Intrathecal and epidural narcotics

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This paper presents an overall review of epidural and intrathecal narcotics. The early laboratory studies and initial clinical applications are presented. This is followed by a description of the mechanism of action of narcotics acting both intrathecally and epidurally, and some of the similarities and differences between narcotics and local anesthetic drugs. Technique, dosages, indications, and contraindications are also discussed.

Pain is described as an unpleasant sensory and emotional experience associated with, or described in terms of, actual or potential tissue damage. Drugs that relieve suffering from pain are termed analgesics.

Stimulation of specialized receptors (nociceptors) which are present in almost every organ system, or their afferent neurons, can result in the transmission of a pain impulse. Inhibition of generation, transmission or perception of the pain impulse can be produced by analgesics. In general, the narcotic analgesics exert their dominant effects at the level of the spinal cord and central (brain) centers. It has been well established that specific opiate receptors exist in the brain, primarily in the limbic system, spinoreticular tracts (such as periaqueductal gray, medial thalamic nuclei, hypothalamus and substantia gelatinosa), spinal trigeminal nucleus, nucleus tractus solitarii, and vagus nerve.

Although there are considerable choices for analgesic therapy, there is no ideal method or ideal drug. With the demonstration of anesthetic and analgesic drug effects in the spinal cord it became apparent that spinal sites were important in mediating analgesic effects. As the body of knowledge about the mechanism of drug-induced analgesia increases, the effects at the spinal cord level assume even greater importance. Researchers have placed heavy emphasis on the interaction of narcotic analgesics with areas of the spinal cord that are thought to function in the transmission of information about painful events in the periphery.

One of the primary aims of anesthesia is to provide intraoperative analgesia. However, the potential side effects of narcotics, in particular respiratory depression, have tempered analgesic treatment of postoperative pain. In 1979, intrathecal and epidural narcotics were introduced that produced intense and very prolonged analgesia. This report will outline this development, and discuss the use, mechanism of action, benefits, and adverse side effects of these narcotics.

History

Clinical application of intraspinal narcotics for pain relief is based on animal work that demonstrated abundant opiate receptors in Rexed's laminal 1, 2, 5, of the dorsal horn of the spinal gray matter. The identification by Snyder of specific opiate receptors in the substantia gelatinosa of the posteriorhorn cell of the spinal cord has opened...
new concepts for the treatment of pain and narcotic addiction. Autogradiographic studies confirmed that abundant opiate receptors exist in the substantia gelatinosa of the dorsal horn, especially in laminae 1 and 2. Light and Perl (1979) showed that central terminals of small unmyelinated fibers were located in the marginal zone (Rexed I) and substantia gelatinosa 2 and 3 of the dorsal horn.

Studies by Yaksh and his colleagues showed that lumbar intrathecal injections of small doses of morphine in cats and rats are followed by prolonged analgesia of the hind limbs. By late 1981, a major review by Yaksh cited over 150 references from his own and other animal studies pertinent to spinal opioids. In 1979, Wang first demonstrated that small doses of morphine given intrathecally and extradurally produced long lasting relief of chronic pain due to malignancies in man. Controlled clinical studies in man have now provided some, but not all of the knowledge needed for optimal clinical use.

**Mechanism of action**

The behavior of intraspinal local anesthetics provides a useful model for understanding the effects of intraspinal narcotics, because the two classes of drugs have some common characteristics, as shown in Table I. Both are ionizable cations of similar molecular weights with similar ionization constants. However, their oil-water partition coefficients are sometimes different and a low degree of solubility, as in morphine sulphate (MSO4), implies that the drug is slow to pass out of the cerebral spinal fluid (CSF) into the lipid tissues of neuraxis.

The pathways of intraspinal local anesthetics and intraspinal narcotics are similar but their targets are different (Table II). Local anesthetics act predominantly on axons, while narcotics act predominantly on presynaptic and postsynaptic membranes of small cell networks in the substantia gelatinosa at the tip of the horn, as well as at the rostral continuation of the substantia gelatinosa in the brain stem.

Narcotics exhibit both specific and non-specific binding to various tissue. Specific binding at opiate receptor sites is reversed by naloxone.

Uptake of parenterally administered narcotics from blood to neuroaxis is limited by the blood-brain barrier (BBB) formed by the lipid endothelial lining of the neuroaxial capillaries. Intraspinal narcotics administered directly in high concentrations enter the CSF and then diffuse from the aqueous phase into the lipid phase of spinal cord tissues, bypassing the blood brain barrier (Table III).

For a highly ionized and hydrophilic drug such as morphine, intrathecal injection will produce extremely high CSF concentration, which will move slowly out of the CSF into spinal cord receptor sites and nonspecific binding sites and clearance sites (arachnoid granulations) (Figure 1). Cep-

<table>
<thead>
<tr>
<th>Table I</th>
<th>Molecular Weight</th>
<th>Pka</th>
<th>Partition coefficient</th>
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<tbody>
<tr>
<td>Lidocaine hydrochloride</td>
<td>234</td>
<td>7.9</td>
<td>2.9</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>288</td>
<td>8.1</td>
<td>27.5</td>
</tr>
<tr>
<td>Morphine sulfate</td>
<td>285</td>
<td>7.9</td>
<td>1.42</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>336</td>
<td>8.4</td>
<td>813</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>386</td>
<td>8.0</td>
<td>1727</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>417</td>
<td>6.5</td>
<td>89</td>
</tr>
</tbody>
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Table II

<table>
<thead>
<tr>
<th>Site of action</th>
<th>Opiates</th>
<th>Local anesthetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nerve roots (long tract in spinal cord).</td>
<td>Blockade of nerve impulse conduction in axonal membrane.</td>
<td>Blockade of sympathetic and pain fibres; often also loss of sensation and motor function.</td>
</tr>
</tbody>
</table>

Reprinted from Cousins: Intrathecal and epidural administration of opioid analgesics. *IARS Refresher Course Lectures*, 1984, with permission from the publisher.
Halad flow of CSF will cause redistribution of the injected drug up to the spinal subarachnoid space to the brain.8

If the narcotics spread cephalad to the basal cisterns and fourth ventricles, they can penetrate the floor of the fourth ventricle to reach opiate receptors in the nuclei of the tractus solitarius, locus ceruleus, vagus, and trigeminal nerves, and the nucleus intercolatus, all of which are structures concerned with central reflex control of respiratory and cardiovascular functions.8

Uptake into the systemic circulation competes for the drug, but results in plasma levels too low to produce any systemic analgesia.8 Low lipid solubility and slow uptake into spinal cord receptors result in slow onset of action and slow egress. Slow egress from the spinal cord results in long duration of action (Figure 1). In the case of a mostly ionized, lipid-soluble drug such as fentanyl (Sublimaze®), there will be only a small amount of un-ionized lipid-soluble drug in the CSF after subarachnoid injection. This small amount of mostly un-ionized, lipid-soluble drug will penetrate spinal cord receptors and non-specific binding sites rapidly, but will also have a rapid egress, unless it has a particular affinity for lipid or high receptor binding.8 For drugs like these, systemic uptake occurs readily, and presumably concentration of residual ionized drug in the CSF is low.

The use of epidural opioids in humans was first reported by Behar in 1979.8 This initial study provided evidence that opioids reached the spinal fluid very rapidly and that analgesia could be obtained in the absence of analgesic blood concentrations. Because sympathetic vasoconstrictor responses and other neurological functions were intact, the term “selective analgesia” came into use.
Compared with the intrathecal route, epidural administration is complicated by pharmacokinetic aspects related to dural penetration, fat deposition, and systemic absorption. This is significant due to the fact that larger doses are used, and higher blood concentrations could result. More detailed epidural opioid pharmacokinetics have been made possible by the study of blood concentrations after separate injections of meperidine have been administered epidurally and intravenously in the same patients. Results showed that vascular absorption of epidurally administered meperidine contributed to analgesia for the first one to two hours, but is not of importance in analgesia that persists for more than two hours. That is, meperidine administered epidurally will exert only a small amount of central action from systemic absorption.

The observation that meperidine reaches the spinal fluid in high concentrations very rapidly suggests that lipid-soluble epidural opioids may gain rapid access to the spinal fluid, via the arachnoid granulations in the dural cuff region (where the reticular spinal artery is readily accessible to the opioid), in addition to dural membrane penetration. Epidural fentanyl has been reported to relieve pain without sedation after cesarean section, at blood concentrations that are consistently less than those known to be analgesic. This indicates that epidural fentanyl may be transferred rapidly to the spinal cord, via CSF and via spinal reticular arteries, leaving only minimal amounts to be absorbed slowly into epidural veins.

Essentially the problem of restricting cephalad spread of analgesia by the extradural route seems to revolve around the selection of agent and dose. At this time, the available evidence suggests that the fat-soluble narcotics such as methadone, meperidine, and fentanyl probably diffuse out of the CSF into the spinal cord lipid tissue fast enough to escape the extensive and delayed rostral spread, seen with such poorly lipid-soluble drugs as morphine.

**Preparation and technique**

Few analgesic methods have met with such rapid and widespread results as centrally administered narcotics. As soon as effectiveness of intrathecal and epidural narcotics was reported, the technique became popular because of its low cost, simplicity of administration and long duration of action. Analgesic effects have been demonstrated by its use in chronic pain, postoperative pain and obstetrical pain (Table IV).

Wang, the first person to use intrathecal morphine on humans, showed effectiveness in the patient with chronic pain. Eight patients suffering from chronic pain were relieved an average of 20 hours after the intrathecal injection of morphine 0.5 or 1 mg. The epidural approach was later used for chronic pain relief: morphine 2-5 mg in an adequate volume 10 ml was found to be effective. Duration was longer with morphine than meperidine or fentanyl, and tolerance was slower to appear when morphine was added to a local anesthetic.

Epidural and intrathecal injections of narcotics were administered for acute pain relief after surgery for trauma. Scientific data have confirmed that unrelieved acute pain results in potentially life-threatening adverse physiological effects such as muscle-splinting and respiratory compromise. New data indicate that the outcome of surgery, and hospitalization time, may be influenced by effective pain treatment. For postoperative comfort intrathecal and, more frequently, epidural narcotics were used without subsequent systemic injections. The intrathecal morphine dosages ranged from 0.2-2 mg and epidural morphine 2-10 mg. Many types of surgery were tested, and intrathecal or epidural injection was found more effective than a placebo, and of longer duration than bupivacaine without the cardiovascular effects. Dosage needed for relief was related to type of pain. Relief lasted from 12-30 hours, varying with the study, type of surgery and methods of evaluation used.

Justification for clinical use of intrathecal and epidural narcotic in obstetrics was the need for long-lasting analgesia without vasomotor effects and motor blockade. Intrathecal morphine 1-2 mg was shown to be effective during labor except during delivery. Epidural injections were either ineffective or minimally effective. The usual explanation for lack of effectiveness is the increased vascularity of the epidural space, with consequent more rapid absorption.

The effectiveness of epidural opioids for labor

<table>
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<tr>
<th>Table IV</th>
<th>Epidural dose</th>
<th>Intrathecal dose</th>
<th>Effectiveness</th>
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<tbody>
<tr>
<td>Chronic</td>
<td>2-5</td>
<td>0.5-1</td>
<td>8-24</td>
</tr>
<tr>
<td>Acute</td>
<td>2-10</td>
<td>0.2-2</td>
<td>12-20</td>
</tr>
<tr>
<td>OB</td>
<td>2-6</td>
<td>1-2</td>
<td>12-20</td>
</tr>
</tbody>
</table>

pains remains controversial. It appears that higher doses are necessary, the duration is not as long, and pain relief during the second stage is variable. It is also necessary to study further the neurobehavioral status of neonates.

In general, the use of systemic narcotics in obstetrics is limited by the possibility of maternal respiratory depression, orthostatic hypotension, nausea and vomiting, delayed gastric motility, decreased uterine activity when administered during early labor, and placental transfer of narcotics resulting in neonatal respiratory depression. Scott and coworkers were the first to use 1.5 mg of intrathecal morphine to provide pain relief during labor. The study was small but two important observations were made. The first patients obtained pain relief but felt contractions, allowing for greater participation in the delivery experience. Second, the 1.5 mg of intrathecal morphine did not provide adequate pain relief for the second stage of labor. In addition the onset of analgesia was slow. Although other authors’ early reports suggested a rapid onset, 45-60 minutes is usually required.

The continuous epidural technique if effective would have a distinct advantage over intrathecal administration because it can be readily adapted to changing clinical situations. Most investigators have reported generally unsatisfactory results using low dose epidural morphine for analgesia during labor. Overall, investigators using 2.0-5.0 mg of epidural morphine or equivalent doses of meperidine have demonstrated that these doses are inadequate.

Administering higher doses of epidural morphine has produced mixed results. Dick and coworkers reported that 6 parturients given 10 mg of epidural morphine experienced inadequate pain relief accompanied by nausea, vomiting, and increased drowsiness. Further investigation is necessary, as these results suggest a dose response.

Analgesia for labor and delivery has been achieved with moderate success using epidural meperidine, fentanyl and lofentanil. These are more lipophilic and have a rapid onset but shorter duration of action than morphine. Studies are currently being done on continuous infusion of epidural fentanyl, and on the use of agonist-antagonist-epidural combinations. Meperidine, fentanyl, morphine, methadone, and vetaendorphin have all been used and compared for epidural, intrathecal use. Morphine has the longest duration of action and is as effective, if not more so, as the other agents. Mixing drugs has also been examined. Experimentally the combination of epinephrine with fentanyl results in a high degree of long lasting analgesia that is less likely to produce tolerance. Yaksh and Reddy have reported that adequate analgesia can be produced in monkeys by administering low doses of an opioid and an alpha-adrenergic agonist. In their study neither dose by itself was capable of producing a high degree of analgesia, but the combination of the two did result in a high degree of analgesia that was less likely to produce tolerance. The results indicate the presence of an important interaction between alpha-adrenergic agonist (in this case epinephrine) and spinally administered opiates. At least experimentally, the addition of epinephrine lowers blood concentrations of the opioid, shortens onset of action and prolongs duration. Nonetheless, this question is still much debated.

Intrathecal and epidural narcotic dosages were first calculated empirically and varied accordingly. Martin et al. attempted to determine the most effective dose of epidural morphine for pain relief, with the fewest side effects postoperatively. From these studies, it can be summarized that after abdominal surgery, epidural morphine 4 or 5 mg is as effective as higher dosages and less likely to cause complications. Dosages of 2 mg or less are less effective. After lower limb surgery 2 mg of epidural morphine is as effective as and less likely to cause side effects than higher doses used during the study. Reports suggest that physical factors, baricity and posture may be effective in limiting rostral spread of opiate activity. Other important and unpredictable variables such as straining, coughing, and vomiting also affect the CSF, and predispose to dangerous cephalad spread of opiate-containing CSF. It would be prudent to restrict dosages to the minimum that is compatible with effective analgesia, and cephalad spread should be impeded by the use of hyperbaric intrathecal solution and by maintaining patients in a head-up position.

Complications and contraindications

Although spinal opiates have no effect on a number of motor or sympathetic functions, side effects consequent to spinal opiates include pruritus, urinary retention, nausea and respiratory depression. Spinal opiates have been observed to produce itching or scratching behavior in man. The sensation has been reported in both chronic and postoperative pain patients after development of analgesia by either epidural or intrathecal opiate injection, possibly continuing for the duration of
analgesia or subsiding spontaneously. Itching is pronounced in the palate and the face. It is poorly relieved by antihistamines. Intravenous naloxone, as little as .04 mg, has been shown to significantly reduce the incidence of pruritis without reducing analgesia.17

The occurrence of itching varies with each study. Reiz and Westberg in their series of 1,200 patients observed itching in 15% of the patients. It has been suggested that the itching may be associated with the presence of preservatives in the injection; however, itching has been observed using solutions having no additives.

The failure to achieve spontaneous micturition, for periods sufficient to require catheterization, has been observed following epidural opiate administration.14 Reiz and Westberg in their series of 1,200 patients observed urinary retention in 15% of the patients, 70% of whom were male. The mechanism underlying the development of urinary retention is not presently clear; however, it has been suggested that morphine increases the tone of the detrusor muscle and the vesical sphincter, thus impeding micturition.14 Naloxone has proven successful in initiating normal micturition. Nausea and vomiting has been reported to occur in 17% of the patients. Vomiting is less common, and both are reversed by naloxone.14

Early respiratory depression may be the result of vascular uptake from the epidural space. Thirty minutes after administering 10 mg of morphine, plasma levels are as high by the epidural route as by the intravenous route (30-50 mg/ml).8 These levels may be high enough to cause a dangerous degree of respiratory depression in patients with severe chronic obstructive lung disease. Delayed central nervous system depression after intrathecal morphine sulfate for postoperative pain, as demonstrated by bradycardia and respiratory depression, has been reported.14

Late respiratory depression is related to lipid/water solubility of the narcotic and to CSF flow both within the subarachnoid and ventricular systems. Respiratory depression caused by morphine follows rostral spread of segmental hyperalgesia. This type of respiratory depression is the most serious complication and may be life-threatening many hours after the patient has returned to his room. Naloxone reverses the respiratory depression, although repeated doses may be necessary. If several bolus IV injections are not effective, then a low dose drip can be started (0.2 mg/hr or 4.0 ml of naloxone in 1000 ml at 125 cc/hr, for example).18 All of these side effects can be attributed to impairment of normal sensory modulation, at either a spinal or a brain stem level. Patients over 70 years of age seem to be in a high risk category. Perhaps brains in patients of this age are more susceptible to respiratory depression from opioids, as is found clinically with intravenous opiates in the geriatric age group.

Just as the technique is the same for insertion of a spinal or epidural local anesthetic as for spinal or epidural opioids, so are the contraindications the same. Absolute contraindications are lack of patient consent, local infection at the site of needle insertion, and increased intracranial pressure, with the risk of brainstem herniation, insecure airway, hypovolemic shock, and coagulopathies.

The key to safe management of intraspinal narcotics lies with effective monitoring of vital signs, especially respiration. However, respiratory rate is a poor index of depression, and apneic episodes may occur with little warning. The delayed rostral spread to brainstem nuclei is an ever-present threat. With morphine the most dangerous time is between 6 and 12 hours after intraspinal administration. Severe respiratory depression and coma were reported to occur 4-11 hours after intrathecal injections of morphine, and were characterized by extreme bradypnea and pinpoint pupils.11

The severity of respiratory depression was shown to be modified by other factors: dosage, association of intramuscular narcotics, age, association of diseases like sleep apnea, position of patient after injection, and history of drug addiction.11 It is proposed that the use of epidural morphine requires close surveillance for 12-24 hours. The use of apnea monitors is essential, but nursing staff personnel must be available and trained to respond. Recovery room or intensive care services are the safest option, but their cost may be prohibitive.

**Conclusion**

New analgesic techniques should be assessed in terms of their ability to provide safe, effective pain relief. In review of epidural and intrathecal narcotics, mechanism of action is via binding to opiate receptors located predominantly in the substantia gelatinosa of the dorsal horn of the spinal cord. Unwanted side effects are generally from rostral flow of the narcotics to the brainstem and binding with various opiate receptors in this area. The more lipid-soluble the agent, the quicker the onset of action, the shorter the duration, and probably the lower the incidence of side effects. If an agent demonstrates a high degree of receptor binding.
and receptor specificity, then even if it is very lipid-soluble, it may have a long duration of action.

Dosages used depend on where the analgesia is required and whether the patient has chronic or acute pain. The age of the patient should be considered, realizing that the elderly patient is more prone to respiratory depression with this therapy.

The intraspinal narcotics represent a promising and attractive field within the wider context of neuropharmacology. As the body of knowledge about the mechanism of drug-induced analgesia increases, the effects at the spinal cord level assume even greater importance, not only to provide an understanding of analgesia, but also as a model site for the study of the interaction between neural systems conveying pain information and drugs that act to inhibit the transmission of that same information.

REFERENCES


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