Intrathecal Drug Administration in Chronic Pain Syndromes

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Abstract: Chronic pain may recur after initial response to strong opioids in both patients with cancer and patients without cancer or therapy may be complicated by intolerable side effects. When minimally invasive interventional pain management techniques also fail to provide satisfactory pain relief, continuous intrathecal analgesic administration may be considered.

Only 3 products have been officially approved for long-term intrathecal administration: morphine, baclofen, and ziconotide. The efficacy of intrathecal ziconotide for the management of patients with severe chronic refractory noncancer pain was illustrated in 3 placebo-controlled trials. A randomized study showed this treatment option to be effective over a short follow-up period for patients with pain due to cancer or AIDS. The efficacy of intrathecal opioid administration for the management of chronic noncancer pain is mainly derived from prospective and retrospective noncontrolled trials. The effect of intrathecal morphine administration in patients with pain due to cancer was compared with oral or transdermal treatment in a randomized controlled trial, which found better pain control and fewer side effects with intrathecal opioids. Other evidence is derived from cohort studies. Side effects of chronic intrathecal therapy may either be technical (catheter or pump malfunction) or biological (infection). The most troublesome complication is, however, the possibility of granuloma formation at the catheter tip that may induce neurological damage. Given limited studies, the evidence for intrathecal drug administration in patients suffering from cancer-related pain is more compelling than that of chronic noncancer pain.

Key Words: evidence-based medicine, intrathecal drug administration, chronic pain, morphine, ziconotide

INTRODUCTION

This review on intrathecal drug administration is part of the series “Evidence-based Interventional Pain Medicine According to Clinical Diagnoses.” Recommendations formulated in this article are based on “Grading strength of recommendations and quality of evidence in clinical guidelines” described by Guyatt et al.¹ and adapted by van Kleef et al.² in the editorial accompanying the first article of this series (Table 1). The latest literature update was performed in June 2013.

The technique of intrathecal drug administration was developed in the 1970s. Analgesia following spinal administration of opiates and the observation that
Intrathecal therapy implies that the drug is administered directly into the area surrounding the central nervous system, which means that the analgesic dose can be substantially reduced. For morphine specifically, the spinal daily dose could be reduced by a factor 12 to 300, compared with the oral daily dose.9 Certain systemically administered analgesics will minimally pass the blood–brain barrier (compartment effect), meaning higher systemic doses are often required. In addition, intrathecal administration of these analgesics may result in fewer side effects.4

Although there are no factors that can predict the effectiveness of this technique, the success of the therapy is mainly associated with careful patient selection (Table 2).4,10 Intrathecal administration of analgesics is only indicated in patients with persistent pain in whom conventional methods of pain management have failed. These methods include extensive pharmacological therapy (analgesics according to the 3-step analgesic ladder including opioid rotation, if indicated combined with antidepressants, anti-epileptic drugs, topical

Table 2. Selection Criteria for Intrathecal Pump Implantation

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<tr>
<th>Clear diagnosis</th>
<th>No psychological or sociological contraindications</th>
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<td>Untreatable side effects of opioids (after opioid rotation)</td>
<td>Failure of several conservative treatments</td>
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<td>Life expectancy ≥ 3 to 6 months</td>
<td>Consider interventional procedures (peripheral nerve catheterization, neurolytic blockades, and cordotomy)</td>
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<td>Positive response during trial period</td>
<td>The patient understands the therapy; no cognitive disorders In patients &lt; 50 years old, consider alternatives including chronic pain rehabilitation programs</td>
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INDICATION AND PATIENT SELECTION

The main indications for intrathecal drug therapy in chronic pain (benign and cancer-related) are neuropathic pain, postherpetic neuralgia, peripheral neuropathy, and mixed nociceptive-neuropathic pain syndromes. Such syndromes include failed back surgery syndrome (FBSS), CRPS type 1, nociceptive pain, visceral pain including chronic pancreatitis, insufficient pain relief, severe side effects to oral, rectal, or transdermal opioid administration.9,10 This technique is also applied in patients with severe spasticity.
treatment and potentially also ketamine), interventional pain management techniques, rehabilitation, and cognitive and behavioral therapy. There should be no (new) surgical indication. As a result, intrathecal drug administration comes at the end of the treatment ladder of patients with chronic noncancer pain. Especially in cases of chronic, noncancer pain syndromes, patients should first undergo extensive psychological evaluation. The presence of psychological factors such as psychopathology, mood disorders, severe distress, and functional pain syndromes (somatization) reportedly reduce the chance of a successful treatment. Untreated addiction is an absolute contraindication for this form of therapy.

The pathophysiological mechanism of the pain syndrome also affects the results of the treatment. The chance of effective pain relief is significantly lower when opioids alone are administered for the treatment of patients with neuropathic pain compared with patients with nociceptive or mixed (nociceptive-neuropathic) pain. This means that every patient candidate should be subjected to extensive multidisciplinary evaluation before the therapy is initiated. This could include, for example, an anesthesiologist and/or neurologist and/or neurosurgeon to evaluate the pain syndrome and a psychologist and/or psychiatrist to evaluate the psychological context and to exclude a psychiatric diagnosis.

For the treatment of chronic noncancer pain, it is essential to begin with a trial period using a temporary intrathecal pain pump to evaluate the patient’s response before a definite intrathecal pain pump is implanted.

The test period can be evaluated (positive if the treatment induces effective pain relief) by means of the following arbitrary objectives: pain relief of at least 50%; significant improvement of the quality of life and sleep; significant increase in daily activities; and pain medication (nonintrathecal) can be reduced or entirely discontinued. Further studies are needed to establish if these objectives during the trial period have a predictive value for the effectiveness of pain relief after implantation of the pain pump.

The polyanalgesic consensus conference suggested a single-shot trial in case of nociceptive pain. Trialing the effect of ITDD for mixed pain or neuropathic pain, continuous infusion over several days may be preferred if the patient tolerates prolonged infusion. In patients with pain due to cancer, intrathecal drug administration can be considered when oral or transdermal analgesics provide insufficient pain relief or produce unacceptable side effects. In these patients, the intrathecally administered drugs may be combinations of more than 1 agent.

Patients with cancer-related pain who are candidates for intrathecal drug administration may have a short life expectancy. In these cases, the switch from oral or transdermal to intrathecal drug administration may be accomplished without a trial period, especially given that implantation of the drug administration pump is rarely performed. Patients are implanted with a subcutaneous port and infused intrathecally with an external pump.

**ACTION MECHANISMS FOR INTRATHECAL DRUG ADMINISTRATION**

**Intrathecal Analgesics and the Posterior Horn of the Spinal Cord**

The intrathecal administration of analgesics relies on the premise that the agent gets intimate access to the spinal pain pathways. A recent review described the different pain pathways and the opportunities for analgesia.

**RECEPTOR AGONISTS AND ANTAGONISTS**

**Opioid Receptor Agonists**

Three types of G-protein-linked opioid receptors can be distinguished, that is, μ, δ, and κ, which are responsible for analgesic and nonanalgesic effects. For example, presynaptic interaction inhibits the release of substance-P and calcitonin gene-related peptide by means of interactions with N-type voltage-dependent calcium channels and reduced calcium influx. Postsynaptic activation of opioid receptors leads to inhibition of adenylate cyclase and also results in opening of potassium channels. The opening of potassium channels causes hyperpolarization, rendering the postsynaptic second-order neuron less responsive.

Morphine is the opioid of first choice for intrathecal administration in chronic pain syndromes. Due to its hydrophilic character, morphine will spread more than fentanyl (and sufentanil) after intrathecal administration and thus extend the area of analgesia. Also, with this opioid, the dose reduction that can be applied when switching from parenteral to spinal administration is the most important, which may result in lesser dose-related side effects.

**κ2-Receptor Agonist**

Interaction with this receptor—located both presynaptically and postsynaptically—like opioids also results in
reduced presynaptic calcium entry and an increased potassium influx postsynaptically, which initiates hyperpolarization of the postsynaptic cell membrane. Clonidine, the most common α2-receptor agonist for intrathecal administration, combined with local anesthetics and morphine is reported to have a synergetic action for pain relief.4 Clonidine is mainly used in combination with opiates to treat neuropathic pain. In addition, intrathecal administration of clonidine (Average daily dose range from 50 to 200 μg) reduces the risk of morphine tolerance and thus lessens the risk for opioid-related adverse effects due to dose escalation.3,15 Side effects include dry mouth, sedation, bradycardia, and hypotension. Sudden discontinuation of long-term intrathecal therapy may lead to rebound hypertension, panic attacks, and psychotic behavior.12

\(\gamma\)-Aminobutyric Acid (GABA) Receptor

Although there are 3 different subtypes of GABA receptors (GABA_A, GABA_B, and GABA_C), only GABA_A and GABA_B have been described in relation to pain management and the treatment of spasticity. GABA_A receptor is coupled to a chloride channel, in which chloride ions enter the cell after activation resulting in hyperpolarization.16 Midazolam, a benzodiazepine with GABA_A agonist activity, is used in intrathecal therapy in combination with local anesthetics in spinal anesthesia.17 Additionally, a single-shot intrathecal administration of midazolam (2 to 5 mg) as a supplement may induce adequate pain relief (lasting more than 4 weeks in 65% of cases) in patients with low back pain and failed back surgery.18

Intrathecal midazolam administration causes dose-dependent sedation. Although no neurotoxicity has been described after single administration in humans, there are no data available about the effects of midazolam after continuous administration.19 In this context, the use of intrathecal midazolam as part of chronic pain management is definitely not preferred.

G-protein-coupled GABA_B receptor increases potassium permeability. As with opioids and α2-receptor agonists, presynaptically decreased opening of voltage-dependent calcium channels results in a decreased release of neurotransmitters. Likewise, postsynaptically increased potassium ion influx also causes hyperpolarization, reducing the activity in second-order neurons. Baclofen, a GABA analog and a GABA_B receptor agonist, is primarily used to treat spasticity by hyperpolarization of postsynaptic second-order motor neurons. Besides reducing spasticity-related pain, baclofen may help decrease neuropathic pain in some cases of central pain syndromes, FBSS, plexopathy and phantom pain; however, supportive evidence for a role of baclofen in analgesia is strongest in animal experiments.4 Side effects include dizziness, muscle weakness, gastrointestinal complaints, sexual dysfunction, decreased cognition, tolerance, and physical dependence, which implies sudden discontinuation may lead to hyperthermia, rebound spasticity, epilepsy, muscle contracture, and even respiratory problems.16

**N-Methyl-d-Aspartate-Receptor Antagonist**

This postsynaptic glutamate receptor (NMDA) is activated via excitatory amino acids, resulting in increased calcium influx. Repeated activation of this receptor, as occurs in neuropathic pain, leads to wind-up and central neuronal hyperexcitability, causing allodynia and hyperalgesia.4,20 Ketamine is the noncompetitive NMDA receptor antagonist that has been most often used. This analgesic is mainly for parenteral administration. Additionally, this analgesic has a narrow therapeutic window and may cause many serious dose-dependent side effects such as mood disorders, changes in perception, and decreased intellectual functioning.20 Finally, there are strong indications that intrathecal use leads to neurotoxicity, both in animals and in humans.21,22 Intrathecal ketamine is only indicated in patients with terminal cancer suffering refractory pain despite extensive (intrathecal) drug therapy.4,16,22

**ION CHANNEL BLOCKERS**

**Na⁺ Channel Blockers**

Local anesthetics block the Na channels of neuronal tissue and disrupt pain transmission. Combination of local anesthetics with opioids may reduce the opioid-related side effects as well as the risk of opioid dose escalation. In addition, a synergetic analgesic effect has been described for intrathecal administration of this combination. Because of the combination with opioids, a low daily dosage of bupivacaine (on the order of 1 to 14 mg) is sufficient to relieve pain.23,24 It is important to note here that intrathecal doses of up to more than 30 mg/day did not cause bladder dysfunction or muscle weakness.25 Safety studies show no neurologic sequelae or toxicity at clinical relevant doses of
intrathecal administration. Few complications are reported.\textsuperscript{26–28}

**N-Type Voltage-Dependent Calcium Channel Blockers**

While there are a number of voltage-dependent calcium channel subtypes (T, L, N, P, Q, and R subtypes), the N-subtype is notably involved in nociception. The only calcium channel blocker for intrathecal use clinically is ziconotide, a synthetic form of peptide, \(\alpha\)-conopeptide.\textsuperscript{4}

The efficacy of this analgesic, administered intrathecally, has been shown in patients with chronic benign and cancer pain syndromes. However, the risk of side effects occurring during therapy with intrathecal ziconotide is very high. Up to 31\% of the treated patients experienced side effects (dizziness, nausea, nystagmus, balance disorders, confusion, constipation, and urinary retention). Ziconotide is used alone as well as in combination with opioids.\textsuperscript{18} In the U.S.A., the FDA imposed the following warning “Severe mental/mood changes (eg, confusion, depression, hallucinations, and decreased alertness) that may occur in some patients. This medication should not be used if there is a history of certain mental disorders (eg, psychosis) because it increases the risk of those side effects.” The advantage of ziconotide is that it results in pain relief without the complications as described for opioid analgesia (tolerance, sexual dysfunction, physical and psychological dependence, and respiratory depression).\textsuperscript{29} However, ziconotide is a weak analgesic as shown in a double-blind placebo-controlled trial,\textsuperscript{30} has a narrow therapeutic window, is easily oxidized when mixed with morphine, which significantly reduces its efficacy,\textsuperscript{31} and is very expensive. All of these factors limit its clinical usefulness.

**INTRATHECAL ADMINISTRATION OF ANALGESICS**

Many analgesics have been proposed for the treatment of neuropathic pain. Within this group, it is possible to make recommendations and create a flow diagram (first-line, second-line, and third-line treatment) for intrathecal treatment, mainly based on expert opinion, supported by studies (primarily observational and case series) and guidelines from literature that are regularly adapted to the latest insights. The most recent guideline suggests a slightly different drug selection for the management of neuropathic pain than for the management of nociceptive pain.\textsuperscript{14,32} (Figure 1)

Only 3 products have been officially approved (on label) for long-term intrathecal administration. These are morphine, baclofen, and ziconotide.\textsuperscript{16,32} First-line analgesics include morphine and ziconotide. Hydromorphone is considered a second-line analgesic, but has not been approved for intrathecal therapy. Combinations of analgesics are often used (mainly as second-line treatment) if the pain relief is insufficient or side effects occur. There is a 30\% to 40\% chance that bupivacaine or clonidine has to be added to morphine or hydromorphone to maintain pain relief. This second-line treatment is applied off-label.\textsuperscript{16,32}

The goal would be to use the lowest possible dose of analgesic(s) that produces adequate pain relief and the fewest side effects for each patient. Analgesics can become neurotoxic due to the intrathecal administration of an excessive daily dose or concentration. The poly-analgesic consensus conference provided guidelines for maximum daily dose and maximum concentration.\textsuperscript{32}

There is a trend toward the use of “high flow—low concentration” to limit neurotoxicity.\textsuperscript{16} A study carried out by Perruchoud et al.\textsuperscript{33} showed that at higher flow rates (up to 4 times), increased drug dilution might result in a decreased effect at the receptor sites. In addition to potential neurotoxicity of the analgesic itself during long-term intrathecal administration, the interactions between the different analgesics in a particular solution can also be neurotoxic.\textsuperscript{34} Clonidine, for example, is not neurotoxic by itself. Intrathecal administration of clonidine, however, can induce spinal hypotension, which may enhance the potential toxicity of other analgesics. There are no preclinical or clinical data with reference to the neurotoxicity of combinations of analgesics.

When different analgesics are combined, the physical and chemical properties of the solution may change.\textsuperscript{34} Before a solution is used in intrathecal therapy, it is essential to know the pH, stability (precipitation of the solution and conversion of analgesics into neurotoxic metabolites), and compatibility of the mixture with the medication reservoir (potential changes of the concentrations of different analgesics by interaction with the reservoir may lead to changes in the clinical efficacy).

Stability studies have been carried out in vitro for most analgesics.\textsuperscript{31,35} However, more researches are needed.\textsuperscript{16}

**Evidence**

**Evidence for Intrathecal Drug Administration in Non-cancer Pain.** Several reviews found intrathecal drug delivery (IDD) to improve pain in permanently implanted patients (moderate evidence for long-term management of chronic noncancer pain).\textsuperscript{10,36–44}
A recent systematic review based on 15 observational (8 prospective and 7 retrospective studies) trials concluded that intrathecal therapy is moderately effective and safe in controlling chronic pain syndromes not readily responsive to other analgesic treatments. Morphine is the most frequently studied drug and the only drug that is approved for intrathecal use by the FDA and EMEA besides ziconotide. Reports on the use of hydromorphone, fentanyl, and sufentanil are found. Nevertheless, the influence of combining the opioid with local anesthetic (bupivacaine) or clonidine and the enhanced analgesia obtained by adding oral naloxone have also been described.

A recent study evaluated the impact of intrathecal morphine administration on pain perception and psychosocial functionality. As a secondary outcome, the level of functional activity was assessed. Thirty patients with chronic noncancer pain not responsive to multimodal analgesic treatment were included in the study. A significant improvement in evaluative component (66%), the affective component (59%), and the sensory component (32%) of the McGill Pain questionnaire over the 24 months follow-up was found. Social, work, and family relationships, and patients’ quality of life improved. Of the 13 patients who were of working age, 12 resumed their professional activities. In the retired patients, this effect was noted as a reduced need for assistance. The morphine infusion rate increased significantly over the observation period.

In a cost-effectiveness analysis, 63 patients suffering FBSS were followed for a 5-year period. Twenty-three patients received a pump implantation, and the remaining patients served as control. The Oswestry Disability Index showed a 27% improvement in the IDD group and 12% in the control group who received conventional therapy. The cost calculation showed that the

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**Figure 1.** Schematic representation of the drug selection for intrathecal therapy of neuropathic pain (A) and nociceptive pain (B). Adapted from: Deer et al.32 1: FDA approved for IT administration. 2: Recommended based on clinical experience and apparent safety. 3: Limited information on efficacy but documented safety. 4: Recommended based on expert consensus.
initial high costs of equipment were recovered after 28 months. The cumulative costs over the 5-year period were lower for the IDD group.47

Retrospective chart analysis of 24 patients to assess the efficacy of intrathecal hydromorphone revealed that accurate pain data were available for 13, 10, and 7 patients at 1, 3, and 12 months after implantation, respectively. The average pain scores decreased significantly.48 When morphine treatment produces intolerable side effects, hydromorphone is frequently used as rotation or switch therapy.49 The effect of opioid rotation between morphine and hydromorphone was assessed in a retrospective trial.50 In 37 patients treated with intrathecal morphine for chronic noncancer pain, mostly from FBSS (51%) who experienced insufficient pain relief or pharmacological complications after 11 months of intrathecal therapy, morphine was switched to hydromorphone. This resulted in the improvement of the pharmacological complications of nausea, vomiting, pruritus, and sedation. Peripheral edema was improved by hydromorphone but tended to recur. The analgesic response was improved by at least 25% in 6 of 16 patients.50

A case series (7 patients) of 2 other alternatives for morphine reported the use of sufentanil citrate and morphine in 0.5% bupivacaine solution. The latter solution provided little or no pain relief without significant side effects, while sufentanil citrate produced significant pain relief.51 Deer et al.41 compared the effectiveness of a combination of bupivacaine with opioids and opioid alone. Patients served as their own comparison arm as they were on opioid alone prior to the addition of bupivacaine. The mean duration of combined treatment (opioid + bupivacaine) was 62 weeks. All patients except 1 reported pain reduction. The need for additional opioids and other analgesics was reduced.

A more recent retrospective study in 17 patients showed significant pain relief and improvement in functionality and quality of life when bupivacaine was added to morphine. The morphine dose was kept constant at 14.10 mg/day, and the bupivacaine dose was initiated at 2.08 mg/day to be increased to 4.83 mg/day. No neurological sequelae were noted.26 A double-blind study by Mironer et al.24 found no added analgesia or improvement in quality of life in 24 patients with chronic noncancer pain when bupivacaine was added to the infusion solution to deliver 4, 6, or 8 mg/day. However, Veizi et al.,52 showed in a retrospective study that initiating bupivacaine alone with the opiate (morphine or hydromorphone) from the outset of intrathecal therapy blunts opioid dose escalation. The average daily dose of bupivacaine in that study was over 10 mg/day.

The use of intrathecal clonidine alone or in combination for the management of complex regional pain syndrome, neuropathic pain, and cancer pain was retrospectively reviewed in 15 patients. All patients received a trial of single-shot and/or short-term infusion of clonidine. Ten patients received an implantable drug delivery system. After initial response to clonidine treatment, 7 patients required additional hydromorphone (3 patients) or morphine (4 patients). In this group of patients, the duration of pain relief is typically shorter than 18 months.53

Intrathecal fentanyl is considered to be another alternative to morphine but published evidence is limited. A case report on 4 patients receiving long-term high doses (up to 20 times the common doses, ranging from 2,000 to 24,000 µg/day) suggested efficacy and safety.54

Animal research55 and clinical observation suggest that selective blockade of morphine excitatory effects by low doses opioid antagonists may enhance analgesia. This assumption was tested in a randomized, double-blind, prospective pilot study.45 Fifteen patients with chronic noncancer pain who received continuous intrathecal morphine were randomly assigned to receive 100 µg naltrexone (group A; n = 3); 10 µg naltrexone (group B; n = 7); or placebo (group C; n = 5), and the daily dose morphine was kept constant over the 7 days study period. Patients receiving the high-dose naltrexone (100 µg; Group A) demonstrated the greatest improvement (P = 0.07) in their daily pain scores. Side effects were common, minor, and similar across treatments. No evidence of opioid antagonist toxicity or opioid withdrawal was observed. The groups were very small thus precluding any statistical significance and conclusion.

Another study showed that opioid taper with a 6-week opioid-free period prior to trialing the patient with a low-dose intrathecal morphine in the treatment of chronic noncancer pain might (1) improve long-term analgesia vs. a combination of oral/IDD system therapy; (2) make it possible to maintain analgesia at microgram doses; and (3) make opioid tolerance reversible in 6 weeks. Further, it appears that a dose–response relationship for effective analgesia may be achieved at < 400 µg/day of intrathecal morphine.56 A similar paradigm was used in a recent prospective study that showed stable intrathecal morphine doses at 6 to 36 months postimplant.57
Breakthrough pain is commonly managed with oral or sublingual fast acting analgesics. Another option is the use of patient-controlled analgesia by means of a specific device, the personal therapy manager (PTM). The effect of this treatment was assessed in an open-label registry. At 12 months follow-up, there was a tendency to reduced pain and improved quality of life. Eighty-five percent of the patients expressed their satisfaction with the PTM. Patients felt they had more control over unpredictable pain fluctuations.

Ziconotide – Ziconotide is FDA and EMEA approved and was recommended as a first-line therapy for nociceptive, mixed, and neuropathic pain in the 2012 Polyanalgesic Consensus Conference recommendations for the management of pain by intrathecal (intraspinal) drug delivery. Clinical relevance of ziconotide in patients with severe refractory chronic pain has been evaluated in 3 placebo-controlled trials, including difficult-to-treat patients.

All 3 studies showed that ziconotide is effective for the treatment of nociceptive, neuropathic, and mixed pain in patients with cancer and without cancer. A clinically significant reduction in VAS score and improvements in function or disease management as measured with the Clinical Global Impression of Change (CGI) and the Categorical Pain Relief Scale (CPRS scale) have been observed. This was assessed in 3 double-blind placebo-controlled trials; visual analog scale of pain intensity improvements compared with baseline ranged from 14.7% to 53.1%. The CGI showed 28.4%, 50.0%, to 23.0% improvement. The majority of patients reported high or complete satisfaction with therapy. Optimal balance between efficacy and tolerability is achieved with a slow dose titration schedule. Ziconotide should be titrated on an individual basis to a desired level of response to ensure efficacy and safety.

The long-term effectiveness of ziconotide is supported by the findings of 2 open-label extension studies: Ziconotide maintains efficacy up to 12 months and does not induce tolerance over this time frame. Increases in dose correspond to reduction in pain scores. Ziconotide can be titrated by the use of bolus injections, continuous infusion, or limited duration infusion. The cost-effectiveness is yet to be proven; current data are based on assumptions and expert opinion. It has been observed that the combination of intrathecal ziconotide and opioid therapy is an option for patients with refractory chronic pain. In a recent study, combining intrathecal ziconotide (in a low dose) with morphine resulted in an adequate and rapid control of oral opioid-refractory cancer pain. The chemical stability of such a mixture, however, is limited.

More controlled, prospective clinical trials to evaluate ziconotide combination therapy are needed.

Evidence for Intrathecal Drug Administration for Cancer Pain. As opposed to the management of chronic noncancer pain, the dose titration for the care of patients at the end-of-life should be performed expeditiously. When dose increases no longer provide supplementary pain relief, drug associations may be used. The proposed treatment algorithms are frequently not FDA approved, although in other nations, this may well be the case. Nevertheless, in this special patient population, well-documented off-label use of certain medications may provide pain relief and improved quality of life.

A randomized controlled trial comparing the efficacy of intrathecal drug therapy in association with conventional medical management with conventional medical management alone showed that at 4 weeks follow-up, 84.5% of patients in the intrathecal treatment group had clinical success vs. 70.8% in the conventional medical management group. The follow-up study found significant reductions in fatigue and reduced consciousness as well as a better survival rates at 6 months.

In an open-label study, 119 patients with refractory cancer pain and/or intolerable adverse effects received an implantable drug delivery system with possibility of patient-activated drug delivery and morphine. Clinical success, defined as 50% pain reduction and reduction in side effects, was achieved in 90% at 1 month, 85% at 2 months, 85% at 3 months, and 91% at 4 months. Intrathecal ziconotide was compared with placebo for the management of pain in patients with cancer or AIDS. In the ziconotide group, 52.9% of patients reported moderate-to-complete pain relief compared with 17.5% in the control group.

A Cochrane review reported a randomized controlled trial and several prospective and retrospective studies. The authors concluded that neuraxial opioid therapy is often effective for treating cancer pain that has not been adequately controlled by systemic treatment. This conclusion was confirmed in a more recent systematic review based on 5 studies examining only patients with cancer pain (1 randomized controlled trial and 4 observational studies). Based on this review, there is a
high quality of evidence for commencing intrathecal administration of analgesics in patients with refractory cancer pain. 38

**SIDE EFFECTS AND COMPLICATIONS**

Neurological complications such as exacerbation of neuropathic pain and paralysis of the lower extremities in 1 patient receiving long-term intrathecal analgesic drugs have triggered further investigation. Radiocontrast myelography and computer tomography revealed catheter-associated intrathecal masses in 3 of 7 screened patients. 73 In 1 asymptomatic patient, the intrathecal mass regressed upon cessation of therapy. In the second asymptomatic patient, treatment was switched from morphine to hydromorphone and the intrathecal mass remained stable over a 1-year period. A review of the data reported in the literature by Medtronic Inc. to the United States Food and Drug Administration revealed 41 cases of intrathecal mass, including 16 published and 25 not previously published cases. 74 All patients suffered chronic pain, and the mean duration of intrathecal treatment was 24.5 months. Most masses were located in the thoracic region. In 39 of the 41 cases, morphine or hydromorphone was associated with other drugs. When baclofen was used as intrathecal medication, no masses were found. Thirty patients underwent spinal surgery to relieve spinal cord or cauda equina compression. One patient died of pulmonary embolism, and 11 patients were nonambulatory at the last follow-up. Surgical specimen revealed noninfectious inflammation, granuloma formation, and fibrosis or necrosis. The authors suggest that the administration of a relatively high concentration of high-dose opioid drugs or the use of drugs and admixtures that are not labeled for intrathecal use may be the cause of intrathecal mass.

A consensus statement on the management of intrathecal catheter-tip inflammatory masses confirms the assumption that the long-term administration of high daily opiate doses alone or mixed with other drugs or the off-label intrathecal use of drugs is most likely the cause of intrathecal mass formation. 15 They recommend close patient monitoring and additional examinations when loss of analgesic drug effect and new gradually progressive neurological symptoms are reported. An early diagnosis of intrathecal mass, before it fills the spinal canal or before the neurological symptoms become severe, may be reversible upon cessation of drug administration through the affected catheter and open surgery may be avoided. 75

This group recommends positioning the catheter in the lumbar thecal sac whenever possible and to keep the daily intrathecal opioid dose as low as possible. 15 Recently, Gupta et al. 76 have published the first case of intrathecal granuloma after sufentanil administration in a 86-year-old woman. These findings illustrate that patients who receive intrathecal drug administration should be monitored regardless of the drug or association used.

A recently published retrospective study found an infectious risk of 2.4% in patients with an IDD system. Most of the infections occurred at the site of the implanted pump and patients with a longer operation time. No difference in infectious rate was found between patients with cancer and without cancer. 77

Another retrospective study reviewed the incidence and management of postdural puncture headache following placement of IDD systems. They found an incidence of 23%, but 79% proved to be self-limited and symptoms resolved with conservative medical management. Epidural blood patch or application of epidural fibrin glue was therapeutically successful for patients with refractory postdural puncture headache. 78

**Side Effects and Complications of Morphine**

Tolerance may develop during intrathecal morphine therapy. Moreover, hyperalgesia, allodynia and myoclonias have been reported at high doses of intrathecal morphine (> 20 mg intrathecal morphine). 79 In these cases, morphine can be replaced by hydromorphone (higher solubility and potency) or fentanyl (higher intrinsic activity resulting in a lower receptor occupancy for identical analgesia which means a smaller risk of tolerance). Experience with long-term intrathecal administration with these opioids is limited. Intrathecal opioid dose escalation occurs more steeply in the younger (under 50 years old) IDD patient population without a concomitant significant decrease in oral consumption of opioids. 80

The side effects of opioid analgesia include urinary retention, constipation, and pruritus. Long-term intrathecal opioid administration may lead to perspiration, gynecomastia, reduced libido, impotence, amenorrhea, hypogonadism, erection disorders, growth hormone, cortisol deficiency, and edema. The development of late respiratory depression (rostral distribution of morphine and opioid receptors reaching the ventral medulla) is a dangerous complication. Sudden discontinuation of
intrathecal administration causes withdrawal symptoms including agitation, diarrhea, hyperthermia, palpitations, and even pulmonary edema. Finally, there is always a risk of psychological dependence.4,8,12,81,82 Intrathecal opioid administration for the management of chronic noncancer pain was demonstrated to be the cause of higher mortality compared with patients with spinal cord stimulation or who underwent discectomy. An epidemiologic study found that 1 year after initiation of the intrathecal opioid treatment, the mortality rate was 3.9%. In the majority of the cases, death was attributed to respiratory distress.83

Another risk is soft tissue injection (often referred to as “pocket fill”) during implantable drug delivery device refills.84 This complication is possibly underappreciated. Large doses of bupivacaine, opioids, ziconotide, and baclofen may have potentially life-threatening consequences.

Side Effects and Complications of Ziconotide

The 3 placebo-controlled pivotal trials showed a significant number of side effects, including abnormal gait, memory impairment, dizziness, confusion, nausea, nystagmus, pain, urinary retention, and vomiting.30,60 Ziconotide produces significantly more vestibular effects than placebo perhaps because ziconotide blocks N-type calcium channels in the granular cell layer of the cerebellum.59 However, the incidence and severity decrease when both the dose and titration frequency are decreased.30,59 The rate of adverse events varied from 92.9%30 to 94.7%.60 The rate of serious adverse events ranged from 30.6%,59 16.5%,60 to 1.8%.30 The dose titration was considerably slower in the later studies,30,60 indicating that slow dose titration can prevent the appearance of major side effects. The 2 open-label extension studies show that neurological adverse events remain common.29,62 There is no evidence of formation of granuloma.29,61

Ziconotide has a narrow therapeutic window because of substantial CNS side effects, which means that treatment with ziconotide is appropriate for only a small subset of patients with severe chronic pain.85 Patients treated with ziconotide should be closely monitored for psychological disorders including psychosis. In an observational follow-up cohort study of cancer patients who suffered intractable pain and received intrathecal ziconotide, 57% of patients experienced side effects which were attributed to other drugs (morphine, clonidine, or ropivacaine) in 57% of cases. Eventually, treatment was discontinued in 7 patients (5 patients due to use of ziconotide). All adverse events disappeared 2 days after treatment discontinuation.86

Evidence Grading

A summary of the evidence grading is given in Table 3.

Recommendations

Intrathecal drug administration is recommended for the management of cancer pain.5 Intrathecal drug administration for the management of noncancer pain is considered later in the range of therapeutic options after exhausting other less invasive options and given favorable psychological profile; this treatment technique can be considered preferentially in a study context.

Clinical Pathway

A clinical pathway for intrathecal drug administration for the management of noncancer pain is given in Table 4.

Technical Aspects of Intrathecal Pain Management

Insertion Technique for an Intrathecal Catheter with a Port for Externalized Pump Infusion. The intrathecal catheter has a subcutaneous port to which the pump can be connected. The catheter is inserted under local anesthesia with the patient lying down or sitting bent forward. Under fluoroscopic guidance, the Tuohy needle is inserted paramedian and interlaminar at a 45° angle. Once the needle has been passed into the subarachnoidal space, the stylet is removed and the catheter is inserted via the needle until the tip of the catheter is located at a level corresponding to the spinal level that is responsible for the pain. If, for example, the pain is located in the L5 or S1 dermatome, the catheter tip should be preferably placed at the level of Th11 in cases of low back pain. The group

<table>
<thead>
<tr>
<th>Technique</th>
<th>Assessment</th>
</tr>
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<tbody>
<tr>
<td>For cancer pain5</td>
<td>Intrathecal medication delivery</td>
</tr>
<tr>
<td>For noncancer pain</td>
<td>Opioids with or without local anesthetics</td>
</tr>
<tr>
<td>Ziconotide</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Summary of Evidence Grading
of Hassenbush, however, promotes the placement of the catheter tip in the thecal sac below the spinal cord to prevent granuloma formation. Once good flow of cerebrospinal fluid via the catheter has been established, a small incision around the needle is made extending to the muscle fascia. The catheter is then affixed and tunneled in midline direction until above the 10th or 11th rib. Subsequently, the port system is connected to the catheter and placed in a subcutaneous pocket. Finally, the system is connected to the external pump by means of percutaneous puncture of the port system. A transparent bandage is used so that any sign of infection at the insertion site can be noticed immediately.

**Possible Complications**

**Postpuncture Headache.** To prevent this, it is suggested to keep the patient in a lying position for 24 hours after surgery.87

**Infection of the System.** Checking the insertion site of the port system every day can reduce this risk.77,88 If infection is suspected, the patient should be

**Table 4. Clinical Pathway**

<table>
<thead>
<tr>
<th>Phase 0</th>
<th>Patient selection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diagnosis: neuropathic pain/ nociceptive pain/mixed pain/ visceral pain</td>
</tr>
<tr>
<td></td>
<td>Unsatisfactory results with conventional medical management, minimal invasive procedures, or strong side effect on systemic medication? Neurosurgical evaluation Psychiatric evaluation: primary psychiatric conditions are contraindications Multidisciplinary paramedical evaluation Nurse Psychologist Physiotherapist</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Intake</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Doctor:</td>
</tr>
<tr>
<td></td>
<td>Patient information</td>
</tr>
<tr>
<td></td>
<td>Evaluation of comorbidities: coagulation disorders, sleep apnea, immune suppression</td>
</tr>
<tr>
<td></td>
<td>Decision of type of catheter, trial medication, hospitalization</td>
</tr>
<tr>
<td></td>
<td>Nurse pain specialist</td>
</tr>
<tr>
<td></td>
<td>Repeat patient information with focus on material, medication, planning of trial period</td>
</tr>
<tr>
<td></td>
<td>Physiotherapist</td>
</tr>
<tr>
<td></td>
<td>Pre-operative evaluation/preparation</td>
</tr>
<tr>
<td></td>
<td>Questionnaires</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase 2</th>
<th>Implantation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thrombosis prevention:</td>
</tr>
<tr>
<td></td>
<td>Antithrombotic stockings, LMW heparin</td>
</tr>
<tr>
<td></td>
<td>Catheter implantation:</td>
</tr>
<tr>
<td></td>
<td>Tip at the level of the painful dermatome</td>
</tr>
<tr>
<td></td>
<td>Trial:</td>
</tr>
<tr>
<td></td>
<td>Between 2 and 7 days, may be longer according to local regulations</td>
</tr>
<tr>
<td></td>
<td>24 hour bed rest</td>
</tr>
<tr>
<td></td>
<td>Initiate the use of the pain diary</td>
</tr>
<tr>
<td></td>
<td>Progressively up titrate 1 single drug at the time</td>
</tr>
<tr>
<td></td>
<td>Reduce the systemic opioids</td>
</tr>
<tr>
<td></td>
<td>Foresee management of secondary side effects: itching, nausea, constipation, urinary retention, allergic reactions</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Phase 3</th>
<th>Trial period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control catheter insertion site (bleeding/infection signs)</td>
</tr>
<tr>
<td></td>
<td>Assess and manage side effects</td>
</tr>
<tr>
<td></td>
<td>Reduce progressively and stop systemic opioids and up titrate spinal opioids</td>
</tr>
<tr>
<td></td>
<td>If temporary catheter—remove</td>
</tr>
<tr>
<td></td>
<td>Definition of positive trial</td>
</tr>
<tr>
<td></td>
<td>50% pain reduction (VAS), Global Perceived Effect, Satisfaction, ADL, sleep, minimal side effects</td>
</tr>
<tr>
<td></td>
<td>If trial is negative:</td>
</tr>
<tr>
<td></td>
<td>Consider a second trial with other medication or a combination</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase 4</th>
<th>Pre-operative control for definitive implantation (if not performed in phase 1)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Appointment with neurosurgeon</td>
</tr>
<tr>
<td></td>
<td>Selection of pump type</td>
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</tbody>
</table>

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<thead>
<tr>
<th>Phase 5</th>
<th>Definitive implantation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thrombosis prevention</td>
</tr>
<tr>
<td></td>
<td>Catheter and/or pump placement</td>
</tr>
<tr>
<td></td>
<td>Pump fill and programmation</td>
</tr>
<tr>
<td></td>
<td>Thoracic bandage</td>
</tr>
<tr>
<td></td>
<td>24 hour hospitalization</td>
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</tbody>
</table>

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<thead>
<tr>
<th>Phase 6</th>
<th>Wound controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Appointments with home care</td>
</tr>
<tr>
<td></td>
<td>Dose adjustment guided by the effect</td>
</tr>
<tr>
<td></td>
<td>Final evaluation: Questionnaires</td>
</tr>
<tr>
<td></td>
<td>Evaluation of pain diary</td>
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</tbody>
</table>
hospitalized and examination of the cerebrospinal fluid (lumbar puncture) is recommended. The literature on the incidence and management of infections of implantable drug delivery devices is rather sparse. Reviewing records of patients younger than 18 years with an implantable baclofen pump shows that superficial wound infections may respond to oral or intravenous antibiotic treatment. In analogy with the strategies developed for the management of infections of cardiovascular implantable devices, intrathecal drug device infections can be classified as: pocket infections, which involve the subcutaneous pocket containing the device and the subcutaneous segment of the leads (ie, not the transvenous segment), and deeper infections that are usually associated with bacteremia and/or endovascular and spinal cord infections. Another classification distinguishes between primary infection, in which the device and/or pocket itself is the source of infection, usually due to contamination at the time of implant, and secondary infection, in which the leads (and then sometimes the device and the pocket) are seeded due to bacteremia from a different source. There are no controlled trials on the therapeutic options of device-related infections. Also, the guidelines are mainly based on clinical observation and expert opinion for cardiovascular devices. When a patient presents a device-related infection, a consultation with an infectious disease specialist is recommended. In many cases, the pump will have to be removed and care should be taken to taper down the dose of administered drugs (opioids, baclofen), administering replacement drugs when the pump is explanted. The antibiotic treatment will be established based on the identified bacteria and their sensitivity.

**Dislocation or Leakage of the Catheter.** This can be confirmed by injecting local anesthetics via the intrathecal system. If no spinal anesthesia occurs, the intrathecal catheter is dislocated. It can also be confirmed by checking the course of the catheter by means of fluoroscopic guidance. The location of the dislocation or leakage can also be identified by means of an injection with contrast fluid via the intrathecal catheter.

**IMPLANTATION OF THE ELECTRONIC MEDICATION PUMP**

If the trial period has been positive and the patient has given consent, an electronically programmed medication pump can be implanted.

**TECHNIQUE**

The port system is removed, and a subcutaneous space is created in the abdominal wall on the same side to insert the pump. Subsequently, the intrathecal catheter (already in situ) is tunneled to this space. The pump is first filled with the required medication and then connected to the catheter. The pump is now programmed: The daily dose is determined, and a priming bolus is given to fill the dead space as well as the catheter.

Risk of surgical reintervention for technical problems:

- Infection of the system:
  - Low-grade infection: local coloring of the skin around the wound or the pump; no fever; no increase in inflammatory parameters; no pain around the implanted pump.
  - No clear data exist on the best management. Possible approaches include replacement of the pump and/or antibiotic treatment.
    - No data exist on the best management. Possible approaches include replacement of the pump and/or antibiotic treatment.
    - However, literature for comparable structures (pacemakers and AICD) differentiates device infections by category: pocket or deeper infections and primary, or secondary infections.
  - Central infection with fever, neck stiffness, headache: lumbar puncture for bacterial analysis, remove the pump, and the catheter as soon as possible and treat the patient empirically with IV antibiotics, get a stricter antibiotic regimen treatment as soon as the identification of the bacteria is known.

- Fluid collection around the pump (seroma)
  - Abdominal binder with possible surgical treatment.

- Dislocation, leakage, or even rupture of the catheter
  - A dye study should be performed to evaluate catheter function. If a leak exists, the catheter should be replaced.
  - Overcome the lack of medication with oral or IV medication.

- Granuloma formation at the tip of the catheter with risk of neurological damage
  - Granuloma might disappear after replacing the intrathecal solution with normal saline.
  - In case of neurological symptoms, neurosurgical resection of granuloma might be necessary.
• Pump software problems
  o Are rare and pump study should be performed if no catheter problems can be detected.
If the pump fails, it should be replaced and IV or oral replacement medication given.

CONCLUSION
The evidence for intrathecal drug administration is higher for the management of cancer pain than for noncancer pain. The success of the treatment is largely determined by a careful selection of patients. This requires multidisciplinary consultation including comprehensive psychological evaluation. However, intrathecal pain management may be accompanied by important side effects and complications. Besides technical problems, such as dislocation and leakage of the catheter (causing acute withdrawal symptoms), infection is a potentially serious complication.

Morphine is still the gold standard for intrathecal administration. Although it relieves the pain, long-term intrathecal morphine therapy may have serious side effects and complications. It is important to inform the patient in advance about possible interference of long-term opioid therapy and sexual dysfunction.

Patients who experience insufficient pain relief despite intrathecal morphine administration may use combinations of analgesics. Due to the lack of adequate research, there are still questions about the effectiveness of this method of pain relief compared with placebo and the spontaneous course of the pain without intrathecal therapy. Moreover, little is known about the neurotoxic potential after long-term intrathecal administration of combinations of analgesics. Finally, there are no data on the physical and chemical stability of these solutions. More researches into this method of pain relief are required to determine its exact use. In this context, this method of pain relief should only be used as the last step in the pain management of patients with chronic pain. Also, these patients should be well informed about the advantages and disadvantages of the therapy before it is decided to implant a pain pump.

ACKNOWLEDGEMENTS
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