Epidural administration of bupivacaine, morphine, or their combination for postoperative analgesia in dogs

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**Objective**—To compare the analgesic effects of epidural administration of morphine (MOR), bupivacaine hydrochloride (BUP), their combination (COM), and 0.9% sterile NaCl solution (SAL) in dogs undergoing hind limb orthopedic surgeries.

**Design**—Blinded, randomized clinical trial.

**Animals**—41 healthy dogs admitted for elective orthopedic surgeries involving the pelvis or hind limbs.

**Procedure**—Analgesic and control agents were administered postoperatively prior to recovery from isoflurane anesthesia. Ten dogs received MOR, 0.1 mg/kg of body weight; 10 received BUP, 0.5%, 1 ml/10-cm distance from the occipital protuberance to the lumbosacral space; 11 received COM; and 10 received SAL epidurally. Dogs were monitored for 24 hours after epidural injection for pain scores, heart and respiratory rates, blood pressure, time to required administration of supplemental analgesic agent, total number of supplemental doses of analgesic agent required, and plasma concentrations of cortisol, MOR, and BUP.

**Results**—Pain scores were significantly lower in dogs in the COM and BUP groups than in dogs in the SAL group. Pain scores also were significantly lower in dogs in the COM group than in dogs in the MOR group. Time to required administration of supplemental analgesic agent was longer for dogs in the COM group than for dogs in the MOR and SAL groups. Total number of supplemental doses of analgesic agent required was lower for dogs in the BUP and COM groups than for dogs in the SAL group.

**Clinical Implications**—Postoperative epidural administration of COM or BUP alone provides longer-lasting analgesia, compared with MOR or SAL. (J Am Vet Med Assoc 1996;209:598-607)

A llieving pain in animals after accidental or surgical injury is a major concern of veterinary care providers. Epidural administration of analgesic agents has proven effective in management of somatosensory and visceral pain confined to the caudal portion of the body. Local anesthetic agents and opioids are used extensively for regional management of postoperative and trauma-induced pain in human beings. Recent reports indicate epidural administration of these agents is becoming more common in veterinary medical practice.

Variable responses of human beings to epidural administration of opioids and local anesthetic agents have been reported. Although local anesthetic agents provide excellent analgesia after epidural administration, duration of analgesia can be inadequate. Additionally, epidural administration of local anesthetics at doses adequate to cause loss of pain sensation can be associated with sympathetic blockade and hypotension, motor paralysis, and hypothermia. Initial investigations of epidurally administered opioids indicated long-lasting analgesia without motor or autonomic blockade. However, the quality of analgesia provided by epidural administration of opioids varies substantially between individuals and is sometimes inadequate for relief of severe pain. Adverse effects after epidural administration of opioids including pruritus, urinary retention, nausea, and respiratory depression also have been reported for human beings. Results of studies comparing the efficacy of epidurally administered opioids or local anesthetics alone or in combination have been inconsistent. There have been reports of more profound and longer-lasting analgesia after use of local anesthetic and opioid combinations compared with administration of single agents, but significant benefits rarely have been observed.

Epidurally administered opioids have been effective in providing analgesia in clinical and experimental studies in veterinary medicine. To our knowledge, a direct clinical comparison of analgesic effects after administration of epidural opioids, local anesthetic agents, or their combination has not been reported. The purpose of the study reported here was to compare the analgesic effects induced by epidural administration of the local anesthetic agent bupivacaine hydrochloride (BUP), the opioid morphine (MOR), or a combination for postoperative pain relief in dogs.

**Materials and Methods**

**Dogs**—The study population included 41 healthy dogs admitted for elective orthopedic surgery involving the pelvis or hind limbs. Dogs with preexisting abnormalities of the lumbosacral space were excluded from the study. Dogs weighed > 20 kg and were between 9 months and 8 years old. Informed owner consent was obtained for each dog prior to admission into the study.

**Experimental protocol**—Medication was not administered before anesthetic induction. After catheterization of the cephalic vein, thiopental or propofol was administered to induce anesthesia and permit tracheal intubation. Isoflurane

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in oxygen was delivered via a circle breathing system to maintain anesthesia. If additional analgesia during the surgical procedure was necessary, 50% nitrous oxide was added to the isoflurane and oxygen mixture. Dogs were excluded from the study if they required opioid analgesics during surgery or if they needed inotropic or other vasodilatative drugs during the 24-hour study period.

Dogs were randomly assigned to 1 of 4 groups. Dogs in the first group were given 0.5% BUP\textsuperscript{a} at 1.0 ml/10-cm distance from the occipital protuberance to the lumberosacral space. Dogs in the second group received 1 mg/ml preservative-free morphine\textsuperscript{b} at a dosage of 0.1 mg/kg of body weight. Dogs in the third group received combination of MOR and BUP (COM) at individual component dosages, and dogs in the fourth group were given sterile 0.9% NaCl solution (SAL). To ensure a blinded study, calculated volumes were augmented with SAL to achieve a total injectate volume of 10 ml for each trial. Individuals performing epidural injections and study observers were unaware of which treatment was administered. The individual associated with treatment assignments did not participate in any aspect of data collection. Epidural injections were performed by PFIH and not from observations of surgical procedures, but before recovery from anesthesia. Each agent was injected into the lumberosacral epidural space while the dog was positioned in lateral recumbency with the surgical site in the most dependent position. All injections of study agents were made over a 60-second period, using a 20- or 22-gauge, 3.5-inch spinal needle.\textsuperscript{c} Needle location was confirmed by a lack of resistance to injection of 1.5 ml of air into the site. This technique has been described as an acceptable method for idiom of the epidural space.\textsuperscript{12,20,24} If correct needle placement could not be confirmed by this approach, location was evaluated fluoroscopically before administration of drug or control agent. After injections were completed, dogs were kept in the same position for 20 minutes before isoflurane anesthesia was discontinued. When the dogs had been exsanguinated and were able to remain unsupported in sternal recumbency, they were allowed to recover in a quiet ward under constant observation.

**Measurements**—After epidural injection of the agent, dogs were monitored for 24 hours by 3 trained observers. Each observer worked an 8-hour shift. Pain scores, assigned by use of a unidimensional scoring system, were recorded at 30-minute intervals.

The scoring system was based on observation of pain-associated behaviors including restless (failure to remain in a constant location during the observation period), positional shifting (recumbency change or change from recumbency to a sitting or standing position), vocalization not associated with environmental stimuli, vocalization associated with postural or positional changes, attention to the surgical incision site, and constant locomotion with unwillingness to assume recumbency. A pain score of 1 was assigned if none of the behaviors was observed. A pain score of 2 was assigned if positional changes (restlessness) were observed every 5 to 10 minutes (tracked by stopwatch) without other pain-associated behaviors. A pain score of 3 was assigned if 2 of the 3 variables represented by vocalization, attention to the surgical incision site, or postural change more than once in 5 minutes was observed. A pain score of 4 was assigned if constant vocalization or constant locomotion with unwillingness to assume recumbency was observed. Significant differences in scoring were not evident when results from observers were compared randomly during, and at the conclusion of, the study.

Any dog with a pain score > 2 received oxymorphone\textsuperscript{d} (0.1 mg/kg, IM or IV) for pain management. Dogs with a pain score of 3 received oxymorphone IM; dogs with a score of 4 received oxymorphone IV (up to a total of 4.0 mg of oxymorphone within a 1-hour period). Elapsed time from epidural injection of agent to administration of the first oxymorphone dose and the total number of oxymorphone doses required during the 24-hour period were recorded. If oxymorphone failed to reduce signs of pain within 15 minutes of IM injection or within 10 minutes of IV injection, acepromazine maleate (0.05 mg/kg, IV) was given (up to a total dose of 4.0 mg during the 24-hour study period) to achieve neuroleptanalgesia. Any dog with a heart rate < 60 beats/minute after administration of oxymorphone was given atropine (0.04 mg/kg, IM). Requirements for these adjunctive drugs were recorded.

Additional data collected during the 24-hour period included respiratory and heart rates and information pertaining to adverse drug effects. Respiratory and heart rates were recorded at 30-minute intervals beginning 30 minutes after epidural injection of the agent. Respiratory rate was determined by counting the number of thoracic excursions during a 60-second period. Heart rate was monitored by auscultation of heart sounds. Indirect blood pressure was monitored by use of oscillometry\textsuperscript{a} and recorded hourly. To minimize the effects of blood pressure cuff placement, the cuff was positioned and maintained over the brachial artery throughout the study period. In addition, elapsed time from when dogs received epidural injections to when they ate and drank, need for urinary bladder decompression by external assistance or catheterization, and any behavioral or physiologic changes (eg, prolonged paralysis, pruritus, or dysphoria) attributable to administration of study agents was recorded.

**Sample collection and analyses**—Before epidural injection of the study agent, a catheter was placed in the dog’s jugular vein for blood sample collection. Blood samples for cortisol, MOR, and BUP concentrations were drawn and placed into sodium EDTA tubes. Samples were collected immediately before epidural injection of agent and at 30 minutes, 1, 2, 4, 8, 12, 16, 20, and 24 hours after injection. Samples were kept at 0 C then centrifuged at 1,800 rpm and 4 C for 10 minutes. The supernatant was decanted, placed into appropriately sized tubes, and frozen at -70 C until analysis. Cortisol concentrations were measured by use of a commercially available radioimmunoassay kit\textsuperscript{a} validated for use in dogs as follows. Calibrator, control, and unknown samples were assayed in duplicate. Assay sensitivity was 1.0 ng/ml. Intra-assay coefficients of variation (and mean ± SD) among 3 canine serum pools measured 5 times in 1 assay were 7.8% (12.5 ± 1.0 ng/ml), 4.9% (33.5 ± 1.8 ng/ml), and 3.4% (113 ± 3.4 ng/ml). Interassay coefficients of variation (and mean ± SD) among 3 canine serum pools measured in 8 different assays were 9.2% (22.5 ± 2.1 ng/ml), 13.8% (32.6 ± 4.5 ng/ml), and 5.5% (117 ± 7.6 ng/ml). Dilutional parallelism was demonstrated by assaying 2 pools of canine serum at 3 volumes (10, 25, and 50 ml) and correcting the measured result for dilution. Corrected values for the first pool were 33.5 ± 1.8, 37.3 ± 1.1, and 30.4 ± 2.4 ng/ml. For the second pool, corrected values were 113 ± 3.4, 117 ± 3.8, and 123 ± 5.2 ng/ml. Recovery of cortisol (1,000, 500, 250, 125, and 62.5 ng/ml) added to canine serum was linear and quantitative (slope = 0.96; r\textsuperscript{2} = 0.997). Cortisol values obtained were compared with the reference range (0 to 50 ng/ml).

Plasma morphine concentrations were measured by high-performance liquid chromatography (HPLC) with electrochemical detection, after solid-phase extraction of MOR from plasma.\textsuperscript{25} The procedure used was a modification of that used by Todd et al.\textsuperscript{25} Assay sensitivity was 2.5 ng/ml. Plasma (0.4 ml) was mixed with 0.4 ml of borate buffer (0.1 N; pH 8.9) and added to an extraction column.\textsuperscript{a} After the sample moved onto the column, the column was eluted with 5.0 ml
of a chloroform and isopropanol solution (95:5). Eluate was collected in a 12-ml conical centrifuge tube and evaporated to dryness under a stream of nitrogen at 55 C. Residue was reconstituted in 200 µl of the mobile phase and analyzed by HPLC. The mobile phase consisted of 95% ammonium acetate buffer and 5% acetonitrile. The buffer was prepared by dissolving 3.85 g of ammonium acetate, 2.0 ml of acetic acid, and 2.0 ml of triethylamine in 1 l of aqueous solution. A 25-cm X 4.6-mm (internal diameter) C-18 reverse-phase column was used at a mobile phase flow rate of 1 ml/min. A glass carbon detector electrode was used at a potential of +0.75 V versus a silver/silver chloride reference electrode. Results were linear from 10 to at least 500 ng/ml. Calibration standards were prepared with each batch of samples, using 6 standards having a concentration range of 10 to 200 ng/ml. Day-to-day coefficients of variation and accuracy were less than ±15% of the measured concentration range.

Bupivacaine concentrations were determined by HPLC with UV detection after liquid extraction of BUP from plasma, by use of a procedure similar to that used for the determination of lidocaine concentrations.29 Assay sensitivity was 30 ng/ml. Lidocaine (20 µl, 100 µg/ml), used as an internal standard, was added to 1.0 ml of plasma, which was contained in a 16 X 125-mm disposable glass culture tube. The plasma was adjusted to pH 7 with 70 µl of NaOH (0.5 N). Methylene chloride (6 ml) was added, and the solution was mixed by use of a rotary mixer for 10 minutes. After centrifugation, the methylene-chloride layer was transferred to a 12-ml conical centrifuge tube and evaporated to dryness under a stream of nitrogen at 55 C. Residue was reconstituted in 200 µl of methanol and analyzed by HPLC. The HPLC column was a 25 x 4.6-mm (internal diameter) C-18 reverse-phase column used with a mobile phase as described for MOR analyses. Mobile phase flow rate was 1.4 ml/min. Detector wavelength was 230 nm. Results were linear from 50 to at least 2,000 ng/ml. Calibration standards were prepared with each batch of samples using 6 standards in the concentration range of 50 to 1,000 ng/ml. Day-to-day coefficients of variation and accuracy were less than ±15% of the measured concentration range. Chromatographic peak areas for MOR and BUP were measured with an electronic integrator. Bupivacaine and MOR were quantitated by comparison with sample peak areas of calibration standards. Bupivacaine and MOR calibration data were fit, using least-squares linear regression analysis. Correlation coefficients for calibration data were typically greater than 0.995.

Analyses of data—Comparisons of occipital protuberance to lumbar sacral space distances, age, and weight among groups were calculated by use of a general linear models procedure. Pain scores were analyzed, using a Kruskal-Wallis test. Time from epidural injection of study agent to administration of the first oxymorphone dose was evaluated by use of median survival analyses. Number of supplemental oxymorphone doses required for adequate analgesia was compared by use of ANOVA. Differences in pain score, time from epidural injection of agent to oxymorphone administration, number of oxymorphone doses required for analgesia, and cortisol concentrations were compared, using repeated measures ANOVA with 2-factor factorial analyses between treatment groups and surgical procedures. Differences in heart rate, respiratory rate, and blood pressure were evaluated by use of repeated measures ANOVA. Mean differences were compared, using Fisler's protected least significant difference method. Correlation analyses were performed to evaluate relationships between pain score and plasma drug concentrations, and between pain score and cortisol concentrations. Criterion for significance was P < 0.05. Statistical analyses were done by use of a commercial statistics software system.

### Table 1—Surgical procedures performed on 41 dogs receiving postoperative epidural administration of selected analgesics or a control agent

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Procedure</th>
<th>HP</th>
<th>CCL</th>
<th>TPO</th>
<th>TA</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUP (10)</td>
<td></td>
<td>1</td>
<td>3</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>MOR (10)</td>
<td></td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>COM (11)</td>
<td></td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>SAL (10)</td>
<td></td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

HP = hip prosthesis placement; CCL = caudal lumbar epidural injection of bupivacaine; TPO = triple pelvic osteotomy; TA = tarsal arthrodesis; BUP = bupivacaine; MOR = morphine; COM = bupivacaine and morphine; SAL = 0.5% NaCl solution.

### Results

**Demographic data**—Distribution of dogs included 10 dogs in the BUP, MOR, and SAL groups, and 11 in the COM group. Mean weight of the dogs was 33.4 kg (range, 23.0 to 55.7 kg). Mean distance from the occipital protuberance to the lumbar sacral space was 78.5 cm (range, 60 to 90 cm). Significant differences between groups of dogs in weight or occipital protuberance to the lumbar sacral space distances were not evident. Statistical interactions between surgical procedure and treatment group assignment were not identified (Table 1).

**Pain scores and oxymorphone requirements**—Pain scores were significantly lower for dogs in the COM group than in the MOR (P = 0.034) or SAL (P = 0.0021) groups, and significantly lower in the BUP group than in the SAL (P = 0.0137) group (Table 2). Overall pain scores between dogs in the BUP and the MOR groups were not significantly different. In addition, significant differences were not identified between dogs in the MOR and SAL groups, whose members had the highest pain scores. Type of surgical procedure did not affect pain scores.

Time from epidural injection of study agent to first required oxymorphone dose was significantly greater for dogs in the COM group than in the MOR (P = 0.032) or SAL (P = 0.008) groups (Table 2). Median time to initial oxymorphone dose for dogs in the COM group exceeded the 24-hour study period. Although time from epidural injection to initial required oxymorphone dose was longer for dogs in the BUP group than in the MOR or SAL groups, the difference was not significant. Time from epidural injection to first required oxymorphone dose did not differ between MOR and SAL dogs. Type of surgical procedure did not affect time to first required oxymorphone dose.

Total oxymorphone dose requirements were significantly lower for dogs in the BUP (P = 0.038) and COM (P = 0.007) groups than for dogs in the SAL group, whereas dose requirements in dogs receiving MOR did not differ from those receiving SAL. Only 3 of 11 dogs in the COM group required oxymorphone administration, whereas 6 of 10 dogs in the BUP group and 8 of 10 dogs in the MOR and SAL groups required oxymorphone supplementation during the trial.

Evaluation of supplemental oxymorphone dose requirements indicated differences between treatment groups (Table 2). Number of IM oxymorphone doses
Table 2—Dose requirements for oxymorphone and acepromazine maleate in dogs after postoperative epidural administration of selected analgesics or a control agent

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>No. of dogs requiring oxymorphone</th>
<th>Time to oxymorphone (h)</th>
<th>Intramuscular administration of oxymorphone (No. of doses)</th>
<th>Intravenous administration of oxymorphone (No. of doses)</th>
<th>No. of dogs requiring acepromazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUP (10)</td>
<td>2.29 ± 0.26&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6</td>
<td>9.1</td>
<td>3.0 ± 0.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0</td>
</tr>
<tr>
<td>MOR (10)</td>
<td>1.45 ± 0.26&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8</td>
<td>5.4</td>
<td>4.4 ± 0.8</td>
<td>0</td>
</tr>
<tr>
<td>COM (10)</td>
<td>1.18 ± 0.26&lt;sup&gt;c&lt;/sup&gt;</td>
<td>≥ 24&lt;sup&gt;0&lt;/sup&gt;&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6.7</td>
<td>0.7 ± 0.3</td>
<td>1</td>
</tr>
<tr>
<td>SAL (10)</td>
<td>1.54 ± 0.26&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8</td>
<td>2.6</td>
<td>0.5 ± 0.2</td>
<td>2</td>
</tr>
</tbody>
</table>

<sup>a</sup> Values reported are mean ± SEM. Values reported are median survival times.

<sup>b</sup> Values in the same column with like superscripts are significantly (P < 0.05) different.

<sup>c</sup> See Table 1 for key.

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**Figure 1**—Plasma cortisol concentrations (mean ± SEM) in dogs before (time 0) and after postoperative epidural administration of bupivacaine (○), morphine (●), the combination of morphine and bupivacaine (△), or NaCl solution (▲). Reference range for cortisol concentrations was 0 to 50 ng/ml.

**Figure 2**—Plasma morphine concentrations (mean ± SEM) in dogs after postoperative epidural administration of morphine (●) or the combination of morphine and bupivacaine (△).

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required to provide adequate analgesia in the 3 COM dogs was higher than in other treatment groups, and significantly different when compared with dogs in the BUP group (P = 0.038). Intramuscular dose requirements also were significantly higher in SAL dogs compared with BUP dogs (P = 0.011). Intramuscular dose requirements for dogs in the MOR group and other treatment groups did not differ. Dogs in the MOR group received more oxymorphone doses IV, compared with dogs in other treatment groups; however, differences were not significant.

Adjunctive drug requirements—Two dogs in the SAL group were given 1 dose of acepromazine, IV, after unsatisfactory analgesic response to oxymorphone administered IV: 1 dog 4 hours after epidural injection of agent, and 1 dog 10 hours after the epidural. One COM dog received a single dose of acepromazine, IV, 6 hours after epidural injection when the dog failed to respond to oxymorphone administered IV (Table 2). Atropine was required for treatment of bradycardia in 2 dogs in the MOR group (heart rates of 41 and 56 beats/min) and 2 in the SAL group (heart rates of 40 and 52 beats/min). Atropine administration resolved the bradycardia.

Cardiorespiratory data—Differences in heart rate, blood pressure, and respiratory rate were evident among groups at certain times; however, overall temporal differences were not observed. Cardiorespiratory indices remained within reference ranges in all dogs throughout the study period. Correlation analyses did not reveal interactions between pain score and heart rate, blood pressure, or respiratory rate measurements.

Plasma cortisol data—Plasma cortisol concentrations were high early in the study period, but were within reference ranges by 12 hours after injection of agent (Fig 1). Cortisol concentrations in dogs in all groups were 1.75 to 2 times greater than the maximum laboratory reference value (50 ng/ml) before epidural injection of agent. Dogs in the BUP group had higher cortisol concentrations than those in the COM (P = 0.031) or SAL (P = 0.043) groups before epidural injection of agent. After epidural injection of agent and...
recovery from anesthesia, plasma cortisol concentrations declined more rapidly in dogs in the COM and MOR groups than in dogs in other treatment groups. Two hours after epidural injection of agent, cortisol concentrations in dogs in the COM group were lower than in dogs in the SAL group (P = 0.046). Four hours after epidural injection of agent, dogs in the COM and MOR groups had significantly lower cortisol concentrations than did dogs in the BUP (P = 0.0017 and 0.0060, respectively) and SAL (P = 0.0114 and 0.0009, respectively) groups. Twelve hours after epidural injection of agent, dogs in the MOR group had lower cortisol concentrations than dogs in the SAL group (P = 0.035). Cortisol concentrations in dogs in the BUP group were higher than in dogs in the MOR (P = 0.031) or COM (P = 0.021) groups 16 hours after epidural injection. Examination of plasma cortisol concentrations revealed several important findings. First, although the aforementioned differences in cortisol concentrations existed, cortisol concentrations in all 4 treatment groups were within reference ranges by 8 hours after epidural injection of agents. Second, differences were not evident when cortisol concentrations in the 2 dogs in the SAL group that did not receive supplemental analgesics were compared with cortisol concentrations in dogs receiving analgesics during the study period. Correlations between cortisol concentration and pain score or between cortisol concentration and heart rate, respiratory rate, or blood pressure were not identified. Additionally, interactions between treatment groups and surgical procedures were not detected.

Plasma MOR concentrations declined from a mean value of 69.5 ng/ml (range, 15.6 to 154.2 ng/ml) at 30 minutes after epidural injection of agent to less than detectable values by 8 hours after injection (Fig 2). Plasma BUP concentrations in dogs declined from a mean value of 328 ng/ml (range, 80 to 786 ng/ml) at 30 minutes after epidural injection of agent to less than detectable concentrations by 4 hours after injection in the BUP group and 12 hours after injection in the COM group (Fig 3). Correlations between pain scores and plasma drug concentrations were not detected.

Dogs in the COM group ate or drank a mean of 5.5 hours after epidural injection of agent, compared with 10 hours for dogs in the BUP group, 10.8 hours for dogs in the MOR group, and 12.5 hours for dogs in the SAL group. One dog in the BUP group vomited after eating, but other adverse gastrointestinal effects were not observed. Fourteen percent of the dogs studied (2 dogs each in the MOR and COM groups, and 1 dog each in the BUP and SAL groups) received manual assistance after they failed to urinate voluntarily (despite distended urinary bladders) within 4 hours of recovery from anesthesia. Adverse effects attributable to epidural drug administration (eg, residual paralysis or delayed emergence from anesthesia) were not observed.

Discussion

Surgical pain in dogs has traditionally been managed using parenteral administration of opioid analgesic agents. Although parenterally administered opioids usually alleviate signs of pain, dosages required to relieve severe signs of surgical pain can be associated with adverse effects, including sedation, hyperresponsiveness to external stimuli, bradycardia, altered gastrointestinal motility, and respiratory depression. Epidural administration of analgesic agents, such as local anesthetics or opioids, has been reported to alleviate pain effectively in surgical patients without altering mentation or adversely affecting physiologic function. Bupivacaine and MOR were selected as the analgesic agents to be used in our study for several reasons. Bupivacaine is the local anesthetic agent of choice in human beings for providing long-term epidural analgesia with minimal motor blockade. The dosage used in this study was chosen on the basis of efficacy. Morphine was chosen on the basis of studies indicating relief of signs of pain after epidural administration in human beings and several other animal species. Morphine doses similar to those used in our study have been shown to provide long-term analgesia in dogs. Epidural administration of COM has been used often for pain management in human beings; however, duration and degree of analgesia after administration has been inconsistent. Investigations using rats and dogs have indicated superior analgesia after administration of COM, compared with the effects of BUP or MOR used alone.

Results of the study reported here indicated epidurally administered BUP or COM provided excellent analgesia; however, analgesic effects of epidural MOR were no better than SAL solution. An earlier report indicated effective analgesia was achieved after epidural administration of MOR (0.075 mg/kg) in dogs with surgically induced signs of pain. In contrast to that study, our study indicated postoperative administration of epidural MOR failed to provide adequate analgesia as evidenced by high pain scores, high oxyphrine dose requirements, and a short duration to supplemental oxygen administration.

Several possible reasons exist for the inconsistent results observed after MOR administration. In human beings, MOR has a long latency period after epidural injection with reported onset of analgesia between 20 and 60 minutes and peak analgesic activity between 40 and 90 minutes after administration. The long latency period of epidurally administered MOR can be attributed to the low lipid solubility of MOR with associated slow absorption into the neuraxis from the aqueous phase of the CSF. Although dogs in our study were maintained under general anesthesia for 20 minutes after epidural injection of agent, this time may not have been adequate for MOR absorption and binding to spinal opiate receptors. Inadequate pain relief has been reported in human beings when epidurally administered MOR has been given to relieve preexisting postoperative pain. Awareness of pain on recovery from anesthesia without adequate analgesia may have contributed to the high pain scores and subsequent high oxyphrine requirements noted in 8 of 10 dogs in the MOR group.

Inappropriate dosing also may have contributed to inadequate analgesia after epidural administration of MOR. Results of studies of human beings have con-
firmed a dose-response relationship between epidural administration of MOR and pain relief after surgical trauma. In a recent study, horses receiving MOR epidurally had a faster onset, longer duration, and greater degree of analgesia after high (0.1 mg/kg) dosages of MOR than after low (0.05 mg/kg) dosages. Unfortunately, dose-response relationships have not been defined for epidural administration of MOR in dogs. Although dosages similar to the one chosen for our study have successfully relieved signs of postthoracotomy and experimentally induced pain in dogs, clinical studies have not proven efficacy of MOR after orthopedic surgery at this dosage. A higher epidurally administered MOR dosage may be necessary for pain relief after orthopedic procedures in dogs.

Epidural administration of BUP provided analgesia superior to SAL solution as evidenced by lower pain scores and oxymorphone requirements for dogs in the BUP group compared with dogs in the SAL group. Duration of analgesia induced by epidural administration of BUP in our study exceeded that of earlier reports. Epidurally administered BUP provided 9 hours of analgesia compared with earlier reports indicating 90 minutes to 7 hours of relief of signs of pain. In human beings, BUP administration before surgery induced sensory blockade lasting 90 minutes to 7 hours, as assessed by pin prick and response to surgical stimulation. Mean time before additional postoperative pain medication requirement was 5.5 hours after BUP administration. In a recent study, duration of surgical anesthesia after administration of epidural 0.75% BUP (0.23 ml/kg) in conscious dogs was 90 minutes. In a study of sedated dogs, a similar dosage of epidurally administered BUP provided 4 to 6 hours of surgical anesthesia. Prolonged duration of pain relief after epidural administration of BUP in our study, compared with that in previous reports, could have been a result of differences in evaluation of signs of pain. In those studies, pain was assessed by monitoring responses to application of a noxious stimulus or ongoing surgical stimulation. In this study, pain relief was evaluated by monitoring pain-associated behaviors in dogs unchallenged by accessory stimuli.

As in other studies, COM provided profound, long-lasting pain relief evidenced by lower pain scores and longer duration of analgesia, compared with MOR or SAL solution. Eight of 11 dogs given COM maintained pain scores < 2 and did not require supplemental analgesics during the study period. Opioid enhancement of local anesthetic block may have contributed to the profound relief of signs of pain observed in our study. Several studies have described synergism between opioids and local anesthetics at different noxious points along spinal pathways. A recent report indicated that BUP increases binding of opioid agonists to spinal opiate receptors in spinal cord membrane preparations in rats. Another study of dogs revealed that intrathecal administration of opioids enhances sensory blockade produced by local anesthetic agents.

Dogs receiving epidurally administered SAL had higher pain scores and required more oxymorphone than dogs given COM. However, signs of pain were not evident in 2 dogs in the SAL group and, therefore, these dogs did not receive analgesics during the study period. Several reasons exist for the apparent lack of pain in these dogs. Individual differences in pain response have been documented in human beings, and similar differences are believed to exist in dogs. Stimulation could have contributed to the lack of pain response. A second explanation is related to the surgical procedure. On the basis of the investigators' clinical experiences, surgical procedures were chosen for the study reported here because they were associated with postoperative pain severe enough to warrant analgesic administration. Stifle arthrotopies for repair of ruptured cranial cruciate ligaments were performed on both dogs receiving SAL solutions and no analgesics. The degree of pain resulting from this procedure may be variable enough to cause a moderate-to-severe pain response in some dogs and a mild pain response in others. Evidence supporting this theory is the lack of significant increases in plasma cortisol concentrations in these 2 dogs, compared with dogs requiring analgesics.

In contrast to the 2 SAL solution-treated dogs that did not have signs of pain, 3 dogs in the COM group had unexpected signs of moderate-to-severe pain 6 hours into the study period. Several reasons exist for inadequate analgesia after epidural administration of COM. As discussed, individual differences in pain response or differences in the degree of surgical pain induced could have contributed to pain-associated behaviors in the 3 dogs. Insufficient drug doses also could have contributed to high requirements for oxymorphone; however, the dosage of BUP used provided excellent analgesia in dogs of earlier reports and in other dogs in our study. Inadequate response to the MOR component of the COM could have resulted in pain-associated behaviors. Evaluation of duration of pain relief in these dogs revealed a new of the COM dogs required the first dose of oxymorphone 8 and 10 hours after epidural injection. Duration of analgesia was similar to that of the BUP group, indicating the MOR component did not provide adequate pain relief after the effects of BUP dissipated.

Measurements of elapsed time from epidural injection of study agent to the first oxymorphone dose indicated a few dogs in each group required oxymorphone within the first hour after epidural injection: 1 dog in the COM group, 1 dog in the BUP group, and 2 dogs in the MOR group. Failure of epidural injection is the probable cause for inadequate pain relief in these dogs. A 12% failure rate has been reported after epidural drug administration in dogs and the failure rate in our study (4/41; 9.76%) was similar. Reasons for failure include inability to palpate anatomic landmarks and poor agent distribution after injection attributable to interference from fat, vascular engorgement, or bony structures.

Acepromazine was administered to 3 dogs after oxymorphone failed to control pain-associated behaviors. Distribution included 2 dogs in the SAL group and 1 in the COM group. In these dogs, a calming effect was observed for 2 to 3 hours after acepromazine administration. Oxymorphone was adequate to reduce subsequent pain-associated behaviors. Addition of a
tranquilizer to an opioid has been shown to enhance the analgesic effects of the opioid and induce a state of hypnosis and analgesia. It is difficult to determine whether dogs requiring acepromazine were in pain or were vocalizing as a result of oxymorphone-mediated dysphoric behavior. Although administration of the tranquilizer may have lead to altered behavioral and cardiorespiratory indices, the decision to administer the drug was made on the basis of a desire to alleviate what was viewed as pain-associated behavior resulting from inadequate regional or systemic analgesia. Cardiorespiratory indices have been used to monitor pain-associated stress response and to identify the need for supplemental analgesics. In the study reported here, heart rate, respiratory rate, and blood pressure measurements were monitored to determine whether a correlation between objective observations and intensity of pain existed, and to assess potential cardiorespiratory adverse effects resulting from drug administration. The investigators acknowledge variations in heart rate, blood pressure, and respiratory rate could have been attributable to concurrent oxymorphone administration rather than epidural administration of agents. Heart rates in all 4 groups were slightly higher at the beginning of the study period than at its conclusion. High heart rates early in the study period could have been associated with increased sympathetic response as dogs recovered from anesthesia. Heart rates in 4 dogs were classified as bradycardic (< 60 beats/min) and required atropine administration. Oxymorphone is reported to cause bradycardia in dogs. Three of the dogs requiring atropine had received oxymorphone in the hour preceding atropine administration. The fourth dog had not received oxymorphone, but had been given MOR epidurally. Plasma MOR concentrations were between 52.5 and 127.5 ng/ml at the time of atropine administration. Although it is possible that MOR contributed to the slow heart rate in the fourth dog, reductions in heart rate have not been observed after epidural administration of 0.1 mg/kg of MOR in halothane-anesthetized dogs.

Sympathetic ganglionic blockade and systemic hypotension associated with epidural administration of local anesthetics have been reported. Although blood pressure values varied throughout the study period in dogs in all treatment groups, they remained within a normal physiologic range. Hypotension after epidural administration of local anesthetic agents was not observed.

Variation in respiratory rates was evident throughout the study period, but significant differences did not exist between groups of dogs. Respiratory depression has been reported after epidural administration of MOR in human beings; however, respiratory depression has not been reported in dogs receiving MOR or COM epidurally. Respiratory depression also has been reported after systemic administration of opioids such as oxymorphone. Mean respiratory rate did not decrease to less than 12 breaths/min in any group of dogs during the study period. Although objective measurements of respiratory function were not made in the study reported here, profound bradypnea or signs of respiratory depression were not observed in dogs during the 24-hour study period.

Cortisol concentrations were measured to determine whether subjective analyses of pain, such as changes in heart rate, blood pressure, and pain scores, correlated with changes in cortisol concentrations. Studies of human beings have shown cortisol concentrations increase rapidly after anesthetic and surgical events such as intubation, hemorrhage, and surgical pain. Plasma cortisol concentrations return to reference values within 24 hours after mild-to-moderate surgical stress, but can remain high for longer periods after major surgical procedures. Regional application of local anesthetic agents and preemptive treatment with opioids have been shown to blunt cortisol stress responses in human beings. Postthoracotomy cortisol concentrations in dogs were lower after epidural administration of MOR than after IV administration of MOR. In another study of dogs undergoing hind limb surgery, differences in cortisol concentrations between dogs receiving MOR or SAL solution epidurally were not observed. Similarly, postoperative epidural administration of analgesic agents did not dampen initial increases in cortisol concentrations in our study. Trends in plasma cortisol concentrations were similar to those recorded for human beings after moderate surgical stress. Cortisol concentrations were high immediately after surgery, but declined to within reference range by 12 hours later, and remained there for the duration of the study period. High cortisol concentrations before epidural injection of the agent were likely a result of sympathetic activity associated with a light plane of anesthesia. Unexpectedly, preepidural cortisol concentrations in the BUP group were higher than in other treatment groups. Reasons for this difference are unclear but also could be related to a light plane of anesthesia at time of epidural administration of the agent. Statistical differences existed among groups at specific times during the latter part of the study period; however, all concentrations were within reference ranges and differences were not considered clinically important. Plasma cortisol concentrations in the 2 SAL dogs not receiving pain medication were not different from dogs given analgesics, indicating the 2 SAL dogs were not experiencing enough pain to cause increases in circulating cortisol concentrations, or that measurement of plasma cortisol concentrations is not a sensitive method of assessing pain in dogs. It was hypothesized that differences in plasma cortisol concentrations could provide an objective means of comparing analgesic techniques and drugs; however, because cortisol concentrations declined in a similar manner in dogs in all groups, it was not possible to determine usefulness of cortisol measurement as a method of pain evaluation.

Plasma MOR concentrations were measured to determine whether they correlated with degree and duration of apparent pain relief. Morphine has been detected in plasma within minutes after epidural injection. Plasma concentrations measured after administration of epidural MOR in our study are similar to those reported for anesthetized dogs. In that study, peak serum concentrations measured 30 minutes after epidural administration of 0.1 mg/kg of MOR were similar to those obtained in our study. Serum concentrations in that study markedly decreased by the end
of the study period, but were still detectable. In the study reported here, peak MOR concentrations were determined at the initial sampling time (30 minutes) after epidural injection. Thereafter, plasma concentrations rapidly declined and were not detectable 8 hours later. This trend was consistently observed in dogs receiving MOR and COM; therefore, the investigators believe the rapid increase in plasma MOR concentrations resulted from rapid absorption of MOR from the epidural space into the vascular compartment as reported in other studies. Studies in human beings indicate vascular absorption may account for a portion of the analgesic effects observed after epidural administration of MOR. Absorption of MOR early in the study period could have contributed to analgesia as supported by the median time to requirement of the first dose of supplemental analgesic (5.4 hours) for dogs in the MOR group. However, correlations between pain scores and plasma MOR concentrations were not observed, indicating systemic MOR concentration is not the sole factor contributing to analgesia after epidural administration.

Plasma BUP concentrations were monitored to determine disposition after epidural injection. Peak plasma concentrations were observed at the first sampling time (30 minutes) after injection. Although the concentration at that time was less that that measured after administration of IV dosages known to produce seizures (18 μg/ml) and cardiovascular collapse (70 μg/ml) in dogs, earlier and more frequent sampling could have provided a better indication of peak BUP concentrations.

Plasma BUP concentrations declined similarly in both groups receiving BUP. Twelve hours after epidural administration, BUP was not detectable in plasma.

Adverse effects that could have been attributed to epidural administration of drugs were recorded. Six dogs required manual expression of distended urinary bladders after voluntary urination was not observed during a 4-hour period after epidural administration of drug. All treatment groups were represented: 1 dog each in the BUP and SAL groups, 2 dogs in the MOR group, and 2 dogs in the COM group. In each dog, manual bladder compression caused voiding. Urinary retention secondary to increased sphincter tone after spinal administration of opioid in human beings can be severe enough to require urinary catheterization. Opioid-induced urinary retention can develop after epidural injection or other parenteral administration and is believed to be caused by interference with parasympathetic function at the spinal cord level leading to diminished detrusor muscle function. Autonomic control of the urinary bladder also is lost after epidural administration of local anesthetic and can lead to urinary retention. Although the 2 dogs in the COM group had not received supplemental analgesics, each dog in the other treatment groups had been given systemic oxymorphone before bladder expression was required. Systemic effects of the opioid may have contributed to the bladder distention observed in these dogs.

Dogs in the COM group were interested in eating and drinking more than 5 hours earlier than dogs in the other treatment groups. Rapid return to adequate nutritional intake after major surgery is beneficial to prevent protein catabolism and to maintain positive nitrogen balance. Additional advantages of early return to voluntary alimentation include earlier withdrawal of IV fluids and more rapid return of normal gastrointestinal activity. Early return to alimentation by dogs in the COM group could have been a result of regional analgesia afforded by agents administered epidurally, whereas longer times in the other treatment groups could have been associated with the sedative effects of systemic oxymorphone.

Accurate and consistent assessments of pain in animals can be difficult to achieve. Veterinary care providers must rely on methods similar to those used in pediatric human medicine to assess pain. These methods include pain scoring systems that rely on subjective observations of responses to pain-inducing stimuli and objective measurements such as changes in heart and respiratory rates and increases in blood pressure and plasma cortisol concentrations. Although pain scoring is based on individual interpretation and may vary between observers, this type of analysis has been used successfully to evaluate and manage pain in human pediatric and veterinary patients. A simple numerical pain scale was chosen in this study for subjective analyses of pain intensity. Observers were trained to respond to specific behaviors associated with surgical pain including vocalization, restlessness, and attention to the surgical site. Use of this pain scale was deemed successful in that administration of analgesics stopped or greatly diminished behaviors associated with pain. The investigators acknowledge the existence of confounding factors that could elicit responses misinterpreted as signs of pain. Stress conditions, including the need to urinate or defecate, cage fear, or lack of human companionship, can cause vocalization and restlessness that may be misinterpreted as nociception. As mentioned previously, not all dogs display obvious physical responses to pain. Lack of signs of pain in stotic dogs can lead to deceptively low pain scores and inadequate administration of analgesic agents. Despite potential limitations, the pain scoring method used in this study appeared to work well, as indicated by significant differences in pain scores and supplemental analgesic requirements among the study groups.

Epidural administration of MOR is commonly used at this institution before or after surgery to provide analgesia; however, its efficacy when applied after orthopedic surgery in our study was disappointing. Higher MOR dosages or epidural administration of MOR preoperatively may offer better analgesia. Bupivacaine and COM provided adequate epidural analgesia, with COM inducing the most profound, long-lasting effects. The study reported here indicated COM induced a high degree of analgesia for management of clinically-apparent pain resulting from hind limb and pelvic orthopedic surgery in dogs. Postoperative administration of BUP also induced a high degree of analgesia, but for a shorter time. Postsurgical epidural administration of MOR was not effective in inducing adequate analgesia at a dosage of 0.1 mg/kg.

References


40. Chapman CR, Turner JA. Psychologic and psychosocial as-


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**Book Review:**


The book is divided into six sections, each of which contain a number of short chapters on specific topics. The sections are Basics of Nutrition, Nutrient Requirements of Dogs and Cats, Pet Foods, Feeding Management Throughout the Life Cycle, Feeding Practices: Problems, Fads, and Fallacies, and Nutritionally Responsive Disorders. At the end of each section is a summary of the key points and a list of references. A glossary of nutritional terms and appendices on nutritional profiles, standard weights of various breeds, and feeding guidelines are presented at the end of the book. This reviewer would have personally preferred that the references be placed at the end of each chapter, rather than at the end of each section.

The authors have presented the information such that readers without extensive training in nutrition can best appreciate some of the complexities of the discipline. Efforts have been made to document scientific arguments with references to actual studies or investigations. In some cases, however, citations represent a specific author's opinion, rather than the result of a study. Difficulty will arise, because many readers will not be able to distinguish between statements of opinion versus statements based on facts. In general, however, the authors have done a credible job in their attempt to present sound nutritional information for the target audience on the basis of available literature.

The first sections on general nutritional principles, nutrient requirements, and feeding management are presented thoroughly. The section on pet food contains up-to-date information on the commercial pet food industry. This section is of interest and should be well received, because two of the authors are employed by a pet food company. Some of the chapters in subsequent sections are treated less thoroughly. The section on nutritionally responsive disorders (ie, diet-disease interaction) and fads and fallacies seems to be decided brief, perhaps in an effort to appeal to the broad-based target audience at which the book is aimed.

In summary, the book serves as a useful introduction to the myriad facets of companion animal nutrition. When used for its intended purpose as an applied reference book for companion animal professionals, readers may find themselves regularly using the book.

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