EPIDURAL ANALGESIA AND ANESTHESIA

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INDICATIONS

Epidural drug administration is a method of administering drugs in close proximity to their site of action either at receptors in the spinal cord or at nerves as they leave the spinal cord. Binding to specific receptors is maximized, producing more profound analgesia and allowing a lower total drug dose to be used compared with systemic administration. This dose reduction may decrease or even eliminate the adverse effects or toxicity that could result from systemic administration of the same drugs. The duration of analgesia may also be more prolonged, because the drug relies on local blood flow for removal from its binding site and delivery to the systemic circulation, where it is then available for metabolism and excretion.

Epidural anesthesia has been advocated as an alternative to general anesthesia for surgical procedures caudal to the diaphragm in dogs that are deemed to be high-risk candidates for general anesthesia.\textsuperscript{7, 25, 27, 32, 45} This technique requires adequate sedation to ensure that the patient does not respond to extraneous stimuli and may not be suitable for all patients or surgical procedures. Oxygen supplementation should be provided.

Epidural anesthetics and analgesics may also be administered as an adjunct to general anesthetic techniques. As dose-dependent cardiopulmonary depression occurs with all inhalant anesthetic agents, anesthetic techniques such as epidural administration of analgesics that reduce the requirement for inhalant agents usually also reduce cardiopulmonary depression. Epidural administration of analgesics before surgery not only provides preemptive and intraoperative analgesia with a minimum alveolar concentration reducing advantage but can also provide excellent postoperative analgesia of prolonged duration.\textsuperscript{5, 28, 52, 54, 57, 99}

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The reduced inhalant requirements associated with the use of epidural analgesia can result in improved hemodynamic function.\textsuperscript{51, 56} The long-lasting analgesia is a particularly effective means of providing postoperative pain control in private practice settings, where 24-hour care may not be available.

Although single epidural injections are effective for intra- and postoperative analgesia, there are also cases of a more chronic nature that can benefit from epidural drug administration. The placement of an epidural catheter allows for multiple injections to be made over a longer period of time.

**CONTRAINDICATIONS**

The two main contraindications for epidural injection are coagulopathies and sepsis. There are numerous blood vessels passing through the epidural space. During needle insertion into the epidural space, it is possible to penetrate or lacerate one of these vessels. Ongoing hemorrhage into the epidural space, a potential risk in an animal with a coagulopathy, could result in increased pressure in the spinal canal. This pressure causes discomfort and may result in pressure on nerves as they pass through the epidural space or even on the spinal cord itself, resulting in paresis or even paralysis.

Sepsis or any type of localized infection such as dermatitis over the injection site is the second major contraindication for epidural puncture, because the risk of introducing infection into the epidural space outweighs the benefits of this method of providing analgesia.

**BASIC TECHNIQUE**

To ensure proper needle placement into the epidural space, the patient must remain still. Patient movement can cause needle displacement, resulting in a misplaced epidural injection, outside the epidural space or, more rarely, an inadvertent spinal or vascular injection. Laceration of a blood vessel in the epidural space, particularly the venous sinus at the bottom of the spinal canal, can cause an epidural hematoma. Because of the nature of most small animal veterinary patients, epidural injections or epidural catheter placement should be performed under profound sedation or general anesthesia unless the patient is extremely quiet or debilitated.

The equipment required to perform epidural injections is minimal. The only required equipment is 20- or 22-gauge spinal needles varying in length from 1.5 to 3.5 in, syringes for injection, and sterile gloves. The shorter needle is ideal for most small animal patients and reduces the chance of deep trauma with missed attempts. Large or obese animals or an angled rather than perpendicular approach to the space requires a longer needle. The passage of the needle into the epidural space is more obvious using a 20-gauge needle; thus, the 22-gauge needle is usually reserved for cat-sized patients. A glass syringe that has been lubricated with sterile saline or a few drops of the epidural solution is useful for checking for lack of resistance to a small test injection of air. A 3-mL plastic syringe is not as sensitive but may suffice. Epidural catheterization requires an epidural catheter, an injection cap, and a blunt Tuohy needle to prevent inadvertent laceration of the catheter as it is inserted. Microfilters are available to insert between the epidural catheter and injection cap. Complete epidural catheter kits are commercially available.
Whether a single epidural injection is being performed or an epidural catheter is being inserted, all equipment must be sterile, and strict attention must be paid to aseptic technique. The injection site should be clipped and cleaned in an aseptic manner. Failure to follow aseptic technique can result in epidural abscesses with or without lumbosacral diskospondylitis, which can be difficult to treat.

Epidural injections may be made with the patient lying in either sternal or lateral recumbency. The epidural injection (outside the dura) is most easily and safely accomplished at the lumbosacral junction in small animals, because the spinal cord and dural sac end cranial to this site in most adult dogs (Fig. 1). Inadvertent subarachnoid puncture is rare, except in puppies and cats, where the spinal cord and dural sac end further caudally. Although this is not a contraindication to epidural puncture in these patients, one does need to bear this in mind while performing an epidural injection. It is important in all cases, especially in cats and puppies, to ensure that the needle tip is not moved around excessively while in the epidural space and to observe for the presence of cerebrospinal fluid (CSF) in the needle hub. If CSF is obtained, the needle may be withdrawn, and the procedure is reattempted or abandoned. Depending on the drugs being injected, drug dosages can be recalculated (see below), and a spinal injection into the CSF (intrathecal injection) can be made.

The lumbosacral junction can be located by palpating the wings of the ileum. The space between the sixth and seventh lumbar vertebrae falls on the imaginary line drawn connecting the cranial margins of the ilial wings. The lumbosacral junction is the vertebral space immediately caudal to L6-7. There is often a subtle depression at this site, because the dorsal spinous processes are more prominent on the lumbar vertebrae than on the sacrum. The needle should be inserted in this depression, with care to stay centered on midline just caudal to the point where the midline of the spine bisects the imaginary line connecting the cranial borders of the ilial wings. To palpate landmarks as the needle is being inserted, the thumb and middle finger of one hand (generally the left hand for right-handed people) may be placed on the most cranial aspect of the wings of the ileum. The index finger of the same hand can be used to locate the

\[ \text{Figure 1. Epidural needle in correct position for injection. CSF = cerebrospinal fluid.} \]
lumbosacral junction and act as a guide for needle insertion (see Fig. 1). The other hand is then free to insert the needle. The needle should be advanced slowly, allowing the practitioner to appreciate the various tissue planes that the needle passes through. Before entry into the epidural space, a "pop" is often felt as the needle passes through the ligamentum flavum.

Once the needle has been advanced to a point where the practitioner thinks that the tip is in the epidural space, the stylet can be carefully removed. The hub of the needle should be observed for the flow of either blood or CSF. If blood is observed, the needle should be withdrawn, and epidural puncture should be reattempted. If CSF is present, the needle has entered the subarachnoid space. An injection can be made into the subarachnoid space provided that the practitioner adjusts the dose of drug accordingly. Generally, a dose reduction of 40% to 50% is recommended. It must be remembered that the animal has then received a spinal injection and not an epidural injection. Spinal injections result in a more rapid onset of effect and also have the potential for more cranial drug migration. Signs of cranial drug migration should be monitored. If no CSF is apparent in the hub of the needle, it is recommended that a small test injection of air be made to confirm that the needle is in the epidural space. If the needle is correctly positioned in the epidural space, there should be no resistance to injection. This lack of resistance is most obvious if a saline-lubricated glass syringe is used, because friction occurs from the rubber on the plunger of a plastic syringe. Because of the negative pressure generated within the epidural space with respiration, correct needle placement can also be verified using the hanging drop technique when the animal is positioned in sternal recumbency. This is done by filling the hub of the needle with sterile saline just before advancing the needle through the ligamentum flavum. As the needle tip enters the epidural space, the saline is drawn into the space by the negative pressure. A small injection of radiopaque dye can also be made to confirm correct epidural location. This last technique may be most helpful with epidural catheter placement, as the hanging drop technique is not feasible and the small diameter of the epidural catheter makes the lack of resistance with a test injection of air difficult to appreciate. It is necessary to stabilize the hub of the needle to prevent inadvertent movement or advancement of the needle during stylet removal and subsequent attachment of a syringe. The shortest possible needle should be used for epidural injection to reduce the chance of the needle tip puncturing the bottom of the vertebral canal, penetrating the abdominal cavity or colon, and risking the introduction of bacteria into the epidural space. Inadvertent placement lateral to the spine also allows this event to occur when long needles are used. Once it has been confirmed that the needle tip is within the epidural space, injection of the chosen drug may be made slowly. Occasionally, a tail twitch is observed either on needle insertion or during injection. Often, an increase in the respiratory rate of the animal occurs during injection, probably in response to the room temperature injectate or pressure, if an injection is made too quickly. In dogs with deep inspirations, it may be possible to perceive increased ease of injection at inspiration as a result of the negative pressure generated in the thoracic epidural space.

Because the epidural space is a fixed-volume space, the volume injected should not be excessive. Cranial migration of the drug and epidural space pressure are dependent on the volume of drug injected. For these reasons, a maximum injectate volume should be determined for each patient. Generally, a volume of 1 mL per 5 kg of body weight blocks up to the first lumbar vertebra. Larger volumes result in more cranial blockade. Some practitioners suggest that epidural injectate volumes are more accurately calculated on the basis of the
crown–rump length of the patient as opposed to body weight. A volume of 1 mL per 10 cm has been recommended. Most anesthesiologists have a maximum recommended volume for epidural injection irrespective of patient size. These authors use a maximum volume of 6 mL. This volume is effective and convenient, and it reduces the possibility of excessive pressure on nerves passing through the space and subsequent postepidural paresis. When local anesthetic blockade of the anterior abdomen is required, a slow injection of 1 mL per 3 to 5 kg body weight may be needed to ensure an anterior effect.

Drug doses should always be calculated on the basis of the lean or ideal body weight of the patient. In obese patients, there may be increased fat in the epidural space, resulting in a more cranial migration or increased pressure in the epidural space with standard volumes of injectate. Injectate volumes should also be reduced by up to 75% in pregnant patients, because pregnancy results in engorgement of the epidural blood vessels, which not only decreases the potential volume of the epidural space but also increases the systemic absorption of drugs injected epidurally. We have found that a volume of 1 mL per 5 kg based on the lean or nonpregnant body weight is safe.

Epidural catheter placement is carried out in a similar manner using a Tuohy needle, which is provided in commercial kits. The distal opening of the needle must be directed forward. This needle is quite blunt, resulting in a more distinguishing “pop” on entry into the epidural space. The stylet is removed, and the catheter is threaded down the needle into the space a sufficient distance to provide security. A radiograph can be taken to verify correct placement, as the catheter is radiopaque. Once the catheter is in place, the needle is carefully removed, and the entry site is protected in a sterile manner (i.e., surgical adhesive drape). If injection resistance develops, the practitioner should assess the filter patency and consider slight withdrawal of the catheter. Catheters can be left in and remain patent for several days.

DRUGS AND DRUG COMBINATIONS

Local Anesthetics

History

In 1901, the effects of epidural cocaine in dogs and people were first reported. Interest in this technique was limited, and it was reserved as an alternative to general anesthesia in veterinary medicine. The epidural administration of local anesthetic agents was advocated for use in any surgical procedure caudal to the diaphragm in dogs but was superior for procedures involving the pelvis, hind limbs, and perineal area. Epidural anesthesia was used much more extensively in human patients, where it was employed as an alternative to general anesthesia and to provide analgesia for obstetric patients. The advantages of epidural anesthesia included minimal cardiopulmonary depression, no organ toxicity from exposure to inhalant anesthetic agents, less fetal depression, and improved pain relief.

Required Modification of Basic Technique

If local anesthetics are used epidurally, it is essential to ensure a slow injection rate so as to provide an even spread of the solution within the epidural space. A patchy block may result from rapid injections. To maximize anesthesia,
it is recommended that the proposed surgical site be placed in a dependent position for 5 minutes after injection to maximize local anesthetic binding on the side to be anesthetized. Failure to do so may result in an incomplete blockade. For a bilateral epidural blockade, the animal should be placed in dorsal or ventral recumbency.8, 27

**Pharmacokinetics**

The mechanism of action of epidural anesthesia produced by local anesthetics is thought to be the result of a combination of three potential mechanisms. Local anesthetics may diffuse into the paravertebral areas through the intervertebral foramina and block nerves distal to their dural sheaths, resulting in multiple paravertebral blocks. A second mechanism involves the diffusion of local anesthetic across the dura into the subarachnoid space, where it then acts on nerve roots. Finally, after diffusion across the dura, local anesthetics may act directly on the spinal cord.6, 13 The primary sites of action thought to be responsible for epidural anesthesia produced by local anesthetics are the spinal nerve roots.13 This theory fits the observed gravity effect on the block.

The time taken for a local anesthetic to penetrate a nerve trunk and the concentration of drug achieved vary inversely with the size of the nerve. Sympathetic nerves are affected first, followed by sensory nerves and finally motor nerves.13, 32 Reports of hypotension in dogs after epidural anesthesia, attributable to sympathetic blockade, have not been consistent or well-documented.8, 20, 27, 32, 37 Recent evidence seems to refute this, and the inhalant-sparing effect becomes much more significant and beneficial during anesthesia.51 Anesthesia produced by intrathecal and epidural local anesthetic injection persists until the local anesthetic agent has been absorbed into the systemic circulation. Highly lipid-soluble local anesthetics such as bupivacaine are absorbed into the systemic circulation at a slower rate, resulting in a longer duration of action13 compared with lidocaine or mepivacaine (Table 1).13 The effects of vascular absorption of local anesthetics have been postulated as a cause of suspected cases of epidurally induced hypotension.6

**Clinical Effects**

Epidural anesthesia results in sensory, motor, and autonomic blockade. Autonomic effects may be of significance if the blockade extends into the thoracic region and interrupts sympathetic nerve fibers.8 Bradycardia may also occur as a result of the blockade of cardioaccelerator nerve fibers if epidural anesthesia extends cranial to the first four thoracic vertebrae.8 Respiratory function is not impaired unless local anesthetics produce motor blockade of the phrenic nerve at C3-5.8

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**Table 1. LOCAL ANESTHETICS USED FOR EPIDURAL ANESTHESIA**

<table>
<thead>
<tr>
<th>Local Anesthetic Agent</th>
<th>Dose (mL/kg)</th>
<th>Duration of Action (minutes)</th>
<th>Time to Onset of Action (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine (2.0%)</td>
<td>0.2</td>
<td>45-90</td>
<td>5</td>
</tr>
<tr>
<td>Mepivacaine (2.0%)</td>
<td>0.2</td>
<td>60-90</td>
<td>5</td>
</tr>
<tr>
<td>Bupivacaine (0.5%)</td>
<td>0.2</td>
<td>120-360</td>
<td>20</td>
</tr>
<tr>
<td>Ropivacaine (0.5%)</td>
<td>0.2</td>
<td>90-420</td>
<td>15</td>
</tr>
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</table>
Epidural anesthesia has been achieved to the level of the first lumbar vertebra with a dose of 0.22 mL/kg and the eleventh thoracic vertebra with a dose of 0.31 mL/kg of 0.75% bupivacaine. Duration of anesthesia ranged from 2 to 6 hours with no adverse hemodynamic effects observed. The relatively short duration of action of lidocaine and mepivacaine limits their use to short surgical procedures. Although bupivacaine has a longer duration of action than lidocaine, it also has a longer latency period of approximately 20 to 30 minutes before the onset of surgical anesthesia (see Table 1).

Peak plasma concentrations of bupivacaine are reached 5 minutes after epidural administration of 1 mL per 4 kg (1.8 mg/kg) of 0.5% bupivacaine and are lower than plasma concentrations after intravenous administration of a similar dose and well below concentrations associated with signs of toxicity in dogs. Induction of motor blockade is in 2.3 ± 2.2 minutes and persists for 158.3 ± 48.8 minutes. The half-life (\( \beta \)) of bupivacaine after epidural administration (168–179 minutes) is approximately five to six times longer than after intravenous administration and is likely a result of the slow release of the lipophilic bupivacaine from the epidural space. An initial decrease in blood pressure and increase in heart rate are correlated with plasma concentrations of bupivacaine after epidural administration. No significant changes in cardiovascular function, respiratory rate, or arterial blood gases are associated with the use of epidural lidocaine or bupivacaine in dogs.

**Opioids**

**History**

The discovery of opioid receptors in the spinal cord led to renewed interest in epidural techniques. Although opioids administered by any route bind to spinal cord opioid receptors, it was speculated that epidural or intrathecal administration would provide preferential delivery and binding of opioids to spinal cord receptors, thereby allowing a lower total dose to be used. This was thought to result in less binding at supraspinal receptors, decreased incidence and severity of adverse effects, and delayed development of tolerance.

In 1979, the first reports on the use of spinal opioids in human patients were made. The use of spinally administered opioids for pain management in a variety of clinical settings, including postoperative pain, cancer pain, chronic pain, obstetrics, was reported with varying degrees of success. The analgesia obtained after epidural administration of meperidine persisted in the absence of blood concentrations previously shown to be associated with analgesia after systemic administration. Analgesia obtained from the administration of epidural morphine and fentanyl has also been demonstrated in the face of plasma drug concentrations below those known to be associated with clinical analgesia. Although a wide variety of opioids, including morphine, meperidine, fentanyl, hydromorphone, methadone, buprenorphine, alfentanil, lofentanil, butorphanol, and nalbuphine, have been used successfully by either the epidural or intrathecal route, much of our knowledge about spinal and epidural opioid analgesia comes from studies of morphine, as this has been the most commonly used opioid.

**Required Modification of Basic Technique**

Although the site of epidural injection does not affect the analgesic actions of morphine, studies have demonstrated that the more lipophilic opioids pro-
duce a more segmental analgesia because of reduced diffusion through the
CSF. These findings are inconsistent, however, when a larger injectate volume
is used. An increased duration of analgesia associated with increasing doses
of morphine has been reported but not consistently shown. Opioids for epi-
dural injection are diluted with an appropriate volume of sterile saline, and use
of the basic technique described previously is suitable.

Pharmacodynamics and Pharmacokinetics

The dorsal horn of the spinal cord is the primary site of action of spinally
and epidurally administered opioids. There seems to be presynaptic as well
as postsynaptic opioid inhibition of afferent transmission. Opioids bind to
presynaptic receptors on the spinal terminals of afferent neurons, inhibiting the
release of excitatory neurotransmitters such as glutamate and substance P.
Opioids also antagonize the effects of excitatory neurotransmitters by inhibiting
the transmission of postsynaptic impulses in ascending tracts and cause in-
creased activity in the descending inhibitory pathways that act on spinal cord
processing of pain.

Epidurally administered opioids are thought to enter the CSF and reach the
spinal cord after penetration of the meninges. Initially, it was thought that the
dura mater was the primary barrier that opioids had to cross to reach their
proposed site of action. Subsequent in vitro studies using live meningeal tissue
suggest that the arachnoid mater may be the primary barrier that opioids
must penetrate. Suggestions that this transfer may be enhanced via arachnoid
granulations in the dural cuff region or by uptake into the posterior radicular
artery have recently been disputed. The transfer of opioids across the meninges
must compete with uptake and systemic absorption by lymphatics and veins
draining the epidural space in addition to a process of reversible sequestration
in epidural adipose tissue.

Plasma concentration curves obtained after epidural morphine administra-
tion are similar to those obtained after intramuscular injections. This observation
demonstrates that rapid systemic absorption occurs. In human beings,
peak plasma concentrations were achieved 15 minutes after the epidural injec-
tion of three different doses of morphine. The peak concentrations were highest
after the highest dose. Plasma concentrations decrease at an equal rate, and
within 60 minutes, the plasma concentrations are below the plasma levels that
are correlated with analgesia after systemic administration, although analgesia
persists. Epidural oxymorphone results in blood levels similar to those ob-
served after intramuscular injection, although the duration of analgesia from
epidural injection is remarkably longer. This is in agreement with the results
in studies of epidural meperidine, which show that vascular absorption con-
tributes to supraspinal analgesia for the initial 1 to 2 hours after administration
but is not associated with the longer lasting nalgesia that persisted beyond the
time when blood concentrations declined below analgesic levels. Peak
CSF concentrations after the administration of epidural morphine were seen
after 60 minutes, with the highest concentrations associated with highest doses
administered. The valveless internal vertebral venous plexus has connections
with intracranial venous sinuses. Investigations using epidurally administered
radioactive-labeled naloxone and morphine revealed that compression of the
vena cava increases the amount of drug being delivered by the blood to the
brain. Changes in epidural venous blood flow thus might influence clearance
of opioids from the epidural space and delivery to the brain.

Opioids also diffuse into adipose tissue in the epidural space. Drugs with
high lipid solubility have a higher affinity for adipose tissue and thus have a tendency to sequester in the epidural fat and lipid layers in the spinal cord. This "depot effect" may explain the longer than expected clinical effects seen with lipid-soluble opioids.33

There seems to be a relation between lipid solubility of an opioid and the onset and duration of analgesia after epidural administration. The more lipophilic opioids enter the CSF more rapidly and thus gain access to opioid receptors in the spinal cord more rapidly.23,63 Lipophilic opioids are also taken up into the systemic circulation more rapidly and are more likely to undergo nonspecific uptake into epidural adipose tissue. This reduces the concentration of opioid available to cross the meninges into the CSF but does provide a depot from which the opioid can slowly be released.36,63 Morphine has the lowest lipid solubility and, consequently, the slowest onset of action and the longest duration of analgesia.16 Low lipid solubility means that morphine crosses the meninges slowly, but once it reaches the CSF, it tends to remain there and is available to be taken up by spinal cord opioid receptors. This slow uptake by receptors is responsible for the slow onset of action but also results in a long duration of analgesia.16

More lipid-soluble drugs such as fentanyl are able to cross the meninges quite rapidly and readily enter the CSF to interact with spinal cord receptors. This results in a more rapid onset of action. Systemic absorption by arteries, veins, and lymphatics creates a persistent concentration gradient for further drug to leave the epidural space and spinal cord and be absorbed into the systemic circulation. This results in a shorter duration of spinally mediated analgesia.16

Oxymorphone is an opioid with moderate lipid solubility. Its onset of action and duration of analgesia would be expected to be intermediate between those of the extremely hydrophilic morphine and the extremely lipophilic fentanyl. Hydromorphone is also used epidurally, and the pharmacokinetics of this drug place it between morphine and oxymorphone.

The dose of drug chosen for epidural administration is dependent on the pharmacokinetics described previously. The more lipid-soluble an opioid is, the closer the epidural dose is to the dose required systemically. As a result lower doses are selected for epidural morphine compared with epidural oxymorphone, which is used at the same dose that is administered systemically (Table 2).

_Clinical Effects_

Epidurally administered opioids, particularly morphine, have been used extensively for postoperative analgesia in both human and veterinary medicine. They have also been used as an adjunct to local and general anesthesia and have been reported to reduce the requirement for these agents.54,63 The duration of analgesia ranges from 4 to 51 hours in human studies38 and from 10 to 24

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Dose (mg/kg)</th>
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<tr>
<td>Morphine</td>
<td>0.1–0.3</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>0.05–0.1</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.03–0.04</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.005–0.01</td>
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hours in canine studies. Spinally administered opioids have been reported to decrease inhalant anesthetic requirements in human patients during surgery. This has been confirmed for epidural morphine in halothane-anesthetized dogs. Because of individual variations in epidural venous drainage and adipose tissue mass, the extent of dural transfer of opioids varies to a great extent. This may contribute to epidural failure in some individuals. A failure rate of 12% has been reported in spite of proper administration technique.

Changes in epidural blood flow result in proportional changes in systemic drug absorption and can affect the duration of action.

Generally, spinally administered opioids produce profound segmental analgesia of long duration that is not associated with any sensory, sympathetic, or motor blockade. Antinociceptive effects occur first and last the longest in somatic segments exposed to the largest amount of drug. Reflex vasoconstriction associated with hypotension and reflex vasodilation caused by hypertension in dogs were shown to be unaffected by epidural morphine administration. Touch, proprioception, and efferent motor activity have been shown to be unaffected in people, primates, cats, and rodents.

Epidural opioids are capable of relieving both visceral and somatic postoperative pain. Electrophysiologic studies indicate that C-fiber nociceptive impulses are blocked to a greater degree by presynaptic opioid inhibition of substance P release than that of Aδ impulses. Spinally administered opioids are therefore better for treating dull aching postoperative pain than acute intraoperative pain.

The use of epidural opioids in people, particularly morphine, has been accompanied by reports of numerous side effects, including pruritus, nausea, vomiting, urinary retention, and respiratory depression. Respiratory depression is the adverse effect of greatest concern. The mechanism of respiratory depression after epidural administration of morphine seems to be related to morphine's low lipid solubility. This results in prolonged concentrations of morphine in the CSF, allowing more rostral spread and an increased potential of the morphine reaching the central nervous system and binding to supraspinal opioid receptors in areas of the brain controlling respiration. Epidural morphine in human beings at doses as low as 0.05 mg/kg has been shown to reduce resting minute volume and increase end-tidal carbon dioxide concentrations for up to 24 hours after administration.

Retrospective studies examining the incidence of delayed respiratory depression revealed a lower rate with epidural (0.25%-0.4%) than with intrathecal (5.5%) administration. Infusion of fentanyl directly into the ventricle of the brain in dogs alone and in combination with 0.75% halothane showed that fentanyl combined with halothane caused a dose-related increase in arterial PCO₂ that was not seen with either drug alone. This supports the assumption that respiratory depression after opioid administration in dogs is primarily of clinical significance when combined with inhalant anesthetic agents or other drugs that contribute to central nervous system depression. Although we observe respiratory depression in anesthetized clinical cases in which higher doses of an opioid are administered epidurally, we do not consider this to be a clinical concern in the postoperative period.

We have observed several less significant side effects in our patients that have received epidural opioid injections. Pruritus can occur and may be more likely if any skin irritation exists from the clipping or skin preparation. The hair seems to grow slowly over the site of the injection in some dogs. Hair regrowth can be complete at the surgical site, although the epidural site is still obvious. Urinary retention can occasionally be troublesome and create discomfort for the animal if the bladder is not evacuated at the end of the surgery. It is advisable
to place a urinary catheter in patients that seem to have difficulty in voiding that is associated with the epidural drug effects or catheter.

The use of epidural morphine at 3 mg/kg in chlorpromazine-sedated dogs resulted in the onset of analgesia in 15 to 20 minutes, surgical anesthesia of 1.3 to 2.5 hours, and postoperative analgesia of 10 to 12 hours. Based on the extremely high dose of epidural morphine used and the duration of surgical anesthesia, it was suggested that anesthesia was the result of supraspinal mechanisms after systemic absorption of morphine rather than spinally mediated analgesia. Adverse effects included excitement in 2 of 30 dogs, which was attributed to misplaced epidural injection, because a further 2 mg/kg of morphine administered epidurally produced good sedation and analgesia.

Epidural morphine at a dose of 0.1 mg/kg decreases halothane requirements in dogs from 1.04% for halothane alone to 0.68% for the forelimb and to 0.60% for the hind limb. Injectate volumes of 0.13 mL/kg compared with 0.26 mL/kg do not affect the analgesia produced.

Segmental analgesia has been demonstrated in dogs and cats, with analgesia occurring first, lasting longer, and being more profound in the somatic segments exposed to the highest concentration of drug. The lower end-tidal halothane concentration required with epidural morphine in dogs resulted in improved hemodynamic parameters compared with those recorded for an equipotent dose of halothane alone. A subsequent study showed that the epidural administration of morphine was not associated with any significant cardiovascular effects during isoflurane anesthesia in dogs.

Epidural administration of 0.1 mg/kg of morphine in a volume of 0.26 mL/kg in dogs resulted in rapid (5 minutes) short-lasting serum concentrations (mean peak concentration in 30 minutes) and delayed (45 minutes) long-lasting CSF concentrations (mean peak concentration at 180 minutes).

Epidural morphine has been reported to result in long-lasting analgesia ranging from 10 to 23 hours in dogs. Epidural morphine has been shown to be at least as effective as intercostal bupivacaine at providing analgesia after lateral thoracotomy in dogs. The reported incidence of complications, including hyperalgesia and pelvic limb paresis, after epidural administration of morphine in 365 dogs and four cats was 0.75%.

Epidural oxymorphone has been administered to dogs at a dose of 0.1 mg/kg with no adverse neurologic effects or histopathologic changes to the spinal cord or dura. Epidural oxymorphone (0.05–0.1 mg/kg) provided a superior degree and duration (7–10 hours) of analgesia in dogs compared with higher intramuscular (0.15–0.2 mg/kg) doses of oxymorphone (2–5 hours) after thoracotomy and hind end orthopedic surgery. Epidural oxymorphone at 0.05 mg/kg provided analgesia with less sedation than intramuscular oxymorphone. This was attributed to higher plasma levels of oxymorphone after intramuscular administration, although levels were not measured. Two of 10 dogs receiving epidural oxymorphone became bradycardic, although only 1 of the dogs receiving intramuscular oxymorphone did. Similar blood levels were achieved in dogs given intramuscular and epidural oxymorphone in another study, and results obtained in research with clinical cases and crossover trials showed common bradycardia. Respiratory depression equivalent to that seen after intravenous administration of oxymorphone was apparent and significantly different than that observed in clinical cases in which epidural bupivacaine alone was administered.

Based on its increased lipid solubility, oxymorphone may produce a more pronounced segmental effect compared with morphine. For this reason, these authors tend to use it to provide epidural analgesia for surgical procedures
involving the hind end and caudal abdomen of patients. Because of the more hydrophilic nature of morphine, it migrates cranially and may be more useful in providing analgesia for the cranial abdomen, thorax, and forelimbs.

**Combinations of Local Anesthetics and Opioids**

**History**

Combinations of opioids and local anesthetics have been administered epidurally in an attempt to optimize analgesia and minimize total drug doses. Advantages of lower administered drug doses include lower incidences of adverse effects and a decreased rate of opioid tolerance development. Although there are numerous clinical studies reporting improved analgesia after the epidural administration of an opioid in combination with a local anesthetic in human patients, conflicting evidence exists when epidural administration of opioids and local anesthetics individually is directly compared with administration of the combination.

**Required Modification of Basic Technique**

The opioid is diluted in local anesthetic rather than in saline. The previously outlined techniques for epidural injections of local anesthetics should be followed.

**Pharmacokinetics**

Opioids and local anesthetics have different sites and mechanisms of action. Studies investigating synergism between these two drug types demonstrated that the administration of naloxone reversed the enhanced analgesia after epidural administration of an opioid–local anesthetic combination. This suggests that activity at the opioid receptors is involved. Some investigators have shown that the presence of bupivacaine enhances morphine’s ability to displace radiolabeled naloxone from rat spinal cord membranes, suggesting that bupivacaine induces a conformational change in spinal cord opioid receptors that enhances morphine binding. Others suggest that low concentrations of local anesthetics in the dorsal root entry area of the spinal cord result in diminished impulse transmission as a result of the small branching C fibers in this area. This results in an increased probability of interruption of action potential propagation in this region. Reduced afferent impulse conduction through this area could facilitate presynaptic inhibition of neurotransmitter release by opioids. The net effect would be an increased antinociceptive effect, with minimal drug concentrations and minimal autonomic and motor disturbances. Intrathecal bupivacaine causes a dose-dependent depression of nociceptive reflexes that is enhanced by the addition of fentanyl in dogs. This results in decreased afferent impulse transmission but causes no enhancement of efferent sympathetic inhibition.

The clinical use of epidural morphine in combination with bupivacaine was first described in dogs as an alternative to general anesthesia for surgery caudal to the last rib. This combination resulted in minimal hemodynamic and respiratory effects and long-term analgesia. Postoperative epidural administration of a combination of morphine and bupivacaine has been shown to provide superior analgesia compared with epidural morphine alone in dogs after hind end orthopedic surgery. The median time requirement of subsequent analgesia administra-
tion was longer than 24 hours compared with 5 hours for epidural morphine alone. There was no correlation between pain scores and plasma drug concentrations.28

Epidural oxymorphone in combination with bupivacaine has been demonstrated to provide significant postoperative analgesia, lasting up to 24 hours.53 Although the combination did not provide significantly decreased halothane requirements during orthopedic surgery compared with the administration of intravenous oxymorphone or epidural bupivacaine, there was a trend toward lower halothane requirements from the typically recommended 1.5 times the minimum alveolar concentration, which resulted in improved cardiovascular performance.51

Clinical Effects

Although a mechanism for a synergistic effect has not been proven, studies on intrathecal and epidural administration of combinations of opioids and local anesthetics have supported the finding that a synergistic analgesic effect does occur in mice, rats, and dogs. The combination has been shown to provide an improved degree and duration of analgesia, even at subanalgic doses, compared with that observed when either drug is given alone.50, 51 In theory, the complete pre-emptive analgesic effect of the local anesthetic should allow more effective analgesia from the epidural opioid. Because there is no significant evidence for detrimental effect with the combination compared with either local anesthetic or opioid alone, it seems reasonable to recommend the use of the combination whenever the local anesthetic could be effective at the site of the surgery such as in procedures caudal to the last rib.

Epidural Administration of Other Drugs

Although not currently in common clinical use, the epidural administration of other groups of drugs including alpha-2 agonists, ketamine, and nonsteroidal anti-inflammatory drugs has been studied. Although benefits do seem to be associated with their use, they are not advocated for use in the small animal clinical setting at this time.

SUMMARY

This review describes the beneficial effects of the use of epidural drugs for pre-emptive analgesia, intraoperative analgesia with an inhalant-sparing effect, and prolonged postoperative analgesia. Epidural morphine, oxymorphone, or hydromorphone is recommended for use in small animals in combination with a local anesthetic of appropriate duration for procedures involving the hind end, although epidural morphine or hydromorphone may be more appropriate for procedures on the thorax and forelimbs. Side effects are few and can usually be easily managed, with the benefits outweighing any detrimental effects that might occur.

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