal (IT) morphine and IT hydromorphone, in a dose 20% of that of morphine, induce an equianalgesic response.” Nonetheless, the discussion in the study states that the morphine-to-hydromorphone conversion rate is 5:1 to 6:1. “No masses were observed at hydromorphone doses (3 and 6 mg/d) that were equianalgesic to morphine doses (18 and 36 mg/d, respectively).”16 This is the conversion rate that we have used in our clinical practice, but there has not been a trial to support the validity of this conversion figure.

Maximum Doses of Hydromorphone

The consensus panel recommends a maximum hydromorphone concentration of 10 mg/cm3 and a maximum dose of 4 mg per day for IT use to prevent granuloma formation. No reference supports this recommendation, however, and the panelists acknowledge that “physicians are advised to titrate doses of these 2 opioids (morphine and hydromorphone) not beyond an a priori upper limit that has been determined from clinical practice.”14 To date, we have treated approximately 60 patients with IT hydromorphone in combination with bupivacaine and/or clonidine at concentrations and doses well beyond those recommended by the panel, without any cases of granuloma. We use magnetic resonance imaging to survey the patients on a yearly basis to make an early diagnosis of this condition. Moreover, we ask patients at their monthly refill visits about symptoms that may be associated with the development of granulomas.

Spinal Cord Lesions Associated With Bupivacaine

The consensus document states that “transient neurologic syndrome (TNS), defined as radicular irritation after spinal anesthesia with local anesthetics, is hypothesized to fall on the lower end of a spectrum of toxic effects caused by local anesthetics.”14 However, no report on TNS after bupivacaine spinal anesthesia exists in the medical literature, although the complication has been associated with the use of lidocaine and mepivacaine.16

Additionally, the guidelines suggest that the combination of bupivacaine and clonidine can result in spinal cord lesions. This conclusion is based on a case report cited in a footnote to the guidelines.17 It is important to recognize that in the case in question, the neurologic deficit appeared 2 years after therapy with bupivacaine and clonidine at doses of 20 mg and 200 mcg per day, respectively. It is unclear if the spinal cord changes were related to neurotoxic effects of the drug, particularly because the rate of administration was 0.5 mL per hour and the edema in the spinal cord extended from the conus medullaris to the T5 level. The spread in cerebrospinal fluid of IT solutions administered at a rate of 0.5 mL per hour has been shown to be limited both in animal models and in humans.18,19 Consequently, it is difficult to understand how the edema in the patient’s spinal cord was so extensive. Moreover, the tip of the catheter had migrated from the T12 to the T10 level, where the lesion was found, raising the possibility that the catheter migration could have resulted from injury to the spinal cord.

Ziconotide as a First-Line Agent

The last polyanalgesic consensus recommended the use of ziconotide for patients in chronic pain when all other options had been exhausted.20 At that time, the
drug had not been approved by the FDA, and only one randomized clinical trial was available.\textsuperscript{22} In contrast, the panelists of the new recommendations have upgraded ziconotide to a first-line agent, at the same level as morphine and hydromorphone.\textsuperscript{14} Because it is acknowledged that “the medications in the current algorithm are arranged in a hierarchy based on evidence on safety, efficacy, and broad clinical parameters gleaned from previous and current consensus literature reviews, ratings of published studies, and expert opinion from 3 polyanalgesic consensus conferences,” the question is whether enough new data on therapeutic efficacy and safety are available to support that recommendation.\textsuperscript{14}

In the study by Staats et al, there are 2 concerns: First, the physiopathology of pain in patients with cancer is disease- and site-specific and may be multifactorial. Thus, treating a patient without a clear description of the source of nociception (somatic, visceral, or neuropathic) could be a problem in the absence of targeted therapies.\textsuperscript{21}

Second, the 2-week follow-up might result in other problems. As previously discussed, ziconotide requires a significant titration window to reach a therapeutic effect, and this is not normally achieved within a 2-week period. Thus, it is possible that the investigators were evaluating a placebo effect at that time. The therapeutic responses beyond that time might have decreased, and the success rate might have been lower if the follow-up had been longer. Consequently, the results of this study do not fully support the use of ziconotide as a first-line agent.\textsuperscript{21}

The consensus supporting ziconotide as a first-line agent is based largely on 2 randomized controlled trials. In the first trial, 169 patients were randomized to ziconotide and 86 patients to placebo for the treatment of severe, chronic noncancer pain over a 6-day period in an inpatient hospital setting.\textsuperscript{22} Doses were started at 2.4 mcg per day and titrated up to 57.6 mcg per day. The mean percentage reduction in pain scores from baseline was 31% for the ziconotide group and 6% for the placebo group. This difference was statistically significant. Moreover, a significantly greater percentage of patients treated with ziconotide (34%) than of those given placebo (13%) responded to treatment ($P<0.001$). Despite this significant reduction in pain, however, of the 169 patients initially treated with ziconotide, only 54 (32%) were considered responders and were eligible for 5 days of treatment as outpatients. A response to treatment was defined as a 30% or greater reduction in pain scale scores from baseline, stable or decreased concomitant opioid analgesic use, and no changes in type of opioid used during the study period.

The incidence of side effects was very high during the titration period, with 95% of the patients treated with ziconotide experiencing at least one adverse event, compared with 72% in the placebo group ($P=0.001$). These side effects included abnormal gait, amblyopia, dizziness, nausea, and nystagmus.

The second trial randomized 112 patients to receive ziconotide, started at 2.4 mcg per day and titrated to a mean dose of 6.96 mcg per day over 3 weeks, and 112 patients to placebo.\textsuperscript{23} The mean percentage reduction in pain in the ziconotide group was 15%, versus 7% in the placebo group ($P=0.0336$). This difference, although statistically significant, was not clinically meaningful. Moreover, the planned sample size of 110 patients in each group provided 80% power to detect an intergroup difference of at least 15 points in the mean percentage change as measured with the VAS. Because the intergroup difference was 8%, the results of the study are underpowered. Additionally, 60% of the patients rated their pain control as poor or fair, and 49% of those in the ziconotide group reported no or little satisfaction with the treatment. The incidence of side effects in the treatment group was also high in this study.

Since the publication of the guidelines, 3 other studies addressing the use of ziconotide in severe, chronic noncancer pain have been published.\textsuperscript{24-26}

In the first study, 644 patients with severe, chronic pain were treated with ziconotide in an open-label, multicenter trial.\textsuperscript{24} In the end, 119 patients were treated for at least 1 year. Median duration of therapy was 2 months, with a range of 1 to 1,215 days. The mean dose was 8.4 mcg per day (range, 0.048-240 mcg/d). Pain scores decreased from 76 to 68 mm after 1 month of therapy and to 73 mm after 2 months of therapy. Virtually all patients experienced adverse events (99.7%), of which 43.5% were mild, 42.3% moderate, and 14.2% severe. Half of those adverse events were considered unrelated to therapy. The authors concluded that “long-term intrathecal ziconotide is an option for patients with severe, refractory pain.” However, the high incidence of side effects and the clinically insignificant reduction in pain do not support therapeutic efficacy under the present protocol design.

The second study evaluated the safety and efficacy of adding IT ziconotide to IT morphine in patients receiving a stable dose of IT morphine.\textsuperscript{25} The mean percentage improvement in pain scores on the VAS was 14.5% (95% confidence interval, -9% to 38%) from baseline to week 5. The mean percentage decrease in oral opioid doses from baseline was 14%. The investigators concluded that the concomitant administration of IT ziconotide and morphine may reduce pain and decrease systemic opioid use in patients receiving treatment with IT morphine alone.\textsuperscript{25} Again, however, both the mean decrease in pain intensity and the reduction in systemic opioid
use are clinically insignificant. The third study generated similarly ambiguous findings.

Taken together, these 3 trials suggest that concomitantly administering ziconotide and morphine does not lead to clinically significant improvement for patients. Moreover, evidence indicates that ziconotide loses stability when administered with either morphine or hydromorphone. Thus, the utility of administering ziconotide with morphine is not clear.

**Conclusion**

The implementation of aggressive analgesic protocols is important in patients with cancer, independently of the stage of their disease, and it is a special priority in patients with advanced disease who are no longer candidates for potentially curative therapy.

Although rarely eliminated, pain can be controlled in the vast majority of patients with the implementation of aggressive comprehensive medical management and/or invasive techniques. In the small but significant proportion of patients whose pain is not readily controlled with pharmacologic therapy, IT therapy with multiple agents is associated with a high degree of success in well-selected patients. To this end, it is very reassuring to be able to conclude that at this point, we have the appropriate tools to adequately treat cancer-related pain in nearly every patient.

**References**


19. Kotob F, de Leon-Casasola OA, Lema M. Intrathecal infusion rates of 1 mL/day improve narrow analgesia with infusion rates of 0.5 mL/day. *Anesthesiology*. 2006;105:1347.


Model IT Protocol for Patients With Cancer Pain

When considering IT therapy with a permanent catheter and a subcutaneous pump, a trial will be necessary to assess the need for multimodal treatment, estimate the doses of the opioid to be used, and confirm the best position for the catheter tip.

The tip of the catheter must be placed at the site where nociception is processed within the spinal cord. We conduct this trial on an outpatient basis to document a 50% decrease in pain. If it succeeds, we implant the permanent device.

Epidural Trial: [7- to 14-day outpatient protocol]

Catheter Position
Dermatomal specific for the area of nociception under fluoroscopic guidance.

Pharmacologic Agents
- Hydromorphone: 0.03-0.12 mg/mL (20-80 mg)
- Bupivacaine: 1-2 mg/mL (0.1%-0.2%)
- Total volume: 600 mL

If the source of the patient’s pain is the lower lumbar or sacral areas, thus precluding the use of high concentrations of bupivacaine, a more dilute solution (0.05%) of the anesthetic can minimize the possibility of motor block. Compensate by adding clonidine, at a dose of 3 to 5 mcg/mL.

Determining doses of epidural opioids (the goal is to determine the requirements of the individual patient) based on the patient’s current opioid use:
- If the patient is receiving more than 300 mcg per hour of transdermal fentanyl or 1,200 mg per day of oral morphine or 600 mg per day of oral oxycodone or 160 mg per day of oral methadone, or more than 300 mg per day of oral oxymorphone, the appropriate concentration of hydromorphone is 0.12 mg/mL.
- If the patient is receiving between 100 and 300 mcg per hour of fentanyl or an equivalent dose of another opioid, the appropriate dose of hydromorphone is 0.06 mg/mL.
- If the patient is receiving less than 100 mcg per hour of fentanyl or the equivalent dose of another opioid, the appropriate dose of hydromorphone is 0.03 mg/mL.

Implanting the IT Pump
If the trial succeeds as defined above, implant an IT system. The following protocol has achieved a rate of success above 80% at our institution:
- Under fluoroscopic guidance, place the tip of the IT catheter in the dermatome corresponding to the area of nociception.
- For severe somatic pain, combinations of local anesthetics and an opioid will be required.
- For neuropathic pain:
  - If the tip of the catheter is below L3-4, initiate therapy with an opioid + clonidine

Table. Potential Pump Errors

1. Effects of magnetic resonance imaging (MRI; Medtronic Medical Device Correction, August 2008)
   All SyncroMed pumps are vulnerable to a delay in the return of proper drug infusion after an MRI. With SynchroMed II pumps, delays have been reported in the logging of motor stall events after an MRI. Although the reported incidence of these phenomena is very low (0.014% and 0.11%, respectively) it is important to carefully check all the pumps after the MRI to ensure that patients are receiving medication. This is particularly important for SynchroMed pumps, as a “Pump Memory Error” may be generated and the pump will not restart infusing unless it is reprogrammed. In contrast, the SynchroMed II may continue infusing even when the interrogation may show a stall state. In either case, the pump will alarm in the face of a stall phenomenon.

2. Missing propelant within the pump
3. Pump motor stall as a result of gear shaft wear
If the tip of the catheter is above L1-2, initiate therapy with an opioid + bupivacaine

**PHARMACOLOGIC AGENTS**

- Morphine 1.0-20 mg per day
- Hydromorphone 0.5-25 mg per day
- Sufentanil 10-100 mcg per day
- Bupivacaine 6-20 mg per day
- Clonidine 250-2,000 mcg per day

Compounding by a trained pharmacist is necessary. Drugs should be concentrated to twice the daily dose, so that the 20 mL programmable pumps may be set to deliver 0.5 mL per hour. In this way, patients will require pump refills monthly and will not have to make frequent visits to the pain specialist’s office.

**TO BEGIN THERAPY:**

**Step 1:**
- Opioid + bupivacaine:
  - Morphine 3-25 mg per day** or hydromorphone 0.5-15 mg per day
  - **6 mg of morphine per day = 1 mg of hydromorphone per day**
  - Bupivacaine: 6-20 mg per day
- Opioid + clonidine:
- Clonidine: 250-2,000 mcg per day

**Step 2: Opioid + bupivacaine + clonidine**

**Step 3: Ziconotide:**
- Initiate therapy with ziconotide at a dose of 2.4 mcg per day (0.1 mcg/h) and titrate to patient response
- Rinse the pump with 2 mL of the 25 mcg/mL solution 3 times, then fill the pump with the remaining medication (16 mL);
- Titration increments should not be more than 2.4 mcg per day or more frequent than once per week;
- Maximum recommended dose: 19.2 mcg per day (0.8 mcg/h)

This approach has some limitations. Ziconotide must not be administered in the epidural space. Consequently, the patient will require progressive titration once the system is implanted. In addition, patients may not allow the practitioner to carry out a titration protocol over 4 to 6 weeks because the starting dose for ziconotide is 2.4 mcg per day with weekly increases of no more than 2.4 mcg per day. Therapeutic effects are not usually seen until a dose of 8 to 10 mcg per day is achieved.

If triple therapy with an opioid, bupivacaine, and clonidine at optimal doses fails, or when considering whether to implement therapy with ziconotide, an evaluation for catheter obstruction, disconnection, catheter migration, or pump malfunction is required.

**Pump:** Computer-program analysis for volume and the volume present within the pump needs to be within 10% of each other, otherwise pump failure is suspected. The Table lists several known pump errors.

**Catheter:** A myelogram performed through the diagnostic port of the pump will be necessary to determine if the device is obstructed, disconnected, or the tip of the catheter is in the correct position. The diagnostic port of the pump can accommodate only a 25-gauge Huber needle. It is important to consider the dead space of the catheter when injecting the contrast medium: 0.196 mL (89 cm total catheter length [81.4 cm for the spinal segment + 7.6 of the catheter interface with the sutureless connector] × 0.0022 mL/cm catheter volume for the model Medtronic 8709 SC).

- A bolus dose may be required after the study is completed because the catheter will be filled with contrast medium. At a programmed rate of 0.5 mL per hour it will take 9.4 hours for the pump to clear the accumulated volume of fluid, resulting in inadequate pain control and possibly symptoms of opioid withdrawal.
- A bolus dose should be programmed after the myelogram to clear the catheter’s dead space of contrast medium. Failure to do so may leave the patient without IT treatment for periods of 16 to 20 hours, depending how much catheter was implanted.

When performing diagnostic port injections, cerebrospinal fluid/therapeutic solution must be withdrawn before injecting contrast medium in order to remove all of the drug from within the catheter. Failure to do so could result in the patient receiving a bolus of up to 0.196 mL of solution along with the contrast medium. Similarly, we suggest aspirating the fluid with a 3-mL syringe (which should collect all the medication in the catheter’s dead space as well as some cerebrospinal fluid) at a very low negative pressure to avoid turbulent flow and the risk for leaving medication within the catheter (cavitations).
Part 2: Noncancer Pain

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Dr. Rauck has received research, speaking and/or consulting fees from Codman, Elan, InSet Technologies, and Medtronic.

Intrathecal (IT) drug delivery systems provide analgesia to patients with cancer pain and to those with intractable pain caused by other conditions. In both groups of patients, this therapy is reserved for those who have failed aggressive trials of oral or systemic analgesics and interventional therapies or those who find the side effects of opiates or other therapies intolerable. Many clinicians continue to use IT drug delivery as one of the “last resorts” for patients whose pain remains uncontrolled.

Background
Analgesic requirements and IT drug delivery differ between patients with cancer pain and those with noncancer pain. Paice and colleagues found that patients with cancer pain characteristically require higher starting doses of IT analgesics, but their doses tend to stabilize more readily than those of patients with noncancer pain. Tolerance appears to be less of a problem in patients with terminal cancer pain than in those with noncancer indications, although distinctions between tolerance and dose escalation secondary to disease progression can be difficult to determine in the clinical setting.

Intrathecal Therapy for Noncancer Pain
Intrathecal drug delivery for noncancer pain is reserved for patients whose pain does not respond to other treatments. Spinal cord stimulation (SCS) is often used before IT analgesia, although patients with diffuse, widespread pain may be considered candidates for IT analgesia without a previous trial of SCS. When IT analgesia is indicated for a patient with noncancer pain, clinicians should discuss expectations with the patient. Like other treatment modalities, IT...
analgesia significantly helps patients manage chronic pain, yet limitations exist. Some patients expect that this modality will eliminate their pain. That rarely occurs, and patients need to understand its benefits and risks before implantation.

Intrathecal analgesia in a patient with noncancer pain commonly begins with an opioid medication. A recent consensus group found that clinicians use both hydromorphone and morphine as first-line opioids for IT drug delivery. Both drugs are hydrophilic and exhibit similar characteristics in the IT space. Hydromorphone is approximately 4 to 5 times more potent than morphine, whether administered intravenously or intrathecally.

However, tolerance has been a significant problem with opioids delivered intrathecally. In addition, as discussed later, granuloma formation following implantation of an IT pump is a potential complication with either hydromorphone or morphine. Daily dosing and, in particular, relatively high concentrations of these drugs appear to increase the risk for granuloma formation.

Ziconotide (Prialt, Elan) is recommended as a first-line drug for patients in whom IT analgesia is indicated. Long-term tolerability with IT ziconotide is enhanced when the initial dose is low (1.2 mcg/d) and titration is slow (increases of 1-2 mcg/wk). Common side effects include dizziness, confusion, ataxia, and impairment of short-term memory.

Second-line IT drugs include clonidine and bupivacaine. Although these drugs typically are combined with an opioid, they can be used as monotherapy. Clonidine has been shown to be an effective stand-alone analgesic in patients with complex regional pain syndrome when administered intraspinally. Bupivacaine is more commonly prescribed as an adjuvant analgesic with an opioid and/or clonidine.

Opioids such as fentanyl and sufentanil can be administered intrathecally. Fentanyl does not appear to trigger granuloma formation, but its long-term efficacy has not been established. The degree of tolerance has also not been described with long-term administration of the lipophilic opioids (fentanyl and sufentanil), although it is expected that these drugs have characteristics similar to those of other opioids.

Intrathecal baclofen has been used for years to treat recalcitrant spasticity. It has also been reported effective by the IT route in patients with dystonia resulting from complex regional pain syndrome. Intrathecal baclofen can be combined with opioids to enhance analgesia; however, whether IT baclofen has an analgesic effect distinct from its antispastic qualities remains open to debate.

Combination IT therapy with morphine and ziconotide has recently been reported in 2 trials. In one study, ziconotide was added to fixed doses of IT morphine and then titrated; in the other, morphine was added to fixed doses of ziconotide and then titrated. Adding morphine to a fixed dose of ziconotide appears to enhance IT analgesia and decrease the use of systemic analgesic agents.

Trialing Methods

An IT trial is performed before a pump is permanently implanted. Clinicians conduct these trials in different fashions for patients with noncancer pain. Options include single-bolus injections and short-term (<5 days) or long-term (>7 days) IT or epidural infusions. A 50% reduction in pain is commonly considered a successful trial. Some drugs lend themselves to specific trials more readily than others. Clonidine can be given by epidural infusion over several days with resultant analgesia in responders. The rate of an epidural infusion ranges from 10 to 50 mcg per hour. Opioids are often trialed in a bolus dose, with conversions calculated according to an IT-to-systemic ratio between 1:50 and 1:100. Ziconotide has commonly been used in long-term trials (up to 3 weeks), although meningitis was reported in 5 of 71 patients with exteriorized catheters during the third week of an IT infusion. Bolus trialing of ziconotide has been discussed by implanters and is currently being examined.

Technology Used for Intrathecal Drug Delivery

Various systems are used for the long-term delivery of drugs into the IT space. Percutaneous catheters, often tunneled to the anterior abdominal wall, can be exteriorized and allow repeated bolus injections. Exteriorized catheter systems (eg, DuPen, Bard Access Systems) are approved for long-term epidural injection, but injection into the IT space is an off-label use. The catheters can be connected to small ambulatory pumps for continuous infusion and/or bolus injections. Exteriorized catheters are used much more frequently in patients with cancer because of the risk for infection, in addition to patient preference for totally implanted systems (see below).

Intrathecal catheters also can be tunneled and connected to subcutaneous ports. Noncoring needles that access the port can be used for injections into the IT space or connected to an ambulatory pump. These systems also carry a significant risk for infection if used for prolonged periods and often are reserved for patients with cancer.

Intrathecal analgesia is most commonly delivered to a patient with noncancer pain through a totally
implanted delivery system. Pumps can provide a constant infusion along a nonmechanical mechanism (eg, Arrow or Codman) at a flow rate that is preset during manufacturing. The flow rate in these pumps cannot be changed, but drug doses can be changed by changing the drug concentration during refills.

The vast majority of implanted systems in the United States are programmable mechanical pumps manufactured by Medtronic. (Ziconotide is approved for use only with the Medtronic SynchroMed and SynchroMed II pumps, and the CADD-Micro, from Smiths Medical). These devices allow continuous infusion with or without preprogrammed boluses, and the infusion rate can be set to vary during a 24-hour cycle. A physician can program the device to administer boluses on a predetermined schedule; alternatively, the patient can self-administer within parameters that the physician sets using a patient therapy manager. Allowing patients to self-administer additional doses gives them a measure of control.

New programmable mechanical IT pumps are currently being developed by 3 different companies: InSet (Prometra), Codman (MedStream), and Advanced Bionics (unnamed). Although the devices currently on the market have proved durable and reliable, the new pumps may advance therapy in different ways, such as by increasing the accuracy of flow delivery, improving pump ergonomics, enhancing battery life, and providing dual chambers to allow drug administration without mixing and possible incompatibility. Some of these devices may be available within the next 12 to 24 months.

Risks, Side Effects, and Complications

Risks of IT drug delivery include those specific to the drugs used and those related to the drug delivery system—specifically, the pumps and catheters. Many of the pharmacologic risks and side effects are similar to those seen with an oral or I.V. route of administration. For example, opioids can cause nausea, vomiting, pruritus, constipation, and respiratory depression (very rare in opioid-tolerant patients, unless a massive overdose is given), whether administered orally or intrathecally. Similarly, clonidine can cause hypotension regardless of the delivery route, although hypotension is a side effect of IT delivery and an intended effect of oral intake.

Several complications merit further discussion. Acute cessation of clonidine can produce life-threatening rebound hypertension if the drug has been administered intrathecally for more than several weeks. This complication can occur, for example, if a patient runs out of drug or a kink in the catheter or another pump malfunction develops. The withdrawal effect can be blocked or mitigated with the oral administration of clonidine. Some physicians have patients keep a prescription of oral clonidine available in case of such an occurrence.

A similar withdrawal reaction can occur with baclofen. In addition, baclofen overdose may produce decreased muscle tone, sedation, and bradycardia. Increases in IT baclofen are usually in the range of 10% to 15% to prevent side effects.

Side effects of opioids that are somewhat specific to IT administration include peripheral edema and granuloma formation. Peripheral edema can be quite troublesome. It is often unresponsive to diuretics such as furosemide, despite the fact that this drug is commonly used as the first-line treatment along with pressure stockings. If the edema is progressive or unremitting, clinicians should change the IT opioid to either hydromorphone (which also carries a risk for edema) or a lipophilic agent, such as fentanyl, which seems less likely to cause this complication.

Formation of granulomas occurs predominantly with the hydrophilic drugs morphine and hydromorphone.14,15 Although granulomas have been reported with clonidine, evidence in a canine model suggests that this drug, when coadministered with an IT opioid, may prevent the complication.16 (Case reports of granuloma formation with clonidine in humans may be secondary to the prior administration of high concentrations of opioids.)

Accurate and prompt diagnosis of an IT granuloma is essential to successful management of the condition. If the symptoms are simply pain and loss of analgesia, the IT drug can be stopped and serial magnetic resonance imaging performed to monitor regression of the granuloma. If serious neurologic symptoms, such as bowel and/or bladder dysfunction, are observed at diagnosis, a neurosurgical consult and surgical removal of the granuloma should be considered. The question of conservative or surgical treatment arises when subtle symptoms are present, such as sensory loss and mild motor dysfunction. Consultation with a neurologist should be considered.

Summary

For patients with noncancer pain refractory to other treatments, IT analgesia offers a legitimate means to obtain meaningful and durable pain relief. With the drugs and devices currently available, IT therapy should be considered for patients whose pain cannot be managed conservatively. Few patients achieve a pain-free status with this aggressive form of therapy. However, for many, pain relief is sufficient to enhance their activities of daily living and improve their quality of life.
References


