Cancer pain results from the growth of cancer in human tissues, as well as 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 using opioids and adjuvants. The implementation of such a strategy may achieve adequate pain control in 90% to 95% of patients. Consequently, 5% to 10% of patients will require some form of invasive therapy.

When specific guidelines are followed, the great majority of patients with cancer-related pain can 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. In addition to its salutary effects on quality of life, mounting evidence suggests that good pain control may positively influence survival.

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 of a patient’s pain is critical for successful management of it.
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 these modalities are highly adaptable to the home care environment.

When it was first introduced, the rationale behind neuraxial opioid therapy was that 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.\(^7,8\) As a result, this type of analgesia would be superior to that obtained with opioids administered by other routes because the total amount of drug is reduced and side effects are minimized. The biggest advantage of neuraxial analgesia 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 expected survival longer than 3 months are candidates for IT therapy with a permanent intraspinal catheter and an implanted subcutaneous pump. Those with expected survival 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 and allow for patient-controlled analgesia.\(^9\)

Clinical Studies

A multicenter prospective randomized clinical trial (RCT) compared IT therapy with comprehensive medical management after 1 month in 202 patients with refractory pain due to cancer.\(^10\) 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 also was 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 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 RCT.

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 compared the cost of implementing therapy with these 2 modalities and showed a “break-even” point at approximately 3 months.\(^12,13\) Epidural therapy, therefore, becomes more expensive than IT therapy after 3 months, one reason to limit it to use in patients whose survival is anticipated to be 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:

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

Equianalgesic Doses of Hydromorphone

The consensus authors concluded IT morphine and IT hydromorphone “in a dose 20% of that of morphine, induce an equianalgesic response.” However, they based this, in part, on a study in which 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).”\(^15\) The researchers state that the morphine-to-hydromorphone conversion rate is 5:1 to 6:1 and that “no masses were observed at hydromorphone doses (3 and 6 mg/d) that were equianalgesic to morphine doses (18 and 36 mg/d, respectively).”\(^15\) Although this is the conversion rate that we have used in our clinical practice, its validity has not been confirmed.

Maximum Doses of Hydromorphone

The consensus panel recommends a maximum hydromorphone concentration of 10 mg/cm\(^3\) 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 yearly magnetic resonance imaging to facilitate early diagnosis of this condition. We also 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 hypoth-
esized to fall on the lower end of a spectrum of toxic
effects caused by local anesthetics.” 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.

Additionally, the guidelines suggest that the combi-
nation of bupivacaine and clonidine can result in spi-
cord lesions. This is based on a case report cited in
a footnote to the guidelines. It is important to rec-
ognize 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, par-
cularly 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. Thus, it is dif-
cult to understand how the edema in the patient’s spi-
cord was so extensive. Also, the tip of the catheter
had migrated from the T12 to the T10 level, where the
lesion was found, raising the possibility that the cathe-
ter migration could have resulted from injury to the spi-
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. At that time, the
drug had not been approved by the FDA, and only one
RCT was available, by Staats et al. There are 2 issues
with the study by Staats et al. First, patients were
treated without a clear description of the source of
nociception (somatic, visceral, or neuropathic), which
could be a problem in the absence of targeted ther-
apies. Second, the 2-week follow-up might result in
other problems. Ziconotide requires a significant titra-
tion 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 suc-
cess rate might have been lower if the follow-up had
been longer. Consequently, the results of this study do
not clearly support the use of ziconotide as a first-line
agent.

In contrast, the panelists of the new recommenda-
tions have upgraded ziconotide to a first-line agent,
at the same level as morphine and hydromorphone.
The question is whether enough new data on therapeu-
tic efficacy and safety are available to support that
recommendation.

The consensus supporting ziconotide as a first-line
agent is based largely on 2 RCTs. In the first trial, 169
patients were randomized to ziconotide and 86 to pla-
celebo for the treatment of severe, chronic noncancer pain
over a 6-day period in an inpatient hospital setting. 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 sta-
tistically significant. Moreover, a significantly greater per-
centage of patients treated with ziconotide (34%) than
of those given placebo (13%) responded to treatment
(P<0.001). Despite this significant reduction in pain, how-
ever, of the 169 patients initially treated with ziconotide,
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 con-
comitant opioid analgesic use, and no changes in type of
opioid used during the study period.

The incidence of side effects was high during the
titration period, with 95% of the patients treated with
ziconotide experiencing at least 1 adverse event (AE),
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. The mean percentage reduc-
tion 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 also was high in
this study.

Since the publication of the guidelines, 3 other stud-
ies addressing the use of ziconotide in severe, chronic
noncancer pain have been published.

In the first study, 644 patients with severe, chronic
pain were treated with ziconotide in an open-label,
multicenter trial. Median duration of therapy was 2
months, with a range of 1 to 1,215 days; 119 patients were
treated for at least 1 year. The mean dose was 8.4 mcg
per day (range, 0.048-240 mcg/d). Pain scores on the
VAS decreased from 76 to 68 mm after 1 month of ther-
apy and to 73 mm after 2 months of therapy. Virtually all
patients experienced AEs (99.7%), of which 43.5% were
mild, 42.3% moderate, and 14.2% severe. Half of those
AEs were considered unrelated to therapy. The authors
concluded that “long-term intrathecal ziconotide is an
option for patients with severe, refractory pain.” How-
ever, the high incidence of side effects and the clinically
insignificant reduction in pain do not support therapeu-
tic 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. The mean percentage improvement in pain scores on the VAS was 14.5% (95% confidence interval, –9% to 38%) 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. 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 usefulness 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;105:4347.
When considering intrathecal 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.

**Practice Tips for Using Intrathecal Pain Pumps**

**Table 1. Pharmacologic Agents Typically Used in IT Pumps**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>1.0-20 mg/d</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.5-25 mg/d</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>10-100 mcg/d</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>6-20 mg/d</td>
</tr>
<tr>
<td>Clonidine</td>
<td>250-2,000 mcg/d</td>
</tr>
</tbody>
</table>

IT, intrathecal

Note: 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.

**Table 2. Potential Pump Errors**

1. Missing propellant within the pump
2. Pump motor stall as a result of gear shaft wear
3. 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.
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) often is 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.⁵ 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).⁶ Common side effects include dizziness, confusion, ataxia, and impairment of short-term memory.⁷

Second-line IT drugs include clonidine and bupivacaine.² 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.⁸ Bupivacaine has been discussed 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 also has 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.⁹ It also has been reported effective by the IT route in patients with dystonia resulting from complex regional pain syndrome.¹⁰ 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.¹¹,¹² 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.¹²

**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 d) or long-term (>7 d) 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 often are 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 wk), although meningitis was reported in 5 of 71 patients with exteriorized catheters during the third week of an IT infusion.¹³ Bolus trialing of ziconotide has been discussed by implanters and currently is 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.) Also available is the Codman 3000 implantable infusion pump (Johnson & Johnson). These devices allow continuous infusion with or without preprogrammed boluses, and the infusion rate can be set to vary during a 24-hour cycle. The 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.

Although the devices currently on the market have proved durable and reliable, 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. A new programmable IT drug pump (Prometra) may be available from InSet Technologies in 2010.

**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 IV 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 usually are 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 often is 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. 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. (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 neurosurgery 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