Long-Term Spinal Opioid Therapy in Terminally Ill Cancer Pain Patients

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Key Words. Analgesics: morphine, opioids · Anesthetic techniques: catheter, epidural, intrathecal, spinal · Pain: cancer

ABSTRACT
In terminally ill cancer patients with refractory pain, long-term spinal opioid therapy may provide a profound analgesia with minimal side effects. The reversibility of the technique and its efficacy throughout the body and for different types of pain are important advantages. For epidural administration, it is preferable to use lipid soluble opioids (sufentanil). For intrathecal administration, morphine is the best choice. The advantages of intrathecal administration over epidural administration are the need for lower doses because of a more direct administration at the receptor site, the easy positioning of the catheter, and less risk for migration of the catheter. In severe refractory pain which does not respond to spinal opioids, the use of non-opioids (e.g., a local anesthetic or an alpha-2 adrenoreceptor agonist) as coanalgesics may be recommended for improving pain relief. Long-term spinal opioid therapy at home has been made possible by technical and organizational development. In home care, only one physician should be the manager for the patient. Coordination should be optimized among patient, family, general practitioner, oncologist, anesthesiologist, home nurse, technician, and pharmacist. The Oncologist 1997;2:70-75

INTRODUCTION
The concept of spinal administration of opioids started in 1971 with the discovery of opioid receptors. In 1973, opioid receptors were isolated in the brain, and in 1976 in the spinal cord. In 1976, Yaksh administered opioids in animals, and in 1979, Behar and Wang described the spinal administration of opioids in man in separate reports [1-3].

After development of spinal administration of opioids, pain relief in cancer pain patients could be achieved in 70% of the patients with opioids as the sole agent; 10%-30% of the patients need additional therapies [4]. The widespread use of this method at home has been made possible by technical and organizational development.

INDICATIONS, REQUIREMENTS AND CONTRAINDICATIONS FOR PATIENTS USING SPINAL OPIOIDS
Patients should be terminally ill and suffering from refractory cancer pain, either due to insufficient pain relief in spite of high-dose opioids or idiosyncratic reactions with systemic opioids. There should be no other reasonable options for treating pain adequately. The efficacy of pain relief using spinal opioids must be established. Location of the cancer and pain sites must be evaluated. The quality of the pain must be assessed because somatic and visceral pain may be relieved with the help of opioids, but neuropathic pain often shows less response on opioid therapy [5]. Moreover, the psychological impact on pain and suffering, anxiety, depression, and anger has to be thoroughly assessed. The physician has to consider that pain in patients suffering from cancer is not always caused by cancer; muscle spasm, obstipation, and concurrent chronic pain problems may also be responsible for pain, each requiring a specific treatment.

Surgery, chemotherapy or radiotherapy may also need to be used to treat the pain adequately. Concerning spinal administration of opioids, the patient’s cooperation is needed and a clear mental state (absence of disorientation or delirium) and a positive attitude toward spinal pain relief are required. The patient also needs family support to improve the quality of home care. Detailed information regarding spinal opioid effects must be given by the physician to patient and relatives. Written and informed consent must be obtained. The effective communication between the patient and family and the care team is imperative.
Relative contraindications for spinal pain relief include an uncooperative family or general practitioner, high cerebrospinal fluid (CSF) pressure (intrathecal catheter), infection at the site of catheter insertion, bleeding disorders, allergies to morphine, a failed trial of spinal opioid therapy, untreated depression, mental confusion, and blockage of drug diffusion because of tumor.

The Advantages and Disadvantages of Spinal Administration of Opioids

The advantages of spinal administration of opioids are:

- the reversibility of the procedure in contrast to neuroablative procedures; a percutaneous catheter can be removed at all times;
- the ability to reach higher concentrations of opioids at the receptor site when compared with systemic administration. The normal dosage of spinal opioids is considerably lower than systemic opioid dosage, therefore producing fewer side effects;
- the effectiveness in pain relief in both halves of the body in contrast to neurolytic blocks, and
- the ability for terminally ill patients to spend their last days at home with an improved quality of dying.

Disadvantages of spinal administration of opioids include dependency on a mechanical delivery system, risk of cellulitis, epidural hematoma, meningitis, epidural infection, and increased health care costs.

Mechanism of Action of Spinal Opioids

Opioids act directly at the spinal cord level by binding to specific opioid receptors in the dorsal horn [6]. Morphine has a presynaptic action which reduces the release of neurotransmitters (substance P, excitatory amino acids) and a postsynaptic action resulting in both a hyperpolarization that reduces activity in the neuronal pathways and facilitation of descending inhibitory spinal pain pathways [7].

The presynaptic action of opioids results from an opening of potassium channels (mu and delta receptors mediated) and a closing of calcium channels (kappa), both leading to a reduction in calcium influx into C-fiber and A delta terminals, thus diminishing neurotransmitter release [8, 9].

Factors Influencing the Efficacy of Spinal Opioids

Factors determining the clinical efficacy of spinal opioid therapy are related to the patient, the delivery system, and the drug (Table 1).

<table>
<thead>
<tr>
<th>Physical and Chemical Properties of Spinal Opioids</th>
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</thead>
<tbody>
<tr>
<td>Density, volume, concentration, pKa, oil:water partition coefficient, molecule weight, and protein binding may all influence the onset, duration, and migration from the site of administration. Lipid solubility is the most important factor. The extremes are sufentanil and morphine with oil:water partition coefficients of 1778 and 1.42, respectively.</td>
</tr>
<tr>
<td>The other opioids have partition coefficients between these values, as listed in Table 2 [10]. Administered in the epidural space, a highly lipophilic drug such as sufentanil has a fast onset with a peak effect between 5 and 15 minutes, whereas the peak effect of morphine, a hydrophilic drug, is reached after one hour. Lipid solubility would also explain the low rostral spread of sufentanil and possibly explain the lower incidence of side effects [11]. However, lipid solubility also produces early onset of respiratory depression after epidural administration due to rapid systemic uptake. Due to its hydrophilicity, morphine diffuses slowly to the receptor, consequently resulting in a peak effect after 60 minutes. CSF clearance is also slow, leading to a relatively long duration of effect (12-24 h) [12]. Morphine slowly migrates rostrally to the brainstem and may induce late-onset respiratory depression [13]. Morphine-naive patients may develop respiratory depression within 12-24 h (1:1200 incidence); however, respiratory depression occurs rarely in patients using morphine chronically [14].</td>
</tr>
<tr>
<td>Other properties of a drug also play a role in the final effect. Protein binding is of little importance for distribution because CSF protein concentrations are low. The volume distribution and metabolism have no role in clinical effect.</td>
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<table>
<thead>
<tr>
<th>Table 1. Factors which influence the efficacy of opioids administered intrathecally and epidurally</th>
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<tbody>
<tr>
<td>Patient-related</td>
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<tr>
<td>• Age, length, weight, gender</td>
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<tr>
<td>• Intra-abdominal pressure</td>
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<tr>
<td>• Anatomical configuration of the spinal cord</td>
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<td>• Cerebrospinal fluid characteristics</td>
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<td>• Speed of diffusion</td>
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<tr>
<td>• Neurologic disease in the spinal cord</td>
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<tr>
<td>Delivery-system related</td>
</tr>
<tr>
<td>• Position of the catheter</td>
</tr>
<tr>
<td>Drug-related</td>
</tr>
<tr>
<td>• Physical and chemical properties of the opioid</td>
</tr>
<tr>
<td>• Dosage</td>
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<tr>
<td>• Solution, specific gravity, baricity</td>
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</tbody>
</table>

For epidural administration, it is preferable to use lipid-soluble opioids (e.g. sufentanil) because epidural fat functions as a depot [11]. Due to the reservoir effect of CSF for hydrophilic opioids, morphine is the best choice for the intrathecal route.

### INEFFECTIVENESS OF SPINAL OPIOIDS

Spinal opioids may be ineffective in intermittent acute somatic pain (pathologic fracture, incidental pain), continuous or intermittent visceral pain (ileus), pain of skin ulcers, neuropathic pain (tumor growth in central nervous system [CNS] tissue), inadequate dosing, failure of the infusion system, obstruction of CSF flow, and emotional collapse [15, 16].

Spinal opioid ineffectiveness during treatment may be expected in long-term intrathecal administration of high-dose morphine solutions decreasing the pH in CSF [17]. Other causes during treatment are increasing tumor growth or tolerance, which are sometimes difficult to differentiate [18].

Tolerance may be caused by receptor downregulation, a phenomenon in which the receptors decrease in quantity or become uncoupled from G protein regulation. Downregulation is characterized by continuous stimulation of agonists on the receptor, leading to a state of desensitization and diminished efficacy with repeated administration. The occurrence of tolerance is unpredictable and may be time-dependent, concentration-dependent, or receptor-selective [19, 20].

### EPIDURAL VERSUS INTRATHECAL ADMINISTRATION

A spinal catheter may be inserted into either the epidural or intrathecal space. When comparing the two routes, few differences were found in efficacy.

Epidural opioid administration reaches the receptor in two ways: systemic absorption and penetration of dura mater and arachnoid. Plasma opioid concentrations after epidural administration are similar to plasma opioid concentrations after intramuscular injections when using lipophilic agents such as sufentanil. The risk of systemic opioid side effects after epidural administration is higher than in intrathecal administration. During intrathecal administration, plasma concentrations above the minimal effective analgesic concentration are measured.

Both the epidural and intrathecal routes have advantages and disadvantages. An advantage of epidural administration is the utilization of the epidural fat to serve as a depot for the drug. A disadvantage of this route is that the catheter may produce fibrosis within the epidural space leading to catheter obstruction [21]. Another disadvantage is that the catheter may migrate into the intrathecal or subdural space, into the intravascular compartment, or out of the epidural space. In a patient with cachexia, a reduction of the epidural fat may lead to a reduced depot reservoir with a higher systemic absorption [22]. A lipophilic drug administered into the epidural space provides a segmental spread of several dermatomes which may lead to failure of analgesia in patients with different localization of pain. At the occurrence of an epidural abscess, a disadvantage is that it may be difficult to diagnose and in a late phase.

The advantages of intrathecal administration of opioids are the use of lower doses, easy insertion of the catheter, and lower incidence of catheter migration. The disadvantages of the intrathecal pathway are the risk of persistent CSF leakage leading to postdural puncture headache and the risk of meningitis.

### INSERTION OF THE CATHETER AND INFUSION SYSTEM

Catheters are tunneled subcutaneously and led to the anterolateral side of the patient. Before the catheter is guided outside the body, three methods of attachment are possible: the catheter is guided directly percutaneously and fixed on the body with a transparent self-adhesive dressing (Tegaderm™), a portal system is inserted, or a totally-implanted catheter is attached to an implanted infusion pump.
The advantages of a portal system are the smaller risk of dislocation of the catheter by inadvertent pressure or traction and, provided that the portal system is kept closed, the reduced risk of infection [23, 24]. However, when multiple punctures are performed, the risk of infection might increase and, moreover, administration via the portal system may introduce logistic problems.

A totally implanted catheter and infusion pump is reserved for patients with a life expectancy of months or years. Its reservoir is refilled percutaneously every 14 to 21 days and provides a constant infusion rate. The main disadvantage is its high cost, and due to the criterion of life expectancy of months, its use in terminally ill cancer patients is not advisable.

**Antioxidants and Antimicrobials Added to Spinal Opioids**

Despite no adverse outcome in histopathological studies, there is a reluctance to administer preservatives spinally. However, the continuous administration of opioids results in a longer storage time after preparation of the opioids, and the addition of antioxidants and antimicrobials may be considered. DuPen et al. warned against using phenol and formaldehyde preservatives.

Epidurally administered morphine combined with these preservatives caused burning pain, disorientation, and confusion [25]. Sensory and motor abnormalities were not found. The use of antioxidants (sodium metabisulfite and EDTA) may cause pruritus and/or neurotoxicity, leading to adhesive arachnoiditis. However, no clinical or neuropathological signs of neurotoxicity were found by Nitescu et al., studying 125 cancer patients who received a mixture of morphine and bupivacaine intrathecally with sodium metabisulfite and EDTA [26].

**Side Effects of Continuous Epidural and Intrathecal Administration of Opioids in Cancer Patients**

The side effects of spinal administration of opioids are urinary retention, generalized pruritus (10%-100%), nausea and vomiting (15%-35%), respiratory depression (rare), myoclonic jerks, and hyperesthesia after high doses of opioids [17, 27, 28].

Contraction of abdominal muscles may relieve urinary retention. However, this form of urinary retention is temporary and incomplete. The incidence of pruritus varies between 0% and 100% with all opioids. In cancer pain patients receiving continuous opioid infusion, pruritus is not a major clinical problem. Nausea and vomiting occur in 15%-35% of patients who receive opioid bolus injections. With continuous infusion, the incidence of pruritus, nausea, and vomiting is much lower. Constipation is not commonly seen after spinal administration of opioids, but frequently occurs after systemic administration.

After high doses of spinal opioids, myoclonic jerks may occur. The treatment of myoclonic jerks is symptomatic with benzodiazepines and reduction or change of the opioid dose [29].

**Spinal Administration of Non-Opioid Adjuvant Drugs**

In cancer pain patients with severe refractory pain not responding to spinal opioids, the use of local anesthetics as an adjuvant to the opioid [30] should be considered for improving the analgesic quality. Coadministration of drugs acting at separate receptors may produce supra-additive or synergistic effects. For instance, application of morphine spinally, combined with a low-dose alpha-2 adrenoreceptor agonist, may show a synergistic effect on analgesia [7].

Clonidine, droperidol, somatostatin, calcitonin, norpinephrine, DADL, ketamine, midazolam, neostigmine, baclofen, lysinacetylsalicylate acid, and local anesthetics have been applied spinally in both experimental and clinical settings.

In Table 3, the drugs administered in combination with opioids are listed. However, to prove efficacy and safety of these adjuvant drugs, histopathological research must be performed to determine long-term effects of their administration [31]. Two studies reporting neurohistopathological findings in 10 and 15 patients, respectively, after continuous infusion of morphine and bupivacaine suggested that a catheter, morphine, and bupivacaine might be used safely for long-term use in cancer patients [32, 33].

**Table 3. Some examples of agents combined with an opioid**

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<tr>
<th>Opioid in combination with:</th>
<th>Agents that reduce excitability</th>
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<tr>
<td></td>
<td>• Local anesthetics (bupivacaine, lidocaine)</td>
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<td></td>
<td>• Ketamine and NMDA (N-methyl-D-aspartate) antagonists (dextromethorphan)</td>
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<td></td>
<td>• NSAIDs (ketorolac, diclofenac)</td>
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<table>
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<tr>
<th>Agents that increase spinal pathway inhibition</th>
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<tbody>
<tr>
<td>• Alpha-2 adrenoreceptor agonists (clonidine, dextrametadamine)</td>
</tr>
<tr>
<td>• Anticholinergic agents (neostigmine)</td>
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</tbody>
</table>

**Home Care Organization**

In the home care setting, only one physician should manage the patient’s analgesic requirements. The general practitioner may be the most appropriate person. However, the coordinating manager must be both willing and knowledgeable. Coordination should be optimized among patient, family, general practitioner, oncologist, anesthesiologist,
A job description for each member of the home care team has to be created. The general practitioner has to be available 24 h. There must be continuous access to hospital specialists, home care nurses, technicians, and pharmacists.

Early detection of side effects and complications and prompt response to acute and unexpected change in intensity of pain during spinal administration of morphine should be provided using some type of practice algorithm, as shown in Figure 1.

Before inserting a permanent spinal catheter, the physician must insure the efficacy of opioids in the terminally ill cancer patient in the home setting. The physician must receive informed consent from the patient and must contact the general practitioner, oncologist, pharmacist, and technician. Permission has to be obtained from the general practitioner and the insurance company. During hospitalization, the catheter is inserted and the optimal dose titrated. The different types of delivery systems should be explained to the patient. The patient must also keep a pain diary. After discharge, communication among the involved providers of care is imperative.

Both hospital and home care nurses provide 24-h availability, following the clinical care protocol, troubleshooting, encouraging the patient to maintain the pain diary, inspecting the catheter insertion site, changing batteries, and contacting other team members when necessary.

The technician also provides 24-h availability for delivery system support. Technicians may be complementary with the home care nurse concerning technical aspects. The team pharmacists must be willing to prepare the medications in an agreed-upon short period of time.

**QUALITY CONTROL**

During treatment, continuous quality control should be performed. Measurement of the effectiveness of pain treatment, functional status, and quality of life is essential. Spinal infusions must be stopped if contamination occurs or in the event of insufficient pain relief despite earnest efforts of one week, insufficient organization support, insufficient medical/paramedical/pharmaceutical support, or patient’s refusal.

**TECHNICAL ASPECTS OF DELIVERY SYSTEMS**

The requirements for an external infusion pump for home care are: small size, easy to handle, capability of administering drugs separately, shock proof, battery alarms and long-term memory storage. Since there is a growing tendency to administer more than one drug to the patient, two options are available. First, each drug may be provided with its own delivery system. To compete with the different pharmacokinetic and pharmacodynamic properties of each drug, this arrangement may be the best solution; the drugs may be titrated more accurately. The main disadvantage is the increase in size of the pump system.

Second, mixing the drugs in the same reservoir offers the advantage of a smaller size of the pump. However, the administration of two drugs is more difficult to titrate and, in some instances, even dangerous.

**CONCLUSION**

In cancer pain patients for whom oral or transdermal drug therapy has not been successful, an epidural or intrathecal catheter for spinal infusion of opioids should be considered. Long-term spinal opioid therapy may provide a profound analgesia with minimal side effects. A subset of these patients requires additional analgesics, such as a local anesthetic or clonidine, which may produce supra-additive or synergistic effects. In the home care setting, coordination should be optimized between patient, family, general practitioner, oncologist, anesthesiologist, home nurse, technician, and pharmacist.

### REFERENCES