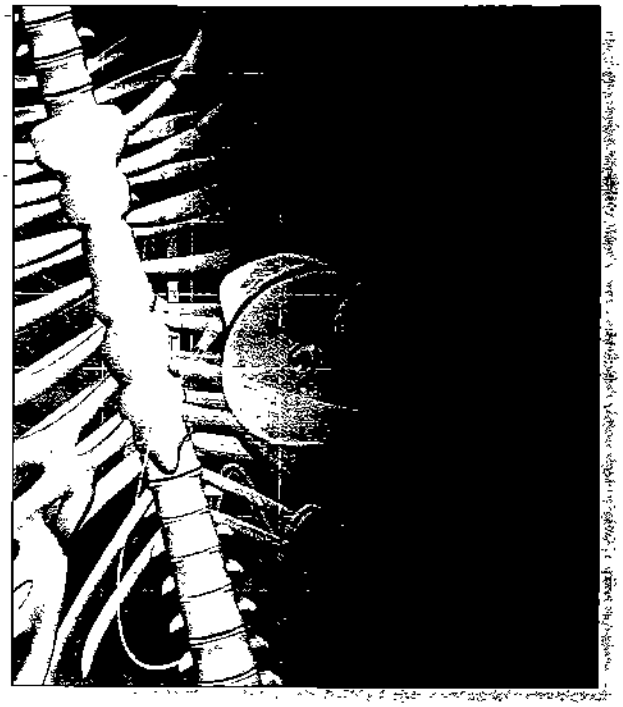
INTRATHECAL PUMPS

Part 2: Noncancer Pain



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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.[1] 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.[2] 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.[3]

However, tolerance has been a significant problem with opioids delivered intrathecally.[4] 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.[5]

Ziconotide (Prialt, Elan) is recommended as a

first-line drug for patients in whom IT analgesia is indicated.[2] 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 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 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 has also 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 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.[13] 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.) 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 by the beginning of 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 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.

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