Comparison of the sedative effects of three nalbuphine doses, alone or combined with acepromazine, in dogs

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OBJECTIVE
To compare sedative, cardiopulmonary, and adverse effects of 3 nalbuphine doses, administered alone or in combination with acepromazine, in dogs.

ANIMALS
6 healthy dogs.

PROCEDURES
Dogs were administered nalbuphine (1.0, 1.5, or 2.0 mg/kg, intravenously [IV]) combined with physiologic saline solution (1 mL, IV; treatments SN1.0, SN1.5, and SN2.0, respectively) or acepromazine (0.05 mg/kg, IV; treatments AN1.0, AN1.5, and AN2.0, respectively) in random order, with a 1-week washout interval between treatments. Sedation scores, heart rate, mean arterial pressure, respiratory rate, and rectal temperature were recorded before and 20 minutes after administration of saline solution or acepromazine (T0), and nalbuphine was administered at T0. Measurements were repeated 15, 30, 60, 90, and 120 minutes after nalbuphine administration.

RESULTS
Treatments SN and AN resulted in at least 120 minutes of mild sedation and 60 minutes of moderate sedation, respectively. Sedation scores were greater for treatments AN1.0, AN1.5, and AN2.0 at various times, compared with scores for treatments SN1.0, SN1.5, and SN2.0, respectively. Administration of nalbuphine alone resulted in salivation and panting in some dogs.

CLINICAL RELEVANCE
All nalbuphine doses promoted mild sedation when administered alone, and moderate sedation when combined with acepromazine. Greater doses of nalbuphine did not increase sedation scores. All treatments resulted in minimal changes in heart rate, respiratory rate, rectal temperature, and mean arterial pressure. Nalbuphine alone resulted in few adverse effects.

Nalbuphine is an opioid agonist-antagonist (κ-opioid receptor agonist and μ-opioid receptor antagonist) used to induce sedation in dogs.1,2 It has minimal adverse effects on cardiopulmonary parameters in dogs2–4 and is an alternative to butorphanol, in that it has the same mechanism of action and similar effects on physiological parameters as butorphanol, but results in less sedation.2 Panting, nausea, vomiting, and stimulation of the CNS are reported adverse effects if nalbuphine is administered rapidly intravenously (IV).5

To date, few studies have been published about the sedative, cardiopulmonary, and adverse effects of nalbuphine when administered at doses > 0.5 mg/kg in dogs.5 The objective of the study reported here was to compare sedative, cardiopulmonary, and adverse effects of 3 nalbuphine doses (1.0, 1.5, and 2.0 mg/kg), administered alone or in combination with acepromazine, in dogs. We hypothesized that nalbuphine would cause dose-dependent increases in sedation scores, that the addition of acepromazine would increase the level of sedation, and that changes in cardiopulmonary parameters would be minimal.

Materials and Methods

Animals
The study was performed at the Instituto de Veterinária of Universidade Federal Rural do Rio de Janeiro, Brazil. Six adult mixed-breed dogs, 3 males and 3 females, between 3 and 4 years of age, and weighing 10.9 ± 1.5 kg (mean ± SD) were used in the study. All dogs were judged to be healthy on the basis of the results of a physical examination, CBC, and serum biochemical profile. Dogs with aggressive behavior or obesity (body condition score > 6/9)
were excluded. The study was approved by the Animal Care and Ethics Committee of the Instituto de Veterinária of Universidade Federal Rural do Rio de Janeiro, Brazil (no. 7033270820).

**Procedures**

Dogs were administered nalbuphine (1.0, 1.5, or 2.0 mg/kg, IV) combined with physiologic saline solution (1 mL, IV; treatments SN1.0, SN1.5, and SN2.0, respectively) or acepromazine (0.05 mg/kg, IV; treatments AN1.0, AN1.5, and AN2.0, respectively) in random order, with a 1-hour washout interval between treatments. Food was withheld for 12 hours and water was withheld for 2 hours prior to the start of each treatment.

For each treatment, dogs were allowed to acclimatize in a small, quiet room with a temperature of 25°C for at least 30 minutes before baseline values for heart rate (HR), respiratory rate (RR), rectal temperature (RT), and mean arterial pressure (MAP) were recorded. HR was determined by auscultation. RR was measured with a digital thermometer (LifeWindow 9X; Digicare Biomedical Technology Inc). Degree of sedation was scored with both a numeric descriptive scale (NDS) from 0 to 3 (0 = no sedation; 1 = mild sedation; 2 = moderate sedation; and 3 = intense sedation) and a simple numerical scale (SNS) from 0 to 10 (0 = no sedation and 10 = the greatest sedation possible). Initially, the dogs were observed on a steel table without interaction for 30 minutes. They were then placed on a nonslip floor in lateral recumbency for the measurement of the other variables. Last, they were placed on a nonslip floor and encouraged to stand and walk. A single observer familiar with each dog’s normal behavior was assigned to perform all evaluations. This observer was blinded to the treatments administered.

A single observer (Angiocath BD Catheter; Becton Dickinson) placed a 22-gauge catheter (Kwik-Cath BD Catheter; Angiocath) in a cephalic vein for drug administration. Dogs were then given physiologic saline (0.9% sodium chloride) solution (1 mL, IV) or acepromazine (0.05 mg/kg, IV; Acepren 0.2%; Univet SP), according to the assigned treatment, over a 1-minute period. Twenty minutes later (T0), sedation scores, HR, RR, RT, and MAP were again recorded. The dogs were then given 1 of the 3 doses of nalbuphine (1.0, 1.5, or 2.0 mg/kg; IV; Nubain; Cristália Produtos Químicos e Farmacêuticos Ltda) diluted in 5 mL saline solution and administered over 5 minutes.

Sedation scores, HR, MAP, and RR were recorded 15 (T15), 30 (T30), 60 (T60), 90 (T90), and 120 (T120) minutes after nalbuphine administration; RT was recorded at T30, T60, T90, and T120. Any episodes of salivation, vocalization, excitation, vomiting, defecation, or panting were recorded.

**Statistical analysis**

The Shapiro-Wilk test was used to determine whether data were normally distributed, and one-way ANOVA with treatment and time as the main factors was used to test for differences in HR, MAP, RR, and RT among treatments and over time. The Bonferroni correction for multiple pairwise comparisons was used to determine which treatments differed. Differences between baseline and values recorded at each subsequent time point and differences between T0 values and values recorded at each subsequent time point were assessed with one-way repeated-measures ANOVA followed by the Dunnett test. Differences among treatments in regard to NDS and SNS sedation scores at all time points and over time were analyzed with the Friedman test followed by a post hoc multiple pairwise comparison with the Bonferroni correction for multiple comparisons. Differences among treatments in regard to sedation scores at all time points and over time were analyzed with the Friedman test followed by a post hoc multiple pairwise comparison with the Bonferroni correction for multiple comparisons.

**Table 1**—Sedation scores (on a scale from 0 to 3 with a numeric descriptive scale and on a scale from 0 to 10 with a simple numeric scale) recorded for 6 dogs administered nalbuphine (1.0, 1.5, or 2.0 mg/kg, intravenously [IV]) combined with physiologic saline solution (1 mL, IV; treatments SN1.0, SN1.5, and SN2.0, respectively) or acepromazine (0.05 mg/kg, IV; treatments AN1.0, AN1.5, and AN2.0, respectively); nalbuphine was administered at time 0, 20 minutes after IV administration of saline solution or acepromazine.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment</th>
<th>T0</th>
<th>T15</th>
<th>T30</th>
<th>T60</th>
<th>T90</th>
<th>T120</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDS (0–3)</td>
<td>SN1.0</td>
<td>0</td>
<td>1.0–2.0</td>
<td>1.0–2.0</td>
<td>1.0–2.0</td>
<td>1.0–2.0</td>
<td>1.0–2.0</td>
</tr>
<tr>
<td></td>
<td>SN1.5</td>
<td>0</td>
<td>1.0–2.0</td>
<td>1.0–2.0</td>
<td>1.0–2.0</td>
<td>1.0–2.0</td>
<td>1.0–2.0</td>
</tr>
<tr>
<td></td>
<td>SN2.0</td>
<td>0</td>
<td>1.0–2.0</td>
<td>1.0–2.0</td>
<td>1.0–2.0</td>
<td>1.0–2.0</td>
<td>1.0–2.0</td>
</tr>
<tr>
<td></td>
<td>AN1.0</td>
<td>1.5</td>
<td>2.0–2.0</td>
<td>2.0–2.0</td>
<td>2.0–2.0</td>
<td>2.0–2.0</td>
<td>2.0–2.0</td>
</tr>
<tr>
<td></td>
<td>AN1.5</td>
<td>1.0</td>
<td>2.0–2.0</td>
<td>2.0–2.0</td>
<td>2.0–2.0</td>
<td>2.0–2.0</td>
<td>2.0–2.0</td>
</tr>
<tr>
<td></td>
<td>AN2.0</td>
<td>1.0</td>
<td>2.0–3.0</td>
<td>2.0–3.0</td>
<td>2.0–3.0</td>
<td>2.0–3.0</td>
<td>2.0–3.0</td>
</tr>
<tr>
<td>SNS (0–10)</td>
<td>SN1.0</td>
<td>0</td>
<td>4.5–6.0</td>
<td>4.5–6.0</td>
<td>5.0–6.0</td>
<td>3.0–5.0</td>
<td>2.5–6.0</td>
</tr>
<tr>
<td></td>
<td>SN1.5</td>
<td>0</td>
<td>4.5–6.0</td>
<td>4.5–6.0</td>
<td>4.0–6.0</td>
<td>4.0–6.0</td>
<td>3.5–6.0</td>
</tr>
<tr>
<td></td>
<td>SN2.0</td>
<td>0</td>
<td>3.0–6.0</td>
<td>3.0–6.0</td>
<td>3.5–6.0</td>
<td>2.5–5.0</td>
<td>1.0–5.0</td>
</tr>
<tr>
<td></td>
<td>AN1.0</td>
<td>4.5</td>
<td>5.0–6.0</td>
<td>5.0–6.0</td>
<td>5.0–6.0</td>
<td>5.0–6.0</td>
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<tr>
<td></td>
<td>AN1.5</td>
<td>3.0</td>
<td>5.0–7.0</td>
<td>5.0–7.0</td>
<td>5.0–7.0</td>
<td>5.0–7.0</td>
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<td>4.0</td>
<td>5.0–6.0</td>
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<td>5.0–6.0</td>
<td>5.0–6.0</td>
<td>5.0–6.0</td>
</tr>
</tbody>
</table>

Data are reported as median (range).
NDS = Numeric descriptive scale. SNS = Simple numeric scale. T = Time.
*Significantly (P < .05) different from the T0 value for the same treatment. **Significantly (P < .05) different from the value for treatment SN1.0 at the same time. †Significantly (P < .05) different from the value for treatment SN1.5 at the same time. ‡Significantly (P < .05) different from the value for treatment SN2.0 at the same time.
the Dunn multiple comparison test. Values of \( P < .05 \) for ANOVA and \( P < .008 \) for the Bonferroni correction were considered significant. All statistical analyses were performed with standard software (SigmaPlot, version 11.0; Systat Software Inc).

## Results

### Sedation

Mild sedation was recorded for treatments SN1.0, SN1.5, and SN2.0 during the 120 minutes of evaluation (Table 1). At T0 for treatments SN1.0, SN1.5, and SN2.0, 1 dog was mildly sedated (NDS score, 1; SNS score, 2). At various time points for treatments SN1.0, SN1.5, and SN2.0, NDS and SNS scores were significantly greater than scores at T0. Two dogs following treatments SN1.0 and SN2.0, and 3 dogs following treatment SN1.5 had moderate sedation (NDS score, 2) at least 1 time point during the study. There were no significant differences among treatments SN1.0, SN1.5, and SN2.0 in regard to NDS and SNS scores.

Administration of acepromazine resulted in mild to moderate sedation (Table 1). At T0, 3 dogs with treatment AN1.0 and 2 dogs with treatments AN1.5 and AN2.0 had moderate sedation (NDS score, 2). Only 1 dog with treatment AN2.0 did not show sedation (NDS score, 0) at T0. For treatments AN1.0, AN1.5, and AN2.0, NDS and SNS scores were significantly greater at various times than scores recorded at T0. At T15, all 6 dogs with treatment AN1.0 and 5 dogs with treatment AN1.5 had moderate sedation (NDS score, 2). With treatment AN2.0, 1 dog had mild sedation (NDS score, 1), 4 dogs had moderate sedation (NDS score, 2), and 1 dog had intense sedation (NDS score, 3) at T15. There were no significant differences among treatments AN1.0, AN1.5, and AN2.0 in regard to NDS and SNS scores.

At various times, NDS and SNS scores were significantly (\( P < .001 \)) greater for treatments AN1.0,

### Table 2—Heart rate, mean arterial pressure, respiratory rate, and rectal temperature for the dogs in Table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment</th>
<th>BL (min)</th>
<th>T0 (min)</th>
<th>T15 (min)</th>
<th>T30 (min)</th>
<th>T60 (min)</th>
<th>T90 (min)</th>
<th>T120 (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>SN1.0</td>
<td>35 ± 12</td>
<td>37 ± 10</td>
<td>31 ± 16</td>
<td>28 ± 11</td>
<td>26 ± 9</td>
<td>23 ± 9b</td>
<td>27 ± 9b</td>
</tr>
<tr>
<td></td>
<td>SN1.5</td>
<td>43 ± 10</td>
<td>35 ± 6</td>
<td>27 ± 8a</td>
<td>27 ± 12b</td>
<td>23 ± 5b</td>
<td>27 ± 4b</td>
<td>20 ± 7b</td>
</tr>
<tr>
<td></td>
<td>SN2.0</td>
<td>33 ± 14</td>
<td>33 ± 15</td>
<td>24 ± 7</td>
<td>23 ± 5</td>
<td>18 ± 2b</td>
<td>23 ± 6b</td>
<td>21 ± 6b</td>
</tr>
<tr>
<td></td>
<td>AN1.0</td>
<td>39 ± 15</td>
<td>31 ± 16</td>
<td>28 ± 11</td>
<td>26 ± 9</td>
<td>23 ± 9b</td>
<td>27 ± 9b</td>
<td>21 ± 4b</td>
</tr>
<tr>
<td></td>
<td>AN1.5</td>
<td>35 ± 9</td>
<td>28 ± 7</td>
<td>19 ± 6b</td>
<td>18 ± 4b</td>
<td>18 ± 2b</td>
<td>19 ± 5b</td>
<td>19 ± 3b</td>
</tr>
<tr>
<td></td>
<td>AN2.0</td>
<td>35 ± 8</td>
<td>23 ± 6</td>
<td>17 ± 3b</td>
<td>17 ± 2b</td>
<td>16 ± 0b</td>
<td>15 ± 3b</td>
<td>16 ± 2b</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>SN1.0</td>
<td>38.9 ± 0.5</td>
<td>38.7 ± 0.6</td>
<td>NA</td>
<td>38.4 ± 0.7</td>
<td>38.3 ± 0.6</td>
<td>38.2 ± 0.6b</td>
<td>38.1 ± 0.6b</td>
</tr>
<tr>
<td></td>
<td>SN1.5</td>
<td>38.3 ± 0.1</td>
<td>38.2 ± 0.2</td>
<td>NA</td>
<td>38.0 ± 0.3</td>
<td>37.9 ± 0.3b</td>
<td>37.9 ± 0.3b</td>
<td>37.8 ± 0.4b</td>
</tr>
<tr>
<td></td>
<td>SN2.0</td>
<td>38.6 ± 0.6</td>
<td>38.3 ± 0.4</td>
<td>NA</td>
<td>38.1 ± 0.5</td>
<td>37.9 ± 0.4b</td>
<td>38.0 ± 0.3</td>
<td>37.8 ± 0.4b</td>
</tr>
<tr>
<td></td>
<td>AN1.0</td>
<td>38.7 ± 0.6</td>
<td>38.4 ± 0.4</td>
<td>NA</td>
<td>38.1 ± 0.5</td>
<td>37.9 ± 0.4b</td>
<td>38.0 ± 0.3</td>
<td>37.8 ± 0.4b</td>
</tr>
<tr>
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<td>38.8 ± 0.3</td>
<td>38.2 ± 0.2</td>
<td>NA</td>
<td>37.8 ± 0.3b</td>
<td>37.5 ± 0.5a</td>
<td>37.6 ± 0.5a</td>
<td>37.4 ± 0.6b</td>
</tr>
<tr>
<td></td>
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<td>38.0 ± 0.3</td>
<td>NA</td>
<td>37.6 ± 0.2b</td>
<td>37.6 ± 0.2b</td>
<td>37.6 ± 0.2b</td>
<td>37.5 ± 0.3ab</td>
</tr>
</tbody>
</table>

Data are reported as mean ± SD.

AN1.0 = nalbuphine (1.0 mg/kg, intravenous [IV]) combined with acepromazine (0.05 mg/kg, IV). AN1.5 = nalbuphine (1.5 mg/kg, IV) combined with acepromazine (0.05 mg/kg, IV). AN2.0 = nalbuphine (2.0 mg/kg, IV) combined with acepromazine (0.05 mg/kg, IV). BL = Baseline (immediately prior to the administration of saline solution or acepromazine). HR = Heart rate. MAP = Mean arterial pressure. NA = Not available (not measured). RR = Respiratory rate. RT = Rectal temperature. SN1.0 = nalbuphine (1.0 mg/kg, IV) combined with physiologic saline solution (1 mL, IV). SN1.5 = nalbuphine (1.5 mg/kg, IV) combined with physiologic saline solution (1 mL, IV). SN2.0 = nalbuphine (2.0 mg/kg, IV) combined with physiologic saline solution (1 mL, IV). AN1.0 = acepromazine (0.05 mg/kg, IV) combined with physiologic saline solution (1 mL, IV). AN1.5 = acepromazine (0.05 mg/kg, IV) combined with physiologic saline solution (1 mL, IV). AN2.0 = acepromazine (0.05 mg/kg, IV) combined with physiologic saline solution (1 mL, IV). T = Time.

\(^{a}\)Significantly (\( P < .05 \)) different from the T0 value for the same treatment. \(^{b}\)Significantly (\( P < .05 \)) different from the baseline value for the same treatment. \(^{c}\)Significantly (\( P < .05 \)) different from the value for treatment AN1.5 at the same time. \(^{d}\)Significantly (\( P < .05 \)) different from the value for treatment SN1.5 at the same time.
AN1.5, and AN2.0 than for treatments SN1.0, SN1.5, and SN2.0, respectively (Table 1).

**Cardiopulmonary variables**

Compared with baseline and T0 values, HR, MAP, RR, and RT were significantly less at various times throughout the study, depending on the treatment administered (Table 2). HR, RR, and RT were not significantly different among treatments SN1.0, SN1.5, and SN2.0. At T30, MAP was significantly ($P = .017$) less with treatment SN1.0 than with treatment SN1.5.

Compared with baseline and T0 values, HR, MAP, RR, and RT were significantly less at various times throughout the study for treatments AN1.0, AN1.5, and AN2.0 (Table 2). MAP, RR, and RT were not significantly different among treatments AN1.0, AN1.5, and AN2.0. Compared with the values recorded after treatment AN1.5, HR was significantly less at T60 following treatment AN1.0 ($P = .029$) and at T120 following treatment AN2.0 ($P = .015$). At various times, HR, MAP, RR, and RT were significantly less for treatments AN1.0, AN1.5, and AN2.0 compared with treatments SN1.0, SN1.5, and SN2.0, respectively (Table 2).

**Adverse effects**

Salivation was recorded in 2 dogs with treatments SN1.0 and SN2.0, and in 1 dog with treatment SN1.5. Panting was recorded in 1 dog with treatment SN1.0 (values for this dog were excluded from analyses of RR). No adverse effects were recorded with treatments AN1.0, AN1.5, and AN2.0.

**Discussion**

Our hypothesis that nalbuphine doses of 1.0, 1.5, and 2.0 mg/kg would cause dose-dependent increases in the degree of sedation was not supported. The results of our study suggested that all doses of nalbuphine, when administered alone, resulted in mild sedation and that administration in combination with acepromazine resulted in moderate sedation. Few adverse effects and no clinically relevant changes in measured cardiopulmonary variables were recorded.

Prior to the study, we had expected that greater doses of nalbuphine would increase the degree of sedation. The fact that this did not happen may suggest that the ability of nalbuphine to induce sedation may have a ceiling effect, as observed in previous studies of antinociceptive effects, reversal of sedative effects, and effects on intraoperative and early postoperative pain.

When administered alone, all doses of nalbuphine used in our study resulted in longer-lasting mild sedation compared with the previously reported duration of sedation when nalbuphine was administered at a dose of 0.5 mg/kg. In our study, all doses of nalbuphine alone resulted in moderate sedation in some dogs, which did not occur when nalbuphine was administered at a dose of 0.5 mg/kg. These results suggest there may be a dose-dependent increase in the duration of sedation when comparing a nalbuphine dose of 0.5 mg/kg with doses of 1.0, 1.5, and 2 mg/kg.

Administration of acepromazine (0.05 mg/kg) promoted mild sedation, similar to that observed in previous studies. All combinations of acepromazine (0.05 mg/kg) and nalbuphine (1.0, 1.5, and 2 mg/kg) used in our study promoted 60 minutes of moderate sedation, which was similar to the sedation observed when the same dose of acepromazine was combined with a 0.5-mg/kg dose of nalbuphine. Thus, when moderate sedation is desired, there does not seem to be any great advantage to using higher doses of nalbuphine.

The results of our study suggested that the use of high doses of nalbuphine promoted minimal reductions in HR, MAP, RR, and RT. Although we evaluated only a few cardiopulmonary variables, our results agreed with those of previous studies.

The rate of IV administration of nalbuphine influences the occurrence of adverse effects. In our study, even when nalbuphine was diluted and administered slowly, some dogs that received nalbuphine alone developed salivation. However, we cannot say whether even slower administration would have prevented salivation. It is likely that the absence of salivation in dogs that received the acepromazine-nalbuphine combinations was a result of the action of the phenothiazine, which has an antiemetic effect and reduces glandular secretions.

Panting is characterized by increased RR as part of a compensatory thermoregulatory response and is commonly observed in awake dogs receiving pure opioid agonists such as morphine and methadone. The occurrence of panting in only 1 dog in our study, even with high doses of nalbuphine, was likely a result of antagonism of the μ-opioid receptor produced by nalbuphine.

The main limitation of our study was the failure to perform a statistical sample size or power calculation, which decreases the reliability of our results. Although the multiparametric monitor and digital thermometer used in the study had been recently in accordance with the manufacturer’s recommendations, the fact that we did not follow American College of Veterinary Internal Medicine guidelines for ensuring temperature and blood present measurement accuracy can be considered a limitation of our study. The evaluation of only a few cardiopulmonary variables were also considered limitations of this study.

On the basis of our results, we concluded that, in healthy dogs, nalbuphine doses of 1.0, 1.5, and 2.0 mg/kg promoted mild sedation when administered alone, and promoted moderate sedation when combined with acepromazine (0.05 mg/kg). All doses produced minimal decreases in HR, MAP, RR, and RT, with no clinical important differences among doses. Salivation and panting were the only adverse effects caused by nalbuphine alone.

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References