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ORIGINAL ARTICLE

Polyanalgesic Consensus Conference 2007: Recommendations for the Management of Pain by Intrathecal (Intraspinal) Drug Delivery: Report of an Interdisciplinary Expert Panel

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ABSTRACT

Background. Expert panels of physicians and nonphysicians in the field of intrathecal therapies convened in 2000 and 2003 to make recommendations for the rational use of intrathecal analgesics based on the preclinical and clinical literature known up to those times. An expert panel of physicians convened in 2007 to update previous recommendations and to form guidelines for the rational use of intrathecal opioid and nonopioid agents. **Methods.** A review of preclinical and clinical published relevant studies from 2000 to 2006 was undertaken and disseminated to a convened expert panel of physicians and nonphysicians. Focused discussions were held on the rational use of intrathecal agents and a survey asking questions regarding intrathecal therapies management was given to the panelists. **Results.** The panelists, after review of the literature from 2000 to 2006 and discussion, created an updated algorithm for the rational use of intrathecal opioid and nonopioid agents in patients with nonmalignant and end-of-life pain. Of note is that the panelists felt that ziconotide, based on new and relevant literature and experience, should be updated to a line one intrathecal drug.

KEY WORDS: *Analgesics, consensus, guidelines, intrathecal, polyanalgesia.*

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Introduction

Intraspinal (intrathecal) infusions of opioids and other analgesic medications have been used increasingly since the late 1980s for the treatment of chronic pain that is refractory to conventional therapies. Recent technological advances have enhanced the safety and reliability of implantable drug delivery systems (IDDS) and have permitted further clinical testing of established medications, drug admixtures, and novel analgesic compounds for use in intrathecal (IT) drug delivery systems. Current thinking in the field of IT drug delivery is informed by preclinical data from physiochemical and animal studies, and by clinical data, although limited, from serial case studies and trials. At present, comparative research on systemic and intraspinal medications helps guide the synthesis of new molecules designed specifically for IT therapeutic use. As the field evolves, more attention is being given to critical device-related variables such as the compatibility of the medication with the drug delivery system that affect concentration, safety and the presence of adverse effects (e.g., inflammatory mass), and outcomes.

In spite of these efforts, clinical research on IT analgesics that meets the "gold standard" of evidenced-based studies has not kept pace with the growing need for innovative approaches to pain management. Rigorous supporting data on the safety and efficacy of a broad cross-section of opioid and nonopioid IT medications remains, to this day, inadequate. This was the case when the first expert panel that addressed this issue convened for the Polyanalgesic Consensus Conference 2000. The panel reviewed existing data suggesting an algorithm for drug selection when using IT polyanalgesia based on "best evidence" and expert opinion, and set forth recommendations for further evidence-based research. The panel published its findings and guidelines in 2000 (1) and presented supplemental reports, including a literature review (2), survey results (3), and discussion of future directions in the field (4).

To meet the challenges of emerging new opportunities, including the availability of experimental medications and new drug formulations, a second expert panel convened for the Polyanalgesic Consensus Conference 2003. The tasks of this panel were to review the pertinent medical literature on intraspinally administered medications published since 1999, update the algorithm for intraspinal drug selection, introduce guidelines for optimizing drug concentration and dosage during therapy, and clarify existing regulations and guidelines relating to the use of compounded medications for IT delivery. The other primary responsibility of the panel was to develop consensus regarding the evidence needed to support the use of a drug for long-term IT infusion. In response to the last task, the 2003 panel elected to base the guideline conclusions on the "best available evidence," inclusive of both an updated literature review and expert consensus. In 2003, very few published studies existed on IT analgesics that provided "type A evidence" generated through the gold standard of double-blind, placebo-controlled, randomized clinical trials. The continued limitation of "type A evidence" has hindered the development of robust clinical data on IT polyanalgesics that can be rated and ranked in accord with Food and Drug Administration (FDA) protocol.

The 2003 panel evaluated the utility of using "minimal evidence" gleaned from validated preclinical pain models and, where feasible, from "tentative" or inferential clinical trials, to support the use of analgesic medications for IT therapy. Essential preclinical "minimal evidence" was defined as data from physiochemical studies on solubility, pH, drug (or drug–drug) stability, compatibility of the drug with the delivery device, and data from validated animal pain models on toxicity, mechanism of action site, pharmacokinetics, and efficacy. Essential clinical "minimal evidence" was described as data regarding side-effects and safety, typically derived from noncontrolled studies or case studies, while desirable "minimal evidence" consisted of pharmacokinetic findings. The problem with this approach, however, is that it ignores other valuable input such as the firsthand clinical observations of physicians who are experienced using IT drug delivery. The consensus opinion of expert panelists constituted an equally authoritative source of data, even if unpublished, that to some degree was comparable with the published data. The logic of the panelists attending the Polyanalgesic Conference 2003 was that "best evidence" should consist of published preclinical and clinical data *plus* expert opinion. The findings and guidelines of the Polyanalgesic Conference 2003 were published in 2004 (5).

Following the same rationale as used in the two previous conferences for updating relevant information and guidelines, a consensus conference of experts in the field of IT therapies, a third polyanalgesic conference, Polyanalgesic Conference 2007, was convened. The guidelines for the drug selection algorithm recommended by the Polyanalgesic Conference 2007 are based on evidence derived from two sources: 1) a broad, although not necessarily exhaustive, literature review of studies published between 2000 and 2006 on both preclinical and clinical data relevant to IT opioid and nonopioid analgesics and 2) the expert consensus of panelists, including clinicians, basic medical science researchers, and clinical investigators. The tasks of the Polyanalgesic Conference 2007 were as follows:

1 Review the conclusions and guidelines of the Polyanalgesic Conference 2000 and Polyanalgesic Conference 2003.
2 Evaluate the current guidelines for IT drug infusion.
3 Review survey responses of fellow peers in the field of IT analgesics for pain management and use the findings to guide discussion during the conference.

4 Review preclinical and clinical data relevant to IT analgesics published since 2000.
5 Formulate consensus opinions on critical issues for IT polyanalgesic therapy.
6 Modify and update the IT analgesic drug selection algorithm, as appropriate, based on "best evidence" from published data and expert consensus opinion.
7 Identify areas, including promising underresearched and experimental analgesic agents, for future evidence-based research that will advance the clinical practice of IT drug infusion therapy.
8 Disseminate the consensus opinions and primary conclusions of the expert panelists to the medical community through data-driven articles published in appropriate peer-reviewed biomedical journals.

The reviewed literature relevant to IT opioid and nonopioid analgesia is reported in the next section of this article. Following this review and update of information will be the consensus panel's recommendations for IT analgesia. These recommendations will be presented in similar fashion to Polyanalgesic Conference 2000 (1) and Polyanalgesic Conference 2003 (5). Also presented will be the panel's recommendations for IT therapies for end-of-life care. It should be understood, at all times, that the recommendations presented in this article represent consensus of expert opinion regarding what is old and what is new, and not what is standard of care. Readers of these guidelines should use these guidelines/recommendations, based on their understanding of the literature and expertise, in a way that might help them formulate knowledge-based decisions when using IT analgesic therapies.

Intrathecal Medications: Literature Update July 2003–January 2007

This literature review is an update to the "Polyanalgesic Consensus Conference 2003: An Update on the Management of Pain by Intraspinal Drug Delivery—Report of an Expert Panel" (5). The review covers preclinical and clinical studies on IT analgesic drug infusions, including opioid, nonopioid, and polyanalgesic medications, published between 2000 and the present (January 15, 2007). It contains summaries of data on a range of medications that are either currently in use, or are potentially indicated, for the IT treatment of pain, particularly intractable pain that has not been successfully managed by conventional therapeutic approaches. The review contains integrated literature synopses of 1) mechanism of action; 2) preclinical data (toxicology, safety and efficacy in animal models, drug stability); and 3) clinical data on safety/complications, efficacy, dosing, coadministration from anecdotal case reports, serial/multiple case report studies, and clinical trials for each IT analgesic medication.

The studies and, to a lesser extent, editorial commentaries, included in this review, address issues of safety, efficacy, drug or drug–drug stability, and device-related issues such as compatibility of an analgesic agent with the drug pump and catheter delivery system. Since the publication (5) of the Polyanalgesic Consensus Conference in 2003, studies on IT medications for pain relief have increasingly provided more data-driven evidence for efficacy, drug tolerability, dosage, adverse events, and the effects of analgesic drug admixtures. While several agents previously under discussion are no longer considered viable treatments for IT use, other compounds may have safe and efficacious therapeutic value, as either single medications or components of combination IT drug infusions.

Intrathecal Opioids

Morphine

Preclinical Data

Opioids act at receptors in the substantia gelatinosa of the spinal cord dorsal horn and produce dose-dependent analgesia (6,7). Furthermore, there also are sex differences in the way animals respond to intrathecal morphine (8). High doses of IT morphine induce thermal nociception and certain components of analgesia through several cellular mechanisms, including blockage of the release of neurotransmitters from primary afferents via presynaptic inhibition of calcium channels (9–11). Additionally, postsynaptic neuronal hyperpolarization results from the opening of G-protein-gated, K^+ channels in the central nervous system that are composed mainly of GIRK1 (G-protein-regulated inwardly rectifying K^+ channel 1)/GIRK2 complexes (7). Increased stimulus-evoked excitatory transmission mechanisms may facilitate the mechanisms underlying opioid-induced abnormal pain. Coadministration of morphine and amlodipine, a putative selective L-type calcium channel blocker, prevented hypersensitivities, presumably by decreasing stimulus-induced excitatory neurotransmitter release (12) in mice. Animals administered amlodipine as a coadjuvant with morphine did not display a rightward shift of the dose–response curve indicative of morphine antinociceptive tolerance.

The antihypersensitivity activity of morphine in animal models of neuropathic pain appears to be completely dependent on A1 adenosine receptor activation (13). Injection of mu opioid receptor adeno-associated viral vector into the sciatic nerve of animals resulted in a significant up-regulation of mu opioid receptors in dorsal root ganglia for up to six months and produced a 5.4-fold increase in the antinociceptive potency of IT morphine (14).

A single dose of IT morphine in rats produced a biphasic response: Long-lasting hyperalgesia involving a three- to five-hour increase in the nociceptive threshold followed by delayed hyperalgesia characterized by a decline in the

nociceptive threshold for one to two days (15). Intrathecal morphine (0.1–10 μg) produced dose-dependent antinociceptive effects, including attenuation of spared nerve injury model (a model of neuropathic pain where the nerve is ligated and not severed) and induced mechanical allodynia in the hairy skin, that were reversed by naloxone (16,17).

Spinal morphine withdrawal syndrome is due to the inability of morphine to suppress the release of excitatory neurotransmitters/neuromodulators from primary afferents following long-term exposure to morphine (18). Spinal pro-inflammatory cytokines and fractalkine, a chemokine, have been identified as possible endogenous regulators of tolerance to the analgesic effects of IT morphine. Delivery of chronic (five days), but not acute (one day), IT morphine induced a rapid increase in pro-inflammatory cytokine protein and/or mRNA in dorsal spinal cord and lumbosacral cerebrospinal fluid (CSF) in rats (19). Intrathecal morphine coadministered with IT IL-1 receptor antagonist (IL-1ra) enhanced acute morphine analgesia while blocking hyperalgesia, allodynia, and analgesic tolerance. Fractalkine produced a similar effect apparently by acting on IL-1 that in turn modulated the effects of IT morphine.

The toxicity of IT morphine has been addressed in earlier studies demonstrating a causal association between IT morphine sulfate infusion and the formation of catheter-tip granuloma in beagle dog and sheep models at doses as low as 1.5 and 12 mg/day, respectively (20,21). Magnetic resonance imaging (MRI) and histopathologic analysis reveal that the formation of catheter-tip inflammatory masses in dogs is dependent on IT morphine sulfate local concentration rather than dose (22,23). Chronic intrathecal morphine at doses of 9 or 12 mg/day produced allodynia in beagle dogs shortly after infusion commenced, a concentration-dependent increase in hind limb dysfunction during the course of the infusion (24) and spastic paraparesis at a dose of (30 μg) after 6 min of aortic occlusion in rats (25).

High-performance liquid chromatography (HPLC) analysis showed that morphine sulfate in an admixture with bupivacaine hydrochloride and clonidine hydrochloride incubated in SynchroMed implantable pumps (SynchroMed, Medtronic Inc., Minneapolis, MN, USA), at 37° for 90 days, remained stable with more than 96% of the original concentration intact. An earlier study showed that di-acetyl morphine (diamorphine) decays to mono-acetyl morphine to morphine in implanted SynchroMed pumps. The analgesia produced by diamorphine and its breakdown products was similar to the analgesia induced by morphine in patients with implanted SynchroMed pumps, for a duration of up to 10 weeks (26).

Clinical Data

The analgesic efficacy of IT morphine is evidenced in an increasing number of case reports and clinical trials, including studies comparing different routes of administration of morphine (27). And, there is evidence that morphine, when given intrathecally, is not only an analgesic, but may in fact be antispasmodic, working centrally (28). A multicentered retrospective study conducted in France analyzed 19 patients implanted with pumps for IT morphine (1–10 mg) treatment of chronic noncancer pain, including postsurgery lumbar and radicular pain in 68.4% of patients (29). The patient satisfaction rate was 90% and the analgesic effect was 67.8% with a 49.2% visual analog scale (VAS) decrease from initial values. While all patients in this study improved in physical activity, only 26.3% of the patients attained their initial functional performance levels. These data are comparable to those of other studies (30–32). Intrathecal analgesia was better in patients with nociceptive pain than in neuropathic or deafferentation pain syndromes. Pharmacologic adverse effects of somnolence, weight gain, nightmares, vomiting, itching, and constipation were reported.

In patients with refractory cancer pain, the use of IT (as well as epidural) analgesia significantly decreases the proportion (86% to 17%) of patients suffering from severe pain at eight-week follow-up (33). A prospective, randomized, double-blind study evaluated pain relief and opioid-related side-effects in opioid-naïve patients with nonmalignant, chronic back pain following administration of intrathecal morphine (range: 0.015–0.25 mg) (34). Dose-effect characteristics of postoperative nausea, vomiting, pruritus, urinary retention, and respiratory depression were assessed in the opioid-naïve test group ($N = 144$) and control ($N = 25$) patients. All patients administered intrathecal morphine reported pain relief when compared to the six patients (25%) of the control group ($p = 0.0005$). The incidence of major respiratory depression was low in the test group overall, but other side-effects varied by individual. Some mild adverse reactions occurred with small doses of IT morphine, suggesting that the onset and incidence of minor opioid-related side-effects in patients receiving IT morphine do not depend on dose. The patient-dependent effects of IT morphine may be partly explained by the theory of bimodal activation of opioid receptors (27).

Slowly increasing chronic respiratory depression is a potentially adverse effect of IT drug delivery of morphine that until recently had not been reported in the literature. In a case report, a 41-year-old man with an implanted IDDS pump (Isomed-60-mL; Medtronic Inc.) delivering IT morphine, 14 mg/day, plus 0.15 mg/day clonidine presented with reduced pulmonary function. He was eventually diagnosed with respiratory depression after an initial misdiagnosis. Clinical correlates of respiratory depression in patients receiving long-term IT administration that tend to go unrecognized include escalating morphine dose without any analgesic improvement, increasing fatigue, exercise dyspnea, and step-by-step loss of pulmonary function (35).

In an assessment of the benefits of hydromorphone compared to morphine, Johansen noted that high levels of

IT morphine-3-glucuronide have been associated with drowsiness, hyperalgesia, allodynia, and myoclonus (36). Continuous IT morphine treatment is associated with inadequate pain relief or intolerable side-effects in 10–15% of patients receiving this therapy (37). Other adverse effects that may result from in IT morphine infusion in high-concentration include the potential for granuloma formation (37–47) and increased noncardiac pedal edema (5). Low testosterone and estrogen leading to reduced libido may result from hypothalamic-pituitary suppression occurring during IT morphine administration (5,29).

A clinical survey by Raphael et al. (48) compared the effects of implanted multiple thoacolumbar lead spinal cord stimulation (SCS) and IT opioid drug delivery (ITDD) in patients with mechanical back pain who had not had prior spinal surgery. ITDD significantly improved quality of life measures more than SCS. While SCS and ITDD each produced a comparable significant reduction in pain, ITDD showed a trend toward greater pain relief than SCS; the trend was not statistically significant.

Hydromorphone

Preclinical Data

Hydromorphone, a semisynthetic hydrogenated ketone of morphine, is a more potent and faster-acting analgesic than morphine due to its greater lipophilic properties. While morphine is a pure mu receptor agonist, hydromorphone activates more than one subtype of opioid receptor including mu opioid receptors primarily and to a lesser extent, delta-opioid and k-opioid receptors (36). Because hydromorphone is more lipid-soluble and has less active metabolites than morphine, it has a smaller supraspinal distribution, which may account for fewer side-effects.

In the study by Johansen et al. (36), the infusion of IT hydromorphone (1.5–12 mg/day) did not cause inflammatory mass, significant gait deficits or histologic abnormalities in sheep. Mild inflammation located 5 cm cranial to the catheter tip was present in two of three sheep administered 12 mg/day and in one of three sheep administered 1.5 mg/day. No granulomatous masses were reported in sheep receiving hydromorphone doses (3 and 6 mg/day) equivalent to morphine doses (= 12 mg/day morphine) that produced granulomas in sheep (36). Future research is needed to determine whether hydromorphone is safer than morphine for continuous IT infusion for chronic pain control (36).

Hydromorphone retained stability at 95% of its initial potency in an infusion system (SynchroMed) at 37° for four months, as evidenced by HPLC method analysis. Ninety-six percent of the intact molecule was recovered from the drug (1.5 mg/mL and 80 mg/mL) stored in plastic syringes for 60 days at 4° and 23°, and for two days at 20° and 37° (49).

Clinical Data

Hydromorphone IT infusions offer a viable therapeutic alternative to IT morphine for patients with intractable pain not alleviated by morphine or intolerable side-effects to morphine. This medication, in particular, is appropriate for use in patient-controlled IDDS for treating breakthrough pain because of its relatively greater analgesic potency and fewer adverse side-effects when compared to morphine. Intrathecal morphine and IT hydromorphone, in a dose 20% of that of morphine, induce an equianalgesic response (36). Intrathecal hydromorphone improved the incidence of side-effects, including nausea and vomiting, pruritus, and sedation, in most patients with chronic nonmalignant pain who had shown poor analgesic response to IT morphine. Short-term, but not long-term, administration of IT hydromorphone mitigated peripheral edema in patients previously treated with IT morphine (37,50).

In a retrospective study ($N = 24$) studying pain relief and side-effects of IT hydromorphone monotherapy for the treatment of non-cancer-related chronic pain, all patients experienced a clinically relevant and statistically significant average reduction in pain without statistically significant increases in adverse effects, including granuloma formation (50). However, a published case report regarding the formation of granuloma in a patient receiving high-dose IT hydromorphone suggests that long-term use of intraspinal opioids, including hydromorphone, possibly at doses (and concentrations) lower than originally suspected, may pose a risk for the development of granuloma (51). As we shall see, this expert panel recommends a maximum concentration and dose of 10 mg/cc and 4 mg/day, respectively, for intrathecal use to, if possible, prevent granuloma.

Fentanyl

Preclinical Data

Fentanyl and sufentanil are potent anilinopiperidine analogs that cross the blood–brain barrier and are rapidly diffused into lipid-rich neural tissues. The partition coefficients (octanol: water) of fentanyl and sufentanil are 100-fold and 1000-fold, respectively, greater than morphine (9).

The potency of fentanyl and sufentanil administered intrathecally was 10–20 times greater than when administered systemically, indicative of the high lipophilicity of these two compounds. Fentanyl activates a lower number of functional receptors than morphine to produce an equivalent analgesic effect. In contrast, down-regulation may affect the maximal analgesic effect produced by morphine. The order of potency on hot plate and tail-flick ED50 (μg) in rats was: sufentanil, 0.2 and 0.3, respectively; fentanyl, 2.4 and 1.9, respectively; and morphine, 4.2 and 5.9, respectively. The same order was reported for the skin-twitch response latency ED50 (μg) in cats: sufentanil 9.5, fentanyl 21.8, and morphine 114.6. The results suggest

that the 4-anilinopiperidine analogs exert their analgesic effect *in vivo* at a spinal cord site (52).

A safety study on the effects of long-term IT fentanyl infusion has not been published (9). In physiochemical studies, fentanyl alone, fentanyl with midazolam, and an admixture of fentanyl/bupivacaine (0.44 mg/mL), epinephrine (0.69 μg/mL), fentanyl (1.25 μg/mL), and fentanyl citrate (20 μg/mL) in polyvinyl chloride portable infusion pumps were stable for varying durations, various temperatures, and in some cases, under conditions of clinical use in a portable infusion pump (9).

Clinical Data

In a randomized trial ($N = 60$) in patients undergoing posterior lumbar spine decompression, IT fentanyl significantly decreased mean pain VAS, increased the time to first patient control analgesia bolus used, and reduced morphine bolus patient control analgesia received by 41% with minimal respiratory depression (53).

Adenosine is known to produce analgesia after IT administration (54). It is known that opioids increase spinal release of adenosine in rats and that IT and systemic opioid–induced analgesia are reduced in animals by adenosine receptor antagonists. A combination of IT morphine and fentanyl ($N = 8$) increased adenosine concentrations dramatically 20 and 60 min after the mixture was administered (55). Intrathecal fentanyl alone or saline ($N = 15$) did not alter adenosine concentrations within a period of 6 min, nor did intravenous remifentanil ($N = 9$).

Sufentanil

Preclinical Data

Intrathecal sufentanil, a 4-anilinopiperidine analog, acts at a spinal cord site to produce analgesic effects and undergoes rapid clearance from the CSF with rapid resorption to the circulatory system (9). The drug requires fewer functional receptors than morphine to provide comparable analgesia. High doses of IT sufentanil administered as repeated bolus rather than continuous IT infusion produced reductions in heart rate, respiratory rate, and body temperature in dogs. Compared to morphine, sufentanil elicits less drug tolerance than morphine. The drug produced a smaller exposure-dependent rightward shift in the dose–response (thermal response latency) curve than morphine (2, 6, and 20 nmol/hour) over a seven-day IT infusion of opioid (9). The greater opioid potency of sufentanil allows it to maintain its efficacy after sustained exposure. The stability of a drug admixture of sufentanil and ropivacaine was found to be equivalent in glass and polyvinyl chloride reservoirs (9).

Clinical Data

In a randomized, double-blind urodynamic study ($N = 40$), IT opioids were associated with a dose-dependent decrease in bladder function. However, the recovery of normal detrusor contractility and sensation of urge was significantly faster after IT sufentanil than after IT morphine (56).

Methadone

Preclinical Data

Methadone is a racemic mixture of D- and L-isomers that produce different effects. The racemic mixture is the form commonly used clinically. Recent studies have shown that the D-isomer of methadone has *N*-methyl-D-aspartate (NMDA) receptor antagonist activity both *in vitro* and *in vivo* (57).

Clinical Data

In a prospective study ($N = 24$) of the IT delivery of preservative-free methadone (20 mg/mL to 60 mg/mL per day) for the treatment of chronic nonmalignant pain in patients who had failed previous IT trials with IT analgesics, 13 patients reported some level of pain reduction during their course of treatment. The authors concluded that methadone was a promising alternative neuraxial agent for the treatment of chronic pain (58).

Meperidine

Preclinical Data

There was no literature found for the preclinical use of meperidine since 2003.

Clinical Data

In a prospective study ($N = 10$), chronic IT delivery of meperidine alone, or meperidine combined with clonidine, significantly decreased intractable neuropathic cancer pain (59). The plasma concentrations of meperidine and normeperidine increased quickly three weeks after the start of IT therapy in three patients. The plasma normeperidine concentration was greater than the meperidine concentration in one patient. It was noted by the authors that these findings are important, because increased levels of meperidine and normeperidine may lead to neurotoxicity of the central nervous system (59).

Intrathecal Local Anesthetics

Bupivacaine

Preclinical Data

Transient neurologic syndrome, defined as radicular irritation after spinal anesthesia with local anesthetics, is hypothesized to fall on the lower end of a spectrum of toxic effects caused by local anesthetics. *In vitro* cultured neurons display alterations in growth of cones and neurites in response to varying concentrations of local anesthetics

(60). In a study on spinal cord neurotoxicity of local anesthetics, IT 2% tetracaine, 10% lidocaine, 2% bupivacaine, and 2% ropivacaine each produced a comparable increase in glutamate concentrations in the CSF of rabbits (61). Local anesthetics injure dorsal and ventral roots by increasing glutamate concentration in CSF and altering motor neurons in the lumbar spinal cord (60,61). Decreased sensory and motor function was associated with chromatolytic deterioration of motor neurons and vacuolation in the dorsal funiculus. Vacuolation was most extensive from lidocaine followed sequentially by tetracaine, bupivacaine, and ropivacaine. The margin of safety, which seemingly correlates with histopathologic changes rather than with glutamate levels, appears to be smallest with lidocaine (61).

In a stability study ($N = 108$), the concentration of IT bupivacaine (7.5 mg/mL) was more than 96% of the original value after incubation at 37° for 12 weeks of continuous exposure to the intact pump-catheter systems or pump delivery system materials (62). Similar stability and concentrations of more than 96% of their original value were reported for three medications in an IT infusion of a combination of morphine sulfate, bupivacaine hydrochloride, and clonidine hydrochloride in SynchroMed implantable pumps incubated at 37° for a duration of 90 day (63,64).

Clinical Data

Although a number of authors have reported improved pain relief when bupivacaine was added to the IT drug mixture, all but one study are uncontrolled and nonrandomized case series (65). A multicenter, double-blind randomized study (66) found that the addition of bupivacaine (up to 8 mg/day) did not provide better pain relief than opioid alone.

In two patients who experienced inappropriate pain relief despite the administration of continuous IT morphine and bupivacaine, complete symptom relief could be obtained when small bolus doses were added (67). It was postulated that continuous flow rates of less than 1 mL per day might be associated with limited mixing in the CSF and that the distribution of the drug in the spinal canal was improved by the injection of boli (67).

A case of unusual spinal lesion as a result of IT delivery of bupivacaine was reported in a 67-year-old female patient with an IT drug delivery device for failed back syndrome (68). The patient presented with new sensory complaints and back pain and an MRI scan revealed a mass impinging on the thoracic spinal cord. Surgical operation and chemical analysis confirmed that the mass was a bupivacaine precipitate located at the tip of the IT catheter. In another case report, bupivacaine (20 mg/mL) was associated with a spinal lesion after nearly three years of uneventful and successful IT management of a neurogenic pain of the lower limb (69).

Ropivacaine

Preclinical Data

Ropivacaine (Naropin, AstraZeneca, Wilmington, DE, USA), a novel long-acting amide local anesthetic agent, is a pure S-enantiomer that blocks sensory nerve fibers more than motor fibers (70,71). The drug has a high pKa and relatively low-lipid solubility (70). In animal models, ropivacaine has less toxicity, but also less potency, than bupivacaine.

Clinical Data

Ropivacaine (Naropin, AstraZeneca) has essentially the same onset, quality, and duration of sensory block as bupivacaine, but it produces less motor block and lower cardiovascular toxicity than bupivacaine in human subjects (70). Ropivacaine and bupivacaine have equivalent effectiveness for subcutaneous infiltration, epidural and intrathecal administration, and peripheral nerve block surgery, as well as obstetrics and postoperative analgesia. Ropivacaine also may be a promising spinal anesthetic drug for outpatient surgical procedures, because it provides short-acting and adequate anesthesia without compromising early ambulation and discharge from the day surgery unit (72).

There are no published reports on long-term IT administration of ropivacaine for the management of chronic pain.

Tetracaine

Preclinical Data

Tetracaine, a sodium channel blocking agent, decreased glutamate release in brain ischemia and exerted a neuroprotective effect in earlier studies (73). A more recent investigation showed that large concentrations of IT tetracaine damage dorsal and ventral roots by increasing CSF glutamate concentrations in CSF, producing chromatolytic deterioration of motor neurons in CSF, and causing vacuolation in the dorsal funiculus. The vacuolation caused by tetracaine was less extensive than that with lidocaine but more extensive than that with bupivacaine or ropivacaine (61).

Clinical Data

No recent study on IT tetracaine for the management of chronic pain could be found in the literature.

Adrenergic Agonists

Clonidine

Preclinical Data

Clonidine, a selective alpha-2-adrenergic agonist, is a lipophilic drug with a rapid onset that produces a short-term

effect (74). The drug induced a dose-dependent antihypersensitivity effect to mechanical stimuli in a rat model of neuropathic pain involving activation of alpha-2 adrenoceptors (75). In a study evaluating the antihyperalgesic and side-effects of IT clonidine (0.3–3.0 μg) and tizanidine (1.0–5.0 μg) in a rat model of neuropathic pain, IT clonidine, 3.0 μg or tizanidine, 5.0 μg significantly reversed both thermal and mechanical hyperalgesia (76). Intrathecal clonidine 3.0 μg, but not tizanidine 5.0 μg, reduced mean blood pressure and heart rate, and induced urinary voiding. Intrathecal clonidine also exhibited a greater sedative effect than tizanidine.

Clinical Data

In a stability study of clonidine, in a clonidine-hydromorphone mixture, no loss in clonidine concentration was reported in 20 paired samples from three patients during the interim between refills (35 ± 13 days) using HPLC analysis (77). The data suggest that clonidine coadministered with hydromorphone is stable for delivery by implantable IDDS for chronic use (77). Bevacqua et al. reported on a case of neuropathic pain treated with intraspinal analgesics in which depression, insomnia, and night terrors developed in association with intraspinal clonidine (78).

Moxonidine

Preclinical Data

Moxonidine, a mixed alpha-2-adrenergic and imidazoline receptor agonist, may be clinically advantageous for chronic neuropathic pain when administered alone or in conjunction with opioid therapy (79). The analgesic effects of IT moxonidine are not dependent on activation of the alpha-2A adrenoceptor subtype (79). Intrathecal moxonidine thus has a better side-effect profile than clonidine. Moxonidine-administered IT displays a synergistic activity with opioid agonists that persists during neuropathic pain (79). Moxonidine has been withdrawn from the market after a controlled study suggested that oral administration in heart failure patients resulted in increased morbidity and mortality (80).

N-Methyl-D-Aspartate Antagonists

N-Methyl-D-aspartate antagonists are known to be analgesic and dextromethorphan, an NMDA antagonist is known to prevent morphine tolerance and enhance antinociception (81,82).

Ketamine

Preclinical Data

The analgesic effect of ketamine is associated with its NMDA-receptor antagonistic properties (83,84). Ketamine may increase the spinal action of morphine, and its active enantiomer S(+)-ketamine, has been considered less neurotoxic than the racemic mixture of ketamine (85). In a randomized, blinded study, IT S(+)-ketamine administered in a clinically relevant concentration and dosage had a toxic effect on the central nervous system of rabbits (86). No significant difference was reported in neurologic status following treatment of rabbits receiving 0.5 mL (2.5 mg) commercially available, preservative-free IT S(+)-ketamine solution ($N = 12$ rabbits) and animals receiving 0.5 mL saline ($N = 6$), once a day for seven consecutive days. Although preservatives in ketamine are implicated in the neurotoxicity of this drug, postmortem histopathologic lesions of the spinal cord and nerve roots, indicative of toxic injury, were observed in 11 out of 12 animals in the S(+)-ketamine group and no histologic alterations were reported in the five control rabbits. Postmortem evidence from another experiment revealed histolopathologies such as central chromatolysis, nerve cell shrinkage, neuronophagia, microglial up-regulation, and gliosis in spinal cord and nerve roots in animals receiving S(+)-ketamine (86). It was concluded by these studies that additional systematic studies of the toxicology of S(+)-ketamine are needed before the neuraxial (intrathecal and/or epidural) use of S(+)-ketamine can be recommended (86).

No published data are available as yet on the pharmacokinetics of continuous IT administration S(+)-ketamine or on the stability of the drug in a IT pump and catheter delivery system. Subcutaneous ketamine administered after IT morphine did not significantly alter the early analgesic effect in rats. However, subcutaneous ketamine nearly prevented the delayed decrease in the nociceptive threshold following IT delivery of morphine (15).

Clinical Data

Clinical data suggest that ketamine may be advantageous in treating postoperative and severe intractable pain syndromes that are not alleviated by increasing IT opioid dose escalation (87,88). Continuous IT administration of S(+)-ketamine in addition to morphine reduced cancer-related neuropathic pain in a single patient case report (83). The same group reported long-term antinociceptive effect in a patient with morphine tolerance (89). The therapy resulted in low plasma levels of S(+)-ketamine and no adverse side-effects over a period of three months.

A patient with severe neuropathic cancer pain successfully improved in response to continuous IT infusion of morphine, bupivacaine, clonidine, and S(+)-ketamine (87). However, the authors of this study advised that IT S(+)-ketamine be used as last resort therapy due to a lack of preclinical safety data or conflicting data on the use of IT S(+)-ketamine, in clinically relevant concentrations. The potential neurotoxicity of the neuraxial use of ketamine and S(+)-ketamine increasingly has raised concern (87).

Other Nonopioid Agents Used Intrathecally

Adenosine

Preclinical Data

Adenosine, along with endomorphins and agmatine (4-aminobutyl guanidine, a putative neurotransmitter is the decarboxylation product of the amino acid arginine and is an intermediate in polyamine biosynthesis), are part of a recently described series of endogenous ligands involved in the inhibition of sensory transduction of noxious stimuli at the spinal level (90). Opioid agents are known to enhance spinal release of adenosine in animal models (55). Adenosine and excitatory amino acids are involved in modulating nociceptive transmission at the spinal level via four types of spinal adenosine receptors, A1, A2A, A2B, and A3 (91–93). The fixed dose and isobolographic analyses of a study on formalin-induced nociception showed that adenosine interacts additively, not synergistically, with MK801 and NBQX (2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline-2,3-dione) in the spinal cord (91,92). Spinal adenosine A1 and A2A receptors appear to affect the modulation of the early (nociceptive) and the late (neuropathic) phase responses of the formalin test. Adenosine A3 receptor may be involved in the regulation of the late phase response (91,92).

Adenosine and adenosine analogs cause antinociception after both systemic and IT delivery administration in animal models (94). Adenosine receptor antagonists decrease analgesia produced by systemic and IT administration of morphine (55). Central adenosine A1 receptor-mediated pain-relieving activation has a slow onset and long duration of action, typically lasting for hours or days and occasionally for months (95). Although A1 adenosine receptor activation decreases hypersensitivity in chronic pain animal models, IT adenosine administration does not induce analgesic response to acute noxious stimuli (96).

When compared to adenosine, capsaicin produced a comparable concentration-dependent glutamate release in normal and nerve-ligated synaptosomes with a threshold of 10 nm in rats. An A1 adenosine receptor antagonist DPCPX (8-cyclopentyl-1,3-dipropylxanthine), but not the A2 adenosine receptor antagonist, DMPX (3′7-dimethyl-1-proparaglyxanthine), inhibited glutamate release from primary afferents in rat spinal synaptosome. No difference in the capsaicin-evoked glutamate release or its inhibition by adenosine synaptosomes was observed between tissue ipsilateral and contralateral to spinal nerve ligation.

Long-term IT administration of adenosine produces hypersensitivity in normal animals. Chronic blockade of spinal adenosine A1 receptors by the A1 antagonist, DPCPX, causes partial prevention of nerve injury-induced hypersensitivity (97). Low doses of adenosine decreased allodynia/hyperalgesia more consistently than they reduced spontaneous pain (95). A study based on the inflammatory pain test in awake rats examined the antinociceptive properties of adenosine and agmatine administered for 60 min on carrageenan-induced thermal hyperalgesia in awake rats (90). While adenosine and agmatine each elicit a small antinociceptive effect during continuous IT delivery, both ligands potentiate the effect of endomorphin-1. A mixture of these endogenous ligands may provide novel therapeutic targets for modulating pain (90).

In an investigation in conscious rats, intracerebroventricular- and IT-administered adenosine agonist R-phenylisopropyladenosine produced a dose-dependent antinociceptive effect via K+ channel activation and reduced minimum alveolar concentration of halothane through activation of A1 receptor subtype (98). Intrathecal T62, (2-amino-3-(4-chlorobenzoyl)-5,6,7,8-tetrahydrobenzothiophen), an allosteric adenosine receptor modulator that enhances adenosine binding to the A1 receptor, reduced hypersensitivity to mechanical stimuli in a rat model of neuropathic pain by a circuit that relies completely on activation of alpha-2 adrenoceptors (75). Intrathecal T62 exhibited a dose-dependent antihypersensitivity effect in this model but had no effect on ambulation or activity level. In a similar study on the efficacy of chronic oral T62 in spinal nerved-ligated rats, A1 adenosine modulators were found to lose efficacy over time, due in part to receptor down-regulation (99). Both mannitol and adenosine in mannitol administered IT increased spinal cord blood flow in rats, suggesting that these medications are not likely to cause neurotoxicity of the spinal cord (94).

Clinical Data

Intrathecal adenosine has been used to successfully treat neuropathic pain in humans (54). In phase 1 studies for safety, Eisenach et al. (100) studied 65 volunteers in two separate trials: an open-label, dose-escalating trial with intrathecal adenosine doses of 0.25–2.0 mg (25 subjects) and a double-blind, placebo-controlled trial of adenosine, 2 mg (40 subjects). Blood pressure, heart rate, end-tidal carbon dioxide, and sensory, motor, and reflex neurologic functions were systematically examined for 24 hours after injection, and volunteers were contacted by telephone at times up to six months after injection. The authors found that adenosine did not affect blood pressure, heart rate, end-tidal carbon dioxide, or neurologic function. Headache was reported by 10 and back pain was reported by 8 of 30 subjects exposed to adenosine in the second double-blind trial, whereas none of these symptoms was reported by the 10 saline-treated subjects. The authors concluded that their data support further investigation of intrathecal adenosine for analgesia in humans and suggest that this agent does not produce a high incidence of severe side-effects. Belfrage et al. (101) performed an open label study of IT adenosine administration studied for the evaluation

of efficacy and side-effects in 14 patients. All patients had chronic neuropathic pain with tactile hyperalgesia and/or allodynia primarily of traumatic origin. The effects of IT adenosine (500 μg [$N = 9$] or 1000 μg [$N = 5$]) was evaluated. Spontaneous and evoked pain (VAS score 0–100) and tactile pain thresholds were assessed before and 60 min after injection. The injection caused transient pain (< 60 min) in the lumbar region in five patients. There were no other side-effects. Spontaneous and evoked pain was reduced (median score from 65 to 24 [$p < 0.01$] and from 71 to 12 [$p < 0.01$], respectively) in parallel with increased tactile pain thresholds in allodynic areas. Areas of tactile hyperalgesia/allodynia were reduced (median reduction 90%; $p < 0.001$). Twelve patients experienced pain relief (median 24 hours). The authors concluded that IT adenosine transiently causes lumbar pain in a subgroup of patients and may reduce various aspects of chronic neuropathic pain. However, in a study ($N = 90$) in females undergoing elective abdominal hysterectomy, IT adenosine, 1000 μg, was not effective in relieving postoperative pain when administered 30 min before delivery of anesthesia (102).

Experimental studies should be conducted to assess the risks of neurotoxicity of IT adenosine before recommending its use in humans (94).

Baclofen

Preclinical Data

Baclofen, a γ-aminobutyric acid (GABA) B agonist, acts on the spinal GABA-B receptor that can regulate the response to acute high-intensity input, the facilitated pain state associated with tissue injury, and the component of the hyperalgesia and allodynia resulting from nerve or spinal injury. The drug produces powerful antinociceptive effects in experimental animal models at doses that produce few or no motor-blocking effects (103).

The stability of an admixture of clonidine and baclofen was assessed in an implantable infusion system maintained at 37° (104). Both clonidine and baclofen concentrations maintained stability and more than 90% of their initial value until at least week 14.

The GABA-B receptor increases the effect of spinal cord stimulation in certain neuropathic conditions (105) and GABA-B and NK1 receptors of spinal dorsal horn neurons have been shown to be involved in secondary hyperalgesia in a monoarthritic rat model (106). The reduction in GABA inhibition may be more important than the increase in substance P-mediated effects in inducing secondary hyperalgesic effects (106).

Clinical Data

Intrathecal baclofen has been used clinically since the late 1980s. It has been increasingly used for the treatment of children (107) with cerebral palsy or adults with severe spasticity due to spinal cord injuries or multiple sclerosis that does not respond to oral therapy (103,108,109). Baclofen is rarely used as an analgesic drug in patients without spasticity, but recent evidence suggests that the drug, given IT, may have therapeutic value in the management of patients even without spasticity (103). In one study ($N = 48$), IT baclofen was administered as an adjunct treatment in patients with neuropathic pain of peripheral origin who responded poorly to SCS (105). Patients receiving SCS plus intrathecal baclofen therapy had an average decline of VAS from 82 to 33 compared with a reduction of VAS, 63 to 33, in patients administered only IT baclofen. This suggests that IT baclofen may be a viable adjunctive treatment to relieve pain in patients who have not achieved satisfactory pain relief with SCS (105).

Baclofen delivered via an IDDS successfully treated an intractable case of postherpetic neuralgia in a 72-year-old male patient (110). The drug was selected as an alternative treatment after conventional pharmacologic therapies and interventional techniques failed to produce pain relief. Pain relief persisted to a large extent (80%) eight months after the implantation of an IDDS (110).

In a prospective study ($N = 62$), gradual escalation of IT baclofen therapy delivered via a programmable pump for patients with spasticity produced no side-effects (111). Yet, IT baclofen use carries risks of severe neurologic consequence and even death from sudden cessation of the drug. Patients with implanted systems for the delivery of high-dose baclofen are at risk for malfunction of the pump and spinal catheter system leading to life-threatening complications such as overdose and withdrawal, particularly in pediatric patients (108,112). A 12-year-old boy receiving chronic IT baclofen presented to a hospital emergency department with the initial symptoms of respiratory arrest, obtundation, fixed pupils, and hypotension that appeared to be indicative of head trauma. He was later properly diagnosed with an IT baclofen overdose and, after recovery during his hospitalization, displayed withdrawal symptoms of hypertension, hyperthermia, and hallucinations (108). Another study reported 32 serious complications, including four serious, catheter-related problems associated with the use of the SynchroMed 10-mL infusion pump for IT baclofen delivery in children (109). Adverse effects in a patient with cerebral palsy and spastic quadriparesis who discontinued IT baclofen included hyperthermia, disseminated intravascular coagulation, rhabdomyolysis, acute renal failure, and multisystem organ failure (113). A programming error in the IT baclofen pump led to these complications. Other pump-related adverse effects of IT baclofen therapy include drowsiness, nausea, headache, muscle weakness, light-headedness, and return to pretreatment level of spasticity. A 19-year-old woman with a generalized dystonia experienced the abrupt onset of adductor spasms of the vocal cords and increased dystonia

following the interruption or IT baclofen treatment (114). The symptoms reversed after the restoration of her IT baclofen. Physicians must be aware that dyspnea associated with increased muscle tone may be an important indicator of baclofen withdrawal in patients with IT baclofen therapy.

Pruritus, a common symptom following IT baclofen withdrawal, is associated with the inhibitory effects of baclofen on the release of substance P at the spinal level (115). While increased spasticity is usually caused by drug tolerance or irritant factors, pruritus appears to be a good clinical indicator of baclofen withdrawal. Pruritus was reported in 10 of 23 cases of IT baclofen withdrawal after the first three months after pump implantation. Dysfunction of the infusion system may provoke pruritus in patients receiving IT baclofen.

Droperidol

Preclinical Data

Droperidol is a dopamine D2-receptor antagonist that appears to have no antinociceptive effect in a rat model, either alone or in combination with morphine, and no histopathological changes were observed in the spinal cord. These results do not support the clinical impression of a droperidol-mediated potentiation of the antinociceptive effect of epidural morphine (116).

Clinical Data

A prospective study ($N = 90$), comparing the analgesic efficacy of the epidural medications tramadol 75 mg, tramadol 75 mg plus droperidol 2.5 mg, and tramadol 75 mg plus clonidine 150 μg, has implications for the therapeutic potential of IT droperidol (117). The addition of epidural droperidol to epidural tramadol decreased the onset time and prolonged postoperative analgesia in patients undergoing lower abdominal surgery. Pain score, respiration rate, and SpO2 values were similar in all groups.

Gabapentin

Preclinical Data

Gabapentin, an anticonvulsant, appears to have a novel action on voltage-dependent calcium ion channels at the postsynaptic dorsal horns that in turn interrupt the events associated with neuropathic pain sensation (118–120). The drug is a GABA analog that was initially reported to show minimal affinity at GABA-A or GABA-B receptors (118). Recent evidence implying that gabapentin is a selective agonist at GABA-B receptors containing GABA(B1a)–GABA(B2) heterodimers is conflicting, however. Supraspinally administered gabapentin produces antinociception via inhibitory action on NMDA receptors (121) and activates the descending noradrenergic system to produce analgesic effects following peripheral nerve injury (122,123). The supraspinal action of gabapentin on mechanical hypersensitivity is mediated by activation of spinal alpha-2-adrenergic receptors with subsequent action by muscarinic receptors (probably M1) and the nitric oxide (NO) cascade (124). The supraspinal effect of gabapentin on thermal hypersensitivity occurs independently of the spinal cholinergic-NO system (124). Recent correlational data on a postoperative pain model suggest that N-type Ca^{2+} channels, but not K(ATP) channels, NMDA or GABA-A receptors, may contribute to the anti-allodynic actions of IT gabapentin (118).

Intrathecal gabapentin enhances the analgesic effects of subtherapeutic dose morphine in a rat experimental pancreatitis model (125). Intrathecal gabapentin (25–200 μg) dose-dependently reduces tactile allodynia via both Ca^{2+}-activated and ATP-sensitive K^+ channels (119,126,127). The drug decreases the formalin-induced release of glutamate and aspartate in the spinal cord dorsal horn and decreases the elevation of glutamate in the noxious stimulus-induced spinal liberation reported in neuropathic rats (119). The activation of the NO-cyclic guanosine 3′,5′-monophosphate-protein kinase G-K+ channel pathway may contribute to gabapentin-induced spinal anti-allodynia (128).

In a study in rats, IT and intraperitoneal gabapentin did not significantly alter the hemodynamics, including significant dose-related differences in blood pressure, from baseline values during a period of 60 min (129). The drug reduces mechanical and cold hypersensitivity when administered both as pretreatment and posttreatment. In the tail-flick latency test, acute gabapentin injection at a dose of 10 μg IT had no enhancing effect on morphine's antinociception in naive rats, but potentiated the antinociception of morphine and attenuated the development of morphine tolerance in morphine-tolerant rats (130).

Local, spinal, or oral tramadol, tramadol–gabapentin, and gabapentin have been shown to produce a dose-dependent antinociceptive effect (131). Low doses of tramadol combined with gabapentin act synergistically to reverse formalin-induced nociception and may be therapeutically effective for managing inflammatory pain (131). In a rat model of postherpetic neuralgia, gabapentin, 10–30 μg, administered IT, significantly affected the mechanical withdrawal threshold in resiniferotoxin-treated rats (132). IT gabapentin alone (up to 300 μg) did not produce antihyperalgesic effects such as reducing hind limb extension, although it did lead to the restoration of certain cage crossing and rearing behaviors levels in an acute rat pancreatitis model (125). Gabapentin and low-dose morphine delivered spinally decreased pain-related behaviors and restored all spontaneous behaviors, including disappearance of hind limb extension, to surgical baseline levels. Intrathecal gabapentin may affect morphine tolerance by suppressing the excitatory amino acid concentration in spinal CSF dialysate (130).

Spinal gabapentin induced full antinociception in injury-induced hyperalgesia but has no effect on acute nociception (133). In the formalin test, gabapentin combined with either clonidine or neostigmine administered spinally reinforced the effects of clonidine and neostigmine (134). In a recent study using the formalin test in rats, gabapentin potentiated the antinociceptive action of MK801 and NBQX in phase 1 as revealed through fixed dose analysis (134). All three compounds reduced the phase 2 flinching response. Isobolographic analysis showed that coadministration of gabapentin-MK801 or gabapentin-NBQX resulted in a synergistic interaction (133). Comparative pharmacologic studies using the formalin test evaluated the effects of gabapentin and adenosine drug mixtures on nociception in rats (135). Fixed dose analysis revealed that IT 5-HT dose-dependently inhibited the phase 1 flinching response, but neither IT gabapentin nor adenosine had any effect on phase 1. An IT mixture of 5-HT with a fixed dose of either gabapentin or adenosine either produced a minimal effect or enhanced the antinociception of 5-HT alone in formalin-induced nociception. Isobolographic analysis showed that all three agents delivered IT dose-dependently reduced the phase 2 flinching response in formalin-induced nociception. An IT mixture of 5-HT with either gabapentin or adenosine may have therapeutic value as an analgesic for both the facilitated state and acute pain in the spinal cord (135).

Ketorolac

Preclinical Data

Ketorolac, a water-soluble nonsteroidal anti-inflammatory agent, is a cyclooxygenase inhibitor of both cyclooxygenase isozymes, COX-1 and COX-2. In a spinal safety study, bolus and continuous infusion of IT ketorolac did not cause spinal pathology and decreased lumbar CSF prostaglandin E2 concentrations in dogs and rats (136). Ketorolac at the highest concentration (four daily bolus deliveries of 5 mg/mL/10 microl) did not induce a drug or dose-related effect upon spinal histology or upon spinal cord blood flow at the lumbar site. Cisternal CSF protein values were increased in all treatment groups and cisternal glucose values were within normal range for all treatment dogs except for three animals that exhibited reduced cisternal glucose levels. The dose had no effect upon spinal histology or upon spinal cord blood flow in rats, although all animals displayed mild pericatheter reaction as confirmed by histological analysis.

Morphine has an inhibitory effect on nocifensor reflexes in rats without circulating estrogen but has no effect on animals with estrogen. Morphine decreases response to uterine cervical distension (UCD) by spinal and supraspinal mechanisms, but its actions are suppressed by estrogen (137). In contrast, ketorolac produces antinociceptive effects at an estrogen-independent, nonspinal site. Chronic IT ketorolac tromethamine, even at large doses, induces potent analgesic activity that showed no adverse neurologic effects during the formalin test in rats (138). Future research in other species is needed to determine the safety of ketorolac tromethamine as an alternative IT analgesic for treating chronic pain.

In a recent study, ketorolac exerted a protective effect against hyperalgesia induced by recurrent withdrawal from chronic spinal morphine use, but it did not significantly change tolerance to spinal morphine (139). Animals pretreated with 60 μg IT ketorolac, exhibited a significant decrease in neuronal death and showed improved hind limb motor function compared to the control rats. Because COX is associated with spinal cord ischemic injury, ketorolac, a COX inhibitor, in theory, may prevent ischemia-related spinal cord injury during thoracoabdominal aortic surgery (140). Intrathecal ketorolac inhibited c-fos in female rats receiving UCD, suggesting that spinal COX is associated with UCD-induced nociception (141).

Midazolam

Preclinical Data

Midazolam, a benzodiazepine-receptor agonist, facilitates the inhibitory action of GABA on neuronal transmission by occupying the benzodiazepine-receptor on a benzodiazepine-GABA-CI channel complex (142). Recent evidence from the tail-flick, hot-plate, and formalin tests of coadministration of intraperitoneal midazolam (2 mg/kg) and subcutaneous morphine (10–100 mg/kg per day) in mice suggests that decreased activity and expression of endogenous spinal NO synthase contributes to the inhibitory action of midazolam on morphine-induced analgesia tolerance (142). Intrathecal midazolam potentiates the antinociceptive effect of opioid medications on the spinal cord, produces a segmental antinociceptive effect in the spinal dorsal cord, and suppresses morphine withdrawal response by blocking the hypersensitization of spinal cord neurons (142,143).

Yet, animal studies have produced conflicting results on the neurotoxicity of midazolam. While IT midazolam (5–15 mg/day for 43 days) was not associated with signs of neurotoxicity in sheep and pigs, IT midazolam (0.1 to 0.3 mg) administered to rats produced significant histologic alterations that appeared to be indicative of neurotoxic side-effects.

The interpretation of these conflicting results is problematic when trying to extrapolate them to humans. One reason is that animals in these studies were given higher concentrations and doses than the concentrations and doses used in human trials. Another reason is that there exists a larger CSF space in humans when compared to rats and rabbits and this larger space permits greater dilution of the drug within the CSF, which may, in turn, ameliorate any toxic effect on the human spinal cord. Lastly, preservative free preparations have been used clinically in humans and

preservative-free formulations are not consistently used in animal experiments (74). No toxicity was reported for drug mixtures containing up to four medications, including midazolam, stored for one to four months in the pump reservoir of patients treated for chronic low-back pain (144).

Clinical Data

Midazolam is used clinically as an adjuvant medication coadministered with opioids or inhaled anesthetics to achieve anesthesia (142). Intrathecal midazolam is synergistic with bupivacaine in postoperative analgesia, and IT midazolam and clonidine resulted in nearly total pain relief without side-effects or tolerance in four patients with chronic noncancer pain (74). Intrathecal midazolam (0.3–12 mg/day) coadministered with morphine produces adequate analgesia without major adverse effects and without rapid onset of morphine tolerance in patients with chronic pain, including nonmalignant back and leg pain (142,144). Intrathecal bolus doses of midazolam, 2 mg, produce segmental analgesia with long-term effects after a one-time application (74).

No neurotoxicity, signs of tolerance, signs of midazolam accumulation, or side-effects such as hypotension, nausea, and drowsiness were observed in case studies of IT midazolam (6.5–70 mg/day) and cases of IT midazolam (600 μg/day) plus clonidine (74,144,145). No signs of toxicity or side-effects were reported in extensive clinical experience with acute boluses of preservative-free, IT midazolam (2.5 mg) (74). While some physicians consider IT midazolam a feasible alternative for the management of intractable chronic pain (74), other experts have called for a reassessment of preclinical safety issues, including data, formulation, kinetics, and potential toxicity, before recommending the clinical use of IT midazolam (146).

Neostigmine

Preclinical Data

Neostigmine is a cholinesterase inhibitor that when given IT appears to elicit nitric oxide release in the spinal cord (130). Data from the formalin test suggest that the antinociception mechanisms of IT neostigmine may involve inhibition of c-fos expression. Neostigmine induces the facilitation of miniature inhibitory postsynaptic currents frequencies in substantia gelatinosa neurons in mice (147).

In a comparative study in rabbits, IT midazolam and neostigmine produced different neurotoxic effects, depending on the dose and the repetition of dosing (148). Pretreatment with IT neostigmine, 2 μg/kg, and clonidine, 2 μg/kg, 30 min later into the lumbar space totally prevented the IT clonidine-induced attenuation of hypercapnic cerebral vasodilation (2 μg/kg) in six rabbits. Normal saline or neostigmine alone did not alter the cerebral reactivity to hypercapnia (149).

Clinical Data

In a prospective trial ($N = 60$) of postoperative safety and analgesic efficacy, IT neostigmine, 50 μg, induced postoperative pain relief for nearly seven hours with fewer side-effects and higher satisfaction ratings than IT morphine, 300 μg (150). While epidural neostigmine reportedly produces postoperative analgesia without nausea in nonpregnant patients (151), case reports suggest that gastro-intestinal side-effects may limit the clinical use of IT neostigmine (152). Future clinical studies are needed to determine the safety and efficacy of neostigmine.

Octreotide

Preclinical Data

Octreotide is a synthetic octapeptide derivative of somatostatin, the growth hormone located in the substantia gelatinosa in the dorsal horn of the spinal cord (153,154). Somatostatin has an inhibitory effect on nociceptive neurons but its pharmacokinetic properties make it undesirable as a novel IT nonopioid analgesic. Octreotide, in contrast, is more stable and has a longer half-life than somatostatin.

Infusions of IT octreotide, 40 μg/hour (equal to approximately 400 μg/hour in human subjects), did not produce neurodegenerative complications when delivered intrathecally in a dog model (154,155). Intrathecal octreotide (sandostatin) (doses of 20, 40, and 80 g) significantly decreased behavioral effects of thermal hyperalgesia and dose-dependently decreased the evoked spinal c-fos expression (the possible equivalent of mechanical allodynia) in rats with chronic constriction injury of the sciatic nerve (153). Paw withdrawal latencies were reduced in all treatment groups compared to the saline group, and in the 40 mg group, paw withdrawal latencies returned to up to 76% of prechronic constriction injury values 120 min after drug delivery. Nearly total inhibition was observed in the expression of c-fos-like immunoreactive neurons in the 80 mg group.

Clinical Data

In an early, blinded, randomized, "N of 1" trial ($N = 2$), limited treatment periods of chronic IT octreotide delivered over a period of five years in these two patients provided pain relief without unwanted drug effects for cancer pain (155). A recent prospective, double-blind study of the use of octreotide ($N = 20$) on adverse effects and toxicity (156) found that IT octreotide (dose range: 405 μg/day to 650 μg/day; maximum rate of delivery, 20 μg/hour) did not cause neurotoxicity or side-effects. The authors caution against making any conclusions to their study, in that, it is conceivable that the time that patients were exposed to the drug was too limited to induce toxicity or to reach an effective therapeutic level.

Data on the overall efficacy and clinical relevance of IT octreotide in this particular patient population is still

being collected. Ongoing research must be conducted to determine the stability of IT octreotide in pump infusion systems. Future research designs that consider specific disease states and various types of pain (ie, neuropathic, nociceptive, or mixed) reflect the more sophisticated trends that are emerging in IT analgesic drug studies.

Ziconotide

Ziconotide (Prialt®, Elan Pharmaceuticals Inc., San Diego, CA, USA; previously known as SNX-111 and CI-1009), a nonopioid analgesic and a voltage sensitive, N-type calcium channel blocker, is a potent synthetic neuroactive peptide equivalent of an omega conotoxin isolated from the venom of a marine snail (National Pharmacy Benefits Management Drug Monograph). Ziconotide, coadministered with morphine, showed additive and/or synergistic effects in rats (157).

Ziconotide–hydromorphone admixtures stored in Medtronic SynchroMed® II pumps at 37° and in control vials at 37° and 5° were found to be more stable than ziconotide–morphine under conditions simulating intrathecal infusions (158). HPLC used to measure drug concentrations showed that the ziconotide–hydromorphone mixture remained 80% stable for 40 days compared to 15 days for ziconotide–morphine as measured by HPLC.

Oxidation of the methionine sulfoxide form of ziconotide is known to result in the degradation of ziconotide. Admixtures that are prepared using a powdered opiate agent and are sparged (to add a gas, in this instance, nitrogen) to remove or decrease the presence of additional dissolved oxygen, should enhance stability. For this reason, both Elan Pharmaceuticals Inc., the manufacturers, of ziconotide (PRIALT®) and the 2007 Polyanalgesic Conference Expert Panelists recommend sparging (with nitrogen) admixtures containing ziconotide plus either powdered morphine or hydromorphone in lieu of using commercial solutions.

Stability

It is known that stability of intrathecal agents at body temperatures is important to the ultimate success of the therapy. Similarly, some agents are not stable at certain concentrations or when mixed with other agents. It is known that ziconotide, at less than 1 μg/cc is not very stable, but appears to have molecular stability at concentrations greater than 1 μg/cc. Furthermore, there may be issues of stability when certain agents are compounded for clinical use (159). Morphine and hydromorphone accelerate the rate of ziconotide degradation, so combinations of ziconotide with lower concentrations of the compounded opioid agent is expected to be more stable.

The 2003 Polyanalgesic Consensus Conference called for future studies to evaluate the stability of ziconotide admixtures with lower concentrations of morphine and hydromorphone (< 30 mg/mL) that fall below the maximum recommended dosage for these two opiates (5). In theory, because fentanyl has higher intrinsic analgesic activity than morphine, a relatively smaller amount of this drug combined with ziconotide should show greater stability. However, future research is needed to determine the stability of fentanyl combined with ziconotide in an intrathecal admixture.

Clonidine, 2 μg/mL, added to ziconotide is quite stable, but bupivacaine added to ziconotide shows slightly less stability. Ziconotide/baclofen admixtures revealed 80% stability through 30 days, rendering this admixture somewhat more stable than a combination containing morphine and ziconotide (160). Combinations of morphine or hydromorphone with bupivacaine are known to be stable (62).

As of this writing, Shields et al. have submitted their data for publication regarding stability of ziconotide/clonidine HCl admixtures with and without morphine sulfate, the stability of an admixture combining ziconotide with bupivacaine, and the stability of an admixture combining ziconotide with commercially formulated or powdered baclofen during simulated intrathecal infusion under laboratory conditions at 37°. A ziconotide/clonidine admixture was 90% stable for 60 days and a ziconotide/clonidine/morphine admixture was 70% stable for 20 days (161). After 30 days, pump ziconotide and bupivacaine concentrations measured an average of 86.9% and 99.4% of their initial concentrations, respectively, and the authors concluded that ziconotide concentration would exceed 90% and 80% of initial concentration for 22 and 45 days, respectively (162). Ziconotide/baclofen admixtures were more stable when prepared using powdered baclofen than commercial formulation. Ziconotide was stable in both admixtures: 82.2% of the initial in the commercially available formulation and 87.4% of the initial in 30 days in the powdered formulation (163).

IT analgesia also might be influenced by how an admixture used is compounded. Combinations of morphine or hydromorphone with bupivacaine are known to be stable (62). Based on these findings, the 2007 Polyanalgesic Conference expert consensus recommends limiting the dose of IT opioid medications when combining ziconotide, in order to increase the efficacy of the admixture. When considering adding opioid to ziconotide refractory patients, it is especially important to limit the concentration and dose of the opioid added to improve results. It also is recommended by the panel that the treating physician modify this recommendation according to the needs of his or her patient.

Clinical Data

Previous recommendations for intrathecal ziconotide used by previous expert panels were to use ziconotide for intractable chronic pain in patients who had exhausted all other therapeutic options, including IT morphine (164). As we shall see, this panel of experts based on new literature

and experience, have recommended moving ziconotide to a level one drug with morphine and hydromorphone. Although apparently working more efficiently for neuropathic pain states (165), this agent has been used for patients with nociceptive pain and mixed nociceptive, neuropathic pain. The drug is administered only as an IT drug delivered via continuous infusion through either an implanted device or an external microinfusion device with a catheter. The drug is associated with improvement on patient perception of pain in double-blind, placebo-controlled studies lasting from 11 to 21 days (164). In randomized controlled studies for nonmalignant pain ($N = 169$) and cancer- or AIDS-related pain ($N = 111$), statistically significant pain relief was achieved overall in patients receiving IT ziconotide as measured by mean percentage change in visual analog scale of pain intensity (VASPI) scores (166,167). Five patients administered ziconotide reported total pain relief (167). Fifty percent of ziconotide-treated patients compared with 17.5% of placebo patients experienced pain relief ($p = 0.001$) (167). In the nonmalignant study, the VASPI score decreased 31.2% from baseline compared to 6.0% for placebo-treated patients (166).

Adverse side-effects reported for ziconotide in trials and case series studies include elevated creatine kinase levels, sedation, somnolence, nausea, headache, lightheadedness, neuropsychiatric symptoms (eg, depression, confusion cognitive or memory impairment, hallucinations, dizziness, confusion, depressed levels of consciousness), ataxia, abnormal gait, slurred speech, double vision, and significant psychologic signs and symptoms or emotional distress (164,168,169). Particular symptoms may correlate with the rate of infusion (170), and successful treatment with ziconotide monotherapy requires psychologic support to decrease both adverse psychologic and physiologic events (168). In a randomized, double-blind, placebo-controlled study on safety and efficacy, slow titration of IT ziconotide to a low-mean dose was associated with significant improvement in pain and better toleration than faster titrations of the drug reported in two earlier placebo-controlled trials impairment (169). Intrathecal ziconotide administered at a low-starting maximum dose 0.5 μg/day with increases of not more than 0.5 μg/day. One a week may mitigate the potential adverse effects associated with this drug (171). Potential contamination of microinfusion devices used to administer ziconotide or any other intrathecal agent may increase the risk of meningitis (164).

Discussion of Consensus Panelists

The expert panelists discussed the published literature, their own broad range of clinical experiences, and other relevant anecdotal reports from colleagues in relation to the use of IT analgesic medications. Evidence-based medicine in this context refers to published data that meet varying levels, or ranks, of scientific merit in establishing causality, or probable causality, between, for example, a drug and an outcome such as efficacy, or a pathologic side-effect. Because only a limited number of class A (randomized controlled trials) of evidence-based studies on IT polyanalgesic therapies have been published, the 2007 Polyanalgesic Conference panelists utilized best available evidence. This decision was in keeping with the precedents established during the previous two conferences in 2000 and 2002. Best available evidence consists of pertinent data, theory, and thought reviewed by clinician-researchers who are consensus experts in the field of IT polyanalgesic therapy and deemed most useful for moving the practice of IT polyanalgesic medicine forward.

The 2007 Polyanalgesic Conference panelists formulated several consensus opinions and recommendations pertaining to key issues of IT therapy that warrant either new or ongoing attention for effective clinical practice. The consensus expert discussions and opinions presented here reflect an integration of published data and clinical anecdotal observations, as well as hypotheses derived logically from best available evidence to date.

Pharmacokinetics of Agents and Their Influence on Outcomes

Outcomes of IT therapies and/or rates of side-effects might be due to variables other than differences between individuals who receive these agents. These pharmacokinetic/dynamic variables might include differences in compounding strategies of these agents, differences in delivery of these agents, the site of a drug's activity, and final position and location of the IT catheter vis-a-vis the spinal cord.

When discussing the risks and benefits of IT bupivacaine, some panelists questioned its analgesic efficacy as an admixture when added to opioids and expressed concern regarding its side-effects, including paresis, sensory loss, and loss of bladder control. Hypothetically, at least, the panelist felt that intermittent boluses and/or higher infusion rates may be more efficacious for achieving analgesia. Confirming this, Buchser et al. in a single-published case report, reported that the every four hours bolus combinations of 0.5 mg of IT bupivacaine plus IT opioid medications and/or other adjuvant medications improved analgesic efficacy over the previous continuous infusion delivery of the same medications for prolonged period of time (67). Discrepancies in outcomes such as this underscore the need to delineate the effects of the drug injection rate on the effects of spinal analgesia. The mode of IT delivery (ie, continuous infusion vs. bolus infusion) may partly explain variable outcomes in different patients receiving the same monotherapy or the same admixtures.

Other factors that might influence efficacy and safety include the baricity of the agent infused and the final location of the IT catheter. It is well-known that pharmacists and physicians compound mixtures of differing baricities,

depending on the concentrations and various combinations wanted and used. To this date, it is unclear of what, if any, significance to outcomes these differences in baricities have. It was felt by some panelists that the diameter of the CSF layer at the catheter tip was important to outcome (safety/efficacy) of the therapy. Some panelists, although not all, felt that the safety and efficacy results are influenced by the location/position of the intrathecal catheter vis-a-vis the spinal cord and the diameter of the CSF space at the tip of the IT catheter. These panelists felt that positioning the catheter within the dorsal IT space, where there is more CSF when compared to the ventral CSF, would result in better analgesia and less risk of granuloma formation. They felt that the deposition of high concentrations and high doses of agents would be diluted by the larger dorsal CSF layer in the low thoracic region. Others, adding to the discussion, questioned whether people with differing disease states such as multiple sclerosis that affects CSF volumes would respond differently and adversely to IT therapy when compared to comparable patients with normal CSF volumes. In spite of the controversy regarding catheter position and the effect of CSF volumes at the catheter tip to outcomes, all of the panelists agreed that future studies are needed to study the effects of CSF volume on outcomes and that ongoing research on the pharmacokinetics of IT drug delivery will play a critical role in enhancing the efficacy of intraspinal polyanalgesics.

Morphine HCl vs. Morphine SO_4

In the United States, morphine sulfate is the form (salt) of morphine used for IT administration, while morphine hydrochloride is the form most often used in Europe. The IT delivery of morphine is causally associated with granuloma formation; however, it is not yet clear whether the different salts of the IT forms of morphine, at equipotent concentrations, have the same potential for inducing inflammatory masses. The panelists recommend that future research is needed to further elucidate whether there is a difference between the salts of morphine regarding granuloma formation.

Polyanalgesic Drug Admixtures

All of the panelists endorsed the use of polyanalgesic admixing when monotherapies fail to produce adequate analgesia and all felt that the literature was robust enough to support such a use. The panelists addressed a published study by Raphael et al. comparing diamorphine (heroin) and morphine for IT analgesic drug delivery alone or in combination with other agents (172). It had been hypothesized that the greater solubility of diamorphine when compared to morphine would allow for greater concentrations of the agent in the IT drug delivery device. One of the results of this study showed that diamorphine decays into *mono-acetyl morphine* immediately following installation into the pump. *Mono-acetyl morphine*, which has an estimated half-life of 50 days, in turn, decays into morphine. This rate of decay was the same for diamorphine alone or when used in combination with either bupivacaine or clonidine.

The efficacy of bupivacaine is related to its site of administration or its rate and form of delivery. The panelists felt that a significant number of patients receiving very low doses of bupivacaine when added to either morphine or hydromorphone showed clinical analgesic improvement and sometimes a reduction in tolerance to morphine. It was felt by some that bupivacaine appears to function more as a membrane stabilizer (due to it actions of calcium channel blockade) rather than as a Na^+ channel blocking agent when administered IT, at low doses. In contrast, it was felt that higher dosing, doses of bupivacaine up to 20–24 mg a day, worked differently by exerting some of its effects via Na^+ channel blockade.

All of the panelists agreed that their own clinical observations paralleled the findings from published studies (173) that a combination of ziconotide and IT morphine produced a significant reduction in pain intensity during its titration phase. In the study by Webster, a mean 26% reduction in VASPI (VAS for pain intensity) was accompanied by weekly decreases in systemic opioid use more than four weeks. Improved pain management also was observed in patients with cancer-related pain refractory to other standard IT therapies, who received a slow titration of ziconotide when added to admixtures of other analgesics. Seven of eight patients who received greater than 20% improvement in the VASPI received admixture therapies of hydromorphone/ziconotide ($N = 3$), hydromorphone/clonidine/ziconotide ($N = 2$), and sufentanyl/ziconotide ($N = 2$). A patient who had had a 10/10 pain score for many years and failed improvement after the administration of multiple combinations of intrathecal analgesics including clonidine/bupivacaine combinations was finally given ziconotide added to a mixture of hydromorphone/baclofen at 1.6 μg per day. The baclofen was included into her original combination therapy to treat spasms of her back musculature. This three-drug combination of hydromorphone/baclofen/ziconotide has produced good analgesia without memory loss that has lasted for more than a year.

Compounding

The only drugs currently approved in the United States for the IT management of pain include preservative-free morphine sulfate solution Infumorph®, Baxter (Deerfield, IL, USA; Astramorph®, AstraZeneca) and ziconotide (PRIALT®). Concentrations of morphine greater than 25 mg/mL require compounded formulations. Ziconotide is not compounded when used as monotherapy. Combinations of morphine and ziconotide, and other drugs and combinations of drugs require compounded formulations.

Compounding demands impeccably clean facilities with high air quality standards, personnel trained in the specifics

of aseptic practices, and thorough knowledge of sterilization and solution stability issues (United States Pharmacopoeia [USP] general chapter). Compounded sterile products intended for delivery into the central nervous system that are incorrectly prepared or contaminated can potentially produce catastrophic effects (174,175).

The United States Pharmacopoeia (USP) and the American Society of Health System Pharmacists (ASHP) have independently issued standards on compounded sterile products that have clinical, legal, and practical significance (176,177). These standards apply to compounding of solutions by various routes, including IT administration.

By 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 nonsterile ingredients or employ nonsterile components and devices that must be sterilized before use. By 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.

Using these standards, no compounded sterile, preservative-free preparation administered via an IT delivery system is classified at Level 1 (low risk). Some compounded preparations are classified at Level 2 (medium risk), and many are classified as Level 3 (high risk). Preparations of a sterile solution from a nonsterile powder are always considered at a Level 3 risk (USP General Chapter <797>, 2004; AHSP guidelines). USP Chapter <797> became effective in January 2004, and its impact continues to unfold on the practice of compounding. State pharmacy boards have primary responsibility for interpreting and enforcing the USP standards. At the national level, the FDA may choose to take enforcement action if they believe the compounding pharmacy is engaged in drug manufacturing.

Considerations for Compounded Formulations for Intraspinal Pumps

Other considerations, relevant to use of commercial formulations labeled for systemic (eg, intravenous, oral) delivery, apply to compounded formulations intended for IT delivery of drugs. These considerations exist in addition to the USP and ASHP sterile compounding recommendations and include the following:

1. Avoiding preservatives, antioxidants, and solubility enhancers, because they may be neurotoxic and/or incompatible with the IDDS.
2. Using buffers that are compatible with the delivery system. For example, 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, one should consider a solution 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). The relatively poor mixing of the CSF compartment can result in prolonged exposure of spinal tissues adjacent to the tip of the catheter. Thus, 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.
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 (159). 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 IT preparations can induce aseptic meningitis (159). Validated bacterial endotoxin test methods for specific and commonly compounded analgesic preparations are reported in the literature (159).

Lipophilicity of Medications

Lipid solubility, lipid content in the cord, and the variability of lipid content in differing areas of the central nervous system may play a significant role in variable patient responses to fentanyl and other lipophilic agents (sufentanil, methadone, clonidine, etc.) when given intrathecally. High lipophilicity results in rapid uptake of the agent by lipids and lipoproteins (spinal cord), less miscigination in cerebral spinal fluid, less supra spinal spread within the CSF, and in the IT drug traveling to the vascular space where intravascular uptake occurs more rapidly than in the case of a more hydrophilic drug. These agents have fewer supraspinal effects and more segmental effects than hydrophilic drugs.

Granuloma Formation

The 2007 consensus panelists have addressed this topic fully in an article published in this issue of *Neuromodulation*, which addresses more fully the etiology, detection, mitigation, and prevention of granulomas (178). All panelists felt that catheter-related granulomas still remain one of the most serious adverse effects and risks of IT pain management (179) and barriers to the widespread use of the therapy. Several factors contribute to the development of intrathecal granuloma, including the agent infused, catheter position, low CSF volume, and the dose and concentration of the drug. Even though some on the panel felt that positioning the catheter into the larger CSF volume of the dorsal IT space of the low thoracic cord, granulomas do occur even in cases where catheters have been inserted into that space.

However, as noted previously in the literature review of this manuscript, concentration of the agent used appears to be the major causal factor of intraspinal, catheter-related granulomas. Inflammatory masses have been reported to be associated with all medications administered IT except for sufentanyl and rarely for fentanyl (9). As of this writing, there have been at least three reports published in the literature of baclofen-related IT granulomas (178,180,181). Even though the literature suggests a granuloma protective effect of clonidine (24,182), there have been reports of patients with IT clonidine, alone, or in combination with other IT agents developing granulomas (23,183). Patients receiving therapies containing clonidine also should be evaluated for granulomas.

Current consensus opinion is that MRI remains the gold standard for surveillance when evaluating the presence of a catheter-related inflammatory mass, although computed tomography/myelogram through the pump offers a more cost-effective technique.

Equianalgesic Conversion Factors for Intrathecal Medications

There is no definitive evidence of a true conversion factor for calculating dose changes when shifting from one IT opioid medication to another and the panelists called for caution when doing so. Oral and systemic hydromorphone is considered in the literature to be 3.5–7 times more potent than morphine, but conflicting evidences for this comparative potency have been reported in the literature. The panelists felt that the IT hydromorphone/morphine potency ratio, in fact, is not known, and that physicians should exert caution when converting morphine to hydromorphone, or vice verse. The panelists felt that physicians should use published studies and equipotency guides as a reference and a guide to conversion, but they also must recognize that there is, as yet, no exact quantifiable conversion formula for these two opioids. In addition, the panelists felt that the risk of changing from a more lipophilic drug to a less lipophilic drug carries a high risk for respiratory depression when using conventional equipotent analgesic charts. Consensus opinion based on safety and caution of the panelists is to start dosing extremely low when shifting from one agent to another, particularly if the change involves shifting to a less lipophilic medication. It was felt by most that adding agent "B" at a low dose to a stable dose of agent "A" and then slowly decreasing the dose of agent "A" while increasing the dose of agent "B" is the safest way to perform IT opioid rotation.

Sudden Cessation of Drug

Catheter disruption, battery failure, or human error may lead unexpectedly to drug withdrawal accompanied by untoward side-effects that may vary, depending on the medication involved (184). Cessation of IT clonidine, for example, is known to cause rebound hypertension with increased risk for stroke, particularly in sensitive patients receiving doses in the higher ranges. Adverse effects associated with the abrupt withdrawal of clonidine may result from mechanical problems such as catheter kinking, inadvertent programming error, or the pump stopping. Consensus recommendations are to give all patients receiving clonidine a prescription for Catapres-TTS patches and/or catapress pills and advise them to immediately contact their physician if they have any signs or symptoms of clonidine withdrawal.

Baclofen withdrawal can, as stated above, be life-threatening. Signs and symptoms of baclofen withdrawal include pruritis, sleepiness, respiratory depression, obtundation, hyperthermia, disseminated intravascular coagulation, increased muscle spasticity, rhabomyolyis, acute renal failure, acute multiorgan failure, and even death (185). According to clinical reports, IT baclofen tolerance may not be a tolerance syndrome *per se*. Rather, it may result from escalating doses of the drug that are administered to patients who have diminished drug delivery due to subtle catheter tears. Conversely, withdrawal from medications like Baclofen also can happen abruptly with system failure or mistakes of refilling or programming (186). Atypical underlying device complications such as this illustrate the need for physicians to be continually vigilant in assessing potential problems arising from intraspinal drug therapy and doing whatever is necessary to diagnose these system failures or mistakes of programming or refilling.

Catheter-Related Issues

Catheter-related issues include catheter material and design, mechanical issues such as dislodgements, tears, small micro fractures, and displacement and complications of the catheter placement such as macrotrauma to the spinal cord and/or granuloma formation. The panelists did not focus on or discuss catheter design or material or management of mechanical catheter issues, but focused

on catheter issues as they relate to analgesic delivery and or inflammatory mass formation. As noted in the literature review and in a separate consensus article written by the panelists (160), there is evidence that an IT inflammatory mass (granuloma) will sometimes disappear if the physician either stops the infusion or pulls the catheter back approximately two segments, or both, as deemed appropriate at the time. The panelists agreed that a third alternative might be appropriate and that alternative is to remove the old catheter and replace it with a new one.

Clinicians may inject nonionic radiocontrast material (myelography) to document the flow rate of CSF around the catheter. When performing this maneuver, it is essential that the physician or other care-giver understand that there does exist a catheter dead space with agent within that dead space and that the agent within that dead space may be of high concentration. Before injecting any material through the side port, the caregiver should empty the dead space, if able, by aspirating from the side port until there is a clear flow of CSF. If unable to aspirate from this dead space, then NO agent should be injected through the side port unless safe and low concentrations, of no clinical consequence, are assured. If a dye study is not safe, a nuclear medicine study can be used in lieu of myelography to determine the innate flow rate of the pump based on a quantifiable amount of radioactivity entering and leaving the pump. If a dye study is safe, the dispersion of the dye after safe injection can then be qualitatively categorized as rapid, moderate, or slow as it moves into the cervical region. A fast dispersion of dye indicates a rapid bulk flow of CSF and that the distribution of the drug will be wider and greater, but a slow dispersion suggests that there may be either a slow CSF bulk flow, a low volume of CSF, or loculation of CSF around the catheter.

Hormonal Adverse Effects

Consensus opinion calls for monitoring for hormonal adverse effects that may result from IT analgesics, particularly opioid medications. While opioid medications are known to cause hypogonadism (187), ziconotide has not been associated with any known incidence of altered testosterone production. According to one anecdotal clinical report, testosterone levels that declined in a male patient who was receiving intrathecal morphine improved after the patient was switched to ziconotide. It is not clear if the reversal in hormonal activity resulted from the cessation of morphine or the delivery of ziconotide. In theory, ziconotide would be expected to exert at least a mild effect on hormonal production, either lowering or increasing testosterone levels, because it is an N-type calcium channel blocker. Additional studies on ziconotide administered in a wide range of titration regimens may clarify the effects of this drug, if any, as both a single agent and an agent in an admixture, on hypogonadism.

Trials

While drug trials are conducted to rule in or rule out efficacy and toxicity, they do not always yield such information conclusively in the time allotted for such studies. Efficacy may take longer to demonstrate than the one- to two-week interval over which most trials take place. Because there are many ways to trial for IT therapy, including single "shots" of epidural or IT medications, the continuous IT or epidural delivery of agents, long-term trials, on the table trials, etc., and because there is no comparative data to compare one way or the other, the panelists felt that trial procedure should be left up to the physician performing them. The panelists felt that until there are data that suggest that trials are unnecessary, trials should be performed before placing IT delivery agents through an IDDS. Trials can be performed with monotherapy or with polyanalgesia.

Patient Monitoring Following Initiation of Therapy

Medtronic Inc. issued a White Paper in 2006 articulating the company's recommendation that the patient monitoring that follows the initiation of IT analgesic therapy, or takes place during dose and drug change, should occur in a hospital setting. Although the panel did not agree that simple dosing changes or low-dose changes of new medications warranted hospitalization in all patients, the consensus position of the 2007 Polyanalgesic Conference is basically in agreement with the view of Medtronic under certain conditions. The panel felt that after the initiation or re-initiation of infusion, continuous IT therapy, patients should be monitored in an adequately equipped facility, having sufficient monitoring equipment, for a sufficient amount of time, if warranted by a combination of risk factors. While the panelists did not designate a precise period of time as sufficient, they noted that all patients should receive appropriate routine monitoring for potential complications in patients receiving relatively high doses of medications during a period of time that a "prudent" physician deems adequate. A period of 24 hours is considered appropriate for evaluating potential complications in vulnerable patients who may benefit from hospital monitoring. Vulnerable patients may include, but are not limited to, the elderly, the very young, opiate naïve patients, patients with poor cardiac reserve or respiratory reserve, etc.

The Conclusions and Recommendations of Polyanalgesic Conference 2007

Algorithm: Selection of Medications for Long-Term Intrathecal Infusion

The published literature on opioid and nonopioid analgesic medications has expanded significantly since the publication of the Second Polyanalgesic Consensus Conference Report in 2004 (5). However, the overall number of new studies

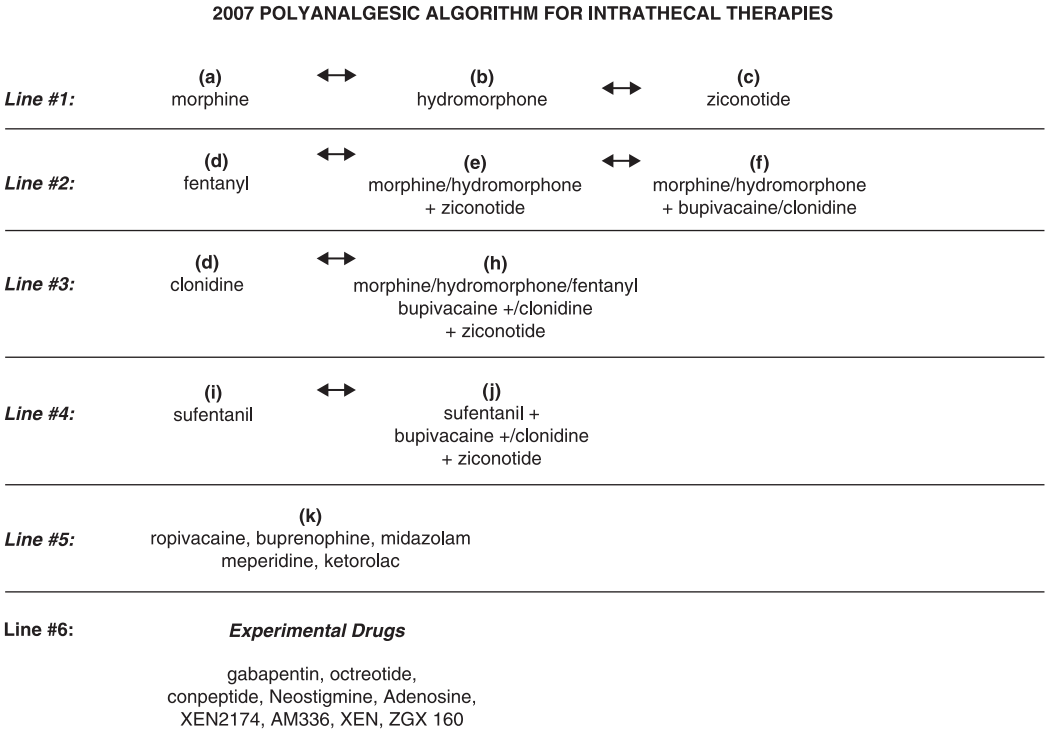

FIGURE 1. Recommended algorithm for intrathecal polyanalgesic therapies, 2007. Line 1: Morphine (a) and ziconotide (c) are approved by the Food and Drug Administration of the United States for intrathecal analgesic use and are recommended for first line therapy for nociceptive, mixed, and neuropathic pain. Hydromorphone (b) is recommended based on clinical widespread usage and apparent safety. Line 2: Because of its apparent granuloma sparing effect and because of its wide apparent use and identified safety, fentanyl (d) has been upgraded to a line 2 agent by the consensus conference when the use of the more hydrophilic agents of line 1 (a,b) result in intractable supraspinal side-effects. Combinations of opioid + ziconotide (e) or opioid + bupivacaine or clonidine (f) are recommended for mixed and neuropathic pain and may be used interchangeably. When admixing opioids with ziconotide, attention must be made to the guidelines for admixing ziconotide with other agents. Line 3: Clonidine (g) alone or opioids such as morphine/hydromorphone/fentanyl with bupivacaine and/or clonidine mixed with ziconotide (h) may be used when agents in line 2 fail to provide analgesia or side-effects occur when these agents are used. Line 4: Because of its proven safety in animals and humans and because of its apparent granuloma-sparing effects, sufenta alone (i) or mixed with bupivacaine and/or clonidine plus ziconotide (j) is recommended in this line. The addition of clonidine, bupivacaine, and or ziconotide is to be used in patients with mixed or neuropathic pain. *In patients with end of life, the panelists felt that midazolam and octreotide should be tried when all other agents in lines 1–4 have failed. Line 5: These agents (k), although not experimental, have little information about them in the literature and use is recommended with caution and obvious informed consent regarding the paucity of information regarding the safety and efficacy of their use. Line 6: Experimental agents (l) must only be used experimentally and with appropriate Independent Review Board (IRB) approved protocols.

pertaining to analgesic medications most commonly used for IT infusion, and the number of studies on new or experimental agents identified by the expert panels of the first and second conferences, remains limited. In keeping with the recommendations proposed by the Second Polyanalgesic Consensus Conference Panel, the clinical practice guidelines and accompanying algorithm for IT drug selection in the 2007 updated version is based on the current best evidence available from published studies and on minimum evidence as defined by the Conference 2003 (5).

The current algorithm for drug selection provides a set of practical clinical guidelines for optimizing the therapeutic use of analgesic medications and drug combinations in a rational and prioritized order. The algorithm is designed for use in 1) screening trials to assess whether or not a new patient is a candidate for pump implantation and 2) changing treatment in a patient already receiving chronic long-term infusion. In addition, the algorithm offers guidance on the appropriate use of experimental medications in cases of difficult, severe intractable pain management, and on agents that warrant additional or new evidence-based research because of their promising safety, toxicology, and efficacy profiles. The medications in the current algorithm are arranged in a hierarchy based on evidence on safety, efficacy, and broad clinical parameters gleaned from previous and current consensus literature reviews, ratings of published studies, and expert opinion from three Polyanalgesic Consensus Conferences (Fig. 1). First line

TABLE 1. Concentrations and Doses of Intrathecal Agents Recommended by the Polyanalgesic Consensus Panelists, 2007

Drug	Maximum concentration	Maximum dose/day
Morphine	20 mg/mL	15 mg
Hydromorphone	10 mg/mL	4 mg
Fentanyl	2 mg/mL	No known upper limit
Sufentanil	50 μg/mL (not available for compounding)	No known upper limit
Bupivacaine	40 mg/mL	30 mg
Clonidine	2 mg/mL	1.0 mg
Ziconotide	100 μg/mL	19.2 μg (Elan recommendations)

medications (morphine, hydromorphone, and ziconotide for neuropathic pain) are supported by extensive clinical experience and published preclinical and clinical data, and are typically used as starting IT therapies. Morphine and more recently, ziconotide, are the only medications approved by the USFDA for IT analgesia.

The expert panelists felt that special rules should apply to patients at end of life. These panelists felt that the algorithm for IT therapy, when used for patients at end of life, should be accelerated. The panelists relied somewhat on a previous expert consensus opinion on the use of intrathecal agents for end of life (188). The use of agents that do not have toxicity data but are supported by anecdotal evidence of safety and efficacy should be accelerated in this patient population and IT agents such as midazolam and octreotide, not recommended for patients with non-malignant pain, should be tried in patients at end of life, when agents in Lines 1–4 have been tried and failed. The physician "do no harm" mandate should be superseded by a mandate to relieve pain and discomfort at end of life. Some patients in this group also might not respond to IT therapy and might require spinal anesthesia, continuous epidural anesthesia, or the use of neurolytic agents such as alcohol or phenol for their relief of end of life pain.

Medications listed below Line 1 are supported by a smaller amount of published preclinical evidence, fewer clinical published studies, less clinical anecdotal experience, or a combination thereof. Second and progressively lower line medications can be administered if intolerable side-effects develop, or if the initial therapy becomes ineffective at a dosage and concentration normally considered safe or convenient (eg, for refills at short intervals) in IT infusions for pain therapy. Selection of a specific drug or drug combination on any level, whether the same or lower levels, should be determined on the basis of clinical judgment, relevant clinical experience, and the patient's individual response to therapy.

Line 1 Approach

Line 1 contains (a) morphine, the only opioid analgesic drug that, as noted, is approved by the FDA for long-term IT administration, (b) hydromorphone, an opioid medication drug that is increasingly used IT because of growing preclinical and clinical evidence-based support from the medical literature, wide clinical experience, and expert consensus opinion, and (c) ziconotide (Prialt®), the only nonopioid analgesic approved by the FDA for long-term IT use. Ziconotide is recommended as a Line 1 drug in this algorithm for nociceptive, mixed, and neuropathic pain. Support for this decision comes from substantial data from preclinical and clinical studies. Ziconitide is considered by the panelists to need a "Special Box" reference, Line 1 medication because of its limited/targeted use due to a variable therapeutic window and wide panel of known adverse effects. Close monitoring of dose/concentration is critical with all three medications in Line 1, but the rationale for exercising caution differs for the opioid and nonopioid medications. Because both morphine and hydromorphone are associated with a known concentration-dependent risk of catheter-tip granuloma formation, physicians are advised to titrate doses of these two opioids not beyond an a *prio*ri upper limit that has been determined from clinical experience (Table 1). If adverse effects develop with either morphine, hydromorphone, or ziconotide; if the dosage is elevated without adequate analgesia, the analgesic can be changed to the alternative Line 1 analgesic (ie, switch morphine to hydromorphone or ziconotide, hydromorphone to morphine or ziconotide, or ziconotide to morphine or hydromorphone) or switch to a Line 2 approach.

Line 2 Approach

Line 2 contains fentanyl (d) alone or morphine or hydromorphone combined with either ziconotide (e) or bupivacaine or clonidine (f). Data are still too limited to accurately calculate the comparative risks vs. benefits of Line 2 single medications and drug combinations. Fentanyl, a lipophilic opioid medication, is a reasonable first choice for a Line 2 drug, especially for patients with nociceptive pain, because cumulative data to date strongly suggest that this medication is rarely related to the development of inflammatory masses. Fentanyl, therefore, is a viable replacement for Line 1 opioid medications in patients who show increased risk for granuloma (ie, early warning signs and symptoms such as decreased analgesia and requirements of

increased dosage). Fentanyl, a highly lipophilic agent, also is a good choice of an IT opioid if the more hydrophilic agents, morphine and hydromorphone, produce intractable supraspinal side-effects such as sedation or nausea and vomiting. If Line 1 medications do not produce adequate analgesia, a combination regimen of morphine (or hydromorphone) plus either ziconotide, bupivacaine, or clonidine can be administered to improve efficacy for mixed and neuropathic pain states. Clinical experience suggests that these combinations are stable, except for the combinations with ziconotide (see discussion on stability). If morphine (or hydromorphone) plus bupivacaine or ziconotide does not improve clinical analgesia, and/or results in dose escalation, switch to morphine (or hydromorphone) plus clonidine. There is reasonably preclinical compelling evidence that clonidine may mitigate or even prevent granuloma formation when coadministered with opioid medications; however, as we saw above, there have been at least three reports of granuloma formation in patients receiving clonidine. Clonidine also is known to have hypotensive side-effects. In regards to bupivacaine, only limited preclinical and clinical data are available. In contrast, clonidine has been studied more extensively but is thought to have a poorer safety profile. The assumption that the addition of either clonidine or bupivacaine will have opioid-sparing effects that decrease the risk for granuloma formation is hypothetical and not proved.

Line 3 Approach

If a Line 2 monotherapy or polytherapy fails to achieve adequate analgesia or if it produces intolerable side-effects, the clinician may try changing to clonidine alone (g) or one of the alternative Line 2 combinations plus ziconotide (h). Line 3 regimens consist of the addition of ziconotide to four possible combinations of either bupivacaine or clonidine added to either morphine or hydromorphone. If the initial drug combination is unsatisfactory, physicians may first switch to another combination (ie, switch to the alternative opioid) within the Line 3 approach before proceeding to Line 4. However, preference should be given first to a combined therapy of either opioid plus bupivacaine. The rationale for using bupivacaine as the preferred nonopioid in the combination is the same as in the Line 2 approach (f). Bupivacaine is higher up on the hierarchy of drug selection when compared to clonidine, because it appears to have a better safety profile than clonidine. Only limited data exist on the safety and efficacy of Line 3 polyanalgesic therapies that include the above combinations plus ziconotide. Although there are few definitive data regarding these combinations, they are feasible options if satisfactory pain relief is not achieved by Line 2 medications. Limited support for the medications and combinations in Line 3 is based on clinical experience of improved pain management upon using such combinations.

Line 4 Approach

Sufentanil, the primary Line 4 medication, can be tried for analgesic efficacy if Line 3 approaches are ineffective. Sufentanil is used in clinical practice, even though there are no long-term safety and efficacy data for this drug. Although sufentanil and fentanyl are both lipophilic opioids with much greater potency than morphine, sufentanil is placed two lines below fentanyl. Minimal evidence suggests that fentanyl is safe and possibly effective. By contrast, there are no long-term safety and efficacy data on sufentanil to support its use. Nonetheless, sufentanil is used in clinical practice and may provide analgesia in patients who develop tolerance to morphine or increased risk for inflammatory mass. Intrathecal infusions of highly lipophilic medications such as sufentanil in theory may cause fewer adverse effects than IT morphine because a smaller amount of a lipophilic agent diffuses to rostral brain centers.* The panelists felt that patients at end of life should be addressed as a special population of patients, and that agents such as octreotide and midazolam, not recommended by the panelists for nonmalignant pain should be tried as a line 4 therapy when all agents in lines 1–4 have failed.

Line 5 Approach

Line 5 constitutes a special box for medications that are available but have limited data on safety, including toxicology and efficacy, or that have either putative or established risks of toxicity, as determined through clinical experience. Medications in this category include ropivacaine, buprenophin, midazolam, meperidine, and ketorolac. There are either no or few published clinical data and/or very limited clinical experience to support the use of agents on Line 5 for chronic IT drug infusions. Similarly, few or no published clinical data and/or very limited clinical experience exists to support the use of these agents as chronic IT drug infusions except for the case of midazolam. Although there are clinical data supporting the use of midazolam in noncancer patient populations, there are data that established IT toxicities for this drug. Data from preclinical models, including toxicology studies, also are limited for Line 5 agents. Medications on Line 5 should be administered only for severe and disabling pain that has not been mitigated by any drug or drug combination above this line.

Line 6 Approach

Line 6 represents a special box of experimental therapies that warrant research as possible future therapies. Medications in this category have no or minimal preclinical and/or clinical data. Line 6 agents include gabapentin, octreotide

*CAVE: a spinal cord lesion has been reported with the use of bupivacaine at a concentration of 20 mg/mL (Perren et al. Pain 2004;109 (1–2):189–194).

conpeptides, neostigmine, adenosine, XEN2174, AM336, and ZGX160 or moxonidine. Use of any drug on Line 6 should be considered only in cases of severe and disabling pain that is refractory to more conventional treatments and only in patients at end of life.

Special Circumstances: Baclofen

Baclofen has FDA approval as a safe effective drug for IT use for the treatment of spasticity. It is currently being used intraspinally to manage pain syndromes in patients with and without spasticity. Clinical experience suggests that IT baclofen may reduce pain in patients with pain arising from spasticity, rigidity, or muscle cramping. However, there is less compelling evidence for its use as an IT agent for the relief of pain. More critically, two recently published reports of baclofen-induced granulomas have raised new concerns over the long-term and possibly even short-term safety of baclofen as an intrathecal analgesic medication.

Special Circumstances: Midazolam

The preservative-free hydrochloride salt of IT midazolam is used with growing frequency in Europe to treat severe pain in advanced cancer. The evidence for safety and efficacy for midazolam is limited. However, the formulation of midazolam solution that is available for commercial use in the United States contains a preservative and most probably should not be used in patients with nonmalignant pain, but may be used in patients with pain refractory to other agents at end of life.

Recommended Dosing and Dose Changes

The panel recommends that when starting IT therapy or when changing drugs used for IT therapy that physicians start low and go relatively slow, guided by each patient's individual needs and clinical presentation. Some patients are robust and young and some patients are frail and old. Some patients are opioid naïve and some are on high doses of systemic analgesics. Physicians should remember that when changing to IT therapy, "do no harm" should always be a guiding principle. Safety, however, must be balanced by the need to relieve pain and suffering. In general, the panel recommends that dosing changes should be accelerated in the cancer population and young and robust and kept to changes weekly in the frail and the old. The panel also recommend between 20% and 30% changes in the nonend-of-life population and up to 50% changes in the end-of-life population, again guided by each individual's needs and tolerances.

The panel fully discussed the upper limits of concentrations and doses, knowing full well the recommendations as set forth by Polyanalgesic Conference 2002. The panel agreed that until further data are available on the upper limits of safety for intrathecal agents, the recommendations as set forth by Polyanalgesic Conference 2002 and set forth in Table 1 are still operable, except for the FDA recommendations for ziconotide.

Conclusions

The Polyanalgesia Conference 2007, a panel of experts known for their expertise in IT therapy, has made updates and recommendations for the rational use of intrathecal agents based on their review of both preclinical and clinical information since 2000. Of most note is that the panel felt that, based on relevant new literature and clinical experience, ziconotide should be upgraded to line one intrathecal therapy along with morphine and hydromorphone. Physicians who treat patients with IT agents should be guided by this information and their own special expertise when treating their patients as individuals. It is to be emphasized that what is presented here are guidelines and should not be misconstrued as standards of care.

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