Proceedings Supplement: Current Status of Intrathecal Therapy for Nonmalignant Pain Management

Clinical Realities and Economic Considerations: Efficacy of Intrathecal Pain Therapy

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Abstract

Studies of analgesia in cancer patients have revealed that intrathecal administration of opioids can deliver potent analgesia with fewer systemic side effects than equivalent doses of systemic opioids. In addition, several trials have examined the safety and efficacy of this modality in patients with pain of nonmalignant origin. In one survey of 35 physicians involving 429 patients treated with intrathecal therapy, physician reports of global pain relief scores were excellent in 52.4% of patients, good in 42.9%, and poor in 4.8%. In another study of 120 patients, the mean pain intensity score had fallen from 93.6 to 30.5 six months after initiation of therapy. In both studies, patients reported significant improvement in activities of daily living, quality of life measures, and satisfaction with the therapy. Constipation, urinary retention, nausea, vomiting, and pruritus are typical early adverse effects of intrathecal morphine and are readily managed symptomatically. Other potential adverse effects include amenorrhea, loss of libido, edema, respiratory depression, and technical issues with the intrathecal system. J Pain Symptom Manage 1997;14:S14–S26. © *U.S. Cancer Pain Relief Committee, 1997.*

Key Words

Opioids, analgesia, intrathecal efficacy, neuropathic pain, nociceptive pain, morphine, naloxone, adverse effects

Introduction

The discovery of highly specific opioid receptors in the nervous system paved the way for the development of intraspinal opioid therapy as a useful therapeutic approach. Studies of cancer patients with intractable pain demonstrated that intrathecal opioids could provide analgesia, often with fewer side effects than with an equianalgesic dose of systemic opioid.[1,2] The analgesic effect was mediated through spinal and supraspinal opioid recep-

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Table 1
Pain Characteristics by Diagnosis

Pain type	Diagnosis		
	Malignant	Noncancer	Total
	(N = 118)	(N = 245)	(N = 363)
Somatic	16(13.6%)	45(18.4%)	61(16.8%)
Neuropathic	30(25.4%)	107(43.7%)	137(37.7%)
Visceral	20(16.9%)	9(3.7%)	29(8.0%)
Mixed	52(44.1%)	84(34.3%)	136(37.5%)

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tors with only minimal influence on motor, sensory, and sympathetic reflexes.[3,4]

Intrathecal opioid therapy is now gaining acceptance by pain specialists as a legitimate approach in selected patients with chronic nonmalignant pain. Although the literature on the use of intrathecal opioid therapy for the management of chronic pain of nonmalignant etiology is limited, there is significant clinical experience to endorse a trial in appropriate patients. The literature is reviewed below.

One caveat in the interpretation of any study relating to the efficacy of a given method of pain control is the stated definition of *efficacy*. Unless efficacy is clearly defined, it is difficult to compare the results of studies and base clinical decisions on their findings. One review noted the imprecision that currently characterizes the use of the term: "Efficacy has meanings that vary greatly with context. . . . At the most basic level, pharmacologists use the term to denote intrinsic efficacy, a construct that refers to the number of receptors in a given system that must be occupied by the drug to yield a given effect. Clinicians often use *efficacy* to describe an outcome in which a favorable balance between analgesia and side effects has been achieved through gradual dose titration."[5] Although this latter definition is the most useful for determining the analgesic outcome associated with a given therapy, most clinicians and patients also seek improvements in overall function and quality of life, and base their therapeutic decisions on these outcomes as well.[6]

There have been various attempts to develop meaningful outcome measures in addition to standard measures of pain relief. These have included interviews with disinterested third parties and measurements of patient satisfaction, for example, would the patient undergo the procedure again to obtain the same result? Other proposed outcome measures have included the need for additional treatment or ongoing use of additional pain medications, impairment of activities of daily living and occupation, and level of neurologic impairment. The lack of consensus complicates the interpretation of efficacy studies. Further questions remain as to the most effective methods of screening patients and the variables that best predict long-term response.

In the absence of pain typology predictors of efficacy and agreement regarding outcomes variables, there is a greater onus on those caring for patients who are candidates for implantable therapies to expend whatever time is necessary to get to know their patients and educate them as to the benefits and limitations of the technology and what their expectations should reasonably be. In the absence of valid pain typology predictors for successful therapy, there can be no substitute for good clinical judgment based on a detailed assessment of each patient.

Retrospective Studies

The United States Experience

Two recently published studies have examined the long-term use of continuous intrathecal opioid therapy in the management of chronic pain of nonmalignant etiology. One, by Paice et al.,[7] surveyed physicians in the United States regarding their standard protocols and practices when treating chronic pain with implanted intraspinal opioid therapy. The authors were specifically interested in identifying dosage changes over time, the use of different screening techniques, and the prevalence of adverse effects and system complications. The study reviewed data derived from 429 patients of 35 physicians

Table 2
Screening Methods by Frequency

Method	Percentage used
Continuous epidural infusion	35.3
Bolus intrathecal injection	33.7
Bolus epidural injection	24.5
Continuous intrathecal screening	6.4

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(Table 1). Approximately two-thirds of the patients had pain of nonmalignant etiology. The most common diagnoses for the entire patient population were failed back surgery (42.4%) and cancer (31%), followed by reflex sympathetic dystrophy (5.6%), postherpetic neuralgia (5.1%), and peripheral nerve injury (3.7%). Ninety-two percent of the patients described in this survey underwent opioid screening. Table 2 illustrates screening methods. The most common screening method was continuous epidural infusion (35.3%), followed by bolus intrathecal injection (33.7%), and bolus epidural injection (24.5%). Continuous intrathecal screening was the least common screening method (6.4%). The findings suggested that in a small percentage of cases invasive procedures were used before an adequate trial of oral opioids and other conservative interventions had been tried. Eleven percent of noncancer patients and 2.3% of cancer patients had never received oral opioids before intraspinal drug therapy. Both nerve blocks and spinal cord stimulation had been tried in a number of patients who had not received adequate trials of more conservative therapies. More noncancer patients had received nerve blocks than had received anticonvulsants or antidepressants. These practices are not consistent with the standard recommendation to try less invasive, less costly syndrome-specific therapies prior to a trial of implantable therapy.

The majority (77.6%) of the patients underwent psychological screening prior to implantation. Of those who did undergo screening, there was a trend toward improved global pain ratings with treatment.

Morphine was the first-line therapy in 95.5% of the cases, and intrathecal administration was the most common delivery route. At 6 months, patients with neuropathic pain only or mixed pain were more likely to require higher doses of intrathecal morphine than other patients. This is similar to the trend observed with systemic opioids and suggests that neuropathic pain is generally opioid responsive, but may require higher doses than commonly used. Local anesthetics, such as bupivacaine were added to morphine in 19.8% of patients. This again suggests that while neuropathic pain is amenable to intrathecal pain therapy, an opioid alone may not always be sufficient to control it. The average morphine dose for those being treated for pain of nonmalignant etiology exhibited a gradual linear escalation. However, when dose escalation was analyzed for all patients who completed 24 months of infusion therapy, the noncancer and cancer patients had similar dosages at 24 months despite the higher dosage in the latter group at initiation. In comparison to the mean dose of 21.0 mg/d reported in an earlier study by Yaksh and Onofrio,[8] the mean dose at 1 year in this survey was 9.2 mg/d for all patients and 14.2 mg/d for cancer patients.

Table 3
Agents Used Intraspinally by Implanted Drug-Administration Device

Agents	N (Total N = 427)
Morphine	300 (69.9%)
Hydromorphone	48 (11.2%)
Morphine and bupivacaine	36 (8.4%)
Morphine and tetracaine	17 (4.0%)
Hydromorphone and bupivacaine	10 (2.3%)
Sufentanil	12 (2.8%)
Bupivacaine	9 (2.1%)
Fentanyl	8 (1.9%)
Sufentanil and bupivacaine	5 (1.1%)
Meperidine and bupivacaine	3 (0.7%)
Fentanyl and bupivacaine	2 (0.5%)
Morphine and fentanyl	1 (0.2%)
Lidocaine	1 (0.2%)
Meperidine	1 (0.2%)
D-ala-D-leu-enkephalin	1 (0.2%)

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A variety of drugs were used (Table 3). While morphine was the most commonly used drug (69.9%), other drugs used in the pump included hydromorphone (11.2%), sufentanil (2.8%), fentanyl (1.9%), bupivacaine (2.1%), meperidine (0.2%), D-ala-D-leu-enkephalin (0.2%), and lidocaine (0.2%). The most frequently used combination was morphine and bupivacaine (8.4%), followed by morphine and tetracaine (4.0%), hydromorphone and

bupivacaine (2.3%), sufentanil and bupivacaine (1.1%), meperidine and bupivacaine (0.7%), fentanyl and bupivacaine (0.5%), and morphine and fentanyl (0.2%). In their discussion, Paice et al.[7] warn of the paucity of data relating to the toxicity of these drugs when delivered intrathecally and their stability alone or in admixtures in the pump.

Physician reports of global pain relief scores were excellent in 52.4% of patients, good in 42.9%, and poor in 4.8%, suggesting significant efficacy of intrathecal pain therapy in terms of pain relief. However, the authors noted that, in this study, physicians tended to overestimate the patients' degree of global pain relief relative to the patients' actual responses. There were no statistically significant differences in pain relief between patients with pain due to malignancy and those with pain of other etiologies. Among patients with pain of nonmalignant etiology, those with somatic pain tended to experience the best pain relief; however, among those with cancer-related pain, overall pain relief was not statistically different among the pain-type groups. The mean percent pain relief for all patients was 61%.

In the survey by Paice et al.[7] the following outcomes were measured: activities of daily living (ADL), employment, percent pain relief and a global measurement of pain relief based on changes in supplemental pain medications, pain intensity score, and activity level. Based on physician reports, approximately 82% of patients showed a slight (24.6%), moderate (34.3%), or great (22.8%) improvement in ADLs, whereas 3.8% and 14.5% experienced a decrease or no change, respectively. Patients with visceral pain were found to show greater improvements in their ADL score than others in both cancer and noncancer groups. Failed back surgery syndrome was the only positive predictor of improvement in ADL.

Of 28 patients who returned to work after the initiation of therapy, 24 had pain of nonmalignant etiology. Those who were able to return to work had a mean pain relief score of 75.6% ± 2.87%, and all who returned to work experienced at least 50% pain relief.

Delivery system complications occurred in 21.6% of 380 patients, and the most common were catheter-related problems. Catheter kinking, cracking, tearing, and withdrawal were significant problems. It should be noted, however, that many of the problems encountered in this survey have decreased with the development of new catheter technologies.[9] The most common drug side effects were nausea and vomiting (25.2%) and pruritus, which was an early side effect in 13.3% of patients. Diminished libido was reported for 4.9% of the patients. Several of the physicians surveyed, however, later contacted the authors to state that they were unaware that this was a common problem and, after more closely questioning their patients, realized its incidence was higher than they had thought.

Table 4
Characteristics of 120 Patients Receiving Continuous Intrathecal Opioid Therapy via Implanted Infusion Pumps

Characteristic	Value
Gender (number of patients)	
Women	60 (50%)
Men	60 (50%)
Age (years)	
Mean ± SEM	54.0 ± 11.2
Minimum	28.0
Maximum	79.0
Follow-up period (years)	
Mean ± SEM	3.4 ± 1.3
Minimum	0.5
Maximum	5.7
Cumulative sum	404

SEM, standard error of the mean.
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The results of this survey must be interpreted cautiously given the likelihood of observer bias, reporting bias, and unknown generalization of the sample. Paice et al.[7] suggest that intrathecal morphine can be efficacious in controlling pain of malignant and nonmalignant etiology. Complications and side effects occur and must be recognized and managed. Based on the results, the authors advocate increased standardization of screening, focusing on the psychological evaluation as well as the history and physical examination. They also note the importance of patient education regarding not only side effects but also the level of pain relief patients can expect.

The European Experience

A study of continuous intrathecal pain therapy in 120 noncancer patients was conducted by Winkelmüller and Winkelmüller (Table 4).[10] The same authors had previously studied 47 patients with implanted intrathecal

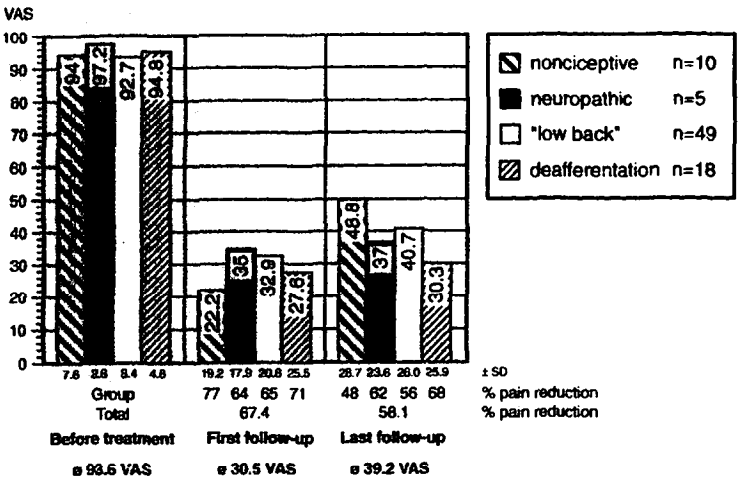

Fig. 1. Figure shows mean pain scores according to visual analogue scale (VAS) before and during treatment. The best long-term relief was experienced by patients suffering from deafferentation pain (68% pain reduction at last follow-up examination). The initial best pain reduction with 77% in the "nociceptive group" diminished to 48% at the last follow-up examination (0 = mean). Reprinted with permission from reference 10.

pumps who were receiving continuous opioids for treatment of nonmalignant pain.[11] Independent of underlying pathology (low back pain, phantom limb pain, neuropathic pain related to spinal cord or nerve lesions, or post-surgical pain), pain was reduced by an average of 79% after a mean follow-up period of 12 months.[11] In addition, other pain-related parameters such as level of activity, mood, and quality and quantity of sleep were significantly improved.

In the more recent study,[10] most of the 120 patients had mixed nociceptive/neuropathic pain following multiple back surgeries (n = 73). Twenty-seven patients had mixed pain: stump and phantom limb pain, postherpetic neuralgia, peripheral nerve injury, brachial and lumbar root avulsions, and pain due to paraplegia. Thirteen patients had nociceptive pain arising from multiple bone or soft tissue surgeries or from meningeal headache, while the remaining 7 patients suffered from neuropathic pain related to chronic peripheral nerve irritation. The mean pain intensity score on a 100-mm visual analogue scale was 93.6 prior to implantation.

According to the selection criteria used by the authors, the patients who received implants were those who had already failed conservative pharmacologic treatments, had experienced an unacceptable level of side effects, or had failed modalities such as spinal cord stimulation. All demonstrated reproducible analgesia following a continuous intrathecal test application of opioids delivered via external pump. Other indications considered in the selection process were psychological influences on pain, pension applications, or ongoing litigation.

Six months after the start of therapy, the average pain intensity score had fallen from 93.6 to 30.5; at the end of the last follow-up period (6 months–5.7 years, mean 3.4 ± 1.3 years), the score was 39.2 (Figure 1). The group of patients with nociceptive pain had the best initial reduction in pain intensity (77%), but this decreased to 48% at the time of the last follow-up. The groups with mixed pain and neuropathic pain showed a therapeutic benefit throughout treatment, again contradicting the view that opioids are not effective for neuropathic pain.

Prior to implantation, 94% of the patients had withdrawn socially and become less active as a result of their pain. At the end of the follow-up period, only 43% still described

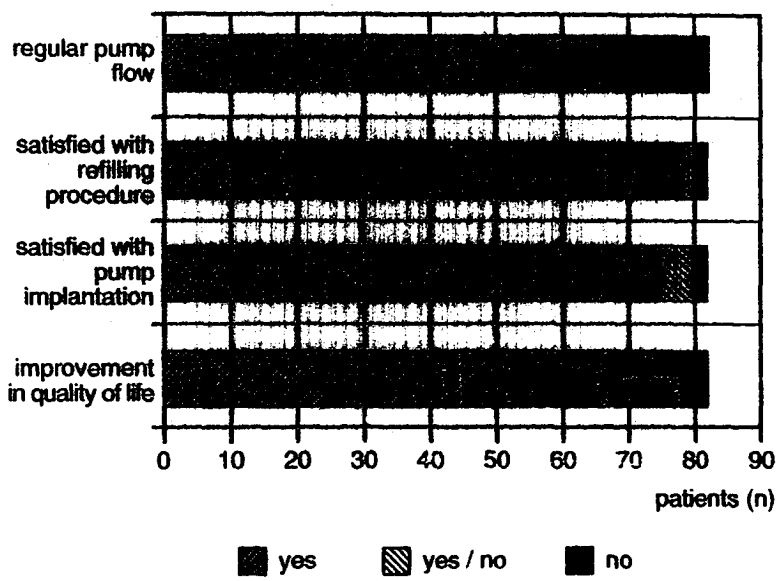

Fig. 2. Figure depicts the acceptance of drug delivery systems in 82 patients with chronic pain of nonmalignant origin. Seventy-five patients (92%) were satisfied with the therapy and 66 patients (80%) reported an improvement in quality of life. The technical refilling procedure was satisfactory in 79 patients (96%); 14 patients (17%) complained of an irregular pump flow. Reprinted with permission from reference 10.

themselves as "passive and withdrawn." Before the initiation of intrathecal opioid therapy, 88% described themselves as depressed and despairing. At the last follow-up, 67% of the patients were either satisfied with their condition or only slightly bothered by pain. Likewise, 81% of patients reported an improvement in their quality of life, 92% were satisfied with their pain therapy, and 96% also were satisfied with their follow-up (Figure 2). Therefore, patients showed significant improvements in social interactions and attitude, and demonstrated a high level of satisfaction with their treatment.

Morphine was the most efficacious and well-tolerated medication in 88 of 120 patients. In some cases, clonidine or bupivacaine was added to the morphine or fentanyl was substituted for morphine. The average starting dosage of intrathecal morphine was 2.7 mg/24 h

Table 2

Mean Morphine Dosages During Intrathecal Treatment in 82 Nonmalignant Pain Patients

	Morphine dosage (mg/d)		
Type of pain	Initial examination mean ± SD (no. of patients)	First follow-up mean ± SD (no. of patients)	Last follow-up mean ± SD (no. of patients)
Nociceptive	2.97±1.45(9)	5.22±2.22(6)	5.47±2.45(7)
Neuropathic	2.30±0.45(5)	3.74±2.30(5)	3.48±2.35(4)
Low back	2.74±1.32(43)	2.93±1.30(22)	4.48±2.41(39)
Deafferentation	2.57±1.92(17)	3.56±2.89(8)	5.18±3.41(16)
Totals	2.70±1.44(74)	3.49±2.03(41)	4.69±2.67(66)

There is no significant difference between the pain groups as far as the infusion dose during treatment is concerned ($P > 0.05$).
Some patients have not been included due to a change in the drug.
SD, standard deviation.
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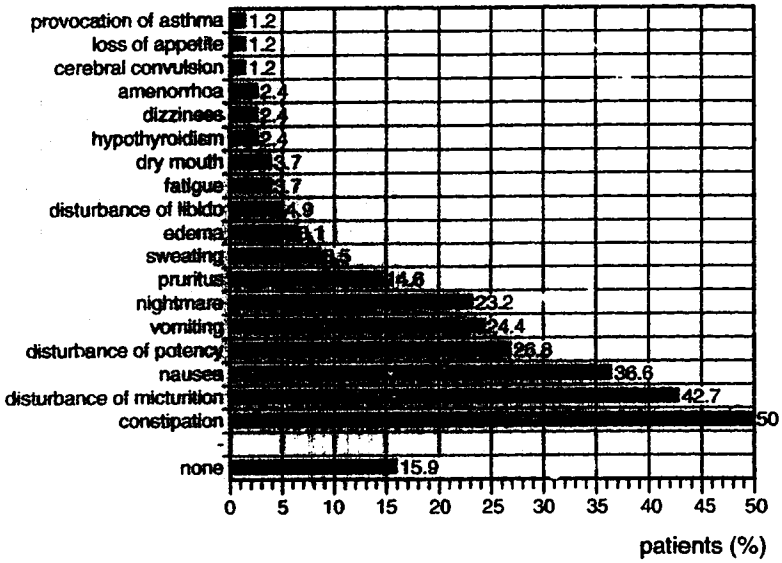

Fig. 3. Figure displays side effects occurring at any time during intrathecal opioid treatment in 82 patients. The most frequent side effects are constipation (50%), disturbance of micturition (42.7%), and nausea (36.6%). No side effects were reported in 15.9% of patients. Reprinted with permission from reference 10.

(Table 5). In the course of treatment, opioid levels were increased in small increments. The largest group of patients had only a 1.6- to 2-fold increase in the infusion dose. Twelve patients required no further increase in medication, and the group with neuropathic pain actually had a slight dosage reduction. Thirty patients did not require any additional systemic medication during intrathecal therapy.

Psychological dependency or behaviors consistent with addiction were not noted to be a problem in any patient, although withdrawal symptoms were observed in situations in which opioid treatment was discontinued or when the pump was prematurely emptied. Three patients developed the need for rapid dose escalation within 4 months and responded to neither drug substitution nor the addition of other drugs. It is noteworthy that, in 4 cases, patients requested pump removal because their primary care physicians refused to continue treatment with what they deemed to be addictive drugs.

Constipation, urinary retention, nausea and vomiting, and pruritus, which are well-known side effects of intrathecal morphine, were common early in the course of therapy. They were successfully managed with appropriate drugs and typically ceased within a few days. Some patients experienced a loss of libido or amenorrhea for the first 6–8 months of therapy but these side effects were self-limited in most patients and disappeared by 12–14 months of therapy. Sweating and edema were lasting side effects in 8.5% and 6.1% of the patients, respectively (Figure 3).

Technical problems, such as skin perforations, irregular flow rates, and refilling problems necessitated the replacement of 14 pumps (16.8%). Infection near the pump pocket necessitated pump replacement in two cases. Six patients requested that their pumps be removed due to increasingly severe side effects despite symptomatic treatment. In 5 patients with extensive scarring of the back musculature due to repeated operations, a therapy-resistant cerebrospinal fluid (CSF) cushion developed in the area of the pump pocket due to a dural leak. Despite sealing

with fibrin glue and muscle patch, the CSF leak could not be stopped in these 5 patients.

Of the 120 patients, 31 were considered treatment failures. Of these 31 patients, 11 did not obtain sufficient pain relief. The remainder had no improvement because of side effects, tolerance, lack of compliance, concomitant illnesses, and surgical and technical reasons.

In their discussion of these results, Winkelmüller and Winkelmüller[10] noted that the overall good results of intrathecal pain therapy could be further improved by (a) better education of both primary care physicians and the public; (b) the addition of other drugs such as clonidine and bupivacaine to augment analgesia when side effects limit morphine dosage escalation to therapeutic levels; (c) further research into the metabolism, pharmacodynamics, and CSF fluid dynamics of medications administered by the intrathecal route; and (d) prospective studies.

A Prospective Study

In an as yet unpublished prospective study, Burchiel and Anderson (unpublished data, 1996) screened 40 patients who had previously failed systemic morphine therapy. Screening was carried out by means of a thorough psychologic examination and either a trial of epidural or intrathecal morphine administration via temporary catheter performed over the course of several days to a week or via lumbar puncture. The 30 patients who reported greater than 50% pain relief during the screening went on to have pumps implanted for intrathecal therapy. The average pain duration for the group prior to implantation was 98 ± 60 months. The most common diagnosis was failed back surgery, and patients had undergone an average of three or more operations. The next most common diagnosis was painful peripheral mononeuropathy, typically due to trauma. Patients were assessed at 6, 12, 18, and 24 months for pain and function. Twenty-four month follow-up is currently available for 20 patients and demonstrated that visual analogue scores for pain and pain coping remain improved. The McGill Pain Questionnaire and the Chronic Illness Problem Inventory (CIPI) scales for sleep, activity, and medication intake either improved or demonstrated a trend toward improvement that persisted through the 24-month follow-up.

The mean equianalgesic dose of morphine increased from 1.96 ± 1.8 mg/d to 6.0 ± 7.0 mg/d during the first 3 months of treatment. However, it remained relatively constant throughout the next 15 months for a mean dose of 9.43 ± 8.8 mg/d at 18 months.

Although most patients experienced some drug-related complications during the first 3 months of therapy, these resolved with standard medical management. Device-related complications occurred at a rate of approximately 20% and included catheter migration from the intrathecal space ($n = 2$), abdominal or subdural catheter obstructions ($n = 2$), pump rotation with catheter coiling ($n = 1$), and subcutaneous seroma ($n = 1$).

Complications of Intrathecal Pain Therapy

In the case of intrathecal pain therapy, adverse events may consist of pharmacologic side effects, complications of surgery, and device-related complications.[12-17]

Pharmacologic Side Effects of Morphine

The side effects of systemic morphine have been well described in the medical literature. The intraspinal administration of this drug also may result in a similar range of side effects, despite the more limited distribution of the drug in the body. Some of these opioid side effects are temporary, normally lasting for the first several days after initiation of therapy and then resolving; other side effects are more enduring.[12]

The cluster of short-term side effects most typically related to opioid administration include pruritus, nausea and vomiting, urinary retention, and constipation.[12,17] In general, all are amenable to symptomatic treatment. All except constipation typically disappear within a few days. In more refractory cases, naloxone HCL or naltrexone HCL may be administered to reduce side effects,[18] but, such treatment usually results in a loss of analgesia. Moreover, naloxone is not a viable long-term option for side-effect management even in those who begin therapy opioid naive.[18] Slow titration of intrathecal morphine may reduce the occur-

rence of nausea, vomiting, and respiratory depression in some cases.

Pruritus. Pruritus is the most common side effect associated with intrathecal opioid administration. In the survey conducted by Paice et al.,[7] the incidence of pruritus was 13.3%. It may occur body wide or be limited to the face, neck, and upper thorax. Pruritus may appear within a few hours of opioid injection, even prior to the onset of analgesia.[13] It is generally not severe. There is some controversy as to whether it is dose related[19] and whether its incidence is higher during intrathecal administration[20] compared with epidural or systemic delivery. If treatment is necessary,the pruritus will often respond to an antihistamine.[12]

Nausea and vomiting. In his review of the side effects of spinal opioids, Chaney[12] notes the incidence of nausea and vomiting following the acute intraspinal delivery of opioids in opioid-naive patients to be approximately 30%. In their survey, Paice et al.[7] found the reported incidence to be 25.2%. Nausea typically occurs within 4 hours of injection and is soon followed by vomiting.[13] These symptoms are usually relieved with antiemetics.

Urinary retention. The incidence of urinary retention varies between 42% and 80% and is more common in elderly men with enlarged prostates.[10,13,21] It is not believed to be dose related.[19,22,23] It is believed to be related to drug interaction with opioid receptors located in the sacral spinal cord,[23] which causes detrusor muscle relaxation and an increase in bladder capacity. Terazosin HCL may be used to treat urinary retention.

Respiratory depression. The most feared effect of spinal opioid administration is respiratory depression. Although the incidence of respiratory depression serious enough to require intervention may be as high as 1% following intraspinal opioid administration to opioid-naive patients, it is likely to be much lower among those who have had exposure to systemic opioids prior to intrathecal trial.[20] In the acute treatment setting (opioid-naive patient), the risk of respiratory depression is bimodal. Early depression (within 2 hours) is presumably due to drug absorption by the systemic vasculature. Delayed depression (which occurs more than 2 hours following opioid administration)[7,22] is the result of cephalad migration of opioid within the CSF and its interaction with opioid receptors in the medullary respiratory center of the brain.[24] Delayed respiratory depression develops slowly and progressively,[22] whereas early respiratory depression usually has a rapid onset. These events are possible in chronic pain patients who have had exposure to systemic opioids, but the risk is attenuated by the tolerance to respiratory depressant effects that develops rapidly during systemic treatment.

Constipation. Because opioids decrease gastrointestinal motility, intraspinal opioids may prolong intestinal transit time.[15] The continuous use of laxatives and stool softeners during opioid therapy is often needed to prevent or decrease constipation.

Decreased libido. According to the previously cited survey by Paice et al.,[7] decreased libido in males may occur more frequently than is generally appreciated by clinicians. Results of animal studies suggest that opioids lower testosterone levels and suppress penile erectile reflexes.[16] These findings also have been confirmed in heroin addicts, along with the finding that testosterone levels return to normal following drug withdrawal.[25] However, there are no prospective data confirming these findings in patients receiving opioids for the management of pain. In an evaluation of six men receiving chronic intraspinal opioids,[26] all reported a reduction in libido, and four had difficulty achieving or maintaining an erection within 1 month of the initiation of therapy. These subjects were found to have serum testosterone levels ranging from 26 to 367 ng/dL, with a mean of 197.7 ng/dL (normal, 350–1500 ng/dL). One patient reported an improvement in libido following morphine dose reduction, while three others were effectively treated with intramuscular testosterone cypionate.

While this report includes a very limited number of patients, it supports anecdotal evidence from patients and physicians suggesting that sexual dysfunction is a frequent side effect of intrathecal opioid therapy. Assessment and management of sexual dysfunction is necessary to increase patient satisfaction with treatment.[26] The same authors recently reported on one case of amenorrhea associ-

ated with the intrathecal administration of morphine.[27] Both male and female candidates for intraspinal analgesia should be alerted to the therapy's potential effects on sexual function and fertility.

Miscellaneous side effects. Other side effects of morphine administration include sweating and peripheral edema. The latter side effect is believed to result from the vasopressin release arising from cephalad migration of opioid in the CSF and interaction with receptors in the posterior pituitary.[28] Persistent sweating may be due to cephalad migration of drug and interaction with opioid receptors in the hypothalamus.

Finally, several side effects of intrathecal opioids have been reported anecdotally, or should be considered based on animal studies. These include central nervous system excitation,[29] and spinal cord damage.[20] Inadvertent use of intrathecal chemotherapy has also caused paralysis in humans.[30] Evidence exists also for the development of transient neurotoxicity following the intrathecal administration of tetracaine.[31]

Surgical Complications

Care must be taken during the implantation of a pump for intraspinal opioid therapy so as to minimize bleeding, the possibility of infection, tissue damage, and CSF leaks which can lead to postspinal headaches.

Bleeding. While some perioperative bleeding is unavoidable, patients with coagulopathies are not candidates for intraspinal opioid therapy until the resolution of the coagulopathy. In his review, Krames[32] warns against closing the surgical wound in the presence of active, uncontrolled bleeding. A hematoma can foster the growth of bacteria and result in postoperative infection.

Bleeding can occur within the epidural space or into the intrathecal sac during placement of an intrathecal catheter.[17] Epidural bleeding, if severe, can lead to symptomatic epidural hematoma, with either spinal cord compression or cauda equina syndrome. If, following surgery, the patient complains of severe back pain or develops paresis of the extremities, urinary retention, perineal sensory loss, or fecal incontinence, immediate assessment using magnetic resonance imaging (MRI) or computerized tomography (CT) of the spine is needed to confirm the diagnosis. In a review of current problems and debates in continuous spinal anesthesia, it is noted that despite the large numbers of patients receiving intraspinal pain therapy, cauda equina syndrome, while feared, is very rare. Over a 50-year period, there have been only 22 reports in the literature.[33]

Infections. Good sterile technique is of paramount importance when implanting foreign bodies. Most surgeons employ preoperative antibiotics and intraoperative antibiotic irrigation. Infections, when they do arise, may be superficial infections of the surgical wound or involve the implanted catheter or the pocket. In the latter instances, removal of the implanted material is imperative. Failure to explant may lead to persistent or generalized infection. More serious infections include epidural and intrathecal infections, which again require immediate explantation of all foreign body materials and the initiation of intravenous antibiotic therapy. A consultation with an infectious disease expert is recommended in all infections serious enough to require explantation.[32]

Intrathecal infections, while rare, may be evidenced by fever, stiff neck, and positive meningeal stretch signs. Diagnosis of infectious meningitis is complicated by the common occurrence of fever and mild meningeal signs as a normal phenomenon after implantation. If the patient does not appear toxic, the complete blood cell count is normal, and the CSF drawn from the pump's side port reveals leukocytosis and elevated protein with negative gram stains, then the patient can be watched carefully until CSF cultures are returned. This situation typically resolves within 48–72 hours.

Untreated epidural infections also can lead to spinal cord or cauda equina compression. Diagnosis should be based on MRI or CT findings. Explantation of all foreign materials is required for treatment.

Tissue damage. Nonspecific tissue reaction around the catheter tip can occur and could potentially lead to cord compression. The development of new pain or neurologic impairments over time could suggest such an occurrence, and diagnosis should be confirmed via MRI.[17]

Incorrect catheter tunneling could lead to perforation of the small or large bowel, the kidney, or even the lung. Such occurrences will be heralded by organ-specific signs and symptoms such as those typical of peritonitis or, in the case of pulmonary perforation, hemoptysis or pneumothorax.[17] Such perforations, although rare, may be surgical emergencies.

Cerebrospinal fluid leaks. CSF leaks into the epidural space are an inevitable result of placement of a catheter smaller than the needle that has been used to puncture the dural sac. CSF leaks may also follow from incomplete sealing of tissue around the catheter at the insertion site, multiple subarachnoid punctures during catheter placement, dislodgment, disconnection, break, puncture, or migration of the catheter. If a CSF leak persists, it can lead to postspinal headache. Krames[32] estimates the rate of such headaches in his group's experience to be approximately 20%. In Nitescu et al.'s study of complications of intrathecal opioids and bupivacaine in a population of 200 cancer patients,[34] the incidence of postdural puncture headache was 15.5%. CSF leaks can be treated by fluoroscope-guided autologous epidural blood patching, in which the patient's venous blood is injected into the epidural space to seal the epidural puncture.[35,36] Recent reports in the literature describe the successful use of subdural blood patches in treating CSF leaks resistant to epidural blood patching.[35,36]

A subcutaneous collection of CSF results in the development of a CSF hygroma, which is typically self-limited and clinically inconsequential. It is important to avoid contaminating these fluid collections, however, because they communicate directly with the CSF within the thecal sac. Such hygromas generally resolve within 1–2 weeks.[17] Their size is limited by the size of the pocket, the expandability of the adjacent tissue, and the duration of healing around the catheter puncture in the dura. Occasionally, hygromas will persist for months. Even in these cases, however, they usually have no clinical significance.

Fluid collections arising in the pump pocket constitute the body's response to a surgically created vacuum.[17,32] These seromas may last for several months and are again of limited clinical significance. If the seroma is bothersome to the patient, abdominal binders can be worn for 6–8 weeks to decrease its size. These seromas normally contain numerous white blood cells, and a positive gram stain or culture is required to demonstrate the presence of infection. In this case, the patient should receive intravenous antibiotics, and the pump pocket should be irrigated with antibiotics. Explantation of the pump and catheter may be required.

Drug Delivery System Complications

In the series by Nitescu et al.,[34] intrathecal catheters functioned well in 93% of 200 patients. The rate of all mechanical complications was 8.5%. Mechanical catheter complications can include breaking, kinking, disconnections, catheter tip obstruction and dislodgment, and accidental withdrawal. Such complications may lead to loss of analgesia. If such loss of analgesia occurs, a mechanical complication should be sought before dosage escalation or workup for disease progression.

Assessment of these problems is performed in several ways. The catheter may be radiographically assessed for signs of kinking, breaking, disconnection, or dislodgment.[17] A CT scan may be performed to confirm the catheter's intrathecal placement. Catheter patency may be assessed by injection of contrast medium or radiolabeled indium. Only a contrast medium indicated for intrathecal use should be used when injecting such an agent into the subarachnoid space. Failure to obey this principle can result in serious adverse events, including severe pain, seizures, or death.[17]

Programmable pump delivery complications may include overfilling, battery failure, pump failure, and pump torsion.[17,32] Again, such system problems are likely to be heralded by loss of analgesia. Confirmation of these complications is made radiographically or by means of fluoroscopy. Programming errors and complications such as inappropriate injection of drug into the side port rather than the reservoir can result in oversedation, respiratory depression, and death. Newer models of programmable pumps have been designed to prevent the possibility of overfilling or inadvertent bolus through a side port.

Conclusion

Intrathecal opioid therapy is a useful approach to patients who have chronic non-

malignant pain that has not responded to more traditional therapies, including failed back surgery and systemic opioid therapy. A growing clinical experience has begun to clarify the short-term and long-term risks. Although current data suggest that intrathecal therapy is effective in improving pain relief and function, additional studies are needed to refine selection criteria and reinforce outcome data. At the present time, careful patient selection based on best clinical judgment, patient education, a high level of vigilance for the development of adverse effects, and attention to surgical technique are all imperative for the success of this therapy.

Moderator Comments

There is agreement in the pain community that intrathecal opioids can offer good pain control to appropriately selected patients. However, the variables that are used to select patients and evaluate efficacy still need further development.

The results of the two retrospective studies[7,10] cited in this paper are encouraging and suggest that some patients can greatly benefit from intraspinal opioid therapy. The assessment of functional improvements appropriate to the patient is essential to judge this therapy. While the results cited in the studies by Paice et al.[7] and Winkelmüller and Winkelmüller[10,11] appear good, future studies are needed to address these issues in more detail. Their ultimate resolution will require additional well-designed, prospective controlled trials that compare this therapy with optimal levels of systemic analgesic therapy and other approaches. Such studies also will need to address patient selection issues, for example, which patient characteristics are most likely to predict a good response to this type of therapy.

These results underscore the need for patient education and increased preimplant interaction with patients. Giving patients realistic expectations for pain relief and functional improvement can only increase their satisfaction with treatment. Patient involvement with treatment also may improve efficacy. Once again, however, prospective studies and greater clinical experience in treating patients with chronic nonmalignant pain are needed to better define outcomes so that expectations can be realistically portrayed to patients. Accumulating experience will add to understanding of the management of drug and surgical complications.

References

1. Coombs DW, Saunders RL, Gaylor M, et al. Epidural narcotic infusion reservoir implantation technique and efficacy. Anesthesiology 1982;56:469–473.

2. Onofrio BM, Yaksh TL. Long-term pain relief produced by intrathecal morphine infusion in 53 patients. J Neurosurg 1990;72:200–209.

3. Yaksh TL. Spinal opiate analgesia characteristics and principles of action. Pain 1981;11:293–346.

4. Yaksh TL, Rudy TA. Narcotic analgesics: CNS sites and mechanisms of action as revealed by intracerebral injection techniques. Pain 1978;4: 299–359.

5. Portenoy RK. Opioid tolerance and responsiveness: research findings and clinical observations. Proceedings of the 7th World Congress on Pain: Progress in pain management, vol. 2. In: Gebhart GF, Hammond DL, Jensen TS, eds. Seattle, WA: IASP Press 1994:595–619.

6. Jamison RN. Comprehensive pretreatment and outcome assessment for chronic opioid therapy in nonmalignant pain. J Pain Symptom Manage 1996; 11:231–241.

7. Paice JA, Penn RD, Shott S. Intraspinal morphine for chronic pain: a retrospective, multicenter study. J Pain Symptom Manage 1996;11:71–80.

8. Yaksh TL, Onofrio BM. Retrospective consideration of the doses of morphine given intrathecally by chronic infusion in 163 patients by 19 physicians. Pain 1987;31:211–223.

9. Penn RD. Catheter implant system for intrathecal drug delivery. [Letter]. J Neurosurg 1996;84:713.

10. Winkelmüller M, Winkelmüller W. Long-term effects of continuous intrathecal opioid treatment in chronic pain of nonmalignant etiology. J Neurosurg 1996;85:458–467.

11. Winkelmüller M, Winkelmüller W. Intrathekale Opiattherapie bei chronischen Schmerzsyndromen benigner Ätiologie Über implantierbare Medikamentenpumpen. Der Schmerz 1991;5:28–36.

12. Chaney MA. Side effects of intrathecal and epidural opioids. Can J Anaesth 1995;42:891–903.

13. Bromage PR, Camporesi EM, Durant PAC, Nielsen CH. Respiratory side effects of epidural morphine. Anesth Analg 1982;61:490–495.

14. Palmer CM. Early respiratory depression following intrathecal fentanyl-morphine combination. Anesthesiology 1991;74:1153–1155.

15. Wattwil M. Postoperative pain relief and gastrointestinal motility. Acta Chir Scand 1988;550: 140–145.

16. Gomez-Marrero J, Feria M, Mas M. Stimulation of opioid receptors suppresses penile erectile reflexes and seminal emission in rats. Pharmacol Biochem Behav 1988;31:393–396.

17. Prager JP. Complications of implantation: diagnosis and management. Presented at Interventional Therapies Workshop, Dannemiller Memorial Educational Foundation in Memphis, TN; September 22, 1996.

18. Cohen SE, Ratner EF, Kreitzman TR, Archer JH, Mignano LR. Nalbuphine is better than naloxone for treatment of side effects after epidural morphine. Anesth Analg 1988;75:747–752.

19. Morgan M. The rational use of intrathecal and extradural opioids. Br J Anaesth 1989;63:165–188.

20. Rawal N, Arner S, Gustafsson LL, Allvin R. Present state of extradural and intrathecal opioid analgesia in Sweden. Br J Anaesth 1987;59:791–799.

21. Bailey PL, Rhondeau S, Schaefer PG, et al. Dose-response pharmacology of intrathecal morphine in human volunteers. Anesthesiology 1993; 79:49–59.

22. Stenseth R, Sellevold O, Breivik H. Epidural morphine for postoperative pain: experience with 1085 patients. Acta Anaesthesiol Scand 1985;29: 148–156.

23. Rawal N, Mollefors K, Axelsson K, Lindgardh G, Widman B. An experimental study of urodynamic effects of epidural morphine and of naloxone reversal. Anesth Analg 1982;62:641–647.

24. Shook JE, Watkins WD, Camporesi EM. Differential roles of opioid receptors in respiration, respiratory disease, and opiate-induced respiratory depression. Am Rev Respir Dis 1990;142:895–909.

25. Wang C, Chan V, Yeung RTT. The effect of heroin addiction on pituitary-testicular function. Clin Endocrinol 1978;9:455–461.

26. Paice JA, Penn RD, Ryan WG. Altered sexual function and decreased testosterone in patients receiving intraspinal opioids. J Pain Symptom Manage 1994;9:126–131.

27. Paice JA, Penn RD. Amenorrhea associated with intraspinal morphine [Letter]. J Pain Symptom Manage 1995;10:582–583.

28. Simantov R, Snyder SH. Opiate receptor binding in the pituitary gland. Brain Res 1977;124:178–184.

29. Krames ES, Gershow J, Glassberg A, et al. Continuous infusion of spinally administered narcotics for the relief of pain due to malignant disorders. Cancer 1985;56:696–702.

30. Saiki JH, Thompson S, Smith F, Atkinson R. Paraplegia following intrathecal chemotherapy. Cancer 1972;29:370–374.

31. Sumi M, Sakura S, Kosaka Y. Intrathecal hyperbaric 0.5% tetracaine as a possible cause of transient neurologic toxicity. Anesth Analg 1996;82: 1076–1077.

32. Krames ES. Intraspinal opioid therapy for chronic malignant pain: current practice and clinical guidelines. J Pain Symptom Manage 1996;11:333–352.

33. Morton CPJ, McCrae AF, Wildsmith JAW. Continuous spinal anesthesia; evolution of a technique. Ann Acad Med Singapore 1994;23(suppl):98S–103S.

34. Niscola P, Sjoberg M, Appelgren L, Curelaru I. Complications of intrathecal opioids and bupivacaine in the treatment of refractory cancer pain. Clin J Pain 1995;11:45–62.

35. Racz G. Subdural blood patch for treatment of spinal headache. Pain Digest 1997 (in press).

36. Shantha TR, Biese J. Subdural blood patch for spinal headache [Letter]. N Engl J Med 1991;325: 1252–1254.