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Neuraxial Medication Delivery

The Development and Maturity of a Concept for Treating Chronic Pain of Spinal Origin

Joshua P. Prager, MD, MS

Study Design. A literature review and synthesis were performed.

Objective. To summarize the history, use, and innovation related to neuraxial drug delivery for the treatment of intractable back pain.

Summary of Background Data. The discovery of opioid receptors in the early 1970s provided a rational basis for the delivery of opioid drugs intraspinally. Epidural or intrathecal infusions deliver drugs directly to opioid receptors, limit systemic exposure, and by decreasing the opioid dosage required for pain relief, generally reduce side effects. The benefits of short-term spinal analgesia led to investigation of longer-term continuous subarachnoid opioid infusions for the management of both cancer pain and noncancer pain, such as that of spinal origin.

Methods.

Results. Unique features of this article include an updated pain continuum, updated indications for intrathecal therapy, a detailed comparison of trial techniques, a detailed comparison of the advantages of different types of pumps, a synopsis of troubleshooting for inadequate efficacy, and an updated statement regarding intrathecal pumps and radiologic procedures, including MRI scanning. Some challenges remain. Large-scale well-controlled studies could answer some perplexing questions regarding efficacy in patients with noncancer or neuropathic pain. Patient selection criteria undoubtedly will be refined and validated as more patients are treated. In addition, further investigation of specifically targeted medications or drug combinations for intraspinal use could increase efficacy, reduce side effects, and expand indications.

Conclusions. Intraspinal medication delivery has become an effective technique for control of intractable pain in appropriately selected patients seen by spine surgeons. [Key words: cancer pain, epidural injection, failed back surgery syndrome, infusion pump, intraspinal injections, intrathecal injection, neuraxial medications, nonmalignant pain, opioids] **Spine 2002;27:2593–2605**

The discovery of opioid receptors[31,53] provided a rational basis for the delivery of opioid drugs intraspinally. By 1979, reports of epidural[8] and intrathecal[63] opioid delivery in humans had entered the peer-reviewed literature. Intraspinal infusions delivered drugs directly to opioid receptors, limited systemic exposure, and by decreasing the opioid dosage required for pain relief, generally reduced side effects, which facilitated the provision of greater analgesia. The benefits of short-term spinal analgesia, primarily for patients with intractable cancer pain, led to investigation of longer-term continuous subarachnoid opioid infusions for the management of both cancer pain[11,14,15,22,27,36,49,51,59,60,62,67] and noncancer pain, such as that produced by failed back surgery syndrome.[4,6,7,12,24,26,28,32,34,37,38,43,55] Pain specialists currently are successfully using opioids to treat patients with chronic noncancer pain, noting that such patients can benefit from sustained analgesia and better function without becoming addicted.[54]

The key to appropriate treatment of pain is proper diagnosis. Pain can be characterized as nociceptive (*e.g.*, somatic pain), neuropathic (pain from nerve injury), or idiopathic. Pure nociceptive pain usually responds well to systemic opioids. Neuropathic pain responds to opioids at higher doses and often is responsive to a large number of antineuropathic medications (Table 1). Failed back surgery syndrome (FBSS) pain usually is a mixed type of pain that is both nociceptive and neuropathic. Nociceptive pain arises from disc or bone injury, reaction to hardware or graft harvesting, or reactive spasm. Neuropathic FBSS pain can arise from nerve injury before surgery, chronic compression, chemical irritation, nerve injury during surgery, scar tissue formation, or arachnoiditis. The challenge in treating FBSS pain is that of treating this mixed etiology of pain. Pain from spinal cord injury may be predominantly neuropathic in nature, whereas mechanical pain such as that in the patient with severe osteoporosis is more nociceptive.

In appropriately selected patients, intraspinal therapy has been refined through accumulated experience from treating tens of thousands of cases (more than 25,000 with implantable pumps[39]), improved drug delivery systems, and new pharmacologic approaches, making it an effective technique for the control of intractable pain.

Intraspinal Drug Delivery Systems

Intraspinal drug delivery can be accomplished by a variety of means including percutaneous catheter, percutaneous catheter with subcutaneous tunneling, implanted catheter with subcutaneous injection site, totally implanted catheter with implanted reservoir and manual pump, and totally implanted catheter with implanted infusion pump.[21] The choice of the system depends on the indication for intraspinal therapy, the need for bolus *versus* continuous infusion, the patient's general medical

From the California Pain Medicine Centers and Reflex Sympathetic Dystrophy Institute and the University of California at Los Angeles School of Medicine, Los Angeles, California.

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Address reprint requests to Joshua Prager, MD, 100 UCLA Medical Plaza, Suite 760, Los Angeles, CA 90095. E-mail: paindoc@UCLA.edu.

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Table 1. Updated Pain Treatment Interventions and Medications[39,40]

Exercise
Meditation, relaxation, yoga, traditional biofeedback and neurobiofeedback
Over-the-counter medications (aspirin, traditional nonsteroidal antiinflammatory drugs) and cyclo-oxygenase inhibitors
Antineuropathic adjunctive medications (tricyclic antidepressants, selective serotonin reuptake inhibitors, GABAergic drugs, other antispasmodics, anticonvulsants, local anesthetics, calcium-channel blockers, substance P-depleting amines, alpha-2 agonists, NMDA receptor antagonists, tramadol) and other adjunctive medications: corticosteroids
Physical rehabilitation: physical therapy, work hardening, occupational therapy, Pilates
Somatic and sympathetic nerve blocks
Cognitive and behavioral therapies
Opioid medications combined with adjuvants
Pure high-potency, time-released opioid medications with breakthrough short-acting opioid medications
Spinal cord stimulation if pain is segmental
Intraspinal infusion analgesia
Neurodestructive procedures

condition, available support services, ambulatory status, life expectancy, and cost. In general, percutaneous tunneled catheters, external pumps, and implanted passive reservoirs can be more cost effective when life expectancy is a matter of weeks to months. A fully implanted pump becomes economical if life expectancy is longer than 3 months.[44]

The first "permanent" catheter for intraspinal drug delivery was developed by DuPen et al[19] in the 1980s. They adapted Broviac catheter technology to create an exteriorized, permanent, three-piece, silicone epidural catheter. The catheter was implanted in 55 patients with cancer patients who had metastatic disease and intractable pain. After 3891 days of catheter use, there were no catheter infections and 18 minor side effects. The rate of hospitalization for pain control was decreased by 90% in these patients. In one series of 350 reported implantations of the DuPen catheter, there were 30 superficial catheter infections, 8 deep catheter infections, and 15 epidural or intrathecal catheter infections, representing a 15.1% infection rate. The DuPen catheter still is marketed for use with an external pump. It may represent a cost–effective alternative for patients with a short life expectancy, such as patients with severe metastatic disease to the spine. However, the DuPen catheter and similar external systems have limited applicability in treating noncancer pain of spinal origin.

Two types of implantable drug delivery systems are marketed currently in the United States.[40,44] The first commercially available implanted pump delivered medication at a fixed rate and consisted of two chambers separated by a flexible bellows in addition to a side port for bolus injections.[53] Outflow was regulated by compressed Freon gas, so changes in altitude and temperature affected drug flow. Because the pump ran at a fixed rate, changes in the rate of medication delivery could be accomplished only by emptying the pump and refilling it

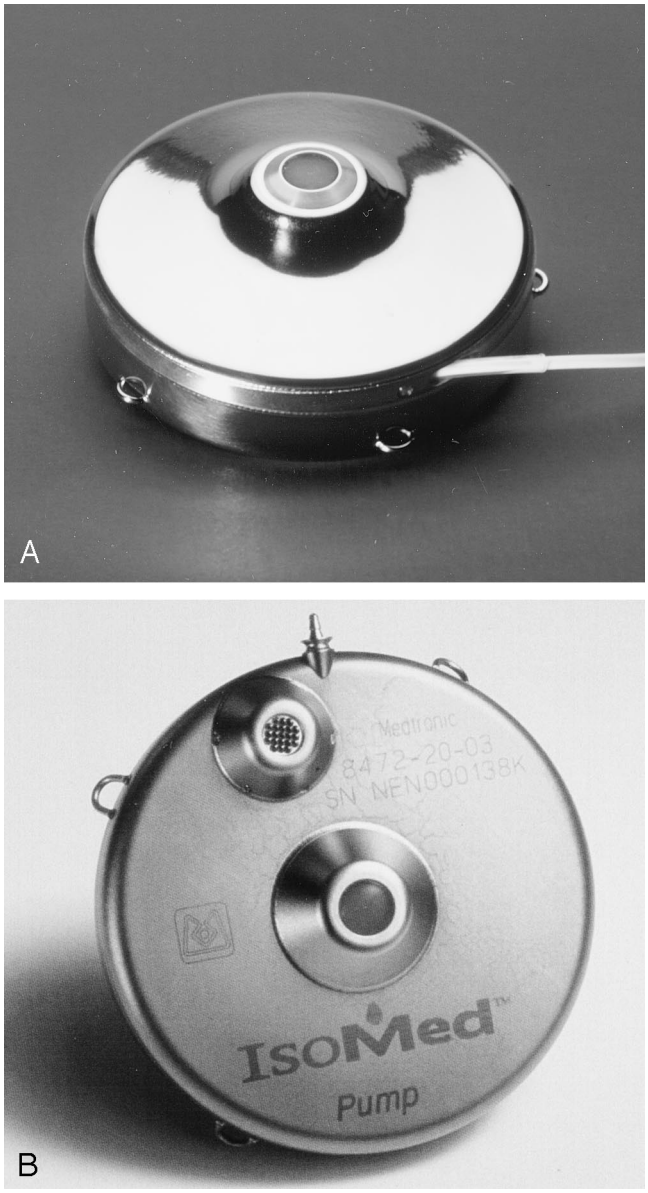

Figure 1. Fixed-rate implantable infusion pumps. **A,** Arrow M-3000 implantable infusion pump (Arrow International, Walpole, MA). **B,** Medtronic IsoMed implantable pump.

with a different concentration of medication. This pump was approved by the Food and Drug Administration (FDA) for epidural administration of preservative-free morphine. The original pump has been superseded by a new model,[31] which has a single raised septum and no side port (Figure 1A). Although essentially the same, the new pump was modified by removing the side port to minimize the potential for overdose. A special needle with a needle shaft aperture and a closed needle tip is used to deliver fluid directly into the catheter rather than the drug reservoir.[21] A second fixed-rate pump is available (Figure 1B).

The third type of implantable delivery system is a programmable electronic pump powered by batteries, which last up to 7 years depending on flow rate.[8] The pump contains a 10- or 18-mL collapsible reservoir and a peri-

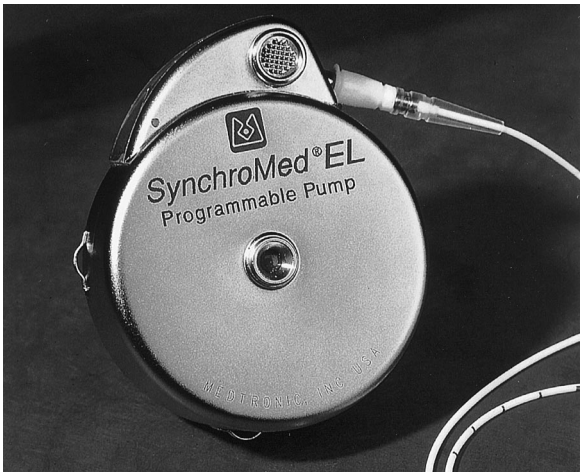

Figure 2. SynchroMed implantable pain pump (Medtronic).

staltic pump that pushes medication through a bacteriostatic filter and catheter. This pump is FDA approved for epidural or intrathecal infusion of preservative-free morphine sulfate for chronic, intractable pain, and baclofen for chronic spasticity. The pump (Figure 2) is programmed, using noninvasive telemetry (Figure 3), to control medication concentration, volume, and dosage. The programmable feature allows flexible dosing options over time and permits precise dose titration. Both pump types require refilling under sterile conditions at least every several months, depending on flow rate.[23]

Figure 3. Programmable telemetry for SynchroMed pump (Medtronic).

Table 2. Comparison of Implanted Pump Characteristics

Consideration	Programmable Pump	Fixed-Rate Pump
Cost	More expensive hardware* Needs to be replaced† Can change rate without changing medication Requires programmer	Less expensive hardware Can be permanent Rate change requires removal of medications to be replaced with different concentration Larger reservoir can reduce number of refills
Environment factors	Will not run when cold‡	Rate affected by pressure and temperature changes
Flexibility	Can run at multiple rates or deliver periodic boluses Can change rate without changing concentration for short term of long term Can be turned off temporarily	Fixed-rate (some have a fixed rate selectable at time of implantation)
MRI compatibility	Compatible§	Compatible
Reservoir volume	18 mL and 10 mL reservoirs	Can have much larger reservoirs
Other features	Programmer displays pump information (rate, medication, concentration last fill, refill date, etc.) Potential for some patient control for incident pain Potential to collect longitudinal information with programming	Can be smaller

*Hardware cost is one component of overall implantation costs. Other costs include operating suite, recovery room, radiology facility and professional fees, anesthesiology professional fees, surgical professional fees, and medications. When considering total cost, hardware cost represents only a small amount.
†Battery lifespan is estimated to be up to 7 years. Surgical costs are incurred for replacement.
‡Only a factor in pump preparation, not at physiological temperatures.
§Please see recently distributed guidelines.

In deciding whether to implant a programmable pump or a fixed-rate pump, several factors are to be considered. Table 2 compares the attributes of the two pump types. The programmable pump provides greater flexibility of medication delivery and clearly is more adjustable. However, a programmable pump is more expensive and needs to be replaced when the battery fails. Hardware is but one component of the entire implantation cost, and when all costs are aggregated, the percentage difference in cost diminishes. As a rule of thumb, programmable pumps are implanted when dosage titration and regulation is anticipated, and fixed-rate pumps may provide a cost–effective choice when dosage is expected to be stable. In practical terms for the patient with chronic pain of spinal origin, dosage regulation is anticipated. Thus, a programmable pump serves the patient better initially. If the patient stabilizes on a regimen, a fixed-rate pump may be considered for replacement to minimize expense. However, the current and future flexibility of programmable pumps make them a superior choice for most important factors, excluding expense.

■ Patient Selection and Screening Trials

The literature is virtually unanimous in emphasizing the importance of appropriate patient selection if intraspinal

Table 3. Updated Indications and Contraindications for Intraspinal Drug Delivery[40,44]

Indications
• Chronic pain with known pathophysiology
• Sensitivity of pain to medication being used
• Failure of more conservative therapy
• Favorable psychosocial evaluation
• Favorable response to screening trial
Contraindications
• Systemic infection
• Coagulopathy
• Allergy to medication being used
• Inappropriate drug habituation (untreated)
• Failure to obtain pain relief in a screening trial
• Unusual observed behavior during screening trial
• Poor personal hygiene
• Poor patient compliance

pain therapy is to be successful. Patients with chronic pain are subject to neurophysiologic, emotional, and behavioral influences, which govern their perception of pain and of pain relief. Therefore, treatment of chronic noncancer pain is multidisciplinary, drawing on cognitive and behavioral psychological therapies, functional rehabilitation, orthopedic and neurologic surgery, medications, nerve blockade, neuroaugmentive and sometimes neurodestructive procedures. The pain treatment continuum in Table 1 lists these interventions and the antineuropathic medications currently used to treat intractable pain.[39]

Indications and contraindications for intraspinal opioid therapy appear in Table 3.[44] Understanding of pathophysiology relates to nociceptive pain as opposed to neuropathic pain. Intraspinal drug delivery has been used primarily for patients with nociceptive pain, which has proved to be opioid responsive. Experience in intraspinal treatment of neuropathic pain is more limited, although several studies indicate that neuropathic pain may respond to intraspinal delivery of escalating doses of opioids, or to nonopioid medications.[29,44] Finally, a screening trial allows both physician and patient to assess intraspinal drug delivery before committing to pump implantation.

Numerous screening protocols exist. Trials can incorporate epidural or intrathecal administration, bolus injection, a series of injections, or continuous infusion, and they can be conducted on an inpatient or outpatient basis. Pure opioid or a mixture containing opioid can be administered. The duration of the trials varies from 24 hours to longer than 1 week. No protocol can be considered superior or definitive on the basis of current research. However, approximating the conditions of long-term therapy during the trial would seem to offer the best chance for assessing efficacy and tolerance.

Table 4 compares the advantages of each trial technique. The choice of protocol is influenced by the patient's overall condition, the physician's preference and experience, the available facilities and resources, the

Table 4. Comparison of Neuraxial Trial Techniques

Epidural Trial	Intrathecal Trial
Decreased risk of intrathecal infection	Most accurately simulates permanent catheter
Lower incidence of post-dural puncture headache (PDPH)	Lower dosage required
No risk of CSF drainage through catheter from disconnect	Smaller needle produces less severe PDPH
More common for outpatient administration	Even distribution of medication in FBSS
Bolus Trial	Continuous Infusion Trial
Ease of administration	Most accurately simulates permanent implant
Does not require pump for trial	Can be titrated
Decreased trial expense if additional bolus is not necessary	Required by some carriers
	Does not produce peaks and troughs of medications
	Facilitates longer trial
	Fewer side effects by avoiding peaks
	Can incorporate placebo without need for second procedure
Pure Opioid Trial	Opioid with Adjuvant Medication Trial
Predicts the effect of pure opioid	May more realistically predict long-term administration
No need to discern which medication had salutary or untoward effects	
Inpatient Trial	Outpatient Trial
Better monitoring may enhance safety	More accurately simulates normal activities
Easier to observe patient	Facilitates longer trial
Sterile technique more likely	More opportunity for titration
	Less expensive per day
Pure Percutaneous Catheter Trail	Tunneled Catheter Trial
Less procedure-related pain during the trial	Decreases chance of CNS infection
Simpler to perform	Facilitates longer trial
Less invasive	Decreases chance of catheter dislodgement
Twenty-four Hour Trial	Longer Trial
Less expensive	Can more accurately simulate normal activities
	More accurately predicts long-term result
	Decreases placebo response
Use of Current Systemic Medications during Trial	Withdraw Systemic Medications during Trial
Eliminates possible systemic abstinence syndrome (abstinence symptoms can confound results)	Can observe the effect and side effects of neuraxial medication without additive effect of systemic medications

practice environment, and the payer coverage. Medicare reimbursement, for example, requires "a preliminary trial of intraspinal opioid drug administration . . . with a temporary intrathecal/epidural catheter."[45] The question of epidural *versus* intrathecal administration continues to be debated, although no study has directly compared the two routes of administration. Although the epidural route is more convenient, an epidural dose must be roughly 10 times an intrathecal dose to provide equivalent analgesia. Proponents of intrathecal administration argue that the larger epidural dose may induce more severe side effects, deterring some patients from agreeing to intrathecal therapy that might be both beneficial and tolerable. For patients with chronic pain of spinal origin, an intrathecal trial optimizes the chance for uniform drug delivery and clearly simulates actual effect more accurately.

Two questions are fundamental: Is the patient's pain responsive to opioid therapy, and can the patient tolerate the planned drug and dosage?[40] The physician and patient should agree in advance on the goals of the trial and on the measures to be used for assessment of the outcome. For example, if returning to work is a goal of long-term intraspinal drug therapy, the patient should be evaluated by a rehabilitation specialist during the screening trial. In general, candidates should not proceed to implantation unless their pain can be reduced by at least 50%.[13,22] Behavioral observation during the trial adds to the information used for making decisions regarding permanent implantation.[56] A psychological interview during or after the trial to discuss how the trial met expectations is valuable.

■ Surgical Implantation

Device manufacturers provide recommended surgical procedures, which can be adapted to surgeon and institutional preference. The surgical procedure has two steps: placement of the catheter and implantation of the reservoir or pump. Implantation technique varies widely, even for a single type of pump, as Krames and Chapple[42] reported in their review of 202 patients in 22 centers. Most of the catheters were inserted between L2 and L4 (87.2%), introduced through the midline (65.1%), or positioned with their tips at T10 to T12 (64.1%). Also, 95% of the catheters were anchored, 43.8% with a right-angle anchor and 44.8% with a butterfly anchor. Catheter position was confirmed in 94.8% of the cases. No correlation was found between any one surgical technique and commonly reported complications.

■ Drug Selection

Intraspinal drugs must be preservative-free. Alcohol, phenol, formaldehyde, and sodium metabisulfite, common drug preservatives, all are toxic to the central nervous system. Any drug packaged in a multidose vial probably contains preservatives and should not be used for intraspinal administration.[66]

Preservative-free morphine sulfate is the only drug approved for intraspinal delivery by the FDA for pain relief. Its long history of clinical use, long duration of action (12–24 hours), and relative ease of use explain why it remains the gold standard for intraspinal therapy. If morphine is poorly tolerated, other opioids (hydromorphone, meperidine, methadone, fentanyl, and sufentanil) also can be used intraspinally. Care must be taken to ensure that the medication preparation is compatible with the pump tubing, and that the medication is pure and preservative free. Some meperidine preparations have rendered the SynchroMed pump (Medtronic, Minneapolis, MN) inoperable by damaging internal tubing (personal communication with Medtronic personnel).

The pharmacokinetic properties of various drugs (their lipid solubility, pH, pKa, molecular weight, and opioid receptor affinity) determine time to onset of action, duration of action, uptake and distribution, and side effects. Lipophilic medications such as sufentanil do not spread more than several neurotomes beyond the delivery site at the catheter tip, whereas hydrophilic medications such as morphine circulate throughout the CSF. Furthermore, the site of drug delivery (epidural *versus* intrathecal) affects distribution. Drugs delivered epidurally must first cross the dura and arachnoid membranes before diffusing to their site of action, whereas drugs delivered intrathecally diffuse passively to the spinal cord. Morphine, which has low lipid solubility and high receptor affinity, diffuses slowly and remains bound for prolonged periods. Unfortunately, the risk of central nervous system side effects (sedation, nausea and vomiting, and respiratory depression) is greater with hydrophilic drugs, such as morphine, than with lipophilic drugs, such as fentanyl or sufentanil. These lipophilic drugs have a rapid onset and prolonged duration of action.[23,39,40]

Dosing of intraspinal drugs is highly individual and depends on the patient's pain type, age, previous need for analgesia, and previous use of opioid medication. Usually, patients with neuropathic pain require higher doses of opioids than patients with nociceptive pain if an opioid is the only medication administered. One advantage with the use of continuous infusion or increasing-dose bolus injections during the screening trial is that dosage can be more precisely titrated.

Drug admixtures can help patients who experience side effects associated with the increasing doses required to provide analgesia or outright tolerance to opioids. Combining drugs with different mechanisms of action can produce synergy, as in the case of morphine combined with bupivacaine. In theory, synergy reduces morphine-associated side effects by decreasing the opioid dose required for analgesia. One caveat applies: Although use of admixtures is increasingly popular and often produces increased analgesia, safety data on many of the combinations is scarce. In fact, there is a paucity of literature even demonstrating the stability of various admixtures in the pump at body temperature up to 3 months.

Satisfactory results with a morphine–bupivacaine combination have been reported in several studies of cancer and noncancer pain, although high concentrations of epidural morphine were required and side effects included transient paresthesias, motor blockade, and

gait disruption.[44] The study of van Dongen et al[17] followed a group of cancer patients treated with intrathecal morphine and bupivacaine through a tunneled percutaneous catheter. Of 17 patients treated with this admixture because morphine alone was insufficient to relieve pain, 10 improved significantly and 4 moderately. The three patients who experienced no improvement also had clinical signs of severe depression. No serious complications were reported. A more recent study by the same group found that intrathecal morphine and bupivacaine slowed the progression of morphine dose, as compared with morphine given alone. These authors attributed the diminished morphine dosage to the synergistic analgesic effect of bupivacaine.[18] Although bupivacaine is a commonly used adjuvant medication, care should be taken to avoid concentrations greater than 0.75% in noncancer patients because neurotoxicity has been demonstrated at greater concentrations in rats receiving long-term infusions.

Lidocaine (a local anesthetic) and clonidine (an α-adrenergic agonist) also have been given with morphine. The morphine–clonidine combination seems to be particularly effective for patients with neuropathic or mixed nociceptive–neuropathic pain.[39,40] In the mid-1990s, the Epidural Clonidine Study Group evaluated 85 patients with severe cancer pain who were taking large doses of opioids without significant pain relief or suffering from severe side effects. They were randomly assigned to receive 30 μg/hour of epidural clonidine or placebo for 14 days and had access to rescue epidural morphine. Pain was documented by visual analog score, McGill Pain Questionnaire, and daily epidural morphine use. Successful analgesia was reported by 45% of the patients receiving clonidine, and by 21% receiving placebo. Among the patients with neuropathic pain, 56% receiving clonidine reported successful analgesia, as compared with only 5% receiving placebo. Pain scores were lower at the end of the study for the patients with neuropathic pain who received clonidine rather than placebo, and morphine use was unaffected. Serious hypotension occurred in two patients receiving clonidine and one receiving placebo.[20] Clonidine has not yet been approved for intrathecal infusion in the United States, but in European and Australian studies, intraspinal infusion was well tolerated for 6 to 12 months.[30,41]

Dexmedetomidine, a highly selective new alpha-2 adrenergic agonist, is known to produce sedation and analgesia in humans.[25] Given intrathecally to rats, it is a very potent antinociceptive.[33] Alpha-2 agonists also seem to potentiate the analgesic effects of opioids. One study in rats evaluated the interactions between systemically (subcutaneous, intravenous, and intraperitoneal) and spinally (epidural and intrathecal) administered alpha-2 agonists (medetomidine, dexmedetomidine, xylazine, clonidine, and detomidine) and opioids (fentanyl or sufentanil).[46] All of the tested alpha-2 agonists potentiated the effects of opioids by reducing the amount of opioid needed to reach specified levels of analgesia and prolonging the duration of analgesia with a fixed dose of opioid. The potentiation appeared to be independent of the route of administration. Dexmedetomidine was second only to medetomidine in its ability to produce deep surgical analgesia when combined with fentanyl.

Recent research that elucidates the neurobiology of pain suggests other methods of pain control. Nerve and tissue damage leads to changes in both the peripheral and central nervous system. Drugs specifically targeted at steps in the neuropathologic cascade are showing promise in reducing both pain perception and side effects. One such drug is ziconotide (SNX 111 or CI-1009), a highly selective, potent, and reversible blocker of neuronal N-type voltage-sensitive calcium channels that produces antinociception in animals. In one study, ziconotide exhibited substantial neuroprotective activity in a model of traumatic diffuse brain injury in rats.[10]

The effect of intrathecally administered ziconotide and morphine on nociception also has been studied in rats.[64] After a 7-day intrathecal infusion, ziconotide enhanced morphine analgesia, but had no effect on ziconotide antinociception. Whereas chronic intrathecal morphine infusion led to rapid tolerance, ziconotide had no loss of analgesic potency during the infusion period. Ziconotide administered with morphine produced a synergistic analgesic effect, but did not prevent morphine tolerance.[64]

In humans, ziconotide has been administered intrathecally to control acute postoperative pain.[3] Mean daily morphine dosage (administered by patient-controlled analgesia) was significantly less in patients receiving ziconotide than in those receiving placebo 24 to 48 hours after surgery ($P = 0.040$). Patient pain perception (measured by visual analog scale) also was markedly lower in patients treated with ziconotide than in patients treated with placebo. Four of six patients receiving the high dose of ziconotide (7 μg/hour) experienced adverse events including dizziness, blurred vision, nystagmus, and sedation, all of which resolved after drug discontinuation. Ziconotide also has be used to treat cancer and AIDS patients experiencing pain not responsive to opioids.[52] Intrathecal ziconotide has demonstrated analgesic efficacy, and the initial reports indicated that adverse events could be controlled with symptomatic treatment. Recently, however, Penn and Paice[52] reported three cases of serious adverse events in patients receiving intrathecal ziconotide.

An expert panel convened in July 2000 released clinical guidelines for intraspinal drug selection, dosage, and administration (Figure 4).[9] The panel found wide variation in practice patterns on the basis of an Internet survey of physicians using implantable pumps. The guidelines reflect the current best available evidence, as judged by experienced clinicians.

Efficacy

Studies on the efficacy of intraspinal morphine report widely ranging success rates for pain relief (Table

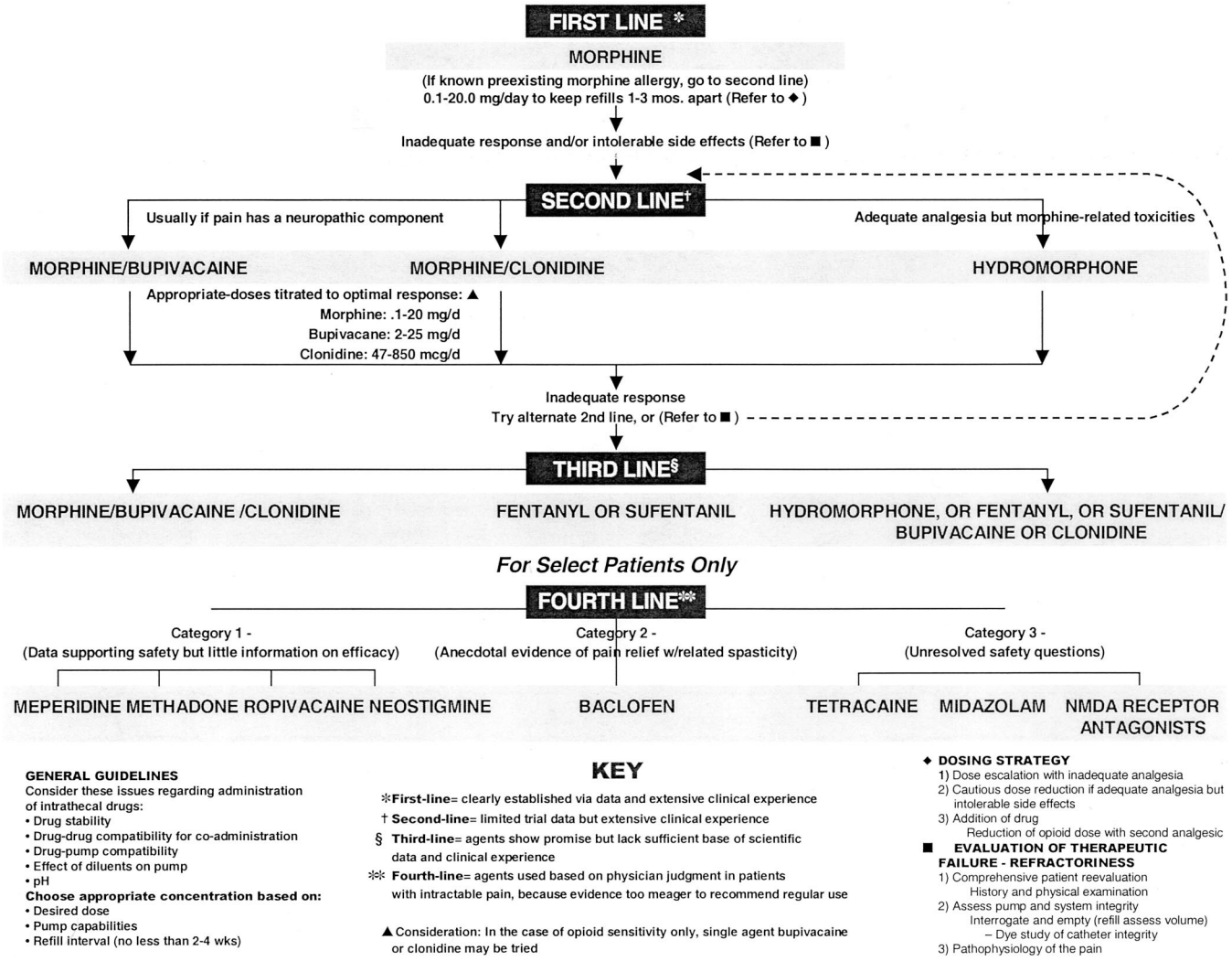

Figure 4. Clinical guidelines for intraspinal infusion.

5).[1,4,5,8,11,14,16,22,28,29,34,36,49–61,63,65] In general, pain relief for cancer patients occurred more frequently (in approximately 80% of cases) and consistently than for noncancer patients. Some studies also included other measures of efficacy, such as improvement in activities of daily living, employment status, and quality of life.

Several key studies have examined the efficacy and reliability of intraspinal drug delivery. Winkelmüller and Winkelmüller[65] investigated the long-term effects of continuous intrathecal infusion for chronic noncancer pain. They followed 120 patients for 6 months to 5.7 years, 73 of whom were FBSS patients with mixed nociceptive–neuropathic pain from multiple lumbosacral operations, including spondylodesis. The best long-term results occurred in the management of deafferentation pain and neuropathic pain, with pain reduction (measured by a visual analog scale) of 68% and 62%, respectively. The mean morphine dosage was 2.7 mg/d initially, which rose to 4.7 mg/d after an average of 3.4 years. Among 28 patients treated more than 4 years, 18 (64.3%) were maintained on constant doses, and 10 (35.7%) required increases to more than 6 mg/d 1 year after therapy began. Tolerance developed in seven patients, three of whom had the pump removed. During the follow-up period, 74.2% of the patients benefited from intrathecal opioid delivery. The average pain reduction was 67.4% after 6 months and 58.1% at last follow-up examination. Most patients (92%) were satisfied with therapy, and 81% reported improvement in quality of life.

Angel et al[2] studied 11 patients (9 with FBSS) referred to a neurosurgery clinic and treated with intrathecal morphine. The patients were observed up to 3 years. Overall, a good to excellent analgesic response was seen in 73% (8/11) of the patients. Unfortunately, the three patients judged to have poor results all had FBSS. The effective response among all the FBSS patients was 67% (6/9). Bladder dysfunction requiring pump removal occurred in two patients. The authors concluded that intrathecal morphine delivery was a viable alternative in the management of FBSS despite its limitations. They cautioned that it should be a last choice option, however.

A retrospective, multicenter study surveyed physicians in the United States regarding intrathecal morphine delivered by the SynchroMed pump.[50] In this study, 35

Table 5. Studies of Intraspinal Morphine for Intractable Pain

Studies (listed in order of publication)	Patient Population (nonmalignant/malignant pain)	Route of Administration	Efficacy	Side Effects
Behar et al.,[8]	6	Epidural	3 complete relief 3 >50% reduction in pain	
Wang et al.,[63]	8	Intrathecal	2 complete relief from separate saline and morphine injections 6 complete relief from morphine alone	
Coombs et al.,[14]	10 (5/5)	Intrathecal	5 Cancer patients: significantly reduced pain 5 noncancer patients: poor pain reduction	
Krames et al.,[36]	17 (1/16)	Intrathecal/ epidural	1 noncancer patient: poor pain relief 16 cancer patients: 50–70% reduction in pain	
Auld et al.,[4]	32	Epidural	66% good 3% side effects	6% complications, mostly catheter-related
Auld et al.,[5]	20 (15 patients with nonmalignant pain)	Epidural	Of 15 patients, 2 had excellent relief, 6 good relief, 1 fair relief, 2 poor relief, 4 no relief	
Brazenor[11]	26	Intrathecal	20 had excellent relief, 3 good relief, 1 poor, 1 none, 1 comatose	
Penn and Paice[51]	43 (8/35)	Intrathecal	8 noncancer patients: all good or excellent pain relief 35 cancer patients: 80% good or excellent pain relief	Early pump failure problems in 6 units were corrected by device modification
Onofrio and Yaksh[49]	53 (0/53)	Intrathecal	67% good or excellent; 19 of 33 improved ambulation Average parenteral opiate doses fell significantly	
Hassenbusch et al.,[28]	69	Intrathecal	41 patients reduced mean pain scores from 8.6 to 3.4	
Follett et al.,[22]	37 (2/35)	Intrathecal	35 cancer patients: good pain relief 2 noncancer patients: good pain relief	Spinal headache (31%), nausea (26%, not necessarily attributable to pump implantation), and lethargy (15%) most common
Kanoff[34]	15		73% good to excellent 40% of patients returned to work	20% catheter-related
Hassenbusch et al.,[29]	18	Intrathecal	61% fair to good	33%
Winkelmüller and Winkelmüller[65]	120	Intrathecal	74% 67% had pain reduction at 6 mo 58% at last follow-up 92% of patients satisfied with treatment 81% of patients reported improved quality of life	17%
Paice et al.,[50]	429 (289/140)	Intrathecal	95% good to excellent 28 patients returned to work	22%
Tutak and Doleys[61]	26	Intrathecal	77% good to excellent	35% catheter-related
Doleys et al.,[16]	36	Intrathecal	60.8% subjective improvement 76.7% decreased oral medications 47.8% improved function 83% of patients rated outcome as good or excellent	Nausea was the most frequent side effect (27.8%) 33% catheter problems requiring surgery Three pumps removed, none for mechanical failure
Anderson and Burchiel[1]	30	Intrathecal	50% had at least 25% pain reduction after 24 mo Activities of daily living improved for at least 12–18 mo	20% device-related

physicians provided 429 case reports detailing screening methods, outcomes, dosing, and adverse effects. Each of the physicians contacted had implanted at least five pumps. Among these patients, 33% were being treated for cancer pain and 67% for noncancer pain. The average length of treatment was 14.6 ± 0.57 months. The patients with somatic pain had the greatest degree of pain relief. After initial dose titration, intrathecal morphine doses increased only twofold, from 5.84 ± 0.65 mg/d to 13.19 ± 1.76 mg/d. The patients being treated for cancer pain had a higher initial dose, which escalated quickly and then reached a plateau. Patients with noncancer pain had a gradual, linear increase in dosage. Adverse drug effects were not frequent, but catheter or system malfunction occurred in 21.6% of the cases.

Although most implantable drug delivery systems are used to treat nociceptive pain, in the Hassenbusch et al[29] study of intraspinal drug therapy for patients with severe neuropathic pain, 11 of 18 patients (61%) had good or fair pain relief after more than 2 years. Average numerical pain scores declined by 39% ± 4.3%, although long-term pain relief eventually failed for 7 of 18 patients (39%). The authors concluded that long-term intrathecal opioid infusions could be effective for treating neuropathic pain, but at higher doses than used for treating nociceptive pain.

A recent prospective study examined the long-term safety and efficacy of intrathecal morphine for patients with severe noncancer pain.[1] Of 40 patients, 30 experienced pain relief during a screening trial and had an intraspinal delivery system implanted. Patients had mixed neuropathic–nociceptive pain (50%), peripheral neuropathic pain (33%), deafferentation pain (13%), or nociceptive pain (3%). Half of the patients (11/22) reported at least a 25% reduction on the visual analog scale after 24 months of treatment. The results of the McGill Pain Questionnaire and Chronic Illness Problem Inventory showed improvement in sleep, social activities, inactivity levels, and medication use throughout the follow-up period. Device-related problems requiring additional surgery were experienced by 20% of the patients.

■ Complications

The complications of intraspinal therapy fall into several categories: procedure-related complications, drug-related side effects, and equipment-related problems. Immediate drug-related side effects include nausea and vomiting, urinary retention (more common in men with benign prostatic hypertrophy), pruritus, and respiratory depression. Each of these conditions can be managed medically with antiemetics, intermittent catheterization, antihistamines, or naloxone, respectively. Respiratory depression, the most serious of these side effects, is relatively rare in patients already exposed to opioids. Delayed side effects include constipation, myoclonus, edema, arthralgias, facial flushing, and diaphoresis. Clinicians increasingly recognize suppression of the hypothalamic–pituitary axis producing endocrine changes. Examples include decreased testosterone production resulting in decreased libido and suppression of thyroid function resulting in hypothyroidism. For this reason, serum lipids, androgens or estrogens, 24-hour urinary cortisol, and serum IGF-1 levels should be monitored during intrathecal therapy.[47] Intraspinal therapy requires conscientious follow-up evaluation, with doses adjusted to balance pain relief against side effects. Many side effects respond to symptomatic treatment.[23]

Unintentional overdosing can be disastrous. Symptoms of massive morphine overdose include muscle rigidity, severe myoclonus, seizure activity, hypertension, cardiovascular collapse, and severe respiratory depression. Should an overdose occur, the patient should be hospitalized immediately. Replacing some cerebrospinal fluid (CSF) with saline and administering naloxone if signs of respiratory depression occur may help.[40]

Catheter-related problems are common, occurring in 10% to 40% of cases. Any abrupt change in pain can signal a catheter problem.[23,44] Troubleshooting for equipment problems demands all of a physician's diagnostic and management skills. A radiograph of the pump and catheter will disclose many catheter problems, but not whether the tip is obstructed or a CSF leak has occurred. Often, surgical inspection and correction are required.[40] Meticulous surgical technique can help to prevent some catheter problems. Catheter position can be checked fluoroscopically, CSF flow confirmed at each step during implantation, and the catheter secured with a purse string suture at the interspinous ligament, and again with a plastic fixation device.[44]

A recent prospective study of 202 patients in 22 centers in the United States and Europe examined results from the use of a catheter[63] modified to overcome some drawbacks of earlier designs.[42] The patients in this study were being treated for noncancer pain (60.4%), spinal spasticity (21.8%), cancer pain (12.4%), or other conditions. The catheter implantation technique varied widely with regard to catheter entry site and tip position, spinal introducer position, and catheter anchoring. Based on 3112.8 months of patient use, the overall catheter-caused complication rate was 0.3% per patient per month. More than 89% of the physicians rated the new catheter as superior to previously available catheters. Table 6 lists the non–medication-related complications associated with this new catheter.

Cerebrospinal fluid leaks are inevitable during intrathecal catheter placement, leading to postspinal headache in up to 20% of patients. Persistent CSF leaks should be treated with autologous epidural blood patching. Cerebrospinal fluid hygromas usually resolve spontaneously, but surgical intervention may be necessary if fluid persistently leaks through the suture line after more conservative measures have failed.[40]

Catheter-tip granulomas, often associated with neurologic sequelae, may develop after intraspinal catheter placement.[47] Granulomas are relatively rare. In a survey of 519 U.S. physicians who implanted drug delivery sys-

Table 6. Summary of Complications Related to a New Intrathecal Catheter[47]

Complication	Procedure-Related	Patient-Related	Mechanical	Total
Dislodged	4	5	1	10
Cut during placement	2	0	0	2
CSF leak/hygroma	2	1	0	3
Pain during insertion	1	0	0	1
Occlusion	0	5	0	5
Disconnection	1	1	0	2
Break	1	2	0	3
Kink	0	1	0	1
Pump pocket/site	3	0	0	3
Total	14	15	1	30
Rate per patient month of follow-up	0.45%	0.48%	0.03%	1.0%

tems, 31 reported a total of 19 cases, 6 of which had not been previously reported in the literature.[57] Two reported cases involved patients with FBSS.[35,48] Patients with a granulomatous mass may present with new pain, numbness, weakness, or changes in bowel and bladder habits. The diagnosis is confirmed by a neurologic examination and MRI. Treatment consists of surgical decompression and removal of the mass and spinal catheter.[47]

Prevention trumps treatment in the management of surgical infections. Prophylactic cephalosporin or vancomycin administration is recommended, along with strict sterile technique. A wound should never be closed in the presence of uncontrolled bleeding because hematomas are active breeding grounds for infections. Epidural hematoma, diagnosed by magnetic resonance imaging (MRI) or computerized tomography (CT), should be treated as an emergency if it impairs neurologic function. Superficial wound infections can be treated with appropriate antibiotics. The implant must be removed if infection invades the catheter or implant pocket. After explantation, the wound should be packed and left open to heal. Intrathecal infections are rare, although many patients spike a fever within the first 3 days after implantation. If the complete blood count is normal, the CSF shows only leucocytosis, and the fever falls within 48 to 72 hours, meningitis probably is not a concern. Untreated epidural infections can abscess and compress the thecal sac, potentially leading to paralysis. Diagnosis relies on clinical signs and symptoms, confirmed by MRI or CT studies. Epidural abscess is treated by removing the pump and catheter and administering antibiotics. Consultation with an infectious disease specialist can be helpful in the selection of antibiotics.[40]

Many patients notice pump pocket seroma for several months after implantation. The use of postoperative abdominal binders may decrease the incidence and severity of this problem. When seroma persists, fluid can be aspirated for gram staining if infection is suspected. Intravenous antibiotics and antibiotic irrigation of the pocket can be performed for proven bacterial infection. Patients should be monitored carefully for the spread of infection during treatment, and the device must be removed if the infection does not respond to treatment.[40]

■ Troubleshooting for Lack of Efficacy

When a patient presents with lack of efficacy from a neuraxial drug delivery system, an algorithm for troubleshooting must be used. The clinician must consider possible tolerance to medication or a change in the patient's back problem as the possible etiology. When these are ruled out, troubleshooting of the system should be initiated. The system can fail to deliver adequate medication when the reservoir volume drops below a critical level, improper programming has occurred, the catheter kinks or obstructs, the catheter becomes dislodged or migrates, the pump malfunctions, or the pump actually stalls.

If the clinician approaches troubleshooting in a systematic fashion, the task becomes relatively simple. The first step involves ensuring that the pump has an adequate amount of medication in its reservoir. If the pump is programmable, a scan of the pump should show whether the pump is programmed properly. Once these basics have been covered, the catheter is evaluated. If the pump has a side port, this can be aspirated to determine whether fluid can be obtained from the catheter. Radiography, particularly fluoroscopic radiography, is a valuable tool for evaluating catheter position. If there is any question regarding catheter function after these preliminary steps, a contrast study can be performed by injecting contrast through the side port of pumps so equipped.

Caveat 1

When performing a contrast study through the side port of the pump, the clinician should be careful not to administer a bolus to the patient while medication is contained in the catheter. If it is not possible to aspirate fluid back before injecting, it may not be advisable to inject contrast medium through the catheter.

Caveat 2

When injecting contrast solution into the intrathecal space, the clinician should use contrast medium indicated only for intrathecal administration. Failure to use an appropriate contrast medium can result in adverse events such as seizures and death. Less severe complications include extreme pain and cramps.

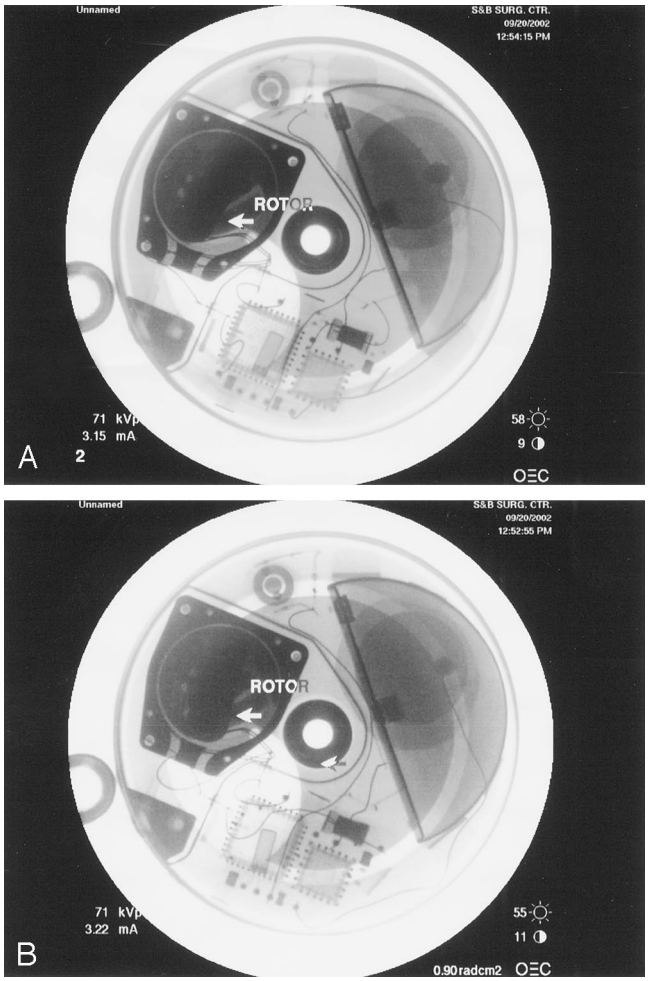

Figure 5. Radiograph of implanted pain pump. **A,** Labeled rotor before rotation. **B,** Rotor after rotation. Notice the change in the movement of the rotor indication that the pump is turning.

Distribution of the contrast solution can demonstrate proper flow within the cerebrospinal fluid, verifying catheter function. Pump function (proper pump roller rotation) can be observed under fluoroscopic guidance (Figure 5). Figure 5A demonstrates the original position of the pump rotor prior to rotor rotation. Figure 5B demonstrates rotation of the rotor. For cases in which conventional contrast radiography leads to a confusing picture, radiolabeled indium can be injected, with the result that serial scans over the ensuing 12 to 24 hours will show diffusion through the cerebrospinal fluid if the catheter is positioned intrathecally.

■ Implanted Pumps and Radiologic Procedures

Patients with FBSS may require diagnostic procedures such as CT or MRI scans. Questions frequently arise regarding the advisability of performing scans for patients with implanted devices. There are no special implications for plain radiographs or CT scans. With modern fixed-rate pumps, exposure of pumps to MRI fields of 1.51 Tesla has demonstrated no impact on pump performance and a limited effect on the quality of the diagnostic information.

For patients with implanted programmable pumps, the manufacturer recently released a document stating:

> The magnetic field of the MRI scanner will temporarily stop the rotor of the pump motor and suspend drug infusion for the duration of MRI exposure. The pump should resume normal operation on termination of MRI exposure. Before MRI, the physician should determine if the patient could safely be deprived of drug delivery. If the patient cannot be safely deprived of drug delivery, alternative delivery methods for the drug can be used during the time required for the MRI scan. If there is concern that suspension of drug delivery during the MRI procedure may be unsafe for the patient, medical supervision should be provided while the MRI is conducted. Before scheduling an MRI scan and on completion of the MRI scan, or shortly thereafter, the pump status should be confirmed using the SynchroMed programmer. In the unlikely event that any change to the pump status has occurred, a Pump Memory Error message will be displayed and the pump will sound a Pump Memory Error Alarm (double tone). The pump should then be reprogrammed and Technical Services notified.[58]

High doses of radiation can damage a pump's circuitry. Care should be taken to exclude the pump from the radiation field during radiation therapy.

■ Future Challenges

During the past decade, intraspinal therapy for intractable pain has evolved into a useful clinical treatment. Nevertheless, many challenges remain. Large-scale, well-controlled studies could answer some perplexing questions regarding efficacy in patients with noncancer or neuropathic pain. Patient selection criteria undoubtedly will be refined and validated as more patients are treated. In addition, further investigation of specifically targeted agents or drug combinations for intraspinal use could reduce side effects and expand indications.

Basic science is elucidating pain mechanisms, providing a basis for the development of new medications and a rationale for new off-label uses of existing medications. With this in mind, clinicians planning new intrathecal catheter placement should consider a location close to the site where pain information enters the spinal cord so that lipophilic medications can achieve optimal effect. Vigilance must be exercised to observe long- and short-term side effects of medications introduced into the spinal fluid. New combinations of medications provide a huge potential for increased efficacy through additive effects and synergy, but the stability of these admixtures and their neurologic impact must be studied.

Microprocessors and miniaturization have enhanced pump development. Programmable pumps are now limited by battery life constraints and size. Improvements in power sources will expand the lifespan of programmable pumps and decrease their size, allowing for larger reservoir volume. At this writing, only one implantable intrathecal system provides an element of patient control, and it is not FDA approved for use in the United States. The current pumps are effective in treating baseline pain, but a system that allows patient control for breakthrough

pain is essential. Finally, given the contrast in the pharmacokinetics and pharmacodynamics of the various medications that will be used simultaneously in pumps in the future, a system that can deliver different medications at different rates would be desirable.

■ Conclusion

Neuraxial medication delivery is now a proven and sophisticated method for managing complex intractable pain, such as that experienced by patients with FBSS. This treatment should be considered when other methods short of neurodestructive procedures have failed. With proper patient selection and medication trial, neuraxial medication delivery is a reversible, nondestructive technique that can benefit patients with FBSS by providing improved pain relief while reducing systemic side effects.

■ Key Points

- Unique features of this article include an updated pain continuum, updated indications for intrathecal therapy, a detailed comparison of trial techniques, a detailed comparison of the advantages of different types of pumps, a synopsis of troubleshooting for inadequate efficacy, and an updated statement regarding intrathecal pumps and radiologic procedures, including MRI scanning.
- Patient selection criteria undoubtedly will be refined and validated as more patients are treated. In addition, further investigation of specifically targeted medications or drug combinations for intraspinal use could increase efficacy, reduce side effects, and expand indications.
- Intraspinal medication delivery has become an effective technique for control of intractable pain in appropriately selected patients seen by spine surgeons.

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