Comparison of the effects of tramadol, codeine, and ketoprofen alone or in combination on postoperative pain and on concentrations of blood glucose, serum cortisol, and serum interleukin-6 in dogs undergoing maxillectomy or mandibulectomy

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Objective—To compare analgesic effects of tramadol, codeine, and ketoprofen administered alone and in combination and their effects on concentrations of blood glucose, serum cortisol, and serum interleukin (IL)-6 in dogs undergoing maxillectomy or mandibulectomy.

Animals—42 dogs with oral neoplasms.

Procedures—30 minutes before the end of surgery, dogs received SC injections of tramadol (2 mg/kg), codeine (2 mg/kg), ketoprofen (2 mg/kg), tramadol + ketoprofen, or codeine + ketoprofen (at the aforementioned dosages). Physiologic variables, analgesia, and sedation were measured before (baseline) and 1, 2, 3, 4, 5, and 24 hours after surgery. Blood glucose, serum cortisol, and serum IL-6 concentrations were measured 1, 3, 5, and 24 hours after administration of analgesics.

Results—All treatments provided adequate postoperative analgesia. Significant increases in mean ± SD blood glucose concentrations were detected in dogs receiving tramadol (96 ± 14 mg/dL), codeine (120 ± 66 mg/dL and 96 ± 21 mg/dL), ketoprofen (105 ± 22 mg/dL), and codeine + ketoprofen (104 ± 16 mg/dL) at 5, 1 and 3, 5, and 3 hours after analgesic administration, respectively, compared with preoperative (baseline) values. There were no significant changes in physiologic variables, serum IL-6 concentrations, or serum cortisol concentrations. Dogs administered codeine + ketoprofen had light but significant sedation at 4, 5, and 24 hours.

Conclusions and Clinical Relevance—Opioids alone or in combination with an NSAID promoted analgesia without adverse effects during the 24-hour postoperative period in dogs undergoing maxillectomy or mandibulectomy for removal of oral neoplasms. (Am J Vet Res 2010;71:1019–1026)

Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>IL</td>
<td>Interleukin</td>
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<td>NIBP</td>
<td>Noninvasive blood pressure</td>
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<td>NRS</td>
<td>Numeric rating scale</td>
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Pain currently is considered to be the fifth vital sign, and as such, it should be regularly assessed and properly managed. Improper treatment of acute pain, including postoperative pain, is a risk factor for the development of chronic pain. Although subjective in essence, pain has been extensively studied over the years, both experimentally and clinically, in domestic animals and humans. Scales used for the clinical assessment of pain have been derived from these studies. Postoperative pain is the result of tissue damage that incites nociception and inflammation, surgical manipulation, and other stimuli, such as anesthesia and stress. Changes in blood glucose, plasma cortisol, and catecholamine concentrations have been evaluated in studies that involved pain recognition in small animals and have yielded important information.
regarding attenuation of the neuroendocrine response to pain. During surgery, various mediators, including prostaglandins, bradykinins, substance P, calcitonin-G–related protein, and cytokines, are released and interact to mediate and modulate pain. Inflammation and stress are associated with an increase in tumor necrosis factor-α and proinflammatory, pain-generating cytokines such as IL-1β and IL-6. Such cytokines may also have anti-inflammatory properties. Interleukin-6 is the primary chemical mediator involved in bone inflammation and bone pain.

Several drugs may be used for the treatment of pain. General guidelines have been offered by the World Health Organization. Those guidelines state that mild pain should be treated with a nonopioid drug (with or without an adjuvant). As pain increases from moderate to severe, mild to strong opioids should be added to the protocol. Ketoprofen is an NSAID commonly used in veterinary medicine. As an anti-inflammatory drug, ketoprofen may be used as a nonopioid agent for the management of mild pain.

Tramadol and codeine are opioids used, either alone or in association with other drugs, in veterinary medicine for the control of mild to moderate pain. Tramadol may be as effective as morphine for postoperative analgesia of bitches undergoing ovariohysterectomy. Metamizole has analgesic, antipyretic, and spasmylytic properties, and prolonged use of this drug does not cause adverse effects in the digestive tract. Metamizole affects the CNS and metabolites of metamizole act in the peripheral nervous system to inhibit synthesis of prostaglandins.

Although numerous clinical studies have been conducted to evaluate analgesics and pain control in dogs, few have been performed in animals with cancer pain that underwent surgical resection of bone and soft tissues. The study reported here was performed with the purpose of evaluating the use of various drugs or drug combinations for the management of pain in dogs undergoing orthopedic or oncological surgery of the mandible or maxilla. Pain and analgesia were clinically assessed through the measurement of physiologic variables, use of pain scales, and clinical observations. Alterations in blood glucose, serum cortisol, and serum IL-6 concentrations were also evaluated.

Materials and Methods

Animals—Client-owned dogs (n = 42) of various breeds, body weights, and ages and both sexes were used in the study. Dogs eligible for inclusion were those evaluated at the Veterinary Hospital of the Faculdade de Medicina Veterinária e Zootecnia of the Universidade de São Paulo. Dogs were assigned to 1 of 5 treatment groups. Eight dogs received tramadol (2 mg/kg, q 8 h for 24 hours), 9 dogs received codeine (2 mg/kg, q 8 h for 24 hours), 9 dogs received ketoprofen (2 mg/kg, q 24 h once), 8 dogs received tramadol + ketoprofen (2 mg of tramadol/kg, q 8 h for 24 hours, and 2 mg of ketoprofen/kg, q 24 h once), and 8 dogs received codeine + ketoprofen (2 mg of codeine/kg, q 8 h for 24 hours, and 2 mg of ketoprofen/kg, q 24 h once). Drugs were administered by a researcher (TLM) who was responsible for anesthesia and assessment of pain and who was not aware of the treatment administered to each dog. Tramadol dosage was based on results of previous studies for control of acute pain in dogs. Co-
data were analyzed for a normal distribution by use of the Kolmogorov-Smirnov test, and nonparametric tests were used to analyze data that did not conform to a Gaussian distribution. Heart rate, respiratory rate, NIBP, and glucose, cortisol, and IL-6 concentrations were analyzed by use of a 2-way ANOVA (group and time effect). Pain and sedation scores were compared within each group by use of the Friedman test followed by the Dunn test and between groups by use of the Kruskal-Wallis test followed by the Dunn post hoc test. Surgery and exubation times were compared by use of a 1-way ANOVA. A χ² test was used to compare rescue analgesia requirements. Data were analyzed by use of statistical software packages. Values of P < 0.05 were considered significant.

**Results**

Of the 42 dogs included in the study, 19 underwent maxillectomy and 23 underwent mandibulectomy. Despite the overall similar numbers for the 2 procedures, there was a significant difference in the number for each procedure among the 5 treatment groups (Table 1). Surgical procedures ranged from small resections of rostral bones to total removal of the mandible on 1 side.

Treatment groups did not differ significantly with regard to body weight, sex, duration of surgery, and extubation time (Table 1). Body weight ranged from 3.0 to 45.3 kg, and surgical time ranged from 30 to 180 minutes. Interval between the end of anesthesia and extubation ranged from 5 to 15 minutes. Dogs ranged from 2 to 19 years of age, which differed significantly among groups. Heart rate, respiratory rate, and NIBP did not differ significantly among groups or time points.

Blood glucose concentrations were significantly increased, compared with baseline values, in all groups, except for tramadol + ketoprofen (Figure 1). The blood glucose concentration was significantly increased in...
dogs receiving codeine at 1 and 3 hours, dogs receiving codeine + ketoprofen at 3 hours, and dogs receiving tramadol + ketoprofen at 5 hours.

Baseline serum cortisol concentrations were near the upper limit of 6 µg/dL. No significant differences were detected among groups at any time point. However, palpation of the surgical site elicited differences in signs of pain (Figure 2). All dogs had a mean baseline NRS score of 1, and most dogs had a baseline NRS score of 0. There was a significant increase in pain score at 2 hours after analgesic administration, compared with the baseline value, for dogs receiving tramadol. Dogs receiving codeine had the greatest mean increase in NRS, although it was not significantly different from the baseline value or from values for the other groups. At 24 hours after analgesic administration, the NRS scores for all treatment groups were similar (range, 1.3 to 1.9).

Fourteen of the dogs required rescue medication. Of these, 13 dogs (2 receiving tramadol, 2 receiving tramadol + ketoprofen, 2 receiving codeine + ketoprofen, 3 receiving codeine + ketoprofen, and 4 receiving ketoprofen) required 1 dose of metamizole and 1 dog (receiving ketoprofen) required 2 doses of rescue medication (metamizole followed 1 hour later by morphine). No significant differences were detected among treatment groups.

Figure 1—Mean ± SD blood glucose concentration measured before surgery (ie, baseline) and at 1, 3, 5, and 24 hours after analgesic administration performed 30 minutes before the end of maxillectomy or mandibulectomy to remove oral neoplasms from client-owned dogs. Eight dogs received tramadol (2 mg/kg, q 8 h for 24 hours [diagonal-striped bars]), 9 dogs received codeine (2 mg/kg, q 8 h for 24 hours [gray bars]), 10 dogs received tramadol + ketoprofen (2 mg of tramadol/kg, q 8 h for 24 hours, and 2 mg of ketoprofen/kg, q 24 h [white bars]), 8 dogs received codeine + ketoprofen (2 mg of codeine/kg, q 8 h for 24 hours, and 2 mg of ketoprofen/kg, q 24 h [black bars]), 9 dogs received codeine (2 mg/kg, q 8 h for 24 hours, and 2 mg of ketoprofen/kg, q 24 h [gray bars]), 8 dogs received tramadol + ketoprofen (2 mg of tramadol/kg, q 8 h for 24 hours, and 2 mg of ketoprofen/kg, q 24 h [white bars]), and 8 dogs received codeine + ketoprofen (2 mg of codeine/kg, q 8 h for 24 hours, and 2 mg of ketoprofen/kg, q 24 h [white bars]). *Within a treatment group, value differs significantly (P < 0.05) from the baseline value.
The study reported here, administration of analgesics in accordance with each of the proposed protocols ultimately resulted in analgesia in dogs undergoing maxillectomy or mandibulectomy. One of the purposes of this study was to determine the drugs or drug combinations that would result in adequate pain management with minimal detrimental repercussions. In this regard, the chosen methods suited this purpose well.

Oral neoplasia is common in dogs and cats, and the oral cavity ranks as the fourth most common site for neoplasms in these species (incidence of 6% and 3%, respectively). The most frequently diagnosed malignant oral neoplasms are melanoma, fibrosarcoma, and squamous cell carcinoma.41-43 Surgeries for the removal of oral neoplasms reportedly are associated with high pain scores,41 which make maxillectomy and mandibulectomy good methods for use in investigating drug-induced analgesia. Although there are protocols for use in postoperative analgesia of oral cavity–related surgeries,41-46 few blinded, prospective veterinary studies have been published on this topic.

In the present study, invasive and malignant tumors of the oral cavity were excised via maxillectomy or mandibulectomy, with removal of a safety margin that included resection of osseous and soft tissues. As stated in the results, surgical time was similar for all dogs. Randomization of dogs among treatments resulted in groups that were not completely homogeneous. Thus, there was a difference with regard to age and type of surgery among groups. Nevertheless, the authors believe that these differences did not compromise the study because differences in age were relatively small and the degree of pain resulting from the type of surgery was estimated to be similar for the 2 procedures. One fact that emphasizes this belief is that the value for preoperative evaluation of pain was similar in all dogs. An observation period of 24 hours after surgery was chosen because this is the most critical time during the postoperative period.47 Pain assessment by use of the NRS and scores of the response to palpation of the surgical site by a single observer has been described in other studies.12,20,21,48-52

In the study reported here, all dogs originally had a preoperative (ie, baseline) mean NRS score ≤ 1. In fact, most dogs had a score of 0, and nearly all of them reportedly were eating normally. This is an interesting finding when compared with results for human studies43-51 in which mild to moderate pain is not uncommon. A speculative reason for this lack of oncological pain could have been a possible adaptation of the dogs to their condition. As expected, an increase in postoperative pain was observed for all treatment groups (mean score ranged from 1 to 3 after analgesic administration). The small difference in analgesia detected at 24 hours was likely attributable to the duration of action of each drug because the action of ketoprofen lasts from 12 to 24 hours19 and that of tramadol lasts for 8 hours.14,34 Thus, tramadol was administered at 8-hour intervals during the 24-hour observation period.

Only dogs receiving tramadol had a significant increase in NRS score (at 2 hours after analgesic administration). However, this does not mean that the administration of tramadol alone was inefficient in pain control.

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because the NRS score was only 2. This observation is in agreement with that in a study in which investigators compared preemptive administration of tramadol (used at the same dosage as for the study reported here), with an equipotent dose of morphine in the evaluation of postoperative (ie, ovariohysterectomy) pain in bitches. The authors of that study concluded that both drugs had similar efficiency in pain control. Dogs treated with codeine alone had a similar increase in NRS score, although it was not significant.

Mean pain scores for the descriptive scale were < 1.1 at all times, which indicated that this scale also provided evidence of adequate pain control. No significant difference was detected in mean pain scores for the descriptive scale among treatment groups.

Rescue analgesia was necessary for some dogs in every treatment group, and the greater need for rescue analgesia for dogs receiving ketoprofen (4/8 dogs) was not significantly different from that for other treatment groups. However, 1 aspect that is clinically important is that the perception of pain may have differed among individual dogs. Therefore, regardless of the regimen chosen for use in pain control, pain must always be continually assessed in every animal.

The sedation observed at 1 hour after analgesic administration could have been attributed, at least in part, to residual effects of the anesthetic regimen used. However, moderate sedation at 1 hour was most evident in dogs receiving codeine + ketoprofen, compared with that for dogs receiving tramadol, with a mean difference in sedation score of 0.8. Indeed, dogs receiving codeine + ketoprofen had a significant decrease in sedation at 4, 5, and 24 hours, compared with the sedation score at 1 hour after analgesic administration.

No significant difference among groups was detected regarding the evaluated physiologic variables. No important change was detected relative to baseline values, which indicated that these medications are safe for use as postoperative analgesics for this specific population.

As a stress factor, pain may be associated with increases in cortisol and glucose concentrations, and changes in these concentrations may provide an accurate means of determining analgesic efficacy. In the study reported here, tramadol + ketoprofen was the only treatment that prevented an increase in blood glucose concentration in relationship to the baseline concentration. When dogs were medicated with only tramadol or only ketoprofen, a significant increase in mean glucose concentrations was detected for each analgesic at 5 hours. Similarly, analgesia provided by codeine + ketoprofen was superior to that of codeine alone because glucose concentration in dogs administered codeine alone increased significantly at 2 time points. However, administration of codeine + ketoprofen was not superior to the use of ketoprofen alone. It should be mentioned that despite these significant increases in glucose concentration, the blood glucose concentration remained within the upper portion of the reference interval. For suppression of pain- or stress-associated hyperglycemia, tramadol + ketoprofen was best, whereas codeine alone had a minimal effect.

Mean serum cortisol concentrations did not exceed 6 mg/mL, which meant that they were high but within the physiologic reference interval, and no significant differences among groups or times were detected, which suggested satisfactory analgesia. Increases in cortisol concentrations were detected for individual dogs, which could empirically be associated with increases in blood glucose concentrations. However, most of these concentrations were only slightly higher than the physiologic reference interval and were detected at 1 hour after analgesic administration, which indicated that stress could have derived from additional factors other than pain (eg, recovery from anesthesia).

Interleukin-6 is a proinflammatory, pain-generating cytokine that has active roles in immunologic responses, neoplasia, osteoclastogenesis, and osteoclast activity, among other processes. There are conflicting results among studies involving proinflammatory ILs and neoplasia that may be explained by differences in methods of measurement, study populations, pathological conditions, and cytokines evaluated. Investigators in a study of humans with squamous cell carcinoma of the oral cavity and oropharyngeal region found a mean IL-6 serum concentration of 87 pg/mL. Unfortunately, few studies have related the physiologic range for this cytokine in dogs, especially dogs with oncological disease. A study in which investigators compared healthy dogs with dogs naturally infected with visceral leishmaniasis revealed mean plasma concentrations of 7.4 ± 3.8 pg/mL and 16.2 ± 6.6 pg/mL, respectively, as determined by use of a human IL-6 ELISA. The study reported here, in which we used a canine IL-6 ELISA, revealed higher concentrations of this cytokine at baseline, which corroborated the general belief that this IL is strongly associated with bone inflammation and bone pain. This is an interesting finding because measurement of IL-6 could be used to indentify populations with injurious diseases that involve inflammation.

An increase in serum IL-6 concentrations should be expected in animals with excessive stress, signs of pain, surgical stimulus, or substantial injury. In a local intervention, only a small increase in plasma IL-6 concentrations is expected, as opposed to the much larger increase in IL-6 concentrations at the surgical site. Conversely, anesthesia and opioid use have been related to diminished serum cytokine concentrations and other inhibition of the immune response. In the present study, serum IL-6 concentrations remained relatively unchanged, with no significant difference among times (including baseline) or treatment groups, independent of whether an opioid was used as part of the analgesic regimens. Such a finding could indicate satisfactory pain control in all treatment groups, which was confirmed by direct evaluation of signs of pain and of a lack of increase in cortisol concentrations, as previously discussed. This could be evaluated in future studies by analysis of other proinflammatory ILs (eg, IL-1β) as well as tumor necrosis factor and C-reactive protein.

Although all animals in the study were of the same species and selected in accordance with specific criteria (ie, species, type of disease, and treatment), the clinical nature of this study posed some limitations on the data obtained, particularly data referring to breeds, which in
turn, reflected on variability in size, body weight, and sex. The number of dogs was also limited, given the criteria and need for owner consent. Because this was a clinical trial involving procedures that were known to cause pain, it was believed that a group of dogs that did not receive analgesia would be of no benefit because rescue analgesia would have to be promptly provided and no further values for subsequent time points would be available for comparison. The clinical nature of this study reflected the advantage of working with real clinical situations that are encountered daily.

Administration of analgesics in accordance with all of the protocols appeared to provide adequate analgesia. Although minor differences could be detected among the analgesic regimens, we suggest that an opioid-NSAID combination is the best alternative for this population of dogs. Furthermore, if the use of an NSAID is contraindicated, then administration of tramadol alone may be a good alternative.

References


