Clinical evaluation of perioperative administration of gabapentin as an adjunct for postoperative analgesia in dogs undergoing amputation of a forelimb

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Objective—To evaluate perioperative administration of gabapentin as an adjunct for analgesia in dogs undergoing amputation of a forelimb.

Design—Randomized, controlled trial.

Animals—30 client-owned dogs.

Procedures—On the day before surgery, a baseline pain evaluation was performed in each dog by use of multiple pain assessment methods. Dogs then received gabapentin (10 mg/kg [4.5 mg/lb], PO, once, followed by 5 mg/kg [2.3 mg/lb], PO, q 12 h for 3 additional days) or a placebo. On the day of surgery, dogs were anesthetized and forelimb amputation was performed. Fentanyl was infused after surgery for 18 to 24 hours; use of other analgesics was allowed. In-hospital pain evaluations were repeated at intervals for 18 hours after surgery, and owners were asked to evaluate daily their dog’s activity, appetite, and wound soreness for the first 3 days after discharge from the hospital. Results were analyzed by use of a repeated-measures ANOVA.

Results—Pain evaluation scores did not differ significantly between gabapentin and placebo groups in the hospital or at home after discharge.

Conclusions and Clinical Relevance—As an adjunct to other analgesics and anesthetics, gabapentin, at the dose and frequency used in this study, did not provide a significant benefit for the management of acute perioperative pain in dogs undergoing forelimb amputation. The small sample size and number of other confounding factors, such as aggressive use of other analgesics, limited the likelihood of detecting a benefit of gabapentin. Other gabapentin doses or dosing regimens warrant further study.

Abbreviations

CCU Critical care unit
CRI Constant rate infusion
GABA γ-Aminobutyric acid
GPS Glasgow Composite Pain Scale—short form
S-WM Semmes-Weinstein monofilament
UMPS University of Melbourne Pain Scale
VAS Visual analogue scale
VGCC Voltage-gated calcium channel

Management of postoperative pain is one of the major challenges of veterinary medicine. Classes of analgesics commonly used in dogs include opioids and NSAIDs, which may be associated with adverse effects such as sedation, dysphoria, gastrointestinal tract dysfunction, or renal toxicity. For this reason, adjunct analgesic techniques that have the potential to improve comfort without adverse effects are of interest. For example, subanesthetic doses of ketamine can improve postoperative pain scores and activity in dogs undergoing amputation of a forelimb.

Gabapentin, a medication originally developed for use as an anticonvulsant, has received considerable attention in the human literature for its ability to decrease chronic neuropathic pain (often related to cancer) and, more recently, to decrease acute postoperative pain. Gabapentin is an alkylated GABA analogue that may modulate pain through binding to α2δ calcium channel subunits, suppressing glutamate and substance P, and, possibly, modulating GABA receptors. Human patients given gabapentin in the perioperative period are often more comfortable and use less analgesic medication.

The clinical trial reported here was conducted to evaluate the use of gabapentin as an adjunct for analgesia in dogs undergoing surgery. The hypothesis for the study was that oral administration of gabapentin during the immediate perioperative period, as part of a multimodal approach to pain management, would improve postoperative comfort and activity in dogs undergoing amputation of a forelimb.

Materials and Methods

Thirty client-owned dogs admitted to the Colorado State University Veterinary Hospital for forelimb amputation...
The dogs were systemically healthy and free of other painful conditions, as determined on the basis of results of physical examination and laboratory tests. The study protocol was evaluated and approved by a university institutional animal care and use committee. Informed consent was obtained from each dog’s owner.

On the day before surgery, a baseline preoperative pain evaluation was performed by a trained veterinary technician prior to initiation of any treatments. Dogs were assigned by use of a randomization procedure to receive gabapentin10 (10 mg/kg [4.5 mg/lb], PO, once on the afternoon preceding surgery, followed by 5 mg/kg [2.3 mg/lb], PO, q 12 h for 3 additional days) or a placebo (gelatin capsule administered PO). Treatments were prepared for each dog by the hospital pharmacy on the basis of each dog’s exact body weight, and dogs in both groups were administered the respective treatments at the same times. Body weights ranged from 34 to 57 kg (74.8 to 125.4 lb) with a mean ± SD of 40.9 ± 7.6 kg (90.0 ± 16.7 lb) and from 28 to 58 kg (61.6 to 127.6 lb) with a mean of 39.5 ± 8.2 kg (86.9 ± 18.0 lb) for dogs in the gabapentin and placebo groups, respectively. Age ranged from 2 to 11 years (mean, 7.1 ± 2.8 years) and from 4 to 12 years (mean, 7.5 ± 2.8 years) for dogs in the gabapentin and placebo groups, respectively.

Dogs were managed in accordance with the hospital’s typical standard of care for animals undergoing forelimb amputation. Preanesthetic medications consisted of glycopyrrolate6 (0.01 mg/kg [0.0045 mg/lb], SC) and methadone6 (0.7 mg/kg [0.32 mg/lb], SC). A catheter was placed in a peripheral vein, and anesthesia was induced by IV administration of fentanyl5 (5 µg/kg), midazolam5 (0.2 mg/kg [0.09 mg/lb]), and propofol2 (2 to 4 mg/kg [0.9 to 1.8 mg/lb]). Dogs were endotracheally intubated, and anesthesia was maintained by administration of isoflurane6 in 100% oxygen, which was supplemented by a CRI of fentanyl (5 to 10 µg/kg/h, IV). The need for the fentanyl CRI was determined on the basis of the anesthesiologist’s assessment of each dog’s response to a painful stimulus during anesthesia and surgery; the fentanyl CRI was decreased to a rate of 2 µg/kg/h approximately 20 minutes before the end of surgery, and the fentanyl CRI was terminated at the end of surgery. Lactated Ringer’s solution was administered at a rate of 10 mL/kg/h throughout anesthesia and surgery. Monitoring during anesthesia included arterial blood pressure (direct or oscillometric), ECG, and pulse oximetry. During surgery, the surgeon infiltrated local anesthetic (approx 1 to 2 mL of 0.75% bupivacaine solution) around the nerves of the brachial plexus immediately prior to transection of the forelimb, in accordance with the standard practice at our hospital; in addition, a 0.5% bupivacaine solution with epinephrine was infiltrated (approx 2 mg of bupivacaine/kg) directly into the skin incision at the time of wound closure.

After completion of surgery, dogs were allowed to recover from anesthesia until they could be extubated; they then were transferred to the hospital CCU for 18 to 24 hours. Fentanyl CRI at a rate of 2 µg/kg/h, IV, was reinitiated within 20 minutes after extubation. The fentanyl CRI could be increased or decreased as necessary, as determined on the basis of the clinical assessment of each dog’s comfort and behavior. Clinical assessments were performed by CCU veterinary technicians or the primary clinician, all of whom were not aware of the treatment group for each dog. Additional analgesics or sedatives could be administered at the discretion of the CCU veterinary technicians or primary clinician; all treatments were recorded in the medical record for each dog.

For the purposes of the study, specific pain evaluations (separate from the clinical evaluations performed by CCU personnel) were performed 0.5, 2, 4, 6, 8, 12, and 18 hours after tracheal extubation by 1 of 4 trained veterinary technicians; the 4 veterinary technicians were not aware of the treatment group for each dog. All 4 veterinary technicians had been trained in the use of the various pain evaluation methods by one of the authors (PWH). The same veterinary technician performed all evaluations on a particular dog, including the preoperative evaluation the day before surgery and all postoperative evaluations.

Four methods of pain evaluation were used in the same order at each time point. The first was the GPS.13 Although the maximum possible GPS score typically is 24, 1 criterion (response of the dog to being walked on a leash) could not be evaluated in the immediate postoperative period; thus, the maximum possible score at those time points was only 20. Therefore, for purposes of the study, all GPS scores were expressed as a percentage of the maximum possible score at each time point. The second method was the UMPS (maximum possible score, 27).11 The third method was the VAS (0 mm = no pain and 100 mm = worst possible pain). The fourth method was wound sensitivity assessed by use of S-WMs.9 At each evaluation time point, the evaluator applied an S-WM to 1 point approximately 0.5 cm from the incision within each of the 4 quadrants around the incision; when a purposeful response (dog turned its head toward the wound or the dog vocalized) was not elicited, the next larger S-WM was applied, and this was repeated until a purposeful response was elicited. Evaluators were aware of the size of the S-WM being used. Potential values for S-WM testing ranged from a minimum of 1.65 (which corresponded to 0.008 g) to a maximum of 6.65 (which corresponded to 300 g).9

Dogs were discharged from the hospital in the late morning or afternoon of the day after surgery (ie, the first day after surgery). For the initial 3 days the dogs were at home (second, third, and fourth days after surgery), owners of the dogs were asked to complete an at-home evaluation form and then mail it to the authors. The 3 behaviors or characteristics evaluated were appetite (scale of 1 to 5 [1 = ate more than usual; 2 = ate about the usual amount; 3 = ate about the usual amount, with coaxing; 4 = ate less than the usual amount, but did eat something; and 5 = did not eat at all]), personality-demeanor-activity (scale of 1 to 5 [1 = more aggressive or restless than usual, 2 = about usual, 3 = slightly less active than usual, but appears to be feeling okay; 4 = less active than usual and slight signs of depression; and 5 = signs of depression, unresponsive; and avoids contact]), and wound soreness (scale of 1 to 3 [1 = not particularly sore or protective of wound; 2 =
slightly sore and avoids touching of the area if possible; and 3 = extremely sore and vocalizes or tries to bite if the area is touched).

The medical record of each dog was examined at the end of the study to evaluate the type and quantity of all analgesic medications administered, with an emphasis on the first 18 hours after surgery when the dogs were cared for in the CCU. The type and quantity of analgesic medications prescribed for administration by the owners after discharge were also evaluated.

A power calculation based on results from a similar clinical study suggested that 10 dogs/group would be sufficient to detect a 30% difference between groups with a power of 0.9; however, it was decided to enroll 15 dogs/group in the event that data collection may be incomplete for some dogs. One dog in the placebo group was withdrawn from the study because it was inadvertently given preanesthetic medications that differed from those in the study protocol. Therefore, data from 14 dogs in the placebo group and 15 dogs in the gabapentin group were included in the statistical analysis. Data analysis was performed by use of commercially available statistical software. For the in-hospital evaluations of GPS, UMPS,VAS, and S-WM, responses were analyzed by use of a procedure for a repeated-measures ANOVA. Treatment was a fixed effect, the baseline evaluation was a covariate, and time was the repeated-measures effect. Dog within treatment group was a random effect. For at-home owner evaluations, binary variables (appetite, activity, and soreness) were analyzed by use of another procedure for a repeated-measures ANOVA. In that analysis, treatment was a fixed effect, day was the repeated-measures effect, and dog within treatment group was a random effect. For all analyses, values of $P < 0.05$ were considered significant.

Results

Of the 14 dogs in the placebo group, 13 had an osteosarcoma and 1 had a soft tissue sarcoma, as determined on histopathologic findings. Of the 15 dogs in the gabapentin group, 13 had an osteosarcoma, 1 had a synovial cell sarcoma, and 1 had an infiltrative lipoma. Baseline scores for GPS were significantly higher in the placebo group (mean ± SE, 19.6 ± 3.0), compared with scores in the gabapentin group (15.6 ± 2.9); therefore, means for preoperative (baseline) pain scores were used as covariates in the analysis. Results of in-hospital evaluations conducted by veterinary technicians using the 4 methods were summarized (Table 1). There were no significant differences in mean scores over time for any of the pain evaluation methods between gabapentin- and placebo-treated dogs.

Review of analgesic administration while the dogs were hospitalized in the CCU or after they were discharged did not reveal marked differences. The CRI for postoperative infusion of fentanyl was similar for both groups (gabapentin group: range, 1.6 to 3.5 µg/kg/h [0.73 to 1.59 µg/lb/h]; mean, 2.4 µg/kg/h [1.09 µg/lb/h]; and placebo group: range, 1.4 to 3.4 µg/kg/h [0.69 to 1.35 µg/lb/h]; mean, 2.2 µg/kg/h [1.0 µg/lb/h]). Similarly, total duration of postoperative administration of the fentanyl CRI was similar between groups (gabapentin group: range, 1 to 30 hours; mean, 17.3 hours; and placebo group: range, 6 to 19 hours; mean, 13.7 hours). In the placebo group, 10 of 14 dogs received NSAIDs (5 received carprofen∗ [4 mg/kg, PO, q 24 h] and 5 received deracoxib† [3 mg/kg (1.4 mg/lb), PO, q 24 h]) while in the CCU, and 9 of the 10 dogs continued to receive an NSAID (5 received carprofen and 4 received deracoxib) after discharge. For the gabapentin group, 5 of 15 dogs received NSAIDs (2 received carprofen and 3 received deracoxib) while in the CCU, and 11 dogs (these 5 plus 6 others) were prescribed an NSAID (4 received carprofen and 7 received deracoxib) for administration by the owners after discharge. Six of 14 dogs in the placebo group received tramadol∗ (5 mg/kg, PO, q 12 h) while in the CCU, and 13 dogs in the placebo group (these 6 plus 7 others) received tramadol after discharge, whereas 5 of 15 dogs in the gabapentin group received tramadol while in the CCU, and 12 dogs in the placebo group (these 5 plus 7 others) received tramadol after discharge. Seven of 14 placebo-treated dogs and 8 of 15 gabapentin-treated dogs received a single dose of acepromazine (0.01 mg/kg, IV) while in the CCU.

Results of evaluations conducted at home by the owners were summarized (Table 2). There were no sig-

<table>
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<th>Method of pain assessment</th>
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<th>4</th>
<th>6</th>
<th>8</th>
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<td>GPS (%)†</td>
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<td>UMPS</td>
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*Baseline GPS scores were significantly ($P < 0.05$) higher in the placebo-treated dogs, compared with scores in the gabapentin-treated dogs; therefore, mean values for baseline GPS scores were used as covariates in subsequent analyses. †The maximum GPS score typically is 24, but 1 criterion could not be evaluated in the immediate postoperative period; thus, the maximum possible score at those time points was only 20. Therefore, all GPS scores were expressed as a percentage of the maximum possible score at each time point.

Table 1—Mean ± SE scores for in-hospital pain evaluation techniques in 15 gabapentin-treated and 14 placebo-treated dogs undergoing amputation of a forelimb.
A growing body of evidence supports the effectiveness of gabapentin in the management of acute or perioperative pain in humans, especially when administered prior to surgery. Gabapentin was originally developed for use as an anticonvulsant, and its pharmacokinetics and metabolism in dogs have been studied. Gabapentin has several desirable characteristics, which include 80% bioavailability after oral administration, with maximum blood concentrations achieved within 3 hours. In dogs, gabapentin undergoes partial biotransformation in the liver, and both the parent drug and metabolite are eliminated via the kidneys, with an elimination half-life of 3 to 4 hours. Although the authors are not aware of any peer-reviewed publications in which the efficacy of gabapentin as an analgesic in dogs has been evaluated, gabapentin is frequently recommended as a component of chronic pain management (eg, in dogs with arthritis or cancer). In humans, gabapentin is used frequently for the treatment of neuropathic pain. For example, investigators in 1 study found that gabapentin administered orally for 6 weeks helped to relieve phantom limb pain. A growing body of evidence supports the effectiveness of gabapentin in the management of acute or perioperative pain in humans, especially when administered prior to surgery. Healthy human volunteers had a significant increase in tolerance to the cold pressor test when gabapentin administration was added to morphine treatment. A number of studies in humans have revealed a reduction in opioid consumption or improvement in pain relief after a variety of surgical procedures, including mastectomy, cholecystectomy, hysterectomy, and spinal surgery, when gabapentin was administered in the perioperative period. However, a more recent study in humans failed to detect a benefit of gabapentin, administered in escalating doses for 30 days beginning immediately after amputation of a leg, on the incidence or intensity of postamputation pain. The reason for these mixed results is unclear.

In the prospective, randomized clinical trial reported here, gabapentin was administered at a total daily dosage of 10 mg/kg for 4 days, but it did not significantly reduce postoperative pain scores or improve appetite and activity in dogs after forelimb amputation. Thus, we could not detect any short-term benefit of gabapentin administration on postamputation pain, which leads to the conclusion that it has no effect. However, several issues should be considered in interpreting these negative results.

The sample size was relatively small and based on the sample size reported in a similar study. In that study, infusion of a low dose of ketamine was associated with significantly lower pain scores and significantly better activity scores in dogs undergoing forelimb amputation. Similar to the dogs in that study, all dogs in the study reported here had cancer, most commonly osteosarcoma, which resulted in varying degrees of pathological changes and pain even before surgery was performed, as indicated by the unexpected significant difference in baseline GPS scores between the placebo and gabapentin groups. Similar to the dogs in the study of infusion of a low dose of ketamine, dogs in the present study received several other analgesic medications, primarily fentanyl. In the years since the aforementioned study of the low dose of ketamine was performed, the use of NSAIDs, tramadol, local anaesthesia, and other medications has increased. Because client-owned dogs were used in the study, withholding of any commonly used analgesic medication was considered unethical. A more standardized analgesic plan that incorporated rescue analgesic medications might have minimized variability, but it also may have made it more difficult to recruit dogs for the study because clinicians are sometimes reluctant to relinquish management of any commonly used analgesic medication. Because client-owned dogs were used in the study, withholding of any commonly used analgesic medication was considered unethical. A more standardized analgesic plan that incorporated rescue analgesic medications might have minimized variability, but it also may have made it more difficult to recruit dogs for the study because clinicians are sometimes reluctant to relinquish management of any commonly used analgesic medication. Because client-owned dogs were used in the study, withholding of any commonly used analgesic medication was considered unethical. A more standardized analgesic plan that incorporated rescue analgesic medications might have minimized variability, but it also may have made it more difficult to recruit dogs for the study because clinicians are sometimes reluctant to relinquish management of.
or chronic postsurgical pain syndromes in which pain persists beyond apparent tissue healing. In earlier studies, investigators determined that gabapentin has antihyperalgesic effects, not antinociceptive effects, which suggests its effect is via a dorsal horn phenomenon, not a peripheral nociceptor. Other studies suggest a noiceptive effect. Hyperalgesia requires some change in downstream (central) pain pathways, which conceivably requires some time. If true, this suggests that gabapentin would not be of use until there is hyperalgesia. In some studies, it has been suggested that gabapentin effects might be time-dependent events. It is possible that a greater duration of follow-up monitoring than was used in the present study might reveal a benefit of gabapentin treatment in preventing the development of chronic or neuropathic pain.

Tests used to evaluate pain or comfort in dogs are not perfect. Much time and attention have been invested in developing accurate pain scoring systems for nonverbal animals, but there is no single technique that is accepted as the criterion-referenced standard. Even within a species, such as dogs, different surgeries, injuries, or types of pain are not equally amenable to a single pain evaluation technique. For these reasons, 4 methods were used to evaluate pain in the hospital and owners were asked to assess 3 characteristics at home after discharge. The GPS and UMS were developed for clinical evaluation of dogs with acute pain. The VAS has been extrapolated from human pain assessment; in addition to the fact that it is nonlinear and prone to bias, its use in nonverbal animals is further complicated by the fact that an observer (rather than the patient) makes the assessment. The S-WMs have been used in both clinical and experimental settings. In a study of rats in which an incision was made on the plantar surface of a hindpaw, withdrawal thresholds to monofilaments were significantly reduced at 2 and 20 hours after incision. Responsiveness to monofilaments was enhanced in αδ-fibers but not C-fibers 1 day after the incision was made in that study. In the study reported here, responsiveness to mechanostimulation by monofilaments was minimal, both before and after surgery. Before amputation, testing of the shoulder area was presumed not to elicit signs of pain because all of the tumors were located more distally in the forelimb; after surgery, wound sensitivity was likely obtunded by the use of bupivacaine infiltrated in the wound. By 8 hours, wound sensitivity was significantly decreased by the use of bupivacaine infiltrated in the incision during closure. Bupivacaine with epinephrine may provide local analgesia for the incision during closure. Bupivacaine with epinephrine may provide local analgesia for the incision during closure. Bupivacaine with epinephrine may provide local analgesia for the incision during closure. Bupivacaine with epinephrine may provide local analgesia for the incision during closure. Bupivacaine with epinephrine may provide local analgesia for the incision during closure.

Interaction with VGCCs is currently the most likely mechanism of action for gabapentin, although other mechanisms have been proposed. The only known binding site for gabapentin is the α2δ subunit of VGCCs. Knock-in replacement of the wild-type α2δ-1 subunit with a mutant (α2δ-1 R217A) incapable of binding pregabalin results in complete loss of the drug's analgesic efficacy. Acute inhibition or blockade of VGCCs by gabapentin is not supported by recent studies; rather, data in those studies suggest that gabapentin, through intracellular binding to the α2δ subunit, delays VGCC trafficking to the cell surface and thereby decreases Ca2+ influx.

Several observations support the notion that gabapentin may be slow in onset in vivo and thus is less efficacious when administered in the immediate perioperative period. These observations include the fact that gabapentin's effect is intracellular, gabapentin does not directly block VGCCs at the cell surface, and expression of VGCCs at the cell surface is delayed in the presence of gabapentin.

Analysis of results of the prospective clinical study reported here did not reveal a significant benefit for the administration of gabapentin at the rate of 10 mg/kg/d in dogs undergoing amputation of a forelimb. Although it is possible that gabapentin has no beneficial effect on acute perioperative pain in dogs when used as part of a multimodal analgesic regimen, adverse effects were not observed. Additional studies with different dosages, different dosing frequencies, and other potentially painful clinical conditions are warranted.

References

From this month’s AJVR

Influence of 7,8-methylenedioxylycoctonine–type alkaloids on the toxic effects associated with ingestion of tall larkspur (Delphinium spp) in cattle

Kevin D. Welch et al

Objective—To determine the contribution of 7,8-methylenedioxylycoctonine (MDL)-type alkaloids to the toxic effects of tall larkspur (Delphinium spp) consumption in cattle.

Animals—Sixteen 2-year-old Angus steers.

Procedures—Plant material from 3 populations of tall larkspur that contained different concentration ratios of MDL-type to N-(methylsuccinimido) anthranoyllycoctonine (MSAL)-type alkaloids was collected, dried, and finely ground. For each plant population, a dose of ground plant material that would elicit similar clinical signs of toxicity in cattle after oral administration was determined on the basis of the plants’ MSAL-type alkaloid concentration. Cattle were treated via oral gavage with single doses of ground plant material from each of the 3 populations of tall larkspur, each animal underwent 1 to 3 single-dose treatments (≥21-day interval between treatments). Heart rate was recorded immediately before (baseline) and 24 hours after each larkspur treatment.

Results—Tall larkspur populations with a lower MDL-type-to-MSAL-type alkaloid concentration ratio required a greater amount of MSAL-type alkaloids to cause the expected clinical signs of toxicity (including increased heart rate) in cattle.

Conclusions and Clinical Relevance—Results indicated that the typically less toxic MDL-type alkaloids contributed in a significant manner to the toxic effects of tall larkspur in steers. Consequently, both the concentration of MSAL-type alkaloids and the total concentration of MSAL- and MDL-type alkaloids should be determined when assessing the relative toxicity of tall larkspur populations. These results provide valuable information to determine the risk of toxicity in cattle grazing on tall larkspur–infested rangelands.