ELSEVIER
SAUNDERS

Neurosurg Clin N Am 15 (2004) 289–296

NEUROSURGERY
CLINICS
OF NORTH AMERICA

Intrathecal methods

Kimberly M. Kaplan, MD, William G. Brose, MD*

Department of Anesthesia, Stanford University School of Medicine, 300 Pasteur Drive, Stanford, CA 94305, USA

Although the use of opioids for intrathecal anesthesia was first reported in 1901 by Brill and colleagues [1], it was not until 25 years ago that the first report of selective blockade of pain by spinal opioids was described by Behar and colleagues [1]. Since its beginning, the promise of selective analgesics derived from intraspinal administration has generated much development in the field of pain management. In fact, many anesthesiologists who had previously relegated themselves to the confines of the operating room discovered that their needles and catheters could reach even beyond the inpatient wards, affording patients outside the hospital the opportunity to receive neuraxial drugs.

The advent of intraspinal analgesia coincided with the increasing demand for pain management, improved quality of life, and palliative care concerns that have directed large sums of health care dollars over the last quarter century.

President Ronald Reagan inadvertently promoted an increase in intrathecal awareness when he received an epidural opioid analgesia for his colectomy in 1985, elevating spinally active medications from merely a curiosity within pain management all the way up to the forefront of accepted pain practice [2].

As with many new discoveries in science, the much sought-after "promise of cure" was not delivered. However, this understandable "quick fix" aspiration of suffering patients sparked a new research frontier in the rapidly evolving field of pain management. The continuous dedication of basic science research has increasingly broadened our thinking and knowledge about the neurophysiology of pain. Sophisticated understanding of the types of receptors and medications that might have an effect at the dorsal horn of the spinal cord have inspired new uses for old drugs and have promoted new drug development. The *Neurosurgery Clinics of North America* have provided a continuing series of empirical trials of different drugs with a recurring theme of help and hope that is combined with undesirable, limiting effects. The goal of this article is to report on the current state of spinal analgesic chemotherapy as it is now known [3].

The scientific basis for spinal analgesic therapy

Small quantities of opiate injected intrathecally produce segmental analgesia [4]. It was this observation that led to the clinical use of spinal opiates during surgical procedures and the relief of postoperative and chronic pain [5]. As with local anesthesia, analgesia begins in the sensory nerves that enter the spinal cord dorsal horn near the area of injection. Presynaptic opioid receptors inhibit the release of substance P and other neurotransmitters from primary afferents, while postsynaptic opioid receptors decrease the activity of certain dorsal horn neurons in the spinothalamic tracts. Opioids will not affect conduction in sensory, motor, and autonomic nerves, so blood pressure, motor function, and nonnociceptive sensory perception are not affected by the spinal opiates.

Published experience of spinal analgesia

For years the discussion of chronic pain acute pain and a pain continuum has been considered as a dichotomy. The recognition that acute postoperative and posttraumatic pain was generally safe to palliate given that the underlying pathology

* Corresponding author.
E-mail address: wbrose@helppain.net (W.G. Brose).

1042-3680/04/$ - see front matter
doi:10.1016/j.nec.2004.02.011

was going to undergo a natural healing process was well accepted. This awareness was one of the principle determinants of recent changes within hospitals and health care systems to adopt pain as the "fifth vital sign," recently introduced by the Joint Commission on the Accreditation of Healthcare Organizations. Cancer pain is also widely accepted as a primary target for palliative analgesic use. Following acute pain, cancer pain management has received much of the focus of medication use and development in recent years. Although acute pain and cancer pain management differ considerably in terms of the underlying pathophysiologic process, the moral imperatives to deliver pain relief and the relatively short duration of therapy align the two. Consequently, much of the work that has been done on analgesic drug development in acute pain is directly translated to cancer pain and vice versa.

The use of analgesics in chronic noncancer pain, however, has been subject to much more rigorous debate. Chronic pain does not share the same time course, and the cultural and social factors that envelop chronic pain sufferers seem to suggest a much more complicated moral dilemma when applying the concepts of palliation to potentially productive members of society. For this reason, the authors do not promote the adoption of acute and cancer pain data to the use of analgesic agents in chronic noncancer pain. Although the moral imperative is clearly great to treat the suffering of these patients, the clinical date would suggest that the best outcome is actually achieved with interdisciplinary approaches to chronic pain rather than spinal analgesic therapies. Nevertheless, within the construct of an interdisciplinary treatment program, we do advocate the consideration of analgesic therapy and specifically intraspinal analgesics.

Our recommendations are that intraspinal analgesics should be used when a specific goal of analgesic treatment has not been achieved through the application of usual oral medications and the intraspinal drug has been proven in a trial period to provide unique efficacy to the patient in achieving the goals set by both the treating physician and the patient. For this reason, we present some information that is derived from acute and cancer pain applications of intraspinal medication use, because it may be applicable to the use of these agents in the chronic setting. We must add, however, that we do not recommend the use of intraspinal medications in chronic noncancer pain outside of a multidisciplinary pain program. Although the unique efficacy of intraspinal chemotherapy makes it tempting to direct as a sole therapy, evidence of benefit in chronic pain falls well short of that demonstrated for multidisciplinary treatment. For the remainder of this article, the term *chronic pain* will specifically refer to chronic noncancer pain.

Transition in goals

When considering any analgesic drug for use in chronic pain, we promote the consideration of three primary points: (1) desired drug effects, (2) undesired drug effects, and (3) medication-related toxicity.

Desired medication effects can be easily described as analgesic endpoints. However, more careful review of that goal would render this description incomplete. The possibility of achieving desired pain relief but with associated undesired effects is the rule rather than the exception. We heave also noted that the measurement of pain or pain relief does not provide a consistent change as these therapies are employed over time. We therefore have advocated the use of an activity-based paradigm that allows the incorporation of desired and undesired defects to produce a single measure that can be individually determined and then followed for each patient or medication trial.

This paradigm relies on the awareness that the problem of chronic pain is not strictly the pain but also its impact on a patient's quality of life. The cumulative effects of pain on an individual's function, productivity, and performance provide most of the tangible loss. The use of therapy to help a patient recoup this loss appears to be a very predictive measure. Therefore, we have developed a trial methodology incorporating the use of intraspinal drugs in which patients identify functional end points and activities that are important to improve their quality of life, and goals are set for achieving these improvements as a basis for determining efficacy of a given medication or dose. We have developed a goal-setting form for our patients that identifies activity changes in vocational, social, or recreational areas of a patient's life that can be monitored and associated with various medication use.

We recommend that all intraspinal drug trials use such an activity-based paradigm to allow clear objective benefits to be determined and documented to support the therapy and justify the

continued use. If a patient does not yet have an implanted device in place, we recommend that a temporary intraspinal catheter be used with individual or combination intraspinal chemotherapy to determine the optimal combination and dose for the patient. We use goal achievement as demonstrated on the activity-monitoring form to make a final determination for permanent pump implantation. We recommend this trial methodology as creating a much more predictable response to permanent pump implantation. We have achieved much greater levels of patient satisfaction and reproducible benefit from evaluating our implantable therapies in this way.

Available drugs

A wide range of opioids have been studied intraspinally. Fentanyl, sufentanil, and meperidine have been studied intraspinally and are routinely used. Other opioids that have been studied are buprenorphine, diamorphine, sufentanil, alfentanil, lofentanil, butophanol, hydormorphone, nalbuphine, methadone, nicomorphine, pentazocine, phenoperidine, meptazinol, and tramadol. At this time, there is a general lack of comparative data for these drugs. The major difference between the various opioids intraspinally is latency of onset, duration of analgesia, and adverse effects. The quality of analgesia appears to be similar for all drugs [6].

Pharmacokinetic pharmacodynamic considerations

As with systemic analgesic therapies, the identification of the site of action, drug delivery to that site, and the consequences of the drug activity at the site are determined by pharmacokinetics and pharmacodynamics of the drugs within the body. Early investigation of kinetic contributions with varying opioid analgesics has suggested that a drug's lipid solubility might influence the distribution. However, further investigation of this novel delivery system has suggested that there is quite rapid distribution of drugs regardless of water/lipid solubility. Although the optimal site of catheter placement relative to opioid effect is still unclear, experience with intraspinally administered local anesthetics suggests that placing the catheter tip in the proximity of the predictably involved dorsal horn segments of the spinal cord is a desirable technique [7].

Single agent therapy

Opioids

Desired effects

Morphine is generally considered by the research community and most pain specialists as the gold standard by which other opioids are compared. Although doses of morphine used have varied widely, the recommended beginning dose is approximately 0.02 to 0.05 mg/h of intraspinal morphine in opioid naïve patients to assess efficacy. If a bolus is to be used, we recommend that the bolus be limited to 0.5 mg to avoid limiting undesired effects.

Undesired effects

Intraspinal morphine has been reported to cause nausea, vomiting, sedation, pruritis, and urinary retention, as well as dose-related respiratory depression. These undesirable consequences of medication use can be effectively measured as an integrated part of therapy by using a goal-setting paradigm such as that introduced above. If the undesired effects limit the performance of a pre-established goal, we recommend changing to a different opioid to determine if the undesired effect may be more specific to morphine than spinal opioids per se. Our recommended drug rotation trials for intraspinal use would include morphine, hydromorphone, and fentanyl.

Toxicity

Intraspinal morphine therapy appears to be safe to the neuraxis when delivered in doses of up to 15 mg/d. Doses of morphine above this level have been associated with ventral root responses. These responses uniformly limit the therapy due to tonic muscle movement that occur unpredictably and uncontrollably [7].

Combination agent therapy

A recent review of intraspinally administered medications by Walker and colleagues provided a review of the evidence to support various analgesic combinations. The summary that follows draws on that evidence.

Opioid and clonidine

Desired effects

Clonidine is an alpha-2-adrenergic agonist that has been used in the treatment of neuropathic cancer pain. In addition, intrathecal opioids and clonidine have also been used successfully in the

management of intractable spasticity [8,9]. It releases acetylcholine intrathecally, and this may be its mechanism of action. When used in combination with an opioid, clonidine allows for an additive decrease in the opioid requirements. The intrathecal dose is commonly 50 to 300 μg/d. Clonidine dosing should be gradually escalated and titrated for each patient to avoid the side effects of hypotension and, more commonly, sedation.

Undesired effects

Clonidine's undesired effects include hypotension and bradycardia. For this reason, we recommend gradual introduction of the medication in patients who are supervised in a hospital setting. With the initial introduction of 1 to 2 μg/h by infusion using an externalized pump or independently adjustable delivery mechanism.

Toxicity

Toxicity presents as indirectly related to hypotension.

Opioid and baclofen

Desired effects

Intrathecal baclofen is now a recognized and well-accepted treatment for the management of severe spasticity, often in association with traumatic spinal cord lesions, cerebral palsy, and multiple sclerosis. Baclofen is a specific γ-aminobutyric acid B receptor agonist. It opens potassium channels and restricts calcium influx into the presynaptic nerve terminal, thereby reducing the release of presynaptic transmitters. This is how it suppresses the release of excitatory neurotransmitters involved in monosynaptic and polysynaptic reflexes. In addition, it inhibits synaptic transmission by blocking presynaptic release of neurotransmitters [10,11]. Thus, it hyperpolarizes neurons and mimics the inhibitory effect of γ-aminobutyric acid on the spinal interneurons. Baclofen is thought to have a possible analgesic effect in addition to its antispasmodic effect. Baclofen can be administered orally, but the side effects are often prohibitive; therefore, we often use it intrathecally. Penn and Kroin [12] first proposed direct intrathecal administration of baclofen to avoid some of the pitfalls associated with oral dosing. Since that time, several studies have confirmed baclofen's relative safety and efficacy intrathecally [13,14]. Dosing is usually 30 to 400 μg/d. Maintenance dosage for long-term continuous infusion of baclofen has ranged from 22 to 1400 μg/d with most patients adequately maintained on 90 to 703 μg/d.

Undesired effects

Some undesired effects include pruritus without rash, hypotension, paresthesias, fever, and altered mental state. Often some of these effects can be symptoms of underdose. Withdrawal can be a life-threatening situation [15].

Toxicity

With the increase in intrathecal baclofen use, several instances of overdose have been reported [16–19]. Symptoms of baclofen overdose include drowsiness, lightheadedness, dizziness, somnolence, respiratory depression, seizures, rostral progression of hypotonia, and loss of consciousness progressing to coma. In most cases reported, coma was reversible without adverse sequelae after the drug was discontinued. There is no specific antagonist, and treatment is initially supportive. Physostigmine may be helpful in reversing respiratory depresssion. The action of physostigmine is unknown. One technique for overdose management involves aspiration of cerebrospinal fluid to decrease the intrathecal baclofen dose [20].

Opioid and local anesthestic

Desired effects

Morphine is often used in combination with bupivacaine because these two agents can act synergistically through different spinal mechanisms. In addition, local anesthetics can be added to morphine when pain is refractory to the single-agent narcotic [10]. When one adds bupivacaine to the intrathecal mixture, the morphine dose can be lowered. Additionally, the treatment efficacy of the refractory cancer pain is increased. This was shown in a study by Sjoberg and colleagues [21]. In this same study, they demonstrated that bupivacaine has a predilection for unmyelinated axons, which help control neuropathic pain that cannot be relieved by morphine alone. Acceptable pain relief was achieved with doses of intrathecal bupivacaine of less than 30 mg/d.

Bupivacaine inhibits sodium, calcium, and potassium channels. Bupivacaine is more effective at the cell bodies than at the axons. It can inhibit sympathetic, sensory, and motor neurons. Local anesthetics are neurotoxic and myotoxic, so it is important to dilute the cerebrospinal fluid when using local anesthetics. Bupivacaine can be used up to 4%. We recommend starting at approximately

3 mg/d; if the patient is elderly, start at 1 mg/d. The accepted limits are 10 mg/d [22].

Undesired effects

Adverse effects of bupivicaine include paresthesias, motor and impairment secondary to loss of sensation, and loss of proprioception, in addition to autonomic effects from the blockade of sympathetic and parasympathetic activity. All of these effects were found to occur with doses of more than 60 mg/d [22].

Toxicity

See Drasner for toxicity of local anesthetics. See Cousins and Bridengaugh [5] for information on bupivcaine-induced cardiotoxicity.

Opioid and N-methyl-D-aspartate antagonists

Desired effects

Ketamine is a phencyclidine derivative with analgesic properties that are believed to be mediated by different mechanisms. Postulated mechanisms by which ketamine analgesia might be mediated include both central and peripheral sites of action. Ketamine binds to opioid receptors, but a significant contribution to its analgesic efficacy may come from interaction with cholinergic, adrenergic, and serotonin systems.

Evidence from animal and human studies indicates that ketamine produces sensory and motor block when injected intrathecally [23,24]. As noted in animal models of protracted inflammatory pain, the initial pain is not attenuated by intrathecal N-methyl-D-aspartate (NMDA) antagonists like ketamine, but delayed pain is substantially reduced when an NMDA antagonist such as ketamine is administered before the initial pain stimulus. Numerous studies performed at the level of the spinal cord have shown that NMDA receptor activation plays a role in the transmission of nociceptive information. Consequently, blockade of the NMDA receptor elicits antiniciception in various models of persistent pain.

There are some reports on the interactions of NMDA antagonists with opioids or with clonidine at the spinal level. Few articles have been published on how the interactions of ketamine and morphine after intrathecal administration affect analgesic properties.

Some present work shows that NMDA receptor antagonists do not produce a behaviorally defined analgesia until doses are used that result in evident motor dysfunction, typically flaccidity.

Toxicity

Large doses of intrathecal ketamine may have neurotoxic potential in humans. Use of this agent alone or in combination is best accomplished in the course of clinical research.

Opioid and neostigmine

Desired effects

Intrathecal neostigmine, a cholinesterase inhibitor, produces antinociception in humans [25]. The combination of intrathecal neostigmine and morphine is believed to produce better analgesia with fewer side effects than the equianalgesic doses of each drug given separately. Neostigmine at 0.3, 0.6, and 5 μg all reduced pain behaviors [26]. Controlled trials of intrathecal clonidine administration over extended periods have not yet been conducted [27].

Local anesthetic and neostigmine

Desired effects. Intrathecal neostigmine can directly stimulate preganglionic sympathetic neurons in the spinal cord and can counteract the hypotension induced by the intrathecal local anesthetic [28]. A combination of neostigmine and local anesthestics may prove to be a combination that provides good hemodynamic stability compared with other combinations [29]. Still, a lot is unknown at this time about the role of spinal neostigmine in pain management.

Undesired effects

In one study, one of the major side effects of intrathecal neostigmine included nausea [27].

Clonidine and neostigmine

Desired effects. Studies have shown that intrathecal administration of neostigmine alone has no analgesic action but reduces the effective dose of intrathecal sufentanil when used in combination [27].

Undesired effects

Common reactions to neostigmine include hypersalivation, fasciculation, abdominal bloating and cramps, diarrhea, flatulence, dypepsia, headache, and dizziness [30].

Toxicity

Overdosage of neostigmine can cause cholinergic crisis, which is characterized by increasing muscle weakness, and can lead to involvement of the muscles of respiration. Atropine may be used to abolish or minimize gastrointestinal side effects

or other muscarinic reactions; care should be taken not to mask signs of overdosage, which could lead to cholinergic crisis.

Midazolam

Desired effects. Benzodiazepines were first introduced for the treatment of anxiety. In addition, they are used for their antianxiety and muscle relaxant properties. Intrathecal injections of the benzodiazepine midazolam have been reported to cause antinociception and potentiate the effects of opioid analgesia. It has been concluded that 2 mg of midazolam intrathecally improves the quality and duration of postoperative pain relief provided by the intrathecal route [31].

Undesired effects

Agitation, involuntary movements, combativeness, and hyperactivity are some of the undesired effects of midazolam.

Toxicity

Respiratory depression and arrest can occur, especially when used in uncontrolled settings. Intrathecally administered midazolam at doses larger than 100 μg/d for 20 days could cause damage to the spinal cord [32].

Droperidol

Desired effects. Evidence from randomized clinical trials shows that adding droperidol to intrathecal morphine allows for a reduced incidence of nausea and vomiting. There was also decreased pruritus and hypotension compared with the administration of intrathecal morphine alone.

Undesired effects

Undesired effects include drowsiness, tachycardia, hypotension, dizziness, chills, and dystonic reactions. Akathisias, hallucinations, and anxiety are also possible [30].

Toxicity

Serious reactions include arrhythmias, tardive dyskinesia, severe hypotension, bronchospasm, laryngospasm, oculogyric crisis, QT prolongation, and delirium. Torsades de Pointes and neuroleptic malignant syndrome are also potential undesired effects [30].

Experimental drugs

Ziconotide

Desired effects

Ziconotide is a selective N-type calcium channel blocker that has been shown to produce analgesia for pain secondary to cancer or AIDS [33]. Ziconotide has also been shown to be efficacious in the treatment of spasticity following spinal cord injury [34]. Some initial reports have shown analgesic efficacy of ziconotide when used intrathecally for cancer and AIDS patients [35]. Ziconotide may be effective in patients who have pain refractory to opioid therapy or for patients who cannot tolerate the side effects of opioids [33]. In case report studies, it appears that doses of 0.4 μg/h should be the starting infusion rate. This dose can be titrated upward according to side effects. Most recently, Staats and colleagues [33] conducted a randomized controlled trial with intrathecal ziconotide that showed clinically significant analgesia in patients who had pain secondary to cancer or AIDS.

Undesired effects

Calcium channels are distributed widely throughout the body, and diverse effects are expected when calcium channel blockers are administered. Adverse effects have been reported with ziconotide, but these tend to be easily managed through dose reduction or symptomatic treatment. Many symptoms were cerebellar in origin, including dysmetria and nystagmus. Other side effects included sedation, confusion, visual and auditory hallucinations, nausea, and diarrhea [35].

Neurotrophin-3 antisense oligonucleotide

When introduced intrathecally, neurotrophin-3 antisense oligonucleotide attenuates nerve injury–induced allodynia [27]. Intrathecal administration of 50 μM of neurotrophin-3 significantly attenuates allodynia [27]. Use of this agent alone or in combination is best accomplished in the course of clinical research.

GDNF

Glial-derived neurotrophic factor (GDNF) has receptors that are expressed by one subtype of dorsal root ganglion cells. Intrathecal administration of GDNF is capable of reducing ectopic discharges within sensory neurons. It has also been shown to reduce mechanical and thermal hyperalgesia following ligation of the sciatic

nerve. Although GDNF needs further investigation, it holds promise for future combination intraspinal therapy [10,36]. Use of this agent alone or in combination is best accomplished in the course of clinical research.

References

[1] Brill S, Gurman GM, Fisher A. A history of neuraxial administration of local analgesics and opioids. Eur J Anaesthesiol 2003;20:682–9.

[2] Bumgarner JR. The health of the presidents: the 41 United States presidents through 1993 from a physician's point of view. Jefferson (NC): MacFarland & Company; 1994.

[3] Walker SM, Mitchell VA, White DM, Rush RA, Duggan AW. Release of immunoreactive brain-derived neurotrophic factor in the spinal cord of the rat following sciatic nerve transaction. Brain Res 2001;890:240–7.

[4] Yaksh TL, Rudy TA. Chronic catheterization of the spinal subarachnoid space [abstract]. Physiol Behav 1976;17:1031–6.

[5] Cousins MJ, Mather LE. Intrathecal and epidural administration of opioids. Anesthesiology 1984;61: 276–310.

[6] Prithvi P, Raj MD. Practical Management of pain. 3rd edition. Labbock, TX: Mosby; 2000.

[7] Loeser JD. Bonica's management of pain. 3rd edition. Philadelphia: Lippincott Williams and Wilkins; 2001.

[8] Loubser PG, Sharkey P, Dimitrijevic M. Control of chronic spasticity following spinal cord injury using intrathecal morphine. Anesth Analg 1988;67:S135.

[9] Middleton JW, Siddall PJ, Walker S, Molloy AR, Rutkowski SB. Intrathecal clonidine and baclofen in the management of spasticity and neuropathic pain following spinal cord injury: a case study. Arch Phys Med Rehabil 1996;77:824–6.

[10] Lazorthes Y, Be JC, Sagen J, et al. Transplantation of human chromaffin cells for control of intractable cancer pain. Acta Neurochir 1995;64:97–100.

[11] Coffey JR, Cahill D, Steers W, et al. Intrathecal balcofen for intractable spasticity of spinal origin: results of a long-term multicenter study. Journal of Neurosurgery 1993;78:226.

[12] Penn RD, Kroin JS. Continuous intrathecal baclofen for severe spasticity. Lancet. p. 125–7.

[13] Penn RD, Kroin JS. Long-term intrathecal baclofen for treatment of spasticity. J Neurosurg 1987;66: 181–5.

[14] Penn RD, Savoy SM, Corcos D, Latash M, Gottlieb G, Park B, et al. Intrathecal baclofen for severe spinal spasticity. N Engl J Med 1989;320:1517–21.

[15] Coffey R, Edgar TS, Francisco GE, Graziani V, Meythaler JM, Ridgely PM, et al. Abrupt withdrawal from intrathecal baclofen: recognition and management of a potentially life-threatening syndrome. Arch Phys Med Rehabil 2002;83: 735–41.

[16] Penn RD, York MM, Paice JA, Muller-Schwefe G. Physostigmine reversal of balcofen-induced sedation. New Eng J Med 1989;320:1517.

[17] Delhaas EM, Brouners JR. Intrathecal balcofen overdose: report of 7 events in 5 patients and review of the literature. International Journal of Clinical Pharmacology, Therapy, and Toxicology 1991;29: 274–80.

[18] Saltuari LM, Kronenberg MF, et al. Balcofen in hereditary spastic paraparesis. Archives of Physical Medicine and Rehabilitation 1992;73:794–7.

[19] Kofler M, Kronenberg MF, Rifiei C, Saltuari LM, Bauer G. Epileptic seizures associated with intrathecal baclofen application. Eurology 1994;44: 25–7.

[20] Rushman S, McLaren I. Management of intrathecal baclofen overdose. Intensive Care Med 1999; 25:239.

[21] Sjoberg M, Appelgren L, Einarsson S, Hultman E, Linder LE, Nitescu P, et al. Long-term intrathecal morphine and bupivacaine in "refractory" cancer pain: I. Results from the first series of 52 patients. Acta Anaesthesiol Scand 1991;35:30–43.

[22] Medtronic Implantable Theories Seminars. Pamela Pierce-Palmer, Pain Faculty, University of California–San Francisco.

[23] Iida H, Dohi S, Tanahashi T, Watanabe Y, Takenaka M. Spinal conduction block by intrathecal ketamine in dogs. Anesth Analg 1997;85:106–10.

[24] Hawksworth C, Serpell M. Intrathecal anesthesia with ketamine. Reg Anesth Pain Med 1998;23: 283–8.

[25] Yaksh TL, Dirksen R, Harty GJ. Antinociceptive effects of intrathecally injected cholinomimetic drugs in the rat and cat. Eur J Pharmacol 1985; 117:81–8.

[26] Hama, Lloyd, Menzaghi. The antinociceptive effect of intrathecal administration of epibatidine with clonidine or neostigmine in the formalin test in rats.

[27] White DM. Neurotrophin-3 antisense oligonucleotide attentuates nerve injury-indueced Abeta-fibre sprouting.

[28] Carp H, Jayaram A, Morrow D. Intrathecal cholinergic agonists lessen bupivicaine spinal block-induced hypotension in rats. Anesth Analg 1994;79:112–6.

[29] Chung C-J, Kim J-S, Park H-S, Chin Y-J. The efficacy of intrathecal neostigmine, intrathecal morphine and their combination for post-cesarean section analgesia. Anesth Analg 1998;87:341–6.

[30] Epocrates. 2004.

[31] Shah FR, Halbe AR, Panchal ID, Goodchild CS. Improvement in postoperative pain relief by the addition of midazolam to an intrathecal injection of buprenorphine and bupivicaine. Eur J Anaesthesiol 2003;20:904–10.

[32] Nishiyama, Hanaoka. Midazolam can potentiate the analgesic effects of intrathecal bupivicaine on thermal or inflammatory-induced pain.
[33] Staats PS, Yearwood T, Charapata SG, Presley RW, Wallace MS, Byas-Smith M, et al. Intrathecal ziconotide in the treatment of refractory pain in patients with cancer or AIDS: a randomized controlled trial. JAMA 2004;291:63–70.
[34] Ridgeway, Wallace, Gerayli. Ziconotide for the treatment of severe spasticity after spinal cord injury.
[35] Penn, Paice. Adverse effects associated with the intrathecal administration of ziconotide.
[36] Boucher TJ, Okuse K, Bennett DL, et al. Reporting of adverse effects in clinical trials should be improved: lessons from acute post-operative pain. J Pain Symptom Manage 1999;18:427–37.