

Special Article

Polyanalgesic Consensus Conference 2003: An Update on the Management of Pain by Intraspinal Drug Delivery—Report of an Expert Panel

Samuel J. Hassenbusch, MD, PhD, Russell K. Portenoy, MD, Michael Cousins, MD, Eric Buchser, MD, Timothy R. Deer, MD, Stuart L. Du Pen, MD, James Eisenach, MD, Kenneth A. Follett, MD, PhD, Keith R. Hildebrand, DVM, PhD, Elliot S. Krames, MD, Robert M. Levy, MD, PhD, Pamela P. Palmer, MD, PhD, James P. Rathmell, MD, Richard L. Rauck, MD, Peter S. Staats, MD, Lisa Stearns, MD, and K. Dean Willis, MD

Department of Neurosurgery (S.J.H.), The University of Texas M. D. Anderson Cancer Center, Houston, Texas, USA; Department of Pain Medicine and Palliative Care (R.K.P.), Beth Israel Medical Center, New York, New York, USA; Pain Management Research Institute (M.C.), University of Sydney & Royal North Shore Hospital, Sydney, Australia; Anesthesia and Pain Management Services (E.B.), Hôpital de zone de Morges, Morges, Switzerland; The Center for Pain Relief (T.R.D.), West Virginia University School of Medicine, Charleston, West Virginia, USA; Swedish Pain Consultation Service (S.L.D.P.), Swedish Medical Center, Seattle, Washington, USA; Department of Anesthesiology (J.E.), Wake Forest University, Winston-Salem, North Carolina, USA; Department of Neurosurgery (K.A.F.), University of Iowa Hospital and Clinics, Iowa City, Iowa, USA; Medtronic, Inc. (K.R.H.), Minneapolis, Minnesota, USA; Pacific Pain Treatment Centers (E.S.K.), San Francisco, California, USA; Northwestern University (R.M.L.), Chicago, Illinois, USA; Pain Management Center (P.P.P.), University of California at San Francisco, San Francisco, California, USA; University of Vermont College of Medicine (J.P.R.), Burlington, Vermont, USA; Piedmont Anesthesia & Pain Consultants, PA (R.L.R.), Winston-Salem, North Carolina, USA; Johns Hopkins University School of Medicine (P.S.S.), Baltimore, Maryland, USA; Valley Pain Treatment Center (L.S.), Scottsdale, Arizona, USA; and Alabama Pain Center (K.D.W.), Huntsville, Alabama, USA

Abstract

Intraspinal drug infusion using fully implantable pump and catheter systems is a safe and effective therapy for selected patients with chronic pain. The options for this approach are increasing, as drugs that are commercially available for systemic administration are adapted to this use and other drugs that are in development specifically for intraspinal administration become available. In 2000 a Polyanalgesic Consensus Conference was

Address reprint requests to: Samuel J. Hassenbusch, MD, PhD, Department of Neurosurgery, C-9.075, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, USA.
Accepted for publication: March 3, 2004.

University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, USA.

organized to evaluate the existing literature and develop guidelines for drug selection. The major outcome of this effort, an algorithm for drug selection, was based on the best available evidence at the time. Rapid changes have occurred in the science and practice of intraspinal infusion and a Polyanalgesic Consensus Conference 2003 was organized to pursue the following goals: 1) to review the literature on intraspinal drug infusion since 1999, 2) to revise the 2000 drug-selection algorithm, 3) to develop guidelines for optimizing drug dosage and concentration, 4) to create a process for documenting minimum evidence supporting the use of a drug for intraspinal infusion, and 5) to clarify issues pertaining to compounding of drugs. Based on the best available evidence and expert opinion, consensus recommendations were developed in all these areas. The panel's conclusions may provide a foundation for clinical practice and a rational basis for new research. *J Pain Symptom Manage* 2004;27:540–563. © 2004 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words

Algorithm, chronic pain, clinical evidence, intraspinal infusion, intrathecal infusion, implantable pump, neuraxial infusion, polyanalgesic drugs, safety and efficacy

Introduction

Intraspinal drug infusion is used for the treatment of chronic pain that is unresponsive to less invasive approaches. The safety and reliability of implantable pumps has facilitated the development of this approach and provided incentives for the development of numerous drugs for neuraxial (i.e., intraspinal – intrathecal or epidural) delivery. Testing is essential, both for drugs currently available for systemic use and for new chemical entities developed specifically for intrathecal administration. The preclinical and clinical trial data should include evidence of safety, efficacy, stability and compatibility with the drug delivery system (pump and catheter), and in the case of drug combinations, drug-drug stability.

Despite numerous studies of existing and novel drugs, only limited data are available to address these issues. In 2000 an expert panel, gathered under the auspices of the Polyanalgesic Consensus Conference 2000, reviewed these data, developed an algorithmic approach to drug selection based on best evidence and expert opinion, and highlighted the need for additional studies.^{1–4} Since 2000, the practice of intraspinal infusion has evolved with the availability of new drugs, new preclinical and clinical data, and advances in medical approaches to chronic pain. To respond to these changes, an expert panel was convened for the Polyanalgesic Consensus Conference 2003. The tasks addressed by the panel included:

1. Review the medical literature since 1999 pertaining to intraspinally-administered drugs;
2. Update the algorithm for intraspinal drug selection;¹
3. Propose guidelines for optimizing drug concentration and dosage during therapy;
4. Develop consensus regarding the evidence required to support use of a drug for long-term intrathecal infusion; and
5. Clarify existing regulations and guidelines pertaining to the use of compounded drugs for intrathecal administration.

Intrathecal Drugs: Literature Update 1999–2003

Articles published between October 1999 (the cut-off date for earlier review^{1–4}) and July 2003 that pertained to the stability, compatibility, toxicity, and analgesic efficacy of drugs in intraspinal infusion, with a focus on intrathecal agents, were identified through a search using PubMed, Biosis, and EMBASE databases. Inpress publications describing recent ziconotide studies were provided by the lead investigators. This search was not intended to be exhaustive and papers were not accepted or rejected on the basis of some a priori minimal level of evidence. The goal was to find all publications that meaningfully updated the literature since the

Polyanalgesic Consensus Conference 2000. This “best evidence” approach, which, in the case of the clinical literature, largely includes the results of surveys and other uncontrolled studies, yielded few definitive findings. Rather, the clinical data provide mostly suggestive results concerning efficacy and a clearer depiction of drug tolerability and dose. The results of this review are described in the following text and summarized in Table 1, which also lists the number of references in the 2000 publication. It should be mentioned that an excellent systematic review on the use of intraspinal drug combinations for the treatment of acute postoperative pain as well as chronic pain was published by Walker and colleagues in 2002.⁵

Opioids

Morphine

Preclinical Data. Perhaps the most significant discovery since the Polyanalgesic Consensus

Conference 2000 is the causal relationship between intrathecal morphine sulfate infusion and the formation of catheter-tip inflammatory masses. Chronic (28-day) intrathecal infusion of morphine sulfate (Infumorph) but not saline in dog and sheep models produced catheter-associated inflammatory masses.^{6–8} In each species, the inflammatory masses became large enough to compress the spinal cord and produce pronounced motor deficits within approximately 1 week after infusion was initiated. The incidence of inflammatory masses increased with increasing dosage/concentration in each species. In beagle dogs and sheep, dosages as low as 1.5 and 12 mg/day, respectively, produced inflammatory masses. Because in both models a constant infusion rate was used with dosage adjusted by adjusting morphine concentration, the effects of these two variables could not be distinguished. Because each animal model used different chronic infusion systems (beagle, ambulatory syringe pump with a polyethylene catheter; sheep, implantable pump

Table 1
Summary of Publications in Literature Update, 1999–2003

Drugs included in literature search	# References 2003 (# References 2000) ^a	Preclinical (Ref #s) ^b	Clinical (Ref #s)
Opioids			
Morphine	14 (61)	6,7,8,18,41,43	9–16
Hydromorphone	6 (1)	19,21,22	23,24
Fentanyl	2 (28)	—	25,26
Sufentanil	2 (10)	—	27,28
Methadone	3 (0)	—	29–31
Meperidine	1 (0)	—	32
Local Anesthetics			
Bupivacaine	7 (36)	33,34	32,33,35–38
Ropivacaine	1 (10)	—	39
Tetracaine	0 (4)	—	—
Adrenergic Agonists			
Clonidine	8 (26)	7,40–42	44–47
Tizanidine	1 (7)	48	—
NMDA Antagonists			
Ketamine	6 (20)	49–51,78	52,53
Other Agents			
Adenosine	1 (0)	—	90
Aspirin	0 (12)	—	—
Baclofen	7 (3)	54	55–60
Droperidol	0 (5)	—	—
Gabapentin	13 (0)	61–73	—
Ketorolac	1 (0)	—	91
Midazolam	9 (5)	74–78	79–82
Neostigmine	2 (8)	—	88,89
Octreotide	0 (2)	—	—
Ziconotide	5 (7)	83	84–87

^aNumber of references (1999–2003) for the specific drug reviewed for the 2003 Polyanalgesic Consensus Conference (number of references for the same drug reviewed for 2000 Polyanalgesic Consensus Conference).

^bIncludes animal studies (neurotoxicity and efficacy/mechanism studies) and stability/compatibility laboratory studies.

with silicone catheter), a contributing role of the delivery system in producing inflammatory masses was unlikely. This possibility is even more remote given that both animal models have been used to screen numerous other intrathecal agents without the occurrence of inflammatory mass.

Clinical Data. Recent studies concluded that intrathecal opioids provided effective analgesia for patients with refractory chronic pain.^{9,10} A prospective, long-term survey (mean follow-up, 29 ± 12 months) of 16 patients found that intraspinal morphine reduced pain scores for all types of pain by an average of 57%. The greatest efficacy was found in patients with neuropathic pain and mixed pain (75% and 61% reductions, respectively).¹¹

The National Outcomes Registry for Low Back Pain collected prospective data on 136 patients with chronic low back pain treated using intraspinal infusion via implanted devices, 81% of whom received morphine.¹² Oswestry Low Back Pain Disability Scale ratings after 12 months improved by 47% in patients with back pain, and by 31% in patients with leg pain.

A retrospective cohort analysis of 23 patients with leg edema during long-term (>24 months) intrathecal morphine administration found a correlation between edema during morphine infusion and pre-existing leg edema and venostasis before morphine infusion began.¹³ The observations also suggested a dose-effect relationship.

Abs et al. retrospectively examined hypothalamic-pituitary function in 93 patients with non-cancer pain.¹⁴ Seventy-three patients received intrathecal morphine (mean dosage, 4.8 mg/day; mean duration, 26.6 months); a 20-patient comparison group had comparable pain syndromes but was not treated with opioids. A majority of patients of both genders in the intrathecal morphine group developed hypogonadotropic hypogonadism. Fifteen percent also developed central hypocortisolism and/or growth hormone deficiency, compared to 0% among the control group. Decreased libido occurred in 96% of men and 69% of women who received intrathecal opioids, compared to 10% and 20% of men and women, respectively, in the control group. Hormone replacement therapy ameliorated decreased libido in 10 of 14

males and 7 of 12 premenopausal females. The authors suggested further investigations to determine the need for systematic endocrine evaluations and replacement therapy in patients treated with long-term intrathecal morphine.

The results of a prospective, multicenter, international, open-label study of an investigational, patient-activated, intraspinal morphine delivery system in patients with cancer pain revealed superior analgesia and fewer opioid-related side effects compared to systemic opioid therapy after 1–13 months of follow-up.¹⁵

Cherry and colleagues reported on a seven-patient case series describing a novel use of intraspinal ($n = 2$ epidural, 5 intrathecal) opioid therapy to manage pain associated with intractable angina.¹⁶ Patients who had failed multiple cardiovascular interventional and systemic medical therapies were successfully treated with self-administered bolus delivery of morphine ($n = 5$) or fentanyl ($n = 2$) using an implantable pump for durations of 2 to 7 years. Starting intrathecal morphine doses were 0.5 to 1.0 mg (delivered in a volume of 1 mL), which were administered at a frequency of 2 to 6 times per day. Side effects reported while on intraspinal opioid therapy for angina included nausea, drowsiness, urinary retention, and diaphoresis.

Coffey and Burchiel¹⁷ analyzed reports of catheter-tip inflammatory masses (granulomas) in 39 patients who received intrathecal morphine or hydromorphone, either alone or mixed with other drugs. The authors noted that patients whose mass was diagnosed during the administration of drugs other than intrathecal morphine had probably been exposed to morphine earlier in their clinical course. Based on this and preclinical studies, another consensus panel has recommended positioning of the catheter tip in the lumbar thecal sac, minimizing opioid dosage and concentration to the extent possible, and providing attentive follow-up of patients to encourage early diagnosis and to reduce the risk of neurological injury.¹⁸

Hydromorphone

Preclinical Data. A recent study in sheep revealed that 28-day intrathecal infusion of hydromorphone was not associated with catheter-tip inflammatory masses.¹⁹ This study was designed

specifically to mimic a similar study that had been conducted previously using intrathecal morphine.⁶ Unlike morphine, which produced inflammatory masses and rear leg lameness in two out of three sheep at dosages ≥ 12 mg/day, hydromorphone was not associated with significant gait deficits or histological changes at any dosage tested (1.5 to 12 mg/day). This finding contrasted with the results of a 1994 study that demonstrated that chronic epidural infusion of either morphine or hydromorphone in sheep was associated with the formation of granulomas.²⁰

Hydromorphone was stable when contained in an infusion system (SynchroMed) and held at 37 °C for 4 months, as analyzed by high performance liquid chromatography (HPLC).²¹ The potency of the 10 mg/mL hydromorphone solution was $>95\%$ of initial potency and it was compatible with the materials of the infusion system. Hydromorphone stability indicated 96% recovery of the intact molecule in a study where the drug was contained in plastic syringes at concentrations of 1.5 mg/mL and 80 mg/mL for 60 days at 4°C and 23°C, and for 2 days at -20°C and 37°C.²²

Clinical Data. In a retrospective study of 37 patients, intrathecal hydromorphone was administered after either inadequate analgesia or unmanageable side effects occurred during treatment with intrathecal morphine sulfate.²³ Pain scores improved during the 10-month (mean) follow-up period. Drowsiness and nausea lessened after patients were switched from morphine to hydromorphone, and leg edema subsided temporarily but eventually recurred after extended hydromorphone exposure.

In another retrospective study, 22 of 24 patients who received intrathecal hydromorphone monotherapy for an average of 1.3 years (range, 10 days to 3.1 years) experienced sustained reduction in pain scores.²⁴

As noted previously, the formation of inflammatory masses at the catheter tip was reported in 9 patients who received hydromorphone, either alone or mixed with other drugs.¹⁷ A subsequent review of the same database plus additional case reports identified an additional 6 cases (total = 15), although the intraspinal analgesic history of most of these patients was

not clear (e.g., previous exposure to intrathecal morphine).⁸

Fentanyl

Clinical Data. In a retrospective analysis of 29 patients who received intrathecal drug therapy for pain, 8 patients received fentanyl 10.5–115 µg/day for a mean duration of 31 months.²⁵ These patients experienced an average of 68% reduction in pain and an average overall satisfaction of 3.25 on a scale of 1 (poor) to 4 (excellent). Another retrospective study ($n = 122$) that examined the complications associated with implantable drug delivery systems included two patients with the combination of fentanyl and bupivacaine;²⁶ neither of these patients experienced serious adverse events.

Sufentanil

Clinical Data. The effects of long-term sufentanil exposure in humans are not known. Although the long-term intrathecal use of sufentanil in two patients (one receiving the combination of sufentanil and bupivacaine) was reported in a study of 88 patients with chronic non-cancer pain, no efficacy/safety results were described.²⁷ As a highly lipophilic drug, sufentanil has a relatively fast onset of effect after epidural administration and a relatively limited rostral spread;²⁸ the latter effect might be associated with a lower incidence of side effects, but this has not been established in comparative clinical trials.

Methadone

Clinical Data. Three studies, two prospective ($n = 24$ ²⁹ and $n = 70$,³⁰ respectively) and one retrospective ($n = 47$ ³¹), were performed to evaluate the use of methadone in intrathecal infusion. The studies involved both cancer and non-cancer patients. Methadone was administered at total daily dosages of 5–60 mg and the duration of treatment ranged from 3 days to 37 months. Overall effectiveness, based on greater than 50% reduction in pain only,^{30,31} or pain reduction combined with improved scores on a quality-of-life questionnaire,²⁹ ranged from 37.5–80%.

Meperidine

Clinical Data. The use of meperidine was described in a single case report. The patient had

neuropathic pain, received intrathecal meperidine 30–60 mg/day for 6 months, and experienced pain relief (immediate improvement in pain score, with adequate analgesia once 60 mg/day was reached) and no side effects.³²

Local Anesthetics

Bupivacaine

Preclinical Data. The stability of a commercially available, intrathecal formulation of bupivacaine HCl (7.5 mg/mL), and compatibility with the SynchroMed (Medtronic Inc., Minneapolis, MN) infusion system have been demonstrated.³³ Bupivacaine concentration remained greater than 96% of initial concentration after chronic exposure to the intact pump-catheter systems or device materials maintained at 37°C for 12 weeks. Moreover, the mechanical integrity and functional properties of the device materials in contact with bupivacaine were maintained.

In a stability study, combinations of morphine sulfate 5 mg/mL plus bupivacaine 2.5 mg/mL, or morphine sulfate 50 mg/mL plus bupivacaine 25 mg/mL, were packaged in 20-mL aliquots in plastic syringes.³⁴ These aliquots were maintained at 4°C or 23°C for 60 days or –20°C or 37°C for 2 days. The potency of morphine in all samples was >97% and the potency of bupivacaine in all samples was >95%. Frozen samples exhibited microparticulates upon thawing, suggesting that freezing of morphine/bupivacaine combinations should be avoided. The combination of morphine 50 mg/mL and bupivacaine 25 mg/mL turned slightly yellow after 7 days at 23°C. This was considered a normal, acceptable color change associated with minimal oxidation of morphine in solution.

Clinical Data. In a randomized, double-blind, multiple-phase crossover trial of 24 patients with chronic nonmalignant pain, the addition of bupivacaine to morphine or hydromorphone produced a statistically significant improvement in quality-of-life scores.³⁵ However, neither a dose-response nor a significant effect on pain scores was observed. For 4 months, patients received intrathecal infusion of four different drug combinations (opioid alone or consecutively with three different bupivacaine concentrations). Every month, pumps were

refilled with either the same opioid they received pre-study, or its mixture with bupivacaine. In random order, patients thus received placebo or bupivacaine (4, 6, or 8 mg/day) plus morphine sulfate (4–22 mg/day) or hydromorphone (7–22 mg/day). Only bupivacaine 6 mg/day produced improvements in quality-of-life scores. One patient reported mild adverse effects from intrathecal bupivacaine (mild numbness in the lower extremities without weakness).

In a prospective cohort study, van Dongen et al. reported that five of 20 cancer patients who had inadequate analgesia with intrathecal morphine alone reported improved pain relief when bupivacaine 5–21.6 mg/day was added to the infusate.³⁶ Intrathecal morphine dosages ranged from 1.2–7.2 mg/day, with a mean treatment duration of 85 and 58 days for the groups receiving morphine alone and morphine/bupivacaine, respectively. The combination of morphine and bupivacaine resulted in a diminished progression of the intrathecal morphine dose during the phase of stable analgesia in comparison with the morphine only group. The investigators reported subjective weakness in the legs and arms of two of the five patients who received a morphine/bupivacaine combination. However, no serious adverse effects were reported and patients were followed until death.

Deer et al. recently determined the effect of bupivacaine in a retrospective study of 109 patients (25 with cancer pain, 84 with nonmalignant pain) who received intrathecal opioid infusions.³⁷ All patients had received intrathecal opioids alone (morphine, average dosage of 8 mg/day, or hydromorphone, average dosage 1.5 mg/day) before being switched to an opioid-bupivacaine (average 10 mg/day, range 2–25 mg) combination. Bupivacaine was added to the infusate of those treated with the opioid alone because of inadequate analgesia. Patients who had a poor response to the opioid alone and were then switched to opioid-bupivacaine combinations reported significantly lower pain scores and experienced a mean opioid dosage reduction of 23%. No major adverse effects and no changes in neurologic exams were reported in patients exposed to opioid-bupivacaine combinations.

In a retrospective study, Mironer and Gruman reported that seven of 12 patients experienced numbness in the lower extremities

with intrathecal bupivacaine 4.2–14 mg/day combined with morphine sulfate 1.5–12.5 mg/day.³² One experienced severe urinary retention, and another experienced orthostatic hypotension. The 12 patients (plus four additional) subsequently received intrathecal hydromorphone alone at 1.5–12.5 mg/day and side effects were reported in one patient. In this hydromorphone-treated subgroup, 13 of 16 patients achieved significant improvement in pain relief.

In a case series of three patients, high dosages of bupivacaine were effective in alleviating pain associated with complex regional pain syndrome (CRPS).³⁸ Patients received bupivacaine at an average dosage of 54 mg/day (maximum 90 mg/day) and were followed for an average of 374 days during infusion and an average of 1,900 days after infusion. Mean pain intensity decreased from 7 (+/-1) to 2 (+/-1) on a numeric scale, but there was no regression of allodynia, edema, or trophic changes.³⁸

Ropivacaine

Clinical Data. Dahm and colleagues compared bupivacaine at a mean (SD) dosage of 48 (+/-45) mg/day with ropivacaine at a mean (SD) dosage of 62 (+/-20) mg/day in 12 patients (nine with cancer pain and three with nonmalignant pain) using a double-blind, randomized, crossover methodology.³⁹ The 12 assessable patients were treated for seven days and all reported improved pain scores during local anesthetic infusion. There were no differences in the efficacy or side effects associated with the two anesthetics, but the required dosage of ropivacaine was 23% higher than the dosages of bupivacaine needed to achieve the same effect (along with a corresponding three-fold increase in average daily cost).

Adrenergic Agonists

Clonidine

Preclinical Data. Clonidine has undergone extensive neurotoxicity testing in animals. For example, Yaksh et al. evaluated 28-day continuous intrathecal infusions of clonidine alone (2 mg/mL) and clonidine combined with morphine in dogs.⁷ Clonidine alone was associated with no evidence of spinal pathology, and was

reported to diminish the magnitude of inflammation that was associated with intraspinal morphine.

Studies have shown that clonidine is stable (i.e., maintained 94% potency) when contained in an infusion pump (SynchroMed) at concentrations of 0.05 mg/mL and 1.84 mg/mL in combination with morphine sulfate at 20 mg/mL and 2.0 mg/mL, respectively, at 37°C for 90 days.⁴⁰ Moreover, all device materials exposed to clonidine (2 mg/mL) for 64 weeks maintained acceptable mechanical performance (e.g., elastomeric properties). In another stability study, combinations of morphine 5 mg/mL or 50 mg/mL and clonidine 0.25 mg/mL or 4 mg/mL were contained in plastic syringes and held at 4°C and 23°C for 60 days, and at -20°C and 37°C for 2 days.⁴¹ Morphine and clonidine retained 98% and 97% of their original potency, respectively, under all storage conditions, with one exception. The combination of morphine 50 mg/mL and clonidine 4 mg/mL held at 4°C, exhibited precipitation within 2 to 4 days. These results suggest that morphine-clonidine combinations should not be refrigerated.

When an admixture of morphine sulfate, bupivacaine hydrochloride and clonidine hydrochloride was incubated in SynchroMed EL pumps at 37°C for 90 days or stored in glass vials at 4°C and at 37°C as controls, the concentrations remained greater than 96% of the original concentrations.⁴² A color change from colorless to light yellow between the 30- and 60-day time points (a change observed also in injectable solutions of morphine sulfate and identified as pseudomorphine⁴³) did not affect the solution's stability. No particulate matter and no clinically significant changes in osmolality were observed during the 90-day study.

Clinical Data. Hassenbusch et al. reported a 20-month prospective phase I/II cohort study of 31 patients (six with cancer pain, 25 with nonmalignant pain) who received intrathecal clonidine alone at a total daily dosage of 144–1,200 µg (mean 872 µg).⁴⁴ Twenty-two patients progressed through the dosage-escalation stage and achieved >50% pain/symptom reduction without intolerable side effects. At 6 months, 77.3% (17/22) of this cohort achieved continued good pain relief, and 59% of the cohort were considered long-term successes (mean

follow-up 16.7 months). Clonidine dosage did not change significantly over time in this group. Moreover, there was no change in patients' Karnofsky performance status. Poor long-term outcome was related to inadequate pain relief ($n = 4$) and intolerable side effects (hypotension [$n = 2$]; impotence, lethargy, and malaise [$n = 1$ each]).

A retrospective study observed that only two of the 10 patients treated with long-term intrathecal infusion of clonidine alone (75–950 $\mu\text{g}/\text{day}$) had good pain relief after 7–11 months of therapy.⁴⁵ The addition of either morphine (0.15–15 mg/day , five patients) or hydromorphone (0.2–8.0 mg/day , three patients) similarly yielded very limited effect; only three of these patients achieved long-term pain relief. Side effects included hypotension (five patients) and sedation (three patients).

In a prospective cohort study, Uhle et al. reported data from 10 patients with neuropathic pain syndromes (two of whom had cancer pain) who received clonidine (average, 44 $\mu\text{g}/\text{day}$) in combination with morphine sulfate or buprenorphine.⁴⁶ These patients realized a 70–100% reduction in pain after the addition of clonidine. Four of eight patients with non-neuropathic pain also appeared to benefit from the addition of clonidine. The most frequent adverse effects were hypotension (10 patients), fatigue (4), dry mouth (3), and impaired bowel function (1).⁴⁶

Siddall et al. compared the efficacy of intrathecal administration of saline, morphine (0.2–1 mg), clonidine (50–100 μg), and the combination of clonidine and morphine.⁴⁷ In the first phase of the study, each patient received saline, clonidine, and morphine in a random sequence. One dose per day of each drug was titrated over 3 days until analgesia (defined as a $>50\%$ reduction from baseline pain score) or the occurrence of side effects. The starting dosages of intrathecal morphine and clonidine were estimated based on previous clinical experience with these drugs. During the second phase of the study, each patient received a combination consisting of 50% of the final dosage of morphine combined with 50% of the final dosage of clonidine. The authors compared the proportion of those patients who had a positive response at any time during the assessment. Of the 15 patients tested, five responded positively to saline, three to the largest dosage

of clonidine alone, four to the largest dosage of morphine alone, and seven to the combination of one-half the largest dosage of clonidine plus one-half the largest dosage of morphine. These data suggest that morphine and clonidine are a worthwhile combination but do not permit a distinction between additivity and synergy in their analgesic effect.⁴⁷

Tizanidine

Preclinical Data. In a dog model, Kroin et al. reported that tizanidine and clonidine at dosages of 3.0–18.0 mg/day yielded equivalent analgesia on a thermal withdrawal test, but that clonidine was associated with greater side effects (hypotension, bradycardia, and bradyarrhythmias).⁴⁸ In the same article, they report on the toxicity of 28-day intrathecal tizanidine infusion administered at dosages of 0 (saline control), 3 and 6 mg/day ($n = 3$ per group) at a constant infusion rate of 40 mL/hr . No significant side effects (body weight, temperature, respiratory rate, heart rate, sedation, or motor coordination) or histopathologic effects (spinal cord gray and white matter) were observed in animals treated with saline or 3 mg/day tizanidine. One animal of three treated with 6 mg/day tizanidine exhibited more subarachnoid inflammatory cells as compared to the control and 3 mg/day -treated animals.

NMDA Agonists

Ketamine

Preclinical Data. Subarachnoid administration of ketamine has been demonstrated to be analgesic in several rodent models.^{49,50} One of these studies also demonstrated synergism with morphine and attenuation of morphine-induced tolerance.⁵⁰ Preclinical studies also have found severe histologic and gross spinal cord toxicity with the intrathecal infusion of other N-methyl-D-aspartate (NMDA) antagonists such as dextrorphan, dextromethorphan, memantine,⁴⁹ and MK-801 and ketamine (T. Yaksh, personal communication).

In a drug stability evaluation, hydromorphone (1.0–47.5 mg/mL) and ketamine hydrochloride (0.5–49 mg/mL) mixtures were stored in glass tubes at room temperature for 24 days.⁵¹ At the end of the test period, the decrease of morphine sulfate or ketamine hydrochloride concentrations were clinically negligible

(decreased by less than 5%); pH and visual appearance were unchanged.

Clinical Data. Intrathecal ketamine at a dosage of 47.2 mg/day yielded enhanced analgesia when added to morphine 13.3 mg/day during treatment of a patient with severe neuropathic pain.⁵² Another case report⁵³ described a 72-year-old woman with abdominal pain due to cancer who received morphine, bupivacaine, clonidine and ketamine, and attained satisfactory pain relief at Day 7. She also developed weakness in the muscles of the abdomen and upper extremities, and acute psychotic changes. Post-mortem histologic analysis of the tissues showed lymphocytic vasculitis close to the infusion site, with lesions predominantly found in the leptomeninges—a previously unreported finding.

Other Agents

Baclofen

Preclinical Data. Using HPLC, Godwin et al. examined the chemical stability of intrathecal baclofen (1,000 µg/mL) and clonidine (200 µg/mL) alone or as an admixture for 10 weeks at body temperature (37°C).⁵⁴ Both of the drugs and the mixture retained greater than 99% of their initial concentrations (baclofen, 99.7%; clonidine, 100.7%; baclofen/clonidine 99.7/101.1%). The authors concluded that baclofen and clonidine alone and as an admixture were sufficiently stable for long-term intrathecal administration.

Clinical Data. Baclofen was evaluated in a randomized, controlled trial that included seven patients who experienced pain and dystonic movements associated with complex regional pain syndrome (CRPS).⁵⁵ During the 0.5- to 3-year (mean 1.7 years) follow-up period, three regained normal hand function and two of three regained the ability to walk. Adverse effects included somnolence ($n = 1$), slight drowsiness (2), muscle weakness related to hypotonia (2), and urinary retention (1).

A retrospective description of 23 patients with either central pain or spasticity-related pain described benefit in 19.⁵⁶ Baclofen was administered as a continuous intrathecal infusion at 150–180 µg/day over a period of 20 to 24 months. Four of the 23 patients also required

morphine, and one patient also received clonidine in addition to baclofen.

In a case report, two patients with CRPS experienced good control of pain, allodynia, and autonomic symptoms with intrathecal baclofen. One patient was treated with baclofen 125–250 µg/day and clonidine 12.5 µg/day (19-month follow-up), and the other was treated with intrathecal baclofen alone (85–250 µg/day; 22-month follow-up).⁵⁷ A similar report of five patients, four of whom received intrathecal baclofen alone (50–460 µg/day) for varied neuropathic or mixed pain syndromes, also described substantial benefit.⁵⁸ No side effects were reported. Finally, a patient with multiple sclerosis and central pain but no spasticity or rigidity reported improvement while receiving baclofen 110–150 µg/day for 20 months.⁵⁹

A potentially life-threatening withdrawal syndrome has been described in spasticity patients when intrathecal baclofen was abruptly discontinued.⁶⁰ The syndrome, which included fever, altered mental status, and profound muscular rigidity, was aborted by the restoration of intrathecal baclofen followed by gradual dose reduction.

Gabapentin

Preclinical Data. The analgesic efficacy of intrathecal gabapentin has been evaluated in rodent models. Administered by bolus intrathecal injection (100–1,000 µg), gabapentin reduced mechanical allodynia and thermal hyperalgesia associated with central sensitization,⁶¹ tissue injury,^{62,63} inflammation,^{64–66} and nerve injury.^{64–71} Gabapentin had no effect on acute nociceptive pain as assessed using the Phase I formalin test in rats^{65,72,73} or the hot-plate test in mice.⁷¹ In these rodent studies, the potency of gabapentin was more than 10-fold greater when the drug was administered intrathecally than subcutaneously or intraperitoneally.⁷² Intrathecal administration yielded no effect on heart rate or blood pressure⁶⁵ but produced mild weakness in the hind limbs at doses greater than 300 µg.^{61,70}

Intrathecal gabapentin and clonidine acted synergistically in a rat model of post-operative allodynia, with an ED₅₀ of 51 µg for gabapentin alone, an ED₅₀ of 31 µg for clonidine alone, and an ED₅₀ of 9 µg for the combination.⁶² The combination of gabapentin and 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX), when administered intrathecally, had a potent synergistic

anti-allodynic effect on neuropathic pain in spinal-nerve ligated rats.⁶⁷ The combination of intrathecal gabapentin and ibuprofen also had a potent synergistic anti-hyperalgesic effect in the formalin model in rats.⁶⁶

Midazolam

Preclinical Data. In studies in cats,⁷⁴ rats,⁷⁵ sheep, and pigs,⁷⁶ there has been no toxicity associated with neuraxial infusion of midazolam. For example, continuous intrathecal infusion of midazolam in sheep (5–15 mg/day vs. saline 125 μ L/hr) or pigs (15 mg/day vs. saline 125 μ L/hr) had no effect on behavior or neurologic function.⁷⁶ All animals, including saline-treated animals, had mild inflammation surrounding the catheter tract in the spinal tissue; the finding in saline-treated animals suggests that the effect was probably related to the indwelling catheter and not midazolam. All midazolam-treated sheep showed greater pain thresholds than at baseline.

In contrast to these studies, histologic/vascular lesions on light/fluorescence microscopy were found in spinal cord specimens from rabbits that received either midazolam or preservative-free midazolam ($n = 6$ each).⁷⁷ Malinovsky et al. also reported neurotoxicity in a rabbit study of intrathecal midazolam.⁷⁸ They administered midazolam (1 mg/mL) via a single percutaneous intracisternal injection and compared it to lidocaine and saline, neither of which caused neurotoxicity. Yaksh and Allen recently presented a detailed review of the preclinical safety issues pertinent to midazolam.⁷⁹

Clinical Data. In a prospective cohort study of 26 patients, four patients received midazolam 0.4 mg/day plus morphine sulfate 0.5 mg/day, clonidine 0.03 mg/day, and bupivacaine 1.0 mg/day, four patients received morphine/bupivacaine/midazolam, and two patients received morphine/midazolam.⁸⁰ Overall, 19 of the 26 patients (73%) achieved good to excellent pain relief, six patients (23%) achieved sufficient pain relief, and one patient reported poor pain relief. No information was provided regarding outcomes according to drug combination received on-study.

Additional information on the efficacy and safety of midazolam was provided by two studies in the acute pain setting.^{81,82} One study

($n = 1,100$) administered intrathecal midazolam (2 mg of isotonic, preservative-free solution, pH 3.5) to 547 patients, and used a control group of 553 patients who did not receive midazolam.⁸¹ In both groups, patients had intraoperative spinal anesthesia, then either received midazolam (or not) for postoperative pain. Eighteen risk factors for adverse neurologic sequelae were studied with respect to the two groups, and the authors reported that intrathecal midazolam was not associated with an increased risk of neurologic symptoms in the midazolam group when compared with controls.

Tucker et al. reported a second study of intrathecal midazolam.⁸² In this randomized trial evaluating relief of labor-related pain ($n = 30$), patients received one of the following regimens: single-agent midazolam 2 mg, versus fentanyl 10 μ g, or a combination of midazolam and fentanyl. Intrathecal midazolam enhanced the analgesic efficacy of fentanyl in a statistically and clinically significant manner, without increasing observed maternal or fetal adverse events.

Ziconotide

Preclinical Data. Ziconotide, previously known as SNX-111, is a neuronal-specific calcium-channel blocker that acts by blocking N-type, voltage-sensitive calcium channels. In a preclinical study performed in rats, acute intraspinal administration of ziconotide and morphine produced additive or synergistic effects.⁸³ Chronic intrathecal ziconotide administration produced neither tolerance nor cross-tolerance to morphine analgesia; conversely, intrathecal ziconotide did not prevent or reverse morphine tolerance.

Clinical Data. A double-blind, placebo-controlled short-term trial of ziconotide in 257 patients with non-cancer pain (78% had neuropathic pain) assessed analgesia for 5 or 6 days in a blinded fashion, followed by an additional 5- to 6-day maintenance period.⁸⁴ Significantly lower pain scores were reported by 31% of the ziconotide-treated patients, compared to 6% of the placebo-treated patients. Moderate to complete pain relief was achieved in 43% of patients in the ziconotide arm versus 18% in the placebo arm. Patients who received ziconotide also decreased their systemic opioid intake and

reported improved quality of life compared to patients who received placebo.

Another placebo-controlled, randomized, short-term trial in 111 patients with cancer- or AIDS-related pain observed a mean pain reduction of 53% in the ziconotide group and 18% in the placebo group during the 5-day maintenance phase.⁸⁵ Pain relief was moderate to complete in 53% of subjects in the ziconotide arm versus 17% in the placebo arm.

Other uncontrolled studies revealed similar results. In groups of patients with varied painful disorders, 32–62% reported pain relief of varying degrees during follow-up periods that lasted from several days to 3.5 years.^{86,87}

Adverse events associated with intrathecal ziconotide have included abnormal gait, nausea, vomiting, urinary retention, dizziness, nystagmus, blurred vision, diplopia, memory impairment, and orthostatic hypotension.^{84,86,87} Side effects usually improved when the ziconotide dosage was decreased.^{86,87} A high incidence of adverse effects was associated with rapid titration of drug.⁸⁵ A retrospective cohort analysis of data from 231 patients treated with long-term ziconotide reported that the prevalence of adverse effects was lower at 6 months than during the first month of treatment for 10 common adverse effects. However, many patients who experienced adverse effects early in their clinical course dropped out of the studies, and were not exposed to ziconotide for 6 months.

Neostigmine

Clinical Data. In a randomized trial conducted in a sample of patients undergoing perianal surgery under spinal anesthesia, Yegin et al. compared intrathecal hyperbaric bupivacaine 10 mg, hyperbaric bupivacaine 10 mg plus neostigmine 25 µg, and hyperbaric bupivacaine 10 mg plus neostigmine 50 µg.⁸⁸ Compared to those who received bupivacaine alone, patients who also received neostigmine experienced a significantly quicker onset of sensory block and a longer time to recover motor and sensory function. Patients who received the higher dose of neostigmine also had a longer period before an analgesic was required in the postoperative period. The frequency of nausea and vomiting was significantly higher in the neostigmine groups.

In a dose-finding study, neostigmine 75 µg, 150 µg, and 300 µg were compared in a group of 80 women who received epidural anesthesia using hyperbaric bupivacaine 8 mg plus fentanyl 10 µg during elective cesarean surgery.⁸⁹ A dose-dependent decline in global pain scores was observed during the first postoperative day. Intraoperative shivering and postoperative sedation increased in the neostigmine groups. There were no differences in nausea and morphine consumption.

Adenosine

Clinical Data. Eisenach et al. compared intrathecal adenosine 2 mg and intravenous adenosine 2 mg in seven patients with chronic neuropathic pain and stable areas of mechanical hyperalgesia and allodynia.⁹⁰ The methodology incorporated the use of a single dose, “double-dummy” approach in a randomized crossover design. Ongoing pain was not affected, but intrathecal adenosine significantly reduced the area of allodynia and mechanical hyperalgesia. Adverse effects included back pain in five patients receiving intraspinal adenosine.

Ketorolac

Clinical Data. Because spinal prostaglandin (PG) synthesis has been hypothesized to play a role in acute pain processes and the generation and maintenance of central sensitization, Eisenach et al. conducted an open-label, Phase I, single dose escalation study ($n = 20$) of intraspinal ketorolac.⁹¹ Study groups received intrathecal injections of ketorolac 0.25, 0.5, 1, or 2 mg ($n = 5$ /group). No adverse effects on sensory or motor function, or deep tendon reflexes were observed. Ketorolac did not reduce pain report to heat stimuli on the lateral calf. With the exception of a mild headache reported by one patient 24 hours after the study, there were no side effects during a 6-month follow-up.

Algorithm: Selection of Drugs for Long-Term Intraspinal Infusion

Although the literature review revealed the limitations in the number and quality of studies pertaining to most of the drugs undergoing consideration for intrathecal infusion, these

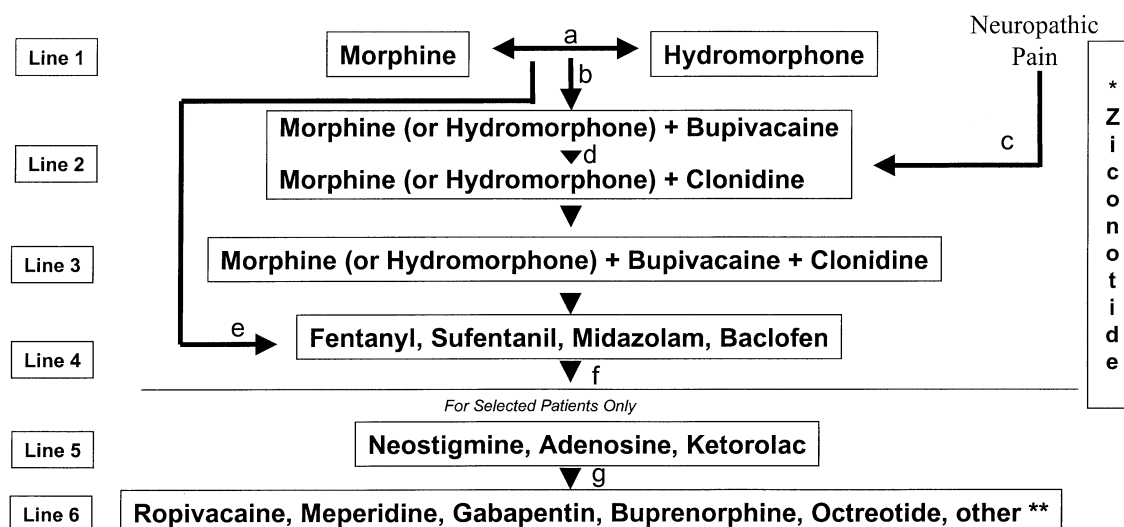
new data reflect the current best evidence. This and the later discussed concept of minimum evidence required to support clinical use were the basis for revision of the algorithm for intrathecal drug selection first proposed in 2000.¹ The updated algorithm was developed as an approach to optimizing drug selection and is relevant both for screening trials¹² to determine whether a patient is a candidate for pump implantation and for treatment changes during chronic long-term infusion.

The algorithm (Fig. 1) arranges drugs in a hierarchy according to evidence of safety, efficacy, and broad clinical experience and this is an update of that published from the previous conference. The drugs on the first line of the algorithm are supported by extensive clinical experience and published preclinical and clinical data. Intrathecal therapy most often commences with a Line 1 drug (morphine or hydromorphone) and only progresses to lower line drugs if intolerable side effects occur, or if the initial agent is no longer effective at a dosage and concentration that is safe or convenient (e.g., refill intervals too short) in clinical

practice. The drugs listed below Line 1 are supported by fewer published preclinical data, clinical experience, or both. Decisions to use a specific drug or drug combination on any level, to use other drugs on the same level, or to use drugs on a lower level are based on the clinical judgment and experience of the individual practitioner, as well as on the patient's response to therapy.

Line 1 Approach

Line 1 contains morphine, the only analgesic drug currently approved by the U.S. Food and Drug Administration (FDA) for long-term intrathecal administration, and hydromorphone, a drug for which usage is supported by the medical literature and broad clinical experience.^{18,23,24} The apparent dosage- or concentration-dependent risk of catheter-tip inflammatory masses suggests that, in the interest of patient safety, physicians respect an a priori upper limit when titrating the dosage of morphine or hydromorphone. If side effects become problematic with either morphine or



*The specific line to be determined after FDA review

**Potential spinal analgesics: Methadone, Oxycodone, NMDA antagonists

a. If side effects occur, switch to other opioid.

b. If maximum dosage is reached without adequate analgesia, add adjuvant medication (Line 2).

c. If patient has neuropathic pain, consider starting with opioid monotherapy (morphine or hydromorphone) or, in selected patients with pure or predominant neuropathic pain, consider opioid plus adjuvant medication (bupivacaine or clonidine), (Line 2).

d. Some of the panel advocated the use of bupivacaine first because of concern about clonidine-induced hypotension.

e. If side effects or lack of analgesia on second first-line opioid, may switch to fentanyl (Line 4).

f. There are limited preclinical data and limited clinical experience; therefore, caution in the use of these agents should be considered.

g. There are insufficient preclinical data and limited clinical experience; therefore, extreme caution in the use of these agents should be considered.

Fig. 1. Update of clinical guidelines for the use of intraspinal drug infusion in pain management.

hydromorphone, or the dosage must be increased to the maximum recommended without adequate analgesia, a reasonable step would be either a switch to the alternative Line 1 opioid (i.e., morphine to hydromorphone or hydromorphone to morphine) or a change to a Line 2 regimen. The latter course may be more appropriate if the pain is neuropathic or the response to either morphine or hydromorphone was characterized by poor analgesia. Indeed, some members on the panel endorsed the view that Line 1 can be omitted altogether by the treating physician if a patient has severe neuropathic pain that has not responded to a systemically delivered opioid.

Line 2 Approach

Line 2 includes morphine or hydromorphone combined with either bupivacaine or clonidine. Few data are available to compare the relative risks or benefits of these combinations. A majority of the panel had concerns regarding the hypotensive side effects of clonidine and, therefore, support the use of bupivacaine as the first drug for addition to a Line 1 agent. Because the safety of intraspinal clonidine has been characterized in preclinical studies to a greater extent than bupivacaine, some panel members were more comfortable adding clonidine before bupivacaine.

As noted, some physicians begin therapy with a combination of an opioid plus bupivacaine or clonidine in the hope of achieving better efficacy for mixed and neuropathic pain states. There are no specific data to support this approach. Whether the addition of clonidine or bupivacaine has opioid-sparing effects, which may reduce the risk of opioid-related side effects or granuloma formation, also is still speculative.

Some physicians administer bupivacaine monotherapy to patients with neuropathic pain that does not respond to a systemically administered opioid. Again, however, no published data support this approach. Intrathecal clonidine monotherapy has been studied, but the case material suggests that relatively few patients maintain long-lasting relief.^{44,45,47} Given these limited data, the panel did not recommend the use of intrathecal clonidine or bupivacaine alone.

Line 3 Approach

If a Line 2 drug combination results in inadequate analgesia or intolerable side effects, the

clinician may change to an alternative Line 2 combination, or add a third drug as a Line 3 strategy. Thus, on Line 3, both bupivacaine and clonidine may be added to either morphine or hydromorphone. If results with the initial Line 3 drug combination are unsatisfactory, another Line 3 drug combination may be considered (i.e., switch to the alternative opioid) before progressing to Line 4.

Line 4 Approach

Few data are available to guide clinical decision making if Line 3 drug combinations are ineffective or tolerated poorly. Line 4 includes the lipophilic opioids fentanyl and sufentanil, and the gamma-amino-butyric acid (GABA) agonists midazolam (GABA_A) and baclofen (GABA_B). The initial strategy for the use of Line 4 agents usually involves a switch from morphine or hydromorphone (Lines 1–3) to fentanyl or sufentanil.

Baclofen is a safe, effective, and approved drug for long-term intraspinal (or oral) administration to treat spasticity. However, analgesic data are limited. The evidence in support of intrathecal baclofen is most clear in those with pain caused by spasticity, rigidity, or muscle cramping. The use of intrathecal baclofen as a primary analgesic in other situations is less well supported.

Intrathecal fentanyl, sufentanil and midazolam are used in clinical practice despite the lack of long-term safety and efficacy data. Sufentanil and fentanyl are potent opioids with an unknown long-term intrathecal safety and efficacy profile. Hypothetically, infusion of a highly lipophilic drug such as sufentanil could result in fewer side effects than a hydrophilic agent like morphine because less drug diffuses to rostral brain centers. The limited clinical experience with sufentanil relegates it to occasional use after fentanyl has been tried without success.

Experience with midazolam is limited to patients with pain associated with advanced cancer. In Europe, midazolam is available as the preservative-free hydrochloride salt, the formulation that also has been studied preclinically. A preservative-containing midazolam solution, such as the formulation that is commercially available in the United States, should not be used without rigorous animal toxicity testing data.

Line 5 and Line 6 Approaches

Few data and only limited experience support the long-term intrathecal infusion of drugs listed on Line 5 (neostigmine, adenosine, and ketorolac) and Line 6 (ropivacaine, meperidine, gabapentin, buprenorphine, octreotide, and others). Line 5 agents have been studied to some degree in preclinical models, including significant toxicity evaluation; Line 6 drugs have had little or no preclinical investigation and minimal to no clinical experience.

Some formulations of meperidine have demonstrated pump compatibility concerns. These remain to be resolved. The use of other drugs, such as oxymorphone, methadone and the NMDA receptor antagonists, has been reported in small surveys. The use of intraspinal methadone raises concerns about toxicity because the commonly available formulation is a racemic mixture that contains the non-opioid d-isomer, which is an NMDA receptor antagonist. Other NMDA antagonists are clearly neurotoxic in animal models.⁴⁹ Given the lack of data, the use of any drug on Line 5 or Line 6 should be considered only when severe and disabling pain is refractory to more conventional treatments.

Ziconotide

Controlled randomized trials have confirmed the analgesic efficacy of ziconotide. This drug is undergoing review by the U.S. FDA. If it becomes available in the United States and elsewhere, its position within the algorithm is likely to evolve as experience in the clinical setting accumulates. The panel noted that the extensive preclinical and clinical data obtained as part of a formal drug development program exceeds the data available for other drugs used for intrathecal infusion and will probably lead to placement of ziconotide on an upper line of the algorithm, unless accumulating experience suggests a narrow therapeutic index in practice.

Rationale for Selection of Drug Dosage and Concentration

Efficacy and toxicity of chronically infused intrathecal drugs depend upon dosage, concentration, and thus infusion rate. The daily dosage may account for side effects related to systemic redistribution, such as sedation, hormone suppression or constipation. Infusion rate and drug

concentration may determine the extent of distribution within the poorly mixed subarachnoid space and thus may influence toxicity and efficacy. Preclinical evidence, for example, suggests that local cerebrospinal fluid (CSF) concentration of opioids at the catheter tip may be related to changes in the meninges, such as mast cell degranulation, and the development of inflammatory masses.^{6,7}

At the Polyanalgesic Consensus Conference 2003, the results of an internet survey of clinicians with experience in intrathecal infusion (see Appendix) was used as reference for dosing and concentration rationale. The potential for varied effects from differences in dosage, infusion rate and concentration has important implications for the trialing of drugs for intrathecal infusion. The panel noted that the time-consuming strategy of conducting trials systematically by varying only one parameter at a time might be best for judging drug effects, but is impractical in most clinical settings. Studies could try to establish dose/concentration guidelines that pertain to all patients, but this will also be very difficult, particularly given the number of drugs now in use. It is more likely that future studies may be able to categorize a set of "optimal" delivery parameters (e.g., high/low infusion rate vs. high/low concentration) associated with different levels of potential risk.

Limited data notwithstanding, the panel perceived a need to develop guidelines for the selection of dosage and drug concentration. These guidelines, which are detailed below, advance the use of relatively high flow rates and relatively low drug concentrations, if possible and practical (Table 2), because this approach is likely to minimize the risk of opioid-induced inflammatory mass formation. To minimize risk overall, an approach that attempts to identify

Table 2
Recommended Maximum Intrathecal
Dosages and Concentrations^a

Drug	Dosage (mg/day)	Concentration (mg/mL)
Morphine	15	30
Hydromorphone	10	30
Bupivacaine	30	38
Clonidine	1.0	2.0

^aThese values represent general recommendations and are dependent upon the specific patient and the clinical experience of the physician; thus, maximum dosage and/or concentration may vary from these values.

the minimally effective dose, rate and concentration by gradual titration from low starting points is preferred.

Morphine

Because the risk of catheter-tip inflammatory mass formation appears to increase with concentration and dose,^{6,7,18} the panel recommended that morphine be infused at a maximum concentration of 30 mg/mL and a maximum dosage of 15 mg/day whenever possible. Morphine-induced hyperalgesia, another dose-dependent effect, also may be reduced or eliminated if this approach is used.^{6,7,92} Surveillance for adverse effects should be especially vigilant at dosages and concentrations above these limits. Hassenbusch et al. recently published consensus recommendations on testing and surveillance, based on a panel review of preclinical evidence and human data.^{8,18}

Hydromorphone

Notwithstanding limited animal data that suggest a lower risk of granuloma formation from hydromorphone than morphine,^{8,18} the panel recommended that hydromorphone be administered at or below a concentration of 30 mg/mL and a total daily dosage of 10 mg, in most cases. This maximal dosage of hydromorphone is greater than the equianalgesic maximal dosage for morphine, but is believed to be safe based on extensive clinical experience. Indeed, it was noted that some experienced practitioners deliver as much as 15 mg/day. At these higher dosages, increased surveillance for adverse effects is prudent.

Bupivacaine

There have been no preclinical studies designed to assess the maximum safe dose and concentration of bupivacaine. Several preclinical studies in rats and rabbits have demonstrated local neurotoxicity,^{93–95} but another study in rabbits, and a dog study, have not.^{96,97} Given the lack of certainty regarding safety, the panel recommended that the concentration and dose of bupivacaine be kept as low as possible to maintain adequate analgesia. Based on clinical observations, the panel further suggested that the occurrence of hyperalgesia be considered a potential early sign of neurotoxicity. The recommended dosage range for bupivacaine is 2 to 30 mg/day and the maximum

recommended concentration is 38 mg/mL (3.8%) based on the aqueous solubility limit of 40 mg/mL. This total daily dosage is likely to preserve lower extremity and bladder function in most patients. In elderly patients and some patients with impaired CSF flow due to scar or other factors, very low doses of bupivacaine may produce sympathetic blockade, somatic sensory blockade, and/or motor blockade. Lower doses may be effective if this occurs. If function is not a concern, such as may occur in the setting of advanced illness, higher bupivacaine doses may be appropriate.

Clonidine

Based on extensive clinical experience and the lack of observed neurotoxicity,⁷ the panel concluded that the previously recommended¹ dosage range for intrathecal clonidine was too low and that a dosage range of 10 µg to 1,000 µg/day is appropriate, although the risk for significant side effects is higher in the upper part of this range. The highest, commercially available concentration of clonidine is 500 µg/mL, but it could be used up to 2,000 µg/mL. The panel further recommended that clonidine treatment be initiated at relatively low dosages (most patients at 100 µg/day, and older and medically frail patients at 10 µg/day) to reduce the risk of side effects, including hypotension, sedation, peripheral edema, and cardiac arrhythmias.^{44,45} The panel noted the potential for a withdrawal syndrome, with rebound hypertension,⁴⁴ and recommended that doses either be tapered prior to discontinuation, or that systemic clonidine be provided if intrathecal therapy is suddenly discontinued. Moreover, some noted from their clinical experiences that the hypotensive side effects of clonidine appear to be dose-related in an unusual way. Hypotension is unusual in dosages up to 200 µg/day and at dosages above 600 µg/day, and is most pronounced in the range of 200–600 µg/day.

Minimal Evidence Requirements for the Use of Intrathecal Analgesic Agents

Intrathecal infusion is evolving and it is likely that efforts will continue to find new agents that are safe and effective via this route. Most of the drugs now used are commercially available for systemic administration and are applied “off

label” for intraspinal use. In contrast to the rigorous testing for safety and efficacy required of new chemical entities, such as ziconotide, developed specifically for intrathecal administration, drugs that are already commercially available potentially could be administered by the spinal route with little or no prior evaluation. The risks associated with this practice, including unanticipated neurotoxicity, are substantial. To reduce this risk, guidelines are needed that define the minimal evidence of safety and efficacy that should be required for a drug to be deemed acceptable for use as an intraspinal analgesic.

To create these “minimal evidence guidelines,” the panel developed specific criteria relevant to safety and efficacy (Table 3). The ultimate goal of this consensus process was

the creation of a tool that would facilitate the rating of drugs that are commercially available for systemic use and are being considered for neuraxial administration. This tool would serve as a useful measurement device to both determine the appropriateness of the agent for use and clarify its placement within the current tiers of the drug-selection algorithm.

Criteria for Minimal Evidence Guidelines

The criteria that should be addressed to clarify whether a drug is appropriate for intrathecal infusion can be divided into preclinical (physicochemical and animal studies) and clinical (Table 3). These criteria mirror the requirements applied to new chemical entities by the U.S. FDA. The panel endorsed the importance of all these criteria but also acknowledged that many of the drugs now included in the drug selection algorithm have not undergone a full evaluation. The relatively recent discovery of the relationship between intrathecal morphine sulfate infusion and catheter-tip inflammatory masses demonstrates the risks associated with taking shortcuts. The panel also noted that the risk/benefit ratio for off-label use in the clinical setting varies with the characteristics of the patient. For example, it may be appropriate to consider a trial of a drug with insufficient evidence relevant to some of the major criteria if a patient has advanced cancer and pain that has been refractory to all reasonable conservative measures.

Preclinical Studies

The preclinical evaluation of compounds, varied concentrations, and different formulations intended for intrathecal delivery is essential because of the risk of neurotoxicity. As noted in an editorial by Eisenach and Yaksh,⁹⁸ a trial of a drug that has not undergone preclinical testing is unethical unless there is a compelling clinical exigency that shifts the risk/benefit ratio. Preclinical safety modeling has become increasingly sophisticated, and is now able to deliver spinal agents continuously for intervals of 1–3 months.⁷⁹ Intraspinal granuloma formation associated with administration of high concentrations of morphine is an important example of cross-species validation that has been demonstrated in preclinical studies.^{6,7}

The physicochemical properties that should be assessed include solubility, pH, stability at

Table 3
Minimum Evidence Required to Support the Use of Drugs for Intrathecal Pain Therapy

Criteria	Weight of each criterion ^a
I. Preclinical Studies	
A. Physicochemical studies	
1. Solubility	E
2. pH	E
3a. Stability at room temperature	
1) in solution	E
2) in device	E
3b. Stability at body temperature	
1) in solution	E
2) in device	E
4. Compatibility with delivery device	E
B. Animal studies	
1. Mechanism/site of action	D
2. Pharmacokinetics	D
3. Toxicity	E
a. Side effects	
b. Neurotoxicity	
4. Efficacy	D
II. Clinical Studies (Human)	
A. Pharmacokinetics	D
B. Side effects	E
C. Safety	E
D. Existence of FDA labeling (U.S. only)	D
1. For intrathecal use	
2. For other route of administration or indication	
3. No approval (no FDA labeling)	
E. Efficacy studies	D
1. Case report	
2. Case series	
3. Historical case-control	
4. Randomized controlled trial	
F. Database (registry of patients receiving drug, safety)	D

^aE = Essential, D = Desirable.

both room temperature and body temperature (both in solution and in the delivery system), drug-drug stability, and drug-device compatibility.^{40,99} The drug must be obtained from a source that can confirm its synthesis and formulation using Good Manufacturing Process (GMP).

Animal studies should provide information on mechanism of action, site of action, pharmacokinetics, toxicity, and efficacy. Animal trials should be predicated on a strong scientific rationale, such as the presence of receptors, channels, or enzymes. When conducting analgesic efficacy and mechanism-focused studies, validated preclinical models of pain processing should be utilized.¹⁰⁰ In animal studies, a concurrent spinal pharmacokinetic assessment also is useful to demonstrate the actual drug exposure experienced in the test spinal cord.¹⁰¹ The animal toxicology studies should include at least one large animal study using dosages that mimic those likely to be used in humans, as well as a maximum dosage and concentration. The latter study should involve at least three animals per dosage group and duration of administration of at least 30 days.

Ideally, some of the preclinical work would determine whether safety and efficacy are affected by drug concentration, drug delivery rate, or even the location of the catheter. The pharmacology of the drug effect should be confirmed with demonstration of dose dependency and, if possible, with the use of pharmacological antagonists. This applies to both analgesic and important non-analgesic effects. The physiologic effects produced by intrathecal delivery in preclinical models should be consistent with the current understanding of the drug's mechanisms of action, including the lack of persistent behavioral or physiological effects that could suggest the potential for neurotoxicity.

Clinical Studies

Clinical studies are needed to evaluate the pharmacokinetics of neuraxial delivery, and both safety and efficacy. Clinical trials vary in quality and the credibility of the findings is related to the extent a trial is controlled. In the absence of blinding and random assignment to study and control groups, data related to subjective effects like analgesia are, at best, tentative. Other factors that strongly influence the reliability, validity, and generalizability

of the results include sample size, number of study centers, inclusion criteria, use of comparator drugs (including the use of active placebos and controls), tested dose ranges, use of breakthrough medications, duration of study, duration of follow-up, prospective assessment of side effects, methods for the evaluation of neurotoxicity, and use of validated measures to assess outcomes other than pain.⁵ Approval of a drug for intraspinal use by a regulatory agency, such as the FDA, would provide evidence that adequate clinical trials had been performed.

The panel suggested that drug combinations and admixtures should be subject to the same criteria for evaluation as single agents because mixing two "safe" drugs could change pharmacokinetics, safety, efficacy, drug stability, and drug-device compatibility. Because it is not practical to test every possible combination or drug:drug ratio, the preferred approach would be evaluation of combinations at the maximum dosages/concentrations of each constituent prior to clinical use. The use of a combination would be reasonable if this type of study generated no negative data and all appropriate stability and compatibility studies had been performed.

The panel recognized that it might occasionally be appropriate for physicians to clinically use drug combinations that lack minimum evidence criteria as long as three conditions were satisfied: 1) each drug separately met suitable minimum evidence criteria, 2) the drugs were stable when combined in solution, and 3) a few published case studies revealed the efficacy and safety of the combination.

Proposed Rating System for Available Drugs

Ideally, each drug proposed for intrathecal infusion would have detailed data pertaining to each of the preclinical and clinical criteria. This is not the case for most drugs now in use, however, and the panel discussed a process for categorizing the existing data in a way that summarizes the evidence. The panel endorsed an approach in which the preclinical and clinical criteria would be broadly rated based on the availability and quality of supporting evidence: no data, rating = 0; minimal quantity or quality (marginal evidence to support drug use), rating = 1; moderate quantity or quality of data (the level at which the data are sufficient to support the use of that agent), rating = 2;

and excellent quality and quantity of data, rating = 3. The rating would be based on a review of the available evidence. One proposed approach for use with the clinical criteria, for example, linked the numeric rating with distinct categories of evidence, specifically multiple randomized clinical trials, single randomized trial or nonrandomized studies, or consensus opinion of experts.

If this type of rating system were developed and validated, it would allow more systematic placement of drugs into the tiers of the drug selection algorithm (Fig. 1). For example, Line 1 would be composed of drugs that are felt to be safe and efficacious, and acceptable for routine clinical use. These drugs would have a rating of 2 or 3 in most categories listed in Table 3. Line 2 would have drugs that probably are safe and efficacious, but should be used with caution. These drugs should have at least a 1 or 2 rating in each category. Line 3 drugs may be safe for clinical use but should be used with significant caution and not as first- or second-line agents. In this rating system, there would be a rating of 1 or 2 for the majority of categories but there may be a 0 rating for isolated categories if the bulk of evidence otherwise supports clinical use of the drug. Line 4 would list drugs whose safety and efficacy have not been demonstrated satisfactorily and should be used only in a research setting or with caution in very limited clinical settings. For these drugs, there would be a 0 or 1 rating for the majority of categories.

The panel believes that this type of strategy would represent a significant advance and would likely increase the overall safety of intrathecal therapy. Further research will serve to refine and verify this model.

Essential, Desirable, Helpful Qualities

In the absence of studies that would substantiate a rating approach to minimal evidence guidelines, the panel proposed a simpler classification of the criteria that could be applied immediately. Specifically, some of the criteria that should be addressed to clarify whether a drug is appropriate for intrathecal infusion should be classified as essential (E) or core, others may be designated as desirable (D), and several could be described as helpful but not essential (N) (Table 3). The criteria considered essential for a new agent include most of the

preclinical physicochemical studies and animal studies involving toxicity, including neurotoxicity and the potential for severe adverse effects (e.g., those affecting the nervous, cardiac, or pulmonary systems). All on the panel supported the need for at least one toxicity study in large animals. Other animal studies were considered desirable, but not essential.

For the clinical studies, the criteria considered essential related to safety and tolerability. Both pharmacokinetics and efficacy were considered desirable but not essential. Valid efficacy data was classified as desirable but not essential to allow a patient with intractable pain who had failed numerous drug trials to be given a promising new agent that had been shown to be safe in high-quality animal studies and in human Phase I studies.

Widespread clinical use can obviate the need for these essential criteria, but only within the dosage and concentration parameters for which the existing literature indicates safety. Regulatory agency approval for intrathecal use implies that all of the essential data have been collected, independently reviewed, and determined to be acceptable.

Issues in Compounding

Preservative-free morphine sulfate sterile solution (Infumorph[®], Baxter; Astramorph[®], AstraZeneca) is the only drug currently approved in the United States for the intrathecal treatment of pain. Therapy with morphine at concentrations above 25 mg/mL, other drugs and combinations of drugs usually require compounded formulations.

Compounding requires extremely clean facilities with high air quality standards, specific training and testing of personnel in aseptic principles and practices, and sound knowledge of sterilization and solution stability principles.¹⁰² Incorrectly prepared or contaminated compounded sterile products are especially dangerous when the product is to be administered directly to the central nervous system.^{103,104}

The United States Pharmacopoeia (USP) and the American Society of Health System Pharmacists (ASHP) have issued standards on compounded sterile products that have practical and legal significance.^{102,105} These standards

apply to the compounding of solutions for neuraxial administration. For the purposes of applying USP Chapter <797>, a compounded sterile product includes preparations prepared according to the manufacturer's labeled instructions and other manipulations when preparing sterile products that expose the original contents to potential contamination, as well as preparations that contain non-sterile ingredients or employ non-sterile components and devices that must be sterilized before use. For the purposes of applying the ASHP guidelines, compounding is defined as mixing of ingredients to prepare a medication for patient use, including dilution, admixture, repackaging, reconstitution, and other manipulations of sterile products.

According to these standards, all compounded sterile, preservative-free preparations administered via an intrathecal delivery system are classified as at least Level 2 (Medium Risk), and many are classified as Level 3 (High Risk) preparations. Preparation of a sterile solution from a non-sterile powder would be considered Level 3.^{102,105}

USP <797> came into effect in January 2004, and the impact on compounding practice is not yet clear. State boards of pharmacy have primary responsibility for enforcing the USP standards, at their discretion. However, the FDA may take enforcement action where they believe the compounding pharmacy is engaged in drug manufacturing.

Considerations for Compounded Formulations for Intraspinal Pumps

In addition to the USP and ASHP sterile compounding recommendations, many considerations relevant to use of commercial formulations labeled for systemic (e.g., intravenous, oral) delivery are also applicable to compounded formulations intended for use in intraspinal pumps. These include the following:

- (1) Avoiding preservatives, antioxidants and solubility enhancers, as they may be neurotoxic and/or may be incompatible with the delivery system.
- (2) Using buffers that are compatible with the delivery system. Acetate buffers are not compatible with the SynchroMed infusion system.

- (3) Using a pH that is physiologically appropriate and is consistent with the drug solubility and delivery system, generally in the range of pH 4–8. For example, morphine and hydromorphone are most stable at lower pH (4–5), but a pH lower than 4 may degrade certain delivery system components.
- (4) Using solutions that are, ideally, isotonic with normal CSF (approximately 300 mOsm/L). Because the relatively poor mixing of the CSF compartment can result in relatively prolonged exposure of spinal tissues adjacent to the tip of the catheter, solutions that are close to isotonic are preferred. The osmotic contribution of each analgesic and each excipient, such as sodium chloride or buffer ions, should be considered. Sterile water for injection may be a better diluent than sterile saline to achieve appropriate tonicity for solutions that contain multiple drug components or drug(s) at high concentration.
- (5) Preparing the solution in a manner that does not alter the solubility of the constituents. The solubility of one agent may be affected by the presence of another. The order in which powdered components are dissolved, the choice of diluent, and the pH of the solution can all affect solubility. Solubility enhancers should be avoided, as they may be neurotoxic or incompatible with the delivery system.¹⁰⁶
- (6) Verifying the chemical and physical stability of the preparation under relevant conditions in accordance with the USP and ASHP publications. Stability information on the most common formulations may be found in the published literature.
- (7) Verifying the sterility of the preparation in accordance with the USP and ASHP publications.
- (8) Ensuring appropriate control of bacterial endotoxins (pyrogens). Bacterial endotoxins are a safety concern, even for a product that is terminally sterilized, because sterilization does not remove endotoxins. Endotoxin-contaminated

intrathecal preparations can induce aseptic meningitis.¹⁰⁶ Validated bacterial endotoxin test methods for specific and commonly compounded analgesic preparations are reported in the literature.¹⁰⁶

Conclusions

The goals of the expert panel participating at the Polyanalgesic Consensus Conference 2003 included a review of recent literature, revision of the algorithm for drug selection developed in 2000, development of guidelines for optimizing drug concentration and dosage, creation of a process for documenting the minimum evidence needed to support the use of a drug in neuraxial infusion, and clarification of the issues pertaining to compounding of drugs. The challenge in meeting these expansive goals largely related to the combination of limited evidence and diversity in clinical experience. Nonetheless, a “best evidence” approach led to consensus in each of these areas. This material and the conclusions it generated should be further refined as knowledge accumulates and clinical experience with intraspinal therapy grows. Although the data pertaining to this therapy are still limited, the guidelines developed by the expert panel are conservative and likely to improve the safety of intrathecal infusion if followed by clinicians. The issues discussed underscore the compelling need for further preclinical and clinical research.

Acknowledgments

The authors thank Tony Yaksh, PhD, Robert Coffey, MD, and Ashley Classen, DO, for their insightful reviews of this article. The Polyanalgesic Consensus Conference 2003 was supported through an unrestricted grant from Medtronic, Inc., Minneapolis, Minnesota.

References

1. Bennett G, Burchiel K, Buchser E, et al. Clinical guidelines for intraspinal infusion: Report of an Expert Panel. *J Pain Symptom Manage* 2000;20:S37–S43.
2. Hassenbusch SJ, Portenoy RK. Current practices in intraspinal therapy—A survey of clinical trends in decision making. *J Pain Symptom Manage* 2000;20:S4–S11.
3. Bennett G, Serafini M, Burchiel K, et al. Evidence-based review of the literature on intrathecal delivery of pain medication. *J Pain Symptom Manage* 2000;20:S12–S36.
4. Bennett G, Deer T, Du Pen S, et al. Future directions in the management of pain by intraspinal drug delivery. *J Pain Symptom Manage* 2000;20:S44–S50.
5. Walker SM, Goudas LC, Cousins MJ, Carr DB. Combination spinal analgesic chemotherapy: A systematic review. *Anesth Analg* 2002;95:674–715.
6. Gradert TL, Baze WB, Satterfield W, et al. Safety of chronic intrathecal morphine infusion in a sheep model. *Anesthesiology* 2003;99:188–198.
7. Yaksh TL, Horais KA, Tozier NA, et al. Chronically infused intrathecal morphine in dogs. *Anesthesiology* 2003;99:174–187.
8. Yaksh TL, Hassenbusch S, Burchiel K, et al. Inflammatory masses associated with intrathecal drug infusion: A review of preclinical evidence and human data. *Pain Med* 2002;3:300–312.
9. Winkelmuller W, Burchiel K, Van Buyten J. Intrathecal opioid therapy for pain: Efficacy and outcomes. *Neuromodulation* 1999;2:67–76.
10. Smith TJ, Staats PS, Deer T, et al. Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: Impact on pain, drug-related toxicity, and survival. *J Clin Oncol* 2002;20:4040–4049.
11. Kumar K, Kelly M, Pirlot T. Continuous intrathecal morphine treatment for chronic pain of nonmalignant etiology: Long-term benefits and efficacy. *Surg Neurol* 2001;55:79–88.
12. Deer T, Chapple I, Classen A, et al. Intrathecal drug delivery for treatment of chronic low back pain: Report from the National Outcomes Registry for Low Back Pain. *Pain Med* 2004;5:6–13.
13. Aldrete JA, Couto da Silva JM. Leg edema from intrathecal opiate infusions. *Eur J Pain* 2000;4:361–365.
14. Abs R, Verhelst J, Maeyaert J, et al. Endocrine consequences of long-term intrathecal administration of opioids. *J Clin Endocrinol Metab* 2000;85:2215–2222.
15. Rauck RL, Cherry D, Boyer MF, et al. Long-term intrathecal opioid therapy using a patient-activated implanted delivery system for the treatment of refractory cancer pain. *J Pain* 2003;4:441–447.
16. Cherry DA, Gourlay GK, Eldredge KA. Management of chronic intractable angina—Spinal opioids offer an alternative therapy. *Pain* 2003;102:163–166.
17. Coffey RJ, Burchiel K. Inflammatory mass lesions associated with intrathecal drug infusion catheters: Report and observations on 41 patients. *Neurosurgery* 2002;50:78–87.

18. Hassenbusch S, Burchiel K, Coffey R, et al. Management of intrathecal catheter-tip inflammatory masses: A consensus statement. *Pain Med* 2002;3: 313–323.
19. Johansen MJ, Satterfield WC, Baze WB, et al. Continuous intrathecal infusion of hydromorphone: Safety in the sheep model and clinical implications. *Pain Med* 2004;5:14–25.
20. Coombs DW, Colburn RW, DeLeo JA, Hoopes PJ, Twitchell BB. Comparative spinal neuropathy of hydromorphone and morphine after 9 and 30 day epidural administration in sheep. *Anesth Analg* 1994;78:674–681.
21. Hildebrand KR, Elsberry DE, Anderson VC. Stability and compatibility of hydromorphone hydrochloride in an implantable infusion system. *J Pain Symptom Manage* 2001;22:1042–1047.
22. Trissel LA, Xu QA, Lien P. Physical and chemical stability of hydromorphone hydrochloride 1.5 and 80 mg/ml packaged in plastic syringes. *Intl J Pharm Compounding* 2002;6:74–76.
23. Anderson VC, Cooke B, Burchiel K. Intrathecal hydromorphone for chronic nonmalignant pain: A retrospective study. *Pain Med* 2001;2:287–297.
24. Du Pen S, Du Pen A, Hillyer J. Intrathecal hydromorphone for intractable nonmalignant pain: A retrospective study. (Submitted to *Pain Med*)
25. Willis KD, Doleys DM. The effects of long-term intraspinal infusion therapy with noncancer pain patients: Evaluation of patient, significant-other, and clinic staff appraisals. *Neuromodulation* 1999;2: 241–253.
26. Kamran S, Wright BD. Complications of intrathecal drug therapy. *Neuromodulation* 2001;4: 111–115.
27. Roberts LJ, Finch PM, Goucke CR, Price LM. Outcome of intrathecal opioids in chronic noncancer pain. *Eur J Pain* 2001;5:353–361.
28. Boersma FP, Heykants J, Ten Kate A, et al. Sufentanil concentrations in the human spinal cord after long-term epidural infusion. *Pain Clinic* 1991;4:199–203.
29. Mironer YE, Tollison CD. Methadone in the intrathecal treatment of chronic nonmalignant pain resistant to other neuroaxial agents: The first experience. *Int Neuromodulation Soc* 2001;4:25–31.
30. Shir Y, Shapira SS, Shenkman Z, Kaufman B, Magora F. Continuous epidural methadone treatment for cancer pain. *Clin J Pain* 1991;7:339–341.
31. Mironer YE, Haasis JC III, Chapple ET, et al. Successful use of methadone in neuropathic pain: A multicenter study by the National Forum of Independent Pain Clinicians. *Pain Dig* 1999;9:191–193.
32. Mironer YE, Grumman S. Experience with alternative solutions in intrathecal treatment of chronic nonmalignant pain. *Pain Dig* 1999;9:299–302.
33. Hildebrand KR, Elsberry DD, Deer TR. Stability, compatibility, and safety of intrathecal bupivacaine administered chronically via an implantable delivery system. *Clin J Pain* 2001;17:239–244.
34. Trissel LA, Pham L. Physical and chemical stability of low and high concentrations of morphine sulfate and bupivacaine hydrochloride packaged in plastic syringes. *Int J Pharm Compounding* 2002; 6:70–73.
35. Mironer YE, Haasis JC, Chapple I, Brown C, Satterthwaite JR. Efficacy and safety of intrathecal opioid/bupivacaine mixture in chronic nonmalignant pain: A double blind, randomized, crossover, multicenter study by the National Forum of Independent Pain Clinicians (NFIPC). *Neuromodulation* 2002;5:208–213.
36. van Dongen RTM, Crul BJP, von Egmond J. Intrathecal coadministration of bupivacaine diminishes morphine dose progression during long-term intrathecal infusion in cancer patients. *Clin J Pain* 1999;15:166–172.
37. Deer TR, Caraway DL, Kim CK, et al. Clinical experience with intrathecal bupivacaine in combination with opioid for the treatment of chronic pain related to failed back surgery syndrome and metastatic cancer pain of the spine. *Spine J* 2002;2:274–278.
38. Lundborg C, Dahm P, Nitescu P, Appelgren L, Curelaru I. Clinical experience using intrathecal (IT) bupivacaine infusion in three patients with complex regional pain syndrome type I (CRPS-I). *Acta Anaesthesiol Scand* 1999;43:667–678.
39. Dahm P, Lundborg C, Janson M, Olegard C, Nitescu P. Comparison of 0.5% intrathecal bupivacaine with 0.5% intraspinal ropivacaine in the treatment of refractory cancer and noncancer pain conditions: Results from a prospective, crossover, double-blind, randomized study. *Reg Anesth Pain Med* 2000;25:480–487.
40. Hildebrand KR, Elsberry DD, Hassenbusch SJ. Stability and compatibility of morphine-clonidine admixtures in an implantable infusion system. *J Pain Symptom Manage* 2003;25:464–471.
41. Trissel LA, Xu QA, Pham L. Physical and chemical stability of low and high concentrations of morphine sulfate with clonidine hydrochloride packaged in plastic syringes. *Int J Pharm Compounding* 2002;6:66–69.
42. Classen AM, Wimbish GH, Kupiec TC. Stability of admixture containing morphine sulfate, bupivacaine hydrochloride, and clonidine hydrochloride, in an implantable infusion system, in press.
43. Vermiere A, Remon JP. Stability and compatibility of morphine. *Int J Pharm* 1999;187:17–51.
44. Hassenbusch SJ, Gunes S, Wachsmann S, Willis KD. Intrathecal clonidine in the treatment of intractable pain: A phase I/II study. *Pain Med* 2002;3: 85–91.

45. Ackerman LL, Follett KA, Rosenquist RW. Long-term outcomes during treatment of chronic pain with intrathecal clonidine or clonidine/opioid combinations. *J Pain Symptom Manage* 2003;26:668–677.
46. Uhle EI, Becker R, Gatscher S, Bertalanffy H. Continuous intrathecal clonidine administration for the treatment of neuropathic pain. *Stereotact Funct Neurosurg* 2000;75:167–175.
47. Siddall PJ, Molloy AR, Walker S, et al. The efficacy of intrathecal morphine and clonidine in the treatment of pain after spinal cord injury. *Anesth Analg* 2000;91:1493–1498.
48. Kroin JS, McCarthy RJ, Penn RD. Continuous intrathecal clonidine and tizanidine in conscious dogs: Analgesic and hemodynamic effects. *Anesth Analg* 2003;96:776–782.
49. Hassenbusch SJ, Satterfield WC, Gradert TL, et al. Preclinical toxicity study of intrathecal administration of the pain relievers dextrophan, dextromethorphan, and memantine in the sheep model. *Neuromodulation* 1999;2:230–240.
50. Miyamoto H, Saito Y, Kirihaara Y, et al. Spinal coadministration of ketamine reduces the development of tolerance to visceral as well as somatic antinociception during spinal morphine infusion. *Anesth Analg* 2000;90:136–141.
51. Walker SE, Law S, DeAngelis C. Stability and compatibility of hydromorphone and ketamine in normal saline. *Can J Hosp Pharm* 2001;54:193–201.
52. Sator-Katzenschlager S, Deutsch E, Maier P, Spacek A, Kress HG. The long-term antinociceptive effect of intrathecal S(+)-ketamine in a patient with established morphine tolerance. *Anesth Analg* 2001;93:1032–1034.
53. Stotz M, Oehen HP, Gerber H. Histological findings after long-term infusion of intrathecal ketamine for chronic pain: A case report. *J Pain Symptom Manage* 1999;18:223–228.
54. Goodwin K, Kim N-H, Zuniga R. Stability of a baclofen and clonidine hydrochloride admixture for intrathecal administration. *Hosp Pharm* 2001;26:950–954.
55. van Hilten BJ, van de Beek WJ, Hoff JI, Voormolen JH, Delhaas EM. Intrathecal baclofen for the treatment of dystonia in patients with reflex sympathetic dystrophy. *N Engl J Med* 2000;343:625–630.
56. Gatscher S, Becker R, Uhle E, Bertalanffy H. Combined intrathecal baclofen and morphine infusion for the treatment of spasticity related pain and central deafferentation pain. *Acta Neurochir Suppl* 2002;79:75–76.
57. Zuniga RE, Perera S, Abram SE. Intrathecal baclofen: A useful agent in the treatment of well-established complex regional pain syndrome. *Reg Anesth Pain Med* 2002;27:90–93.
58. Zuniga RE, Schlicht R, Abram SE. Intrathecal baclofen is analgesic in patients with chronic pain. *Anesthesiology* 2000;92:876–880.
59. Becker R, Uhle EI, Alberti O, Bertalanffy H. Continuous intrathecal baclofen infusion in the management of central deafferentation pain. *J Pain Symptom Manage* 2000;20:313–315.
60. Coffey RJ, Edgar TS, Francisco GE, et al. Abrupt withdrawal from intrathecal baclofen: Recognition and management of a potentially life-threatening syndrome. *Arch Phys Med Rehabil* 2002;83:735–741.
61. Partridge BJ, Chaplan SR, Sakamoto E, Yaksh TL. Characterization of the effects of gabapentin and 3-isobutyl-gamma-aminobutyric acid on substance P-induced thermal hyperalgesia. *Anesthesiology* 1998;88:196–205.
62. Cheng JK, Pan HL, Eisenach JC. Antiallodynic effect of intrathecal gabapentin and its interaction with clonidine in a rat model of postoperative pain. *Anesthesiology* 2000;92:1126–1131.
63. Hwang JH, Yaksh TL. Effect of subarachnoid gabapentin on tactile-evoked allodynia in a surgically induced neuropathic pain model in the rat. *Reg Anesth* 1997;22:249–256.
64. Lu C, Westlund K. Gabapentin attenuates nociceptive behaviors in an acute arthritis model in rats. *J Pharmacol Exper Ther* 1999;290:214–219.
65. Yoon MH, Yaksh TL. The effect of intrathecal gabapentin on pain behavior and hemodynamics on the formalin test in rats. *Anesth Analg* 1999;89:434–439.
66. Yoon MH, Yaksh TL. Evaluation of interaction between gabapentin and ibuprofen on the formalin test in rats. *Anesthesiology* 1999;91:1006–1013.
67. Chen SR, Eisenach JC, McCaslin PP, Pan HL. Synergistic effect between intrathecal non-NMDA antagonist and gabapentin on allodynia induced by spinal nerve ligation in rats. *Anesthesiology* 2000;92:500–506.
68. Wallin J, Cui JG, Yakhnitsa V, et al. Gabapentin and pregabalin suppress tactile allodynia and potentiate spinal cord stimulation in a model of neuropathy. *Eur J Pain* 2002;6:261–272.
69. Jun JH, Yaksh TL. The effect of intrathecal gabapentin and 3-isobutyl gamma-aminobutyric acid on the hyperalgesia observed after thermal injury in the rat. *Anesth Analg* 1998;86:348–354.
70. Cho HS, Kim MH, Choi DH, et al. The effect of intrathecal gabapentin on mechanical and thermal hyperalgesia in neuropathic rats induced by spinal nerve ligation. *J Korean Med Sci* 2002;17:225–229.
71. Laughlin TM, Tram KV, Wilcox GL, Birnbaum AK. Comparison of antiepileptic drugs tiagabine, lamotrigine, and gabapentin in mouse models of acute, prolonged, and chronic nociception. *J Pharmacol Exper Ther* 2002;302:1168–1175.

72. Grabow TS, Dougherty PM. Gabapentin produces dose-dependent antinociception in the orofacial formalin test in the rat. *Reg Anesth Pain Med* 2002;27:277–283.
73. Kaneko M, Mestre C, Sanchez EH, Hammond DL. Intrathecally administered gabapentin inhibits formalin-evoked nociception and the expression of Fos-like immunoreactivity in the spinal cord of the rat. *J Pharmacol Exp Ther* 2000;292:743–751.
74. Nishiyama T, Matsukawa T, Hanaoka K. Acute phase histopathological study of spinally administered midazolam in cats. *Anesth Analg* 1999;89:717–720.
75. Nishiyama T, Hanaoka K. The synergistic interaction between midazolam and clonidine in spinally-mediated analgesia in two different pain models of rats. *Anesth Analg* 2001;93:1025–1031.
76. Johansen MJ, Gradert TL, Satterfield WC, et al. Toxicity and efficacy of continuous intrathecal midazolam infusion in the sheep model. *Anesth Analg*, in press.
77. Erdine S, Yucel A, Ozyuvaci E, et al. Neurotoxicity of midazolam in the rabbit. *Pain* 1999;80:419–423.
78. Malinovsky JM, Cozian A, Lepage JY, et al. Ketamine and midazolam neurotoxicity in the rabbit. *Anesthesiology* 1991;75:91–97.
79. Yaksh TL, Allen JE. The use of intrathecal midazolam in humans: A case study of process. *Anesth Analg*, in press.
80. Rainov NG, Heidecke MD, Burkert W. Long-term intrathecal infusion of drug combinations for chronic back and leg pain. *J Pain Symptom Manage* 2001;22:862–871.
81. Tucker AP, Lai C, Nadeson R, Goodchild CS. Intrathecal midazolam I: A cohort study investigating safety. *Anesth Analg*, in press.
82. Tucker AP, Mezzatesta J, Nadeson R, Goodchild CS. Intrathecal midazolam II: Combination with intrathecal fentanyl for labor pain. *Anesth Analg*, in press.
83. Yong-Ziang W, Da Gao M, Phillips S. Interactions of intrathecally administered ziconotide, a selective blocker of neuronal N-type voltage sensitive calcium channels, with morphine on nociception in rats. *Pain* 2000;84:271–281.
84. Unpublished data.
85. Staats PS, Yearwood T, Charapata SG, et al. Intrathecal ziconotide in the treatment of refractory pain in patients with cancer or AIDS: A controlled clinical trial. *JAMA* 2004;291:63–70.
86. Brose W, Gutlove D, Luther R, Bowersox SS, McGuire D. Use of intrathecal SNX-111, a novel, N-type, voltage-sensitive, calcium channel blocker, in the management of intractable brachial plexus avulsion pain. *Clin J Pain* 1997;13:256–259.
87. Staats PS, Luthardt F, Shipley J, Jackson C, Fisher K. Long-term intrathecal ziconotide therapy: A case study and discussion. *Neuromodulation* 2001;4:121–126.
88. Yegin A, Yilmaz M, Karsli B, Erman M. Analgesic effects of intrathecal neostigmine in perianal surgery. *Eur J Anaesthesiol* 2003;20:404–408.
89. Kaya FN, Sahin S, Owen MD, Eisenach JC. Epidural neostigmine produces analgesia but also sedation in women after cesarean delivery. *Anesthesiology* 2004;100:381–385.
90. Eisenach JC, Rauck RL, Curry R. Intrathecal, but not intravenous adenosine reduces allodynia in patients with neuropathic pain. *Pain* 2003;105:65–70.
91. Eisenach JC, Curry R, Hood DD, Yaksh TL. Phase I safety assessment of intrathecal ketorolac. *Pain* 2002;99:599–604.
92. Yaksh TL, Harty GJ. Pharmacology of the allodynia in rats evoked by high-dose intrathecal morphine. *J Pharmacol Exp Ther* 1988;244:501–507.
93. Li DF, Bahar M, Cole G, Rosen M. Neurological toxicity of the subarachnoid infusion of bupivacaine, lignocaine or 2-choloprocaine in the rat. *Br J Anaesth* 1985;57:424–429.
94. Sakura S, Bollen AW, Ciriales R, Drasner K. Local anesthetic neurotoxicity does not result from the blockade of voltage-gated sodium channels. *Anesth Analg* 1995;81:338–346.
95. Yamashita A, Matsumoto M, Matsumoto S, et al. A comparison of the neurotoxic effects on the spinal cord of tetracaine, lidocaine, bupivacaine, and ropivacaine administered intrathecally in rabbits. *Anesth Analg* 2003;97:512–519.
96. Ready LB, Plumer MH, Haschke RH, Austin E, Sumi SM. Neurotoxicity of intrathecal local anesthetics in rabbits. *Anesthesiology* 1985;63:364–370.
97. Kroin JS, McCarthy RJ, Penn RD, Kerns JM, Ivankovich AD. The effect of chronic subarachnoid bupivacaine infusion in dogs. *Anesthesiology* 1987;66:737–742.
98. Eisenach JC, Yaksh TL. Safety in numbers: How do we study toxicity of spinal analgesics? *Anesthesiology* (Editorial Views) 2002;97:1047–1049.
99. Grouls RJE, Korsten EHM, Yaksh TL. General considerations for the formulation of drugs for spinal delivery. In: Yaksh TL, ed. *Spinal drug delivery*. Amsterdam: Elsevier Science BV, 1999:371–393.
100. Yaksh TL. Spinal systems and pain processing: Development of novel analgesic drugs with mechanistically defined models. *Trends Pharmacol Sci* 1999;20:329–337.
101. Yaksh TL, Rathbun ML, Provencher JC. Preclinical safety evaluation for spinal drugs. In: Yaksh TL, ed. *Spinal drug delivery*. Amsterdam: Elsevier Science BV, 1999:417–437.
102. USP General Chapter <797> Pharmaceutical Compounding—Sterile Preparations. U.S. Pharmacopeia, January 1, 2004.

103. Jones TF, Felera CA, Simmons BP, et al. Neurologic complications including paralysis after a medication error involving implanted intrathecal catheters. *Am J Med* 2002;112:31–36.
104. Cooper JF, Thoma L. Screening extemporaneously compounded intraspinal injections with the bacterial endotoxins test. *Am J Health Syst Pharm* 2002;59:2426–2432.
105. American Society of Health-System Pharmacists. ASHP guideline on quality assurance for pharmacy-prepared sterile products. *Am J Health Syst Pharm* 2003;60:1440–1446.
106. Trissel LA. Trissel's™ stability of compounded formulations, 2nd ed. Washington, DC: APhA Publications, 2000.

Appendix

Dosing and Concentration Survey Among Experienced Physicians

An internet survey was conducted among a small group of highly-experienced physicians regarding dosing and concentrations of various intrathecal drugs infused long-term to control pain. The aim was to characterize the practices of experienced clinicians.

Survey Methodology

Invitations to participate in the survey were e-mailed to 345 physicians considered to be leaders in the field of pain management. In order to qualify for participation in the study, physicians were required to have implanted intrathecal pumps for pain management for at least 3 years, to have implanted at least six pumps for pain medications during the 12 months preceding the survey, and to have been treating at least 20 pain patients with implanted pumps at the time of the survey. Only 40 physicians (12%), nine of whom were co-authors of this article, completed the survey. Because the number of physicians answering questions about a particular drug or drug combination for a certain type of patient was even smaller (often less than 10), the results are not statistically reliable, but the data do provide an initial overview of current practice among experienced clinicians.

Survey Findings

The 40 responding physicians had a mean (median) number of years in practice of 11 (8).

The mean number of years of implanting intrathecal medication pumps was 9 (range, 4–18; median, 8 years) and the mean (median) number of pumps implanted in the past year was 17 (12). At the time of the survey, the mean (median) number of patients (managed by the physician group) with implanted medication pumps was 49 (47), and the mean percent of patients with implanted pumps who had cancer pain was 19%. The distribution of specialties was as follows: anesthesiology, 78%, neurosurgery, 10%, and other, 12%.

When questioned about the use of drugs and drug combinations to treat pain, physicians indicated that they used morphine most often, alone and in combination with other drugs. Hydromorphone was used by almost as many physicians, alone and in combination, but on fewer patients. Fentanyl was used much less often, and sufentanil was rarely used. A consistent trend was the wide variations in concentrations and daily dosages administered of morphine alone, hydromorphone alone, and fentanyl alone. Physicians often adjusted the dosages of drugs or drug combinations by a fixed percentage at each adjustment, most often between 10% and 20%, whether increasing or decreasing the dosage. Physicians made an average of five to eight adjustments to a dosage before switching to a different drug or drug combination. Physicians seemed willing to try more dosage adjustments for morphine and hydromorphone and combinations containing these agents than for fentanyl or sufentanil or combinations containing these agents, and they usually kept patients on a drug or drug combination for 1 to 2 weeks for non-cancer pain before making a dosage adjustment. They allowed more time at a given dosage for morphine and hydromorphone or combinations containing these drugs than for fentanyl or sufentanil or combinations containing these drugs. Approximately one-half of their non-cancer patients treated with each drug or drug combination responded well to it and experienced a sustained response for at least 6 months. Approximately one-half of the respondents' patients who began on single drug therapy eventually received polytherapy.