Neutering surgeries are the most commonly performed surgeries in veterinary hospitals in the United States. Castration and ovariohysterectomy are likely causes of pain in animals. To the authors’ knowledge, few recent studies have been reported regarding use of analgesic drugs in animals undergoing neutering in the United States; however, on the basis of the authors’ experience and results of studies conducted in other countries, analgesic protocols for such animals may be inadequate. Results of another study indicate a common reason that veterinarians do not administer analgesics to patients undergoing surgery is a belief that owners will not pay for such treatments. However, one of the most inexpensive classes of analgesic drugs, local anesthetics, are underused.

Effects of intratesticular injection of bupivacaine and epidural administration of morphine in dogs undergoing castration

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Objective—To determine the intraoperative and postoperative analgesic efficacy of intratesticular or epidural injection of analgesics for dogs undergoing castration.

Design—Randomized controlled trial.

Animals—51 healthy male dogs.

Procedures—Dogs were assigned to a control group that received analgesics systemically (hydromorphone [0.1 mg/kg [0.045 mg/lb], IM] and carprofen [4.4 mg/kg [2.0 mg/lb], SC]; n = 17), an epidural treatment group that received analgesics systemically and morphine (0.1 mg/kg [0.045 mg/lb]) epidurally (17), or an intratesticular treatment group that received analgesics systemically and bupivacaine (0.5 mg/kg [0.23 mg/lb/testis]) intratesticularly (17). Dogs were anesthetized and castrated by veterinary students. Responses to surgical stimulation were monitored intraoperatively, and treatments were administered as required. Pain scores were assigned via a modified Glasgow composite pain scale after surgery. Serum cortisol concentrations were determined at various times. Rescue analgesia included fentanyl (intraoperatively) and hydromorphone (postoperatively).

Results—Compared with control dogs, dogs in the intratesticular bupivacaine and epidural morphine treatment groups received significantly fewer doses of fentanyl intraoperatively (11, 1, and 5 doses, respectively) and hydromorphone postoperatively (14, 7, and 3 doses, respectively) and had significantly lower postoperative pain scores (mean ± SEM score at first assessment time, 7.1 ± 0.5, 4.8 ± 0.2, and 4.5 ± 0.4, respectively). At 15 minutes after removal of the testes, serum cortisol concentrations were significantly higher than they were immediately prior to surgery for all groups and values for the intratesticular bupivacaine treatment group were significantly lower versus the other 2 groups.


Abbreviations

ETCO2 End-tidal carbon dioxide
ETISO End-tidal isoflurane
SpO2 Saturation of hemoglobin with oxygen as measured via pulse oximetry
TID Time of intraoperative physiologic data determination
TPP Time of postoperative pain assessment

Local and regional administration of analgesic drugs is a commonly used technique in human patients for treatment of pain caused by various procedures. Such analgesic techniques include administration of opioids and local anesthetic drugs in the epidural space and injection of local anesthetic drugs in surgical sites or near nerves. For humans and other animals, multimodal analgesia (eg, local and regional administration of analgesic drugs in addition to systemic administration of such drugs) may improve analgesia versus systemic administration of analgesic drugs alone. Beneficial effects of multimodal analgesia that includes local and regional administration of drugs have been
studied extensively for dogs undergoing orthopedic procedures, but the effects of such techniques in dogs undergoing soft tissue procedures, such as castration, have only recently been evaluated and comparative effects of different techniques (eg, intratesticular local anesthesia and epidural analgesia) have not been evaluated in a single study. Results of other studies including animals other than dogs suggest that local and regional administration of local anesthetic drugs provides moderate to high levels of analgesia for humans and other animals undergoing castration or other types of testicular surgery. Human males undergoing testicular surgery for whom a local anesthetic drug (bupivacaine) is injected in the spermatic cord have less pain versus such patients receiving systemically administered opioids and NSAIDs alone. Intratesticular injection of lidocaine before castration of anesthetized horses improves analgesia versus that of control horses undergoing castration without receiving that treatment. Similarly, local anesthesia relieves signs of pain for pigs, calves, and lambs undergoing castration. Although epidural administration of analgesic drugs is not commonly used for dogs undergoing castration, epidural administration of such drugs has been used for cattle and alpacas undergoing castration and humans undergoing other types of testicular surgeries. Therefore, use of such analgesic techniques may be appropriate for dogs undergoing castration. Results of a recent study indicate epidural administration of lidocaine (with or without opioid drugs) induces adequate analgesia for castration of dogs. Other advantages of local and regional administration of analgesic drugs for anesthetized human patients include decreased incidence of stress-induced complications (eg, development of cardiac dysrhythmias and ischemia) and an ability to maintain a light plane of anesthesia, which results in a faster recovery from anesthesia.

The objective of the study reported here was to determine and compare the intraoperative and postoperative analgesic efficacy of analgesic drugs injected in the epidural space in combination with systemic administration of opioid drugs and NSAIDs for healthy male dogs undergoing castration. Our hypothesis was that epidural administration of analgesic drugs would improve perioperative analgesia for dogs versus that of systemic administration of opioids and NSAIDs alone.

**Materials and Methods**

**Animals**—Fifty-one healthy male dogs admitted to the Washington State University College of Veterinary Medicine Veterinary Teaching Hospital for routine castration were enrolled in this study. Dogs included in the study were 4 months to 4 years old, weighed 4.5 kg (9.8 lb) or greater, and were not receiving any medications at the time of admission. All dogs included in the study were determined to be healthy on the basis of results of physical examinations and PCV and serum total protein concentration analyses. Dogs with dangerously aggressive or excessively fearful behavior were excluded from the study to prevent injury to personnel handling the dogs during postoperative assessments. Dogs that had conditions (eg, lumbosacral skin disease) that precluded epidural administration of drugs were also excluded from the study. Dogs that underwent castration surgeries > 3 hours in duration or that had major surgical complications (as determined by the anesthesiologist on duty) were eliminated from the study. All dogs enrolled in the study were brought to the hospital for castration by personnel of a local animal shelter, and permission was granted by shelter administrators for inclusion of the dogs in the study.

**Anesthesia**—All dogs were anesthetized by use of standard clinical protocols. Food was withheld from dogs overnight (approx 8 hours), but water was not withheld. Carprofen (4.4 mg/kg [2.0 mg/lb], SC) was administered to dogs before surgery. Acepromazine (0.02 mg/kg [0.009 mg/lb]) and hydromorphone (0.1 mg/kg [0.045 mg/lb]) were combined in the same syringe and administered IM to dogs. Approximately 20 minutes after administration of acepromazine and hydromorphone, dogs were placed on an examination table, hair was clipped from skin superficial to the right or left cephalic vein, and that area was aseptically prepared by a veterinary student anesthetist. A 20-gauge, 2.75-cm catheter was percutaneously placed into the right or left cephalic vein of each dog, flushed with heparinized saline (0.9% NaCl) solution, and secured with tape. Propofol was administered to effect (dose range, 3.4 to 5.5 mg/kg [1.5 to 2.5 mg/lb]) IV through the catheter until the anesthetic depth of dogs allowed endotracheal intubation. For each dog, auffed endotracheal tube of an appropriate size was orotracheally placed and secured to the maxilla. The endotracheal tube was connected to a rebreathing system attached to an anesthetic machine intended for use with small animals. Oxygen was delivered through the endotracheal tube via the rebreathing system, the endotracheal tube cuff was inflated, and isoflurane administration was started. The isoflurane vaporizer was set at a dial setting of 3% to 4% with an oxygen flow rate of 2 L/min for the first 5 to 15 minutes of anesthesia. Then, the vaporizer dial setting was decreased to between 1.5% and 2% to maintain a light plane of anesthesia during preparation of dogs for surgery. Oxygen flow rates were approximately 20 to 40 mL/kg/min (9.1 to 18.2 mL/lb/min); a minimum of 300 mL of oxygen/min was delivered to each dog during anesthesia. Dogs were allowed to breathe spontaneously during anesthesia. After dogs were moved to the operating room, a sampling tube was attached to a port on a connector between the endotracheal tube and the rebreathing system for side-stream measurement of ETiso concentration, which was started at 1.0 times the minimum alveolar concentration (approx 1.3% ETiso concentration) and then adjusted as needed to maintain a light surgical plane of anesthesia. The ETiso concentration was decreased by 10% to 20% when dogs lacked a response to surgical stimulation; when dogs responded to surgical stimulation, additional anesthetic or analgesic drugs were administered.

After induction of anesthesia, a 20- or 22-gauge 2.75-cm catheter was percutaneously placed by use of aseptic technique in a right or left dorsal pedal artery for direct measurement of arterial blood pressures. A calibrated blood pressure transducer was placed at the level of the right atrium of the heart and zeroed to atmospheric pressure. Electrocardiogram leads were placed for monitoring of a lead II trace, a pulse ox-
imeter probe was placed on the tongue for measurement
of SpO2, and a temperature measurement probe was placed in the esophagus. Airway gas samples for
determination of ETCO2 concentrations were obtained
via the same tube that was used for measurement of
ETiso concentrations. Variables were measured with
the same monitor that was used to measure ETiso con-
centrations. The monitor was automatically calibrated
to room air daily for measurement of ETCO2, concentra-
tions. Monitors had been calibrated for measurement
of ETiso concentrations at the time they were installed
several months prior to the study; the manufacturer’s
instructions indicated that the monitors required calibra-
tion only once per year. Anesthetists manually deter-
mined heart and respiratory rates, mucous membrane
color, and capillary refill time every minutes. All dogs
received lactated Ringer’s solutionb during anesthesia
(20 mL/kg, IV, during the first hour of anesthesia and
10 mL/kg [4.5 mg/lb], IV, during the subsequent period
of anesthesia).

Intratesticular and epidural injection of analgesic
drugs—Dogs were assigned to 1 of 3 treatment groups
(17 dogs/group) via a randomization procedure by use
of time stamps on anesthesia admissions forms. Treat-
ment groups included dogs that did not receive intra-
testicularly injected or epidurally administered analge-
sic drugs (control group), dogs that received epidural
administered preservative-free morphine (0.1 mg/kg;
epidural morphine group), and dogs that received in-
tratesticularly injected bupivacaine (1 mg/kg [0.45 mg/ lb] divided equally between the 2 testes; intratesticular
bupivacaine group). Intratesticular injection or epi-
dural administration of analgesic drugs was performed
immediately after induction of anesthesia. For epidural administration of morphine, dogs were positioned in sternal recumbency; hair was clipped from an area of skin (8 × 8 cm) dorsal to the lumbosa-
cral vertebral articulation, and that area was aseptically
prepared. A 20-gauge 5.5-cm epidural needle was in-
serted through the skin, the stylet was removed, and
a drop of saline solution was placed in the hub of the
needle. The needle was slowly advanced into the lum-
boSacral epidural space until the saline solution was as-
pired into the space (ie, hanging drop technique) or
until the needle penetrated the ligamenta flava. Proper
placement of the needle in the epidural space was con-
firmed when little resistance was felt during injection
of saline solution. Following confirmation of proper
placement of the needle in the epidural space and the needle was with-
drawn. Positioning of animals after epidural injection
of opioid drugs alone is not as important as when local
anesthetic drugs are used; therefore, dogs were imme-
diately positioned in dorsal recumbency. For intrates-
ticular injection of bupivacaine, scrotal skin was asepti-
cally prepared and bupivacaine was injected by use of a
22-gauge, 2.2-cm needle directly into the parenchyma of
each testis after aspiration to confirm that the needle
was not in a blood vessel.

To decrease confounding of results attributable to
injection of fluid into the epidural space or testes and
to ensure personnel assessing severity of pain were un-
aware of treatments dogs had received, dogs that did not receive preservative-free morphine in the epidural
space (control and intratesticular bupivacaine group
dogs) received an equivalent volume of saline solution
that was administered epidurally via the same method
and dogs that did not receive intratestically injected
bupivacaine (control and epidural morphine group
dogs) received an equivalent volume of saline solution
that was injected in the testes via the same method.

Surgery and intraoperative pain assessments and
treatments—All dogs were castrated by veterinary stu-
dents who were supervised by faculty surgeons or sur-
gery residents. Castrations were performed by use of a
standard prescrotal approach.27

When a noxious stimulus (ie, surgical stimulation)
resulted in a heart rate, respiratory rate, or mean arterial
blood pressure ≥ 20% higher than the baseline (Tmax = 0
minutes) value, dogs received additional anesthetic or
analgesic drugs. These criteria were determined on the
basis of clinical experience of the investigators and pub-
lished guidelines. Dogs with a 20% increase in values
of any of those variables received fentanyl (2 µg/kg [0.9
µg/lb], IV). Alternately for dogs that seemed to have in-
adquate anesthetic depth, the isoflurane vaporizer dial
setting was increased so that the ETiso concentration
increased by 10% to 20%. The number of times addi-
tional analgesic or anesthetic drugs were administered
to dogs was not limited and was determined only on the
basis of values of physiologic variables and assessment
of anesthetic depth. The number of such treatments for
each dog was recorded, and data were statistically ana-
lyzed. The time required for intratesticular injection
of bupivacaine, time required for epidural administration
of morphine, time from completion of intratesticular or
epidural injection of drugs to the start of surgery, times at
which intraoperative rescue analgesia (ie, fentanyl) was
administered, and duration of surgery were recorded.

Postoperative care and assessment and treatment
of pain—Following completion of the surgical proce-
dure, anesthesia was discontinued and dogs were moved
to a recovery area. Dogs were extubated when spontane-
ous swallowing was observed. Dogs were warmed with
an external warming device until rectal temperature was
≥ 37.78°C (100°F). After dogs were determined to be in
stable condition, they were placed in a holding cage in
the anesthesia recovery area for observation during the
remainder of the postoperative period of the study. Af-
ter the postoperative study period ended, catheters were
removed and dogs were moved to hospital kennels. Pain
scores were determined by use of a modified composite
Glasgow pain scale (short form).28 Because ambulation
was not possible for all dogs immediately after anesthe-
tia, the portion of that form that required walking of dogs
outside kennels (ie, section B) was not completed so that
all dogs were evaluated by means of the same criteria.
The section of the form that required observation of dogs
in kennels was used to observe dogs without handling
in various locations because dogs were not always in a
kennel at the times pain scores were determined. Each
dog was evaluated via the modified composite Glasgow pain scale when it could first voluntarily raise its head or when it first responded to palpation of the incision (TPP = 0 hours) and 1 (TPP = 1 hour) and 4 (TPP = 4 hours) hours following that initial assessment. Each dog was evaluated via the modified composite Glasgow pain scale by an observer (TEP) who was unaware of the treatment group of the dog. At each postoperative pain assessment time, dogs with a modified composite Glasgow pain scale score of ≥ 5 received postoperative rescue analgesia (hydromorphone [0.1 mg/kg, IV]). The number of doses of hydromorphone administered and the time at which postoperative rescue analgesia (hydromorphone) was administered to dogs were recorded and data were analyzed statistically. Dogs that received hydromorphone were reassessed within 10 minutes after administration of the drug; if analgesia of a dog was inadequate at that time (on the basis of a pain score that remained > 5 despite treatment), the dog received dexmedetomidine (2 µg/kg, IV) and was removed from the study. Adverse effects that were potentially attributable to intratesticular or epidural injection of drugs (ie, local tissue reactions [attributable to bupivacaine or morphine injection], cardiovascular or neurologic effects [attributable to bupivacaine injection], and failure to urinate following surgery [attributable to epidurally administered morphine]) were recorded.

Physiologic data and blood sample collection—Although data were collected every 5 minutes during anesthesia, times at which dogs were transported to and from operating rooms varied among dogs. Therefore, physiologic data of dogs were analyzed for standardized times. Physiologic data collection was started 15 minutes prior to the start of surgery (T0 = 0 minutes [this time coincided with the start of draping]; time of the start of surgery was the time that skin incision was started) and continued every 5 minutes for 45 minutes after that time (Tpp = 5 to 45 minutes). Heart rate, respiratory rate, arterial blood pressures (systolic, mean, and diastolic), SpO2, esophageal temperature, ETiso concentration, ETco2 concentration, and data regarding responses of dogs to the surgical stimulus were recorded for each of those times. Heart rate, respiratory rate, and pain scores were recorded at Tpp = 0, 1, and 4 hours. A blood sample (2 mL) was collected from the IV catheter of each dog immediately prior to the start of surgery (baseline), 15 minutes after both tests had been removed, and at 1 and 4 hours after extubation for determination of serum cortisol concentrations. Blood samples were placed into tubes with no additives and immediately refrigerated (approx 4°C). Within 4 hours after collection, serum was separated by use of a high-speed centrifuge and frozen at −20°C. Serum samples were shipped on ice to a laboratory for performance of cortisol assays within 30 days after collection.

Cortisol assay—Serum cortisol analysis was performed by personnel at a commercial laboratory at Michigan State University College of Veterinary Medicine by use of a solid-phase radioimmunoassay procedure in which iodine 125 (125I)-labeled cortisol competed with cortisol in a serum sample for binding to antibodies immobilized on the surface of a polypropylene assay tube. Supernatant was decanted, and radiolabeled cortisol was quantified with a gamma radiation counter. Assay data were converted to serum cortisol concentrations (in nmol/L) by use of a calibration curve.

Statistical analysis—Normality of errors of data for all dogs combined was determined via the Shapiro-Wilk test. Variables with a parametric distribution of data were analyzed via repeated-measures ANOVA with a Bonferroni post hoc test. Data for number of doses of opioids administered intraoperatively and postoperatively (ie, rescue analgesia) were nonparametrically distributed and were analyzed with the Kruskal-Wallis test. Numbers of dogs that received intraoperative and postoperative rescue analgesia in each group were analyzed via the Fisher exact test. For all data, a P value of < 0.05 was considered significant. Data analyses were performed with statistical software.

### Results

Mean ± SEM weight, age, anesthesia duration, surgery duration, time from completion of intratesticular or epidural injection of analgesic drugs to the start of surgery, and ETiso concentration (pooled data for all times) for each group of dogs were summarized (Table 1). No

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Epidural morphine</th>
<th>Intratesticular bupivacaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>21 ± 8</td>
<td>23 ± 11</td>
<td>21 ± 9</td>
</tr>
<tr>
<td>Age (mo)</td>
<td>12 ± 8</td>
<td>16 ± 10*</td>
<td>16 ± 12*</td>
</tr>
<tr>
<td>Anesthesia duration (min)*</td>
<td>85 ± 32 (50–145)</td>
<td>86 ± 18 (55–110)</td>
<td>81 ± 13 (65–115)</td>
</tr>
<tr>
<td>Surgery duration (min)†</td>
<td>44 ± 19 (20–75)</td>
<td>41 ± 11 (30–70)</td>
<td>40 ± 11 (25–70)</td>
</tr>
<tr>
<td>Time from epidural and intratesticular injection to surgery (min)‡</td>
<td>31 ± 6 (15–40)</td>
<td>39 ± 11 (20–60)</td>
<td>28 ± 7 (15–40)</td>
</tr>
<tr>
<td>ETiso concentration (%)</td>
<td>1.19 ± 0.02</td>
<td>1.10 ± 0.02*</td>
<td>1.03 ± 0.02*</td>
</tr>
</tbody>
</table>

Data are mean ± SEM values unless stated otherwise.

*Value is significantly (< 0.05) different from the value for the control group. †Data are mean ± SEM (range) values. ‡Dogs that did not receive morphine epidurally (control and intratesticular bupivacaine group dogs) received an equivalent volume of saline (0.9% NaCl) solution that was administered epidurally via the same method and dogs that did not receive bupivacaine intratesticularly (control and epidural morphine group dogs) received an equivalent volume of saline solution that was injected in the testes via the same method.
significant differences were detected among treatment groups regarding weights of dogs or duration of surgeries. Dogs in the control group were significantly younger than dogs in the epidural morphine or intratesticular bupivacaine groups. Although not all surgical procedures for dogs were completed before the last data collection time during surgery (TID = 45 minutes), both testes had been removed for all dogs before that time (which we considered the portion of the procedure likely to cause the most pain). Although surgeries for some dogs were completed prior to TID of 45 minutes, data for an adequate number of dogs (14 control group, 15 intratesticular bupivacaine group, and 16 epidural morphine group dogs) were available for that time for performance of statistical comparisons.

The ETiso concentrations were significantly different among groups of dogs, but values within each group were not significantly different among data collection times. No significant differences in heart rates, respiratory rates; mean, systolic, or diastolic arterial blood pressures; \( \text{SpO}_2 \); or \( \text{ETCO}_2 \) concentrations during anesthesia were detected among groups of dogs, and values of these variables were considered clinically normal for anesthetized dogs. Mean arterial blood pressure for control group dogs was significantly higher at TID of 25 minutes than it was before that time. No significant differences in heart or respiratory rates were detected among groups of dogs at any postoperative assessment time or among postoperative assessment times for any of the groups.

The number of doses of opioid drugs administered to epidural morphine and intratesticular bupivacaine group dogs intraoperatively (lentamyl) and postoperatively (hydromorphone) were significantly lower than the number of doses administered to control group dogs (Figure 1). The number of dogs that received intraoperative rescue analgesia (fentanyl) was significantly different among groups of dogs; 8 of 17, 5 of 17, and 1 of 17 dogs in the control, epidural morphine, and intratesticular bupivacaine groups, respectively. Each of the dogs in the intratesticular bupivacaine and epidural morphine groups received fentanyl during the intraoperative period, respectively. Each of the dogs in the intratesticular bupivacaine and epidural morphine groups received fentanyl doses administered to control group dogs (3 dogs received 2 doses). Most (11/17) fentanyl doses were administered from TID of 25 minutes to TID of 35 minutes (which was typically the time during which clamps were first applied to a spermatic cord during the procedure). Most (19/24 [79%]) hydromorphone doses administered to dogs were administered at TID = 0 hours.

Pain scores at TID = 0 and 1 hour were significantly higher for control group dogs than they were for intratesticular bupivacaine and epidural morphine group dogs (Figure 2). For each group of dogs, pain scores were significantly lower at TID = 1 and 4 hours than they were at TID = 0 hours. Mean pain score for the control group at TID = 4 hours was significantly lower than the pain score for that group at TID = 1 hour. The number of dogs that received postoperative rescue analgesia (hydromorphone) was significantly different among groups of dogs; 14 of 17, 3 of 17, and 7 of 17 dogs in the control, epidural morphine, and intratesticular bupivacaine groups received hydromorphone during the postoperative period, respectively. One dog in the control group had severe signs of pain postoperatively and was treated with both hydromorphone and dexmedetomidine. Data for this dog were included in statistic-
al comparisons of data collected intraoperatively but were excluded from analyses of data collected postoperatively. None of the other dogs were treated with dexmedetomidine postoperatively.

The interassay and intra-assay coefficients of variation for the serum cortisol assay were 8% and 3%, respectively. The serum cortisol concentrations had a wide range of values. Serum cortisol concentrations for each group of dogs were summarized (Figure 3). Serum cortisol concentrations in samples obtained 15 minutes after both testes had been removed were significantly lower for the intratesticular bupivacaine group than they were for the control group. Serum cortisol concentrations for the control group were significantly higher in samples obtained 15 minutes after both testes had been removed than they were at any other time.

The mean ± SEM time for intratesticular injection of bupivacaine by the veterinary students was 0.8 ± 0.5 minutes. The mean ± SEM time for epidural administration of morphine was 2.8 ± 1.5 minutes. These data were not statistically analyzed.

Discussion

Results of the present study indicated that intratesticular injection of bupivacaine or epidural administration of preservative-free morphine augmented the analgesia induced by systemically administered hydrocortisone and carprofen in dogs undergoing castration. Dogs with intratesticularly or epidurally administered analgesic drugs received significantly fewer opioid drugs during and after surgery and had lower pain scores after surgery versus control dogs that did not receive those treatments. Small differences in values of these variables between the intratesticular bupivacaine and epidural morphine groups were detected; these values were not significantly different and were likely attributable to differences in times of onset and duration of action of analgesic drugs administered to dogs in those groups. Few differences were detected among groups at each time or among times within each group regarding values of physiologic variables, which was not surprising because depth of anesthesia was carefully controlled and dogs with signs of pain were immediately treated. Cortisol concentrations in serum samples obtained 15 minutes after removal of the testes were significantly higher than baseline concentrations for all groups of dogs and were significantly higher for control group dogs than they were for intratesticular bupivacaine group dogs at that time. These results suggested that acute surgical stimulus caused an increase in serum cortisol concentrations and that intratesticular administration of bupivacaine abrogated that response. Other differences among serum cortisol concentrations were small, and high variability in data precluded further conclusions. Thus, the basis of these results, we recommend intratesticular administration of bupivacaine or epidural administration of morphine in addition to standard systemically administered analgesic treatments for dogs undergoing castration. In addition, we recommend that signs of pain be assessed via multiple methods during studies in which the efficacy of analogesics is assessed because results of serum cortisol assays were inconclusive at some times in this study but results of analysis of the intraoperative and postoperative pain assessments and the number of doses of opioids administered to dogs indicated clear differences among groups.

Intratesticular and epidural injection of analgesic drugs was performed in this study because both techniques were easily performed and inexpensive; therefore, these techniques may be practical methods for veterinarians in private practice. Intratesticular administration of analgesic drugs in particular was easily performed and is commonly used to provide analgesia for animals of various species undergoing castration or other types of testicular surgery. Some veterinarians use this method of analgesia for dogs undergoing castration, and results of 2 recent studies indicate the efficacy of intratesticular injection of local anesthetic drugs. Animals likely have more pain at the time the spermatic cord is cut, crushed, or torn during castration than at any other time during that surgery, and injection of local anesthetic drugs into the spermatic cord provides analgesia for piglets and horses undergoing that procedure. However, injection of analgesic drugs into the spermatic cord is more difficult and time-consuming than intratesticular injection of such drugs, and results of both of those studies indicate that similar analgesia is attained via either of those methods. The finding that these methods provide equivalent levels of analgesia is likely attributable to rapid distribution of lidocaine into the spermatic cord following injection of the drug into the testes; $^{14}C$-radiolabeled lidocaine injected into the testes of piglets is detectable in spermatic cords within 3 minutes and up to 40 minutes (the last time of data collection in the study) following injection. However, authors of that study concluded that the concentration of lidocaine in the spermatic cord at 40 minutes after injection may have been lower than the analgesic tissue concentration. In the present study.
the mean ± SD time between intratesticular injection of bupivacaine and the start of surgery was 28 ± 7 minutes and another 5 to 10 minutes elapsed before ligation of spermatic cords of dogs; therefore, the tissue concentration of bupivacaine at that time may not have resulted in maximal analgesia. However, because dogs in the intratesticular bupivacaine group received fewer doses of rescue analgesics intraoperatively and postoperatively, had lower cortisol concentrations at 15 minutes after testis removal, and had lower pain scores at T_{pe} of 0 and 1 hour versus control group dogs, we concluded that intratesticular injection of bupivacaine induced analgesia during the intraoperative and postoperative periods. The analgesic efficacy of intratesticularly administered bupivacaine (despite the prolonged interval between injection and spermatic cord ligation) could have been attributable to several reasons. Bupivacaine, which has a longer duration of action than lidocaine,9 was used in the present study. Although the duration of analgesia following intratesticular injection of bupivacaine has not been determined, bupivacaine likely had a longer duration of action in the testes than lidocaine would have. Also, times to peak tissue concentration of lidocaine, but not duration of analgesia, have been determined for animals after intratesticular injection.13 Therefore, local anesthetic drugs (including lidocaine) may provide analgesia at 40 minutes after injection into the testes.

Although intratesticular injection of local anesthetic drugs may induce analgesia in spermatic cords, there are potential sources of pain during castration that may not be alleviated with such a treatment. Because intratesticularly administered lidocaine is not absorbed into cremaster muscles in pigs,13 pain attributable to surgical trauma of cremaster muscles in dogs may not be alleviated by such treatments. In the present study, none of the dogs with intratesticularly administered bupivacaine seemed to react to application of clamps to spermatic cords, although most dogs in the control and epidural morphine groups that received fentanyl received that drug immediately after clamps were applied. This finding suggested that application of clamps to spermatic cords of dogs caused pain. Therefore, either surgical trauma to cremaster muscles did not cause pain (because dogs in the intratesticular bupivacaine group did not seem to react to such surgical trauma) or intratesticular administration of bupivacaine desensitized cremaster muscles in dogs. Another potential source of pain in dogs undergoing castration that may not have been alleviated via intratesticular injection of local anesthetic drugs was surgical trauma to the skin and stimulation of tissues at the incision site because incisions were typically cranial to the scrotums of dogs (ie, prescrotal surgical approach). In the present study, 1 dog in each group received fentanyl immediately after the skin was incised. Injection of local anesthetic drugs in surgical incisions may have improved analgesia in the dogs. After surgery, dogs in the intratesticular bupivacaine group received a significantly higher number of doses of hydromorphone than dogs in the epidural morphine group and significantly fewer doses of hydromorphone than control group dogs. This finding could have been attributable to a shorter duration of analgesia induced by intratesticularly injected bupivacaine versus that induced by epidurally administered morphine. However, dogs in the intratesticular bupivacaine group that received hydromorphone during the postoperative period did not seem to have the longest time between intratesticular bupivacaine injection and the end of the surgery; therefore, pain in those dogs may have been from another source (eg, skin that was not locally anesthetized). Also, bupivacaine may have had a shorter duration of action in those dogs because of rapid uptake via vascular or lymphatic systems, which would have decreased the duration of analgesia induced by the local anesthetic drug.

Bupivacaine has a small therapeutic index when administered IV.33 Because the testes are highly vascularized, aspiration should be carefully performed before intratesticular injection of bupivacaine to ensure that the drug is not administered IV. Adverse effects of local anesthetic drugs are uncommon and include local tissue reaction, CNS signs (eg, muscle fasciculations and seizures), and cardiovascular collapse.33 No adverse effects of bupivacaine were detected in dogs in this study, and adverse effects of intratesticular injection of local anesthetic drugs have not been reported for animals of other species, to the authors’ knowledge.

Analgesic drugs are administered epidurally with increasing frequency for dogs undergoing ovariohysterectomy35-38 and have been used for dogs undergoing castration.26 Various analgesic drugs are administered in the epidural space, including local anesthetic drugs and opioids. Morphine is a useful opioid for epidural analgesia because it is highly hydrophilic. Lipophilic opioids (eg, fentanyl) administered epidurally are rapidly absorbed into epidural fat and the systemic circulatory system, resulting in minimal contact time with spinal opioid receptors and a duration of analgesia that is not significantly different from the duration of action following systemic administration of the drug.39 Conversely, hydrophilic opioids (eg, morphine) are minimally absorbed following epidural administration and stay in contact with opioid receptors in the spinal cord for a longer period of time than do lipophilic opioids, inducing a longer duration of action and further cranial distribution of analgesia. Analgesia following epidural administration of morphine lasts up to 24 hours in small animals39; morphine is commonly administered epidurally for analgesia, and we chose to use it in this manner in the present study because of the long duration of action. Morphine administered in the epidural space at the lumbosacral junction has been used to provide analgesia for animals undergoing surgeries of hind limbs,11,40,41 the perineum,42 and the abdomen,41,43 and may even induce analgesia of forelimbs.44 The extent of cranial distribution of a drug in the epidural space depends on characteristics of the drug and the volume injected. In dogs, methylene blue (0.26 mL/kg [0.12 mL/lb]) injected epidurally at the lumbosacral junction is distributed cranially to the 11th to 13th thoracic vertebrae.39 The volume (1 mL/4.5 kg or 0.22 mL/kg [0.1 mL/lb]) of morphine epidurally administered to male dogs in the present study should have migrated far cranially to induce analgesia of genitourinary tracts of those dogs.

A disadvantage of epidural administration of morphine is that the time to onset of analgesia may be 30
to 60 minutes. This delay to onset of analgesia may have been a reason that dogs in the epidural morphine group received a higher number of doses of analgesic drugs intraoperatively versus that of dogs in the intratesticular bupivacaine group in the present study. The time from epidural administration of morphine to the start of surgery (ie, skin incision) was 39 ± 11 minutes, which may have been shorter than the time to onset of epidural analgesia in some dogs. However, the time from injection of analgesic drugs to the start of surgery was longer for that group than it was for the intratesticular bupivacaine group; therefore, more dogs with epidurally administered morphine may have had analgesia than would have if times to the start of surgery had been similar between these groups of dogs. The difference in time to the start of surgery between those groups was attributed to delays in availability of operating rooms and not to intentional delays to increase the efficacy of epidurally administered analgesics. The time to onset of analgesia for animals receiving an epidurally administered opioid can be decreased via concurrent epidural administration of a local anesthetic drug. The combination of a local anesthetic drug and morphine provides more effective (and frequently longer duration of) analgesia versus either drug alone and use of a combination of such drugs would probably be clinically useful because of enhanced amount, faster onset, and longer duration of analgesia. A combination of epidurally administered opioids and local anesthetic drugs induces effective analgesia in dogs after castration. However, it is the opinion of some clinicians that the volume of local anesthetic injected in the epidural space should not exceed 0.2 mL/kg (0.09 mL/lb). Nerves in the sympathetic trunk, which have a role in regulation of hemodynamic variables including heart rate and vascular tone, branch off from the thoracolumbar region of the spinal cord. If this area of the spinal cord is desensitized with local anesthetics, profound hypotension and decreased cardiac output can develop. The recommended volume of epidurally administered local anesthetic drugs (0.2 mL/kg) results in analgesia of the areas of the body with pudendal nerve branches (branching from the spinal cord at the level of the first lumbar vertebra), but does not result in local anesthesia of the thoracolumbar trunk. Opioids in the epidural space do not cause desensitization of sympathetic nerves; therefore, the volume of opioids is not as important as the volume of local anesthetics injected epidurally.

Another reason that epidurally administered morphine may not have been as effective as intratesticularly injected bupivacaine in this study was the fact that it was more difficult to ensure that drugs were injected into the epidural space than it was to ensure that drugs were injected into testicular parenchyma. We used the hanging drop technique and detection of a lack of resistance to injection to determine proper placement of the epidural needle for morphine administration. During the hanging drop technique, a drop of saline solution is placed in the hub of the epidural needle as it is advanced. Once the needle enters the epidural space, the fluid should be aspirated from the needle into the space because of subatmospheric epidural pressure. This technique is successful for epidural injection 88% of the time in medium-sized dogs in sternal recumbency with a 20-gauge spinal needle. Because the technique does not always indicate entry of a needle into the epidural space, low resistance to injection was also used to determine appropriate needle position. Low resistance to injection may indicate appropriate placement of drug in the epidural space in up to 95% of animals; however, performance of this technique requires experience to determine the appropriate amount of pressure required for injection of fluid into the epidural space. Thus, successful injection of a drug into the epidural space cannot be confirmed with either the hanging drop technique or via lack of injection resistance, especially for inexperienced personnel. Epidurally administered drugs do not provide analgesia in approximately 7% of dogs. In the present study, dogs receiving epidurally administered morphine had lower postoperative pain scores and required fewer doses of opioids postoperatively than did control group dogs, suggesting that most epidural injections were performed correctly. However, there was a high degree of variability in values of data for the epidural morphine group (particularly serum cortisol concentrations), which may have indicated that some epidural injections did not induce analgesia in dogs.

Because one of the primary benefits of epidural administration of morphine is a long duration of action, a longer period of data collection might have allowed detection of more differences in analgesia among groups of dogs in the present study. The long duration of action is likely the reason that fewer dogs in the epidural morphine group received analgesic drugs postoperatively versus dogs in either of the other groups. One dog remained sedated 80 minutes after epidural administration of morphine and received butorphanol IV (0.2 mg/kg), which caused the dog to regain a normal level of consciousness within 10 minutes after the injection. Prolonged sedation in this dog could have been attributable to the dose of hydromorphone that was administered preoperatively; such a duration of action of hydromorphone is unusual because the duration of action of this drug is typically 2 to 4 hours after IV administration. Prolonged sedation could also have been attributable to systemic absorption of morphine from the epidural space, which was also unlikely because morphine is highly hydrophilic and typically remains in the epidural space with minimal systemic absorption. Sedation following injection of morphine in the epidural space is unlikely to develop. Thus, prolonged sedation of that dog was most likely caused by an exaggerated response to anesthetic and opioid drugs. No other adverse effects were detected in any of the other dogs receiving epidurally administered morphine. Results of other studies indicate epidural administration of morphine to dogs causes minimal to no adverse effects. Adverse effects (eg, pruritus, urine retention, signs of nausea, vomiting, and respiratory depression) are estimated to develop in <11% of small animal patients receiving epidurally administered morphine.

A limitation of any veterinary analgesic study is that pain assessment of animals is difficult, primarily because animals cannot verbally communicate that they have pain and they may hide signs of pain from humans. Thus, pain in animals should be assessed...
via determination of various variables including physiologic, behavioral, and endocrine responses to noxious or painful stimuli. In the present study, we assessed intraoperative pain of dogs via determination of responses to surgical stimulation, responses to administration of analgesic drugs, and measurement of physiologic (heart rate, respiratory rate, and arterial blood pressure) variables; postoperative pain was assessed via determination of behavior (responses to palpation of incisions and movement outside of cages) and physiologic (heart and respiratory rates) variables. These variables were useful for assessment of pain because they were easily and quickly determined, allowing rapid treatment of pain when needed. Intraoperatively, indications for rescue analgesia included increases in values of heart rates or mean arterial blood pressures by > 20%. However, values of heart rates and mean arterial blood pressures can increase because of other factors including hypercarbia, hyperthermia, and hypoxemia, but these causes were ruled out via monitoring of dogs and performance of anesthesia in a manner that supported physiologic variables within reference limits. Postoperative use of physiologic variables is difficult because heart and respiratory rates can be affected by factors other than pain, such as stress, excitement, and fear. Not all of the dogs in this study were well socialized, and it was likely that postoperative physiologic data were not an accurate indication of pain for these animals.

Because values of physiologic variables are not specific for detection of pain, serum cortisol concentrations have been used to assess pain in animals of many species, including dogs, cats, horses, cattle, and sheep. However, serum cortisol concentrations are also an insensitive measure of pain and can be increased by other factors (eg, stress, excitement, and fear). Differing serum cortisol concentrations among similar groups of animals are likely attributable to treatment differences. Thus, animals exposed to a painful stimulus should have higher serum cortisol concentrations than animals receiving analgesic drugs that are exposed to that same stimulus. However, because handling of animals can cause substantial increases in circulating cortisol concentrations, especially for animals that are not accustomed to handling, serum cortisol concentration may not be a useful marker for detection of pain. In fact, in 1 study, serum cortisol concentrations did not indicate pain, whereas behavioral scores and other markers of pain (eg, circulating substance P concentrations) did indicate pain in castrated calves. Findings of the present study supported the fact that increases in serum cortisol concentration do not always indicate pain. Serum cortisol concentrations determined in this study indicated that the dogs likely had pain 15 minutes after removal of the testes, considering that serum cortisol concentration was higher at this time than it was at any other time and the untreated control dogs had serum cortisol concentrations that were higher than the serum cortisol concentrations for dogs in the treatment groups. However, during the rest of the study, the serum cortisol concentrations were highly variable and no conclusions regarding pain could be made by use of those data, whereas pain scores and criteria for rescue analgesia indicated the dogs had pain. Dogs included in this study were from animal shelters, and many of those dogs were not socialized and were resistant to handling. Thus, the finding that serum cortisol concentrations may not always have been indicative of pain in dogs of this study could be attributed to increases in serum cortisol concentrations because of stress and handling. In retrospect, other markers (eg, substance P) may have been more useful for detection of pain in dogs. Other factors that may have contributed to variability in serum cortisol concentrations included the fact that cortisol concentrations may undergo diurnal fluctuation and serum was not collected from dogs at similar times of the day, and control group dogs were significantly younger than dogs in the other 2 groups. Young humans may have a smaller circulating cortisol concentration response to stress than old humans. Ages of dogs in each group may have been similar if a more robust randomization scheme had been used in the present study.

Subjective pain scores have been used to assess signs of pain for animals of several species, including dogs. Pain scoring systems are insensitive, and scores can be skewed by patient factors such as excitement, fear, and bias or knowledge base of the person assigning the scores. However, pain scoring systems have been investigated for use with animals of many species, and the modified composite Glasgow pain scale has been validated for assessment of acute signs of pain in dogs. This pain scale has been used in several studies in which pain in dogs was assessed. Evaluation of signs of pain by a single observer who is unaware of the treatments administered to dogs, as in the present study, decreases variability in pain scores. In the present study, control group dogs had significantly higher pain scores at T of 0 and 1 hour than dogs in either of the other 2 groups. However, at T of 4 hours, no difference in pain scores were detected among the groups. This result was not surprising because dogs included in this study were clinical patients and were treated for pain whenever needed. The control group dogs had more postoperative pain scores > 5 and received more doses of hydromorphone than dogs in either of the other groups. Most of these doses of hydromorphone were administered following T of 0 hours, which was expected because the first dose of hydromorphone (administered preoperatively) was expected to have analgesic effects for only 2 to 4 hours and would have been ineffective by T of 0 hours. Despite the possibility of residual effects of anesthesia at that time, we were able to detect signs of pain in dogs (especially when surgical incisions were palpated). One dog in the control group had severe signs of pain and was dysphoric at T of 0 hours; that dog received both hydromorphone and dexametomidine. Because dexametomidine decreases circulating concentrations of cortisol and is a potent sedative, postoperative data for that dog were excluded from statistical analysis. Also, all dogs received carprofen, which is effective for treatment of postoperative soft tissue pain in dogs. Results of the present study for T of 4 hours may have been different if we had eliminated dogs from the study that required postoperative rescue analgesia or if we had al-
located dogs that required such treatment to another group for statistical comparisons. However, the objective of this study was not to develop analgesic techniques that would supplant standard protocols (eg, systemic administration of opioids and NSAIDs), but to determine whether intratesticular or epidural injection of analgesic drugs augmented such standard analgesic protocols.

A major limitation of this study was that surgical stimuli were likely inconsistent among dogs, which could have affected the data. Because the dogs included in this study were part of our clinical caseload, surgeries were performed by veterinary students supervised by surgery residents and faculty, and anesthesia was performed by veterinary students supervised by anesthesia residents, technicians, and faculty members. However, duration of surgery and degree of tissue manipulation would have been more consistent among groups of dogs if 1 experienced surgeon had performed the castrations. Also, intraoperative assessment of pain and responses of anesthetists to signs of pain in dogs may have been more consistent if 1 experienced anesthetist had performed all anesthetics. Postoperative signs of pain were assessed by a single observer who was unaware of treatments received by dogs, which likely decreased variability of pain scores during that period. However, despite variability among surgeons and anesthetists, we determined statistical differences among groups regarding pain scores and administration of rescue analgesia. Another study has been conducted in which signs of pain were assessed for dogs undergoing anesthesia and surgery performed by students. Results of that other study indicated dogs had complications attributable to ineptitude of experience. No complications attributable to administration of drugs or performance of anesthesia were detected in the present study, even though student anesthetists were inexperienced. However, students were closely supervised by experienced anesthesia personnel, which may have prevented such complications. Amount of experience of a surgeon may not affect the degree of postoperative signs of pain in a dog after neutering; the analgesic techniques used in the present study may be useful for veterinary surgeons with any amount of experience.

Another limitation of the present study was that monitors used for measurement of ETiso concentrations were not calibrated daily. Although the manufacturer’s instructions indicated that daily calibration of such monitors was not necessary, daily calibration would have ensured that ETiso concentrations were accurate. Infrequent calibration of monitors may not be problematic for determination of the anesthetic plane of a patient because this variable is clinically assessed via determination of heart rate, respiratory rate, mean arterial blood pressure, and response to a surgical stimulus and not via determination of ETiso concentrations. However, infrequent calibration of monitors may have affected our ability to detect significant differences in ETiso concentrations among groups of dogs. Thus, ETiso concentration data were reported but conclusions regarding this data were not determined.

Concerns for veterinary practitioners regarding performance of supplemental analgesia techniques include the time required for administration and the cost of drugs. However, intratesticular injection of bupivacaine and epidural administration of morphine were inexpensive and rapidly administered (mean ± SEM time to completion, 0.8 ± 0.5 minutes and 2.8 ± 1.5 minutes for intratesticular and epidural injections, respectively) in the present study. On the basis of US prices at the time this study was completed, intratesticular injection of bupivacaine cost approximately $0.60 and epidural administration of morphine cost approximately $3.20 (for a dog that weighed 10 kg [22 lb]) for each dog. This cost included costs of drugs, needles, and syringes but did not include a fee for administration of drugs by personnel. Epidural administration of morphine was more expensive than intratesticular injection of bupivacaine because of the price of an epidural needle. Because of ease of administration, low cost, and effective analgesia, intratesticular injection of local anesthetic drugs could easily be included in the analgesic protocol for dogs undergoing castration in most veterinary practices. Epidural administration of morphine was effective in this study and has been used for analgesia of dogs undergoing castration in another study. Results of the present study indicated that epidural administration of morphine or intratesticular injection of bupivacaine decreased intraoperative and immediate postoperative signs of pain in dogs undergoing castration without causing adverse effects. Because both of these analgesic techniques can be performed easily, rapidly, and inexpensively (particularly intratesticular administration of local anesthetic drugs), use of such techniques in analgesic protocols should be considered by veterinary practitioners.

b. Acrepomazine maleate, Boehringer Ingelheim Vetmedica Inc, St Joseph, Mo.
c. Hydromorphone HCl, Baxter Healthcare Corp, Deerfield, Ill.
d. Abbott Laboratories, North Chicago, Ill.
e. Propoflo28, Abbott Laboratories, North Chicago, Ill.
f. Isoflo, Abbott Laboratories, North Chicago, Ill.
g. Datascope Panorama, Mindray DS USA Inc, Mahwah, NJ.
h. Lactated Ringers injection USP, Hospira, Lake Forest, Ill.
i. Preservative-free morphine HCl, 1 mg/mL, Hospira, Lake Forest, Ill.
j. Senscaine, bupivacaine HCl, 0.2%, APP Pharmaceuticals LLC, Schaumburg, Ill.
k. GraphPad Prism, GraphPad Software, La Jolla, Calif.

References


From this month’s AJVR

Pharmacokinetics of meloxicam after intravenous, intramuscular, and oral administration of a single dose to Hispaniolan Amazon parrots (Amazona ventralis)

Christine M. Molter et al

Objective—To compare pharmacokinetics after IV, IM, and oral administration of a single dose of meloxicam to Hispaniolan Amazon parrots.

Animals—11 healthy parrots.

Procedures—Cohorts of 8 of the 11 birds comprised 3 experimental groups for a crossover study. Pharmacokinetics was determined from plasma concentrations measured via high-performance liquid chromatography after IV, IM, and oral administration of meloxicam at a dose of 1 mg/kg.

Results—Initial mean ± SD plasma concentration of 17.3 ± 9.0 µg/mL was measured 5 minutes after IV administration, whereas peak mean concentration was 9.3 ± 1.0 µg/mL 15 minutes after IM administration. At 12 hours after administration, mean plasma concentrations for IV (3.7 ± 2.5 µg/mL) and IM (3.5 ± 2.2 µg/mL) administration were similar. Peak mean plasma concentration (3.5 ± 1.2 µg/mL) was detected 6 hours after oral administration. Absolute systemic bioavailability of meloxicam after IM administration was 100% but was lower after oral administration (range, 49% to 75%). Elimination half-lives after IV, IM, and oral administration were similar (15.9 ± 4.4 hours, 15.1 ± 7.7 hours, and 15.8 ± 8.6 hours, respectively).

Conclusions and Clinical Relevance—Pharmacokinetic data may provide useful information for use of meloxicam in Hispaniolan Amazon parrots. A mean plasma concentration of 3.5 µg/mL would be expected to provide analgesia in Hispaniolan Amazon parrots; however, individual variation may result in some birds having low plasma meloxicam concentrations after IV, IM, or oral administration. After oral administration, plasma meloxicam concentration slowly reached the target plasma concentration, but that concentration was not sustained in most birds. (Am J Vet Res 2013;74:375–380)