Evaluation of sedative and cardiorespiratory effects of romifidine and romifidine-butorphanol in cats

André L. Selmi, DVM, MS; Glenda R. Barbudo-Selmi, DVM, MS; Carla F. Moreira, DVM; Christine S. Martins, DVM, MS; Bruno T. Lins, DVM; Guilherme M. Mendes, DVM; Concepta McManus, PhD

Objective—To determine sedative and cardiorespiratory effects of romifidine alone and romifidine in combination with butorphanol and effects of preemptive atropine administration in cats sedated with romifidine-butorphanol.

Design—Randomized crossover study.

Animals—6 healthy adult cats.

Procedures—Cats were given saline solution followed by romifidine alone (100 µg/kg [45.4 µg/lb], IM), saline solution followed by a combination of romifidine (40 µg/kg [18.1 µg/lb], IM) and butorphanol (0.2 mg/kg [0.09 mg/lb], IM), or atropine alone (0.04 mg/kg [0.02 mg/lb], SC) followed by romifidine (40 µg/kg, IM) and butorphanol (0.2 mg/kg, IM). Treatments were administered in random order, with a 1-week interval between treatments. Physiologic variables were determined before and after drug administration. Time to recumbency, duration of recumbency, time to recover from sedation, and subjective evaluation of sedation, muscle relaxation, and analgesia were assessed.

Results—Bradycardia developed in all cats that received saline solution and romifidine-butorphanol or romifidine alone. Preemptive administration of atropine prevented bradycardia for 50 minutes in cats given romifidine-butorphanol. Oxyhemoglobin saturation was significantly decreased 10 minutes after romifidine-butorphanol administration in atropine-treated cats.

Conclusions and Clinical Relevance—Results suggested that administration of romifidine alone or romifidine-butorphanol causes a significant decrease in heart rate and that preemptive administration of atropine prevents bradycardia for 50 minutes. (J Am Vet Med Assoc 2002;221: 506–510)

Various α2-adrenoceptor agonists, particularly xylazine hydrochloride and medetomidine, are used to induce sedation and analgesia in dogs and cats. Romifidine is an α2-adrenoceptor agonist that has rarely been evaluated in cats in recent years,1,2,3 despite its extensive evaluation in dogs. According to some reports,1,2 romifidine dosages from 10 to 120 µg/kg (4.5 to 54.4 µg/lb) induce adequate sedation in dogs. Like other α2-adrenoceptor agonists, romifidine seems to have important anesthetic-sparing effects.

Similarly to other agents in this class, romifidine causes adverse effects such as bradycardia, bradypnea, and hypothermia in dogs and cats2,4,5 and a biphasic change in arterial pressure characterized by initial hypertension followed by hypotension in dogs.6,7

Butorphanol is an opioid agonist-antagonist drug used for postoperative pain control and as a sedative, especially when combined with α2-adrenoceptor agonists.5,8 When combined with romifidine, it causes a significant decrease in heart and respiratory rates in dogs.7

Results of studies7,8 indicate that preemptive administration of anticholinergics prevents bradycardia induced by α2-adrenoceptor agonists but prolongs the hypertension caused by α2-adrenoceptor agonists. Routine use of an anticholinergic with medetomidine may be disadvantageous because of prolonged and severe hypertension.7 Preemptive administration of glycopyrrolate in dogs prevents romifidine-induced bradycardia but causes a significant increase in arterial pressure.8 When romifidine (100 µg/kg [45.4 µg/lb]) is combined with ketamine (20 mg/kg [9 mg/lb]) and atropine (0.05 mg/kg [0.02 mg/lb]) in cats, it causes a significant decrease in heart rate, respiratory rate, and rectal temperature.7

Despite the great number of studies4,8,9 of romifidine in dogs, to our knowledge, the cardiorespiratory effects of IM administration of romifidine alone or in combination with butorphanol in cats and the effects of preemptive administration of atropine in cats sedated with romifidine and butorphanol have not been compared. Therefore, the purpose of this study was to compare sedative and cardiorespiratory effects of IM administration of romifidine alone and romifidine-butorphanol as well as the effects of preemptive atropine administration in cats sedated with romifidine-butorphanol.

Materials and Methods

Cats—Six male domestic shorthair cats were used in this study. Mean ± SD age was 2.0 ± 0.4 years; mean weight was 2.5 ± 0.67 kg (5.5 ± 1.7 lb). Cats were housed in approved facilities, fed a standard commercial diet, and given water ad libitum. All cats were considered to be healthy on the basis of results of a physical examination, serum biochemical analyses, and CBC. Vaccinations were current for all cats, and all cats had been dewormed recently. The study protocol was approved by the institution’s animal care and use committee.

Study design—A random order crossover design was
used. Treatments consisted of SC administration of saline (0.9% NaCl) solution (0.5 ml) followed 10 minutes later by administration of romifidine alone (100 µg/kg, IM), administration of saline solution followed 10 minutes later by a combination of romifidine (40 µg/kg [18.1 µg/lb], IM) and butorphanol (0.2 mg/kg [0.09 mg/lb], IM) or administration of atropine (0.04 mg/kg [0.02 mg/lb], SC) followed 10 minutes later by a combination of romifidine (40 µg/kg, IM) and butorphanol (0.2 mg/kg, IM). A minimum interval of 1 week was allowed between treatments. The study was masked in that the observer was unaware of the drug regimen that had been used.

Baseline values were determined immediately prior to drug administration. Noninvasive oscillometric systolic arterial blood pressure (SAP), diastolic arterial blood pressure (DAP), and arterial hemoglobin oxygen saturation (SpO2) were determined 6 times by use of a multiparametric monitor, and means were calculated for each variable. Heart rate (HR) was obtained by use of a stethoscope placed on the lateral aspect of the left thorax. Respiratory rate (RR) was measured by observing thoracic excursions. Rectal temperature (RT) was measured by use of a digital thermometer. Monitoring of blood pressure was achieved by placing a cuff circumferentially around the left antebrachium of the cat; cuff width was approximately 40% of the total diameter of the limb. An infrared sensor for SpO2 determination was placed on the cat's lips during all measurements.

After baseline data (–10 minutes) were collected, cats were given atropine or saline solution. Ten minutes later, romifidine alone or romifidine-butorphanol was administered IM. The latter were drawn up separately and combined in a single syringe immediately prior to administration. Heart rate, RR, SAP, DAP, MAP, SpO2, and RT were measured 10 minutes after administration of atropine or saline solution and 5, 10, 20, 30, 40, 50, and 60 minutes after administration of romifidine or romifidine-butorphanol. Time from administration of romifidine or romifidine-butorphanol to lateral recumbency (when the cat was considered totally relaxed, lying in lateral recumbency on a solid surface) was recorded, as well as duration of lateral recumbency (from start of lateral recumbency to when the cat lifted its head a few centimeters for the first time) and time to recover from sedation (from end of lateral recumbency to when the cat was considered totally relaxed, lying in lateral recumbency). One cat given saline solution followed by romifidine-butorphanol did not assume lateral recumbency until 20 minutes later, and this cat was eliminated from statistical analyses. One cat that received romifidine alone recovered from sedation after 30 minutes and was also eliminated from statistical analyses. For the remaining cats, time to lateral recumbency after IM drug administration was < 3 minutes with no significant differences among treatment regimens. Duration of lateral recumbency was longer in the romifidine-alone group, but this difference was not significant. Cats that received saline solution followed by romifidine alone acquired lateral recumbency after 2.5 ± 1.0 minutes. Duration of sedation and time of recovery were 89.5 ± 56.7 and 3.2 ± 4.5 minutes, respectively.

Cardiorespiratory variables and evaluating adequacy of sedation, analgesia, and muscle relaxation did not know which treatment cats had received.

Statistical analyses—Cardiorespiratory variables were compared among drug treatments by means of ANOVA for repeated measures followed by the Tukey test to compare values within and between groups. Sedation, muscle relaxation, and analgesia were analyzed by use of a Friedman test in each group to assess changes from basal values with time and to compare the differences among groups at each time point. Time to assumption of lateral recumbency, duration of lateral recumbency, and time to recover from sedation were compared by use of a Student t test. For all analyses, values of P < 0.05 were considered significant. Data are given as mean ± SD.

Results

Before sedation there were no significant differences among treatment groups for any variable. One cat given saline solution followed by romifidine-butorphanol did not assume lateral recumbency until 20 minutes later, and this cat was eliminated from statistical analyses. One cat that received romifidine alone recovered from sedation after 30 minutes and was also eliminated from statistical analyses. For the remaining cats, to lateral recumbency after IM drug administration was < 3 minutes with no significant differences among treatment regimens. Duration of lateral recumbency was longer in the romifidine-alone group, but this difference was not significant. Cats that received saline solution followed by romifidine alone recovered from lateral recumbency after 2.5 ± 1.0 minutes. Duration of sedation and time of recovery were 89.5 ± 56.7 and 3.2 ± 4.5 minutes, respectively.

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minutes, respectively. When cats were given saline solution followed by romifidine-butorphanol, time from drug administration to lateral recumbency was 3.0 ± 0.6 minutes. Duration of lateral recumbency was 58.2 ± 3.5 minutes and time to recover from sedation was 3.1 ± 1.3 minutes. When cats were given atropine, time from administration of romifidine-butorphanol to lateral recumbency was 3.1 ± 0.4 minutes. Duration of lateral recumbency was 53.5 ± 4.1 minutes and time to recovery from sedation was 3.5 ± 1.5 minutes.

Sedation, muscle relaxation, and analgesia did not differ among groups before IM administration of romifidine or romifidine-butorphanol. Sedation scores increased significantly in all groups after IM administration of sedative drugs. However, scores after drug administration were not different among groups over time (Fig 1).

Time to recovery from sedation was longer in cats given atropine followed by romifidine-butorphanol, but not significantly. Duration of lateral recumbency was longer in cats given romifidine alone, but not significantly.

Vomiting was observed in 4 cats given saline solution followed by romifidine-butorphanol. One cat given atropine followed by romifidine-butorphanol vomited after administration of the sedative drug combination. None of the cats that received romifidine alone vomited, but all salivated.

Heart rate was significantly decreased in cats given romifidine alone or romifidine-butorphanol 5 minutes after drug administration, compared with baseline values. In cats given atropine before administration of romifidine-butorphanol, HR was significantly increased 10 minutes after atropine administration; HR returned to baseline values 5 minutes after romifidine-butorphanol administration, although HR was significantly decreased 50 minutes after drug administration (Table 1). Heart rate was higher from 5 through 40 minutes in cats given atropine and romifidine-butorphanol, compared with cats given saline followed by romifidine alone or romifidine-butorphanol, but differences were not significant. When compared with cats that received romifidine alone, HR was significantly higher in both groups of romifidine-butorphanol-treated cats after 50 minutes of drug administration. The lowest HR recorded when cats were given saline solution and then sedated with romifidine-butorphanol was 76 beats/min (10 minutes after romifidine-butorphanol administration), whereas in cats that received romifidine alone the lowest HR was 64 beats/min.

Arterial hemoglobin oxygen saturation was significantly lower 5 minutes after romifidine-butorphanol administration in cats treated with atropine, compared with baseline values, and differed significantly from romifidine and butorphanol-romifidine-treated cats (Table 1). Mean arterial blood pressure, SABP, DABP, and RR were not significantly affected over time. However, at 20 and 60 minutes after administration of romifidine alone in cats treated with saline solution, MABP was higher than in cats that received the romifidine-butorphanol combina-

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Table 1—Mean ± SD values for cardiorespiratory variables determined at various times (~10 to 60 minutes) in 6 cats sedated with romifidine alone (100 µg/kg [45.4 µg/ft], IM) or a combination of romifidine (40 µg/kg [18.1 µg/ft], IM) and butorphanol (0.2 mg/kg [0.09 mg/ft], IM), after IM administration of atropine (0.04 mg/kg [0.02 mg/ft], SC) or saline (0.9% NaCl, 0.5 ml/solution)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>SR</td>
<td>168.4 ± 32.1</td>
<td>166.4 ± 13.7</td>
<td>116.1 ± 17.2</td>
<td>83.8 ± 20.6</td>
<td>90.6 ± 18.1</td>
<td>87.8 ± 14.0</td>
<td>78.5 ± 14.5</td>
<td>81.3 ± 17.2</td>
</tr>
<tr>
<td>RR (breaths/min)</td>
<td>SR</td>
<td>54.9 ± 6.3</td>
<td>53.2 ± 5.2</td>
<td>52.9 ± 5.2</td>
<td>53.9 ± 5.2</td>
<td>52.8 ± 5.6</td>
<td>46.4 ± 11.5</td>
<td>42.0 ± 5.2</td>
<td>43.4 ± 10.3</td>
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<tr>
<td>SABP (mm Hg)</td>
<td>SR</td>
<td>117.0 ± 12.2</td>
<td>119.6 ± 3.3</td>
<td>108.0 ± 14.8</td>
<td>118.6 ± 8.8</td>
<td>120.0 ± 7.54</td>
<td>115.0 ± 4.2</td>
<td>118.0 ± 13.5</td>
<td>116.8 ± 10.3</td>
</tr>
<tr>
<td>DABP (mm Hg)</td>
<td>SR</td>
<td>84.8 ± 8.6</td>
<td>87.0 ± 13.66</td>
<td>78.2 ± 13.4</td>
<td>80.6 ± 10.0</td>
<td>86.2 ± 19.3</td>
<td>76.4 ± 3.0</td>
<td>80.7 ± 14.3</td>
<td>79.2 ± 9.5</td>
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<tr>
<td>MABP (mm Hg)</td>
<td>SR</td>
<td>94.1 ± 7.5</td>
<td>96.6 ± 4.5</td>
<td>90.0 ± 16.8</td>
<td>98.2 ± 8.9</td>
<td>102.4 ± 7.8</td>
<td>95.8 ± 2.4</td>
<td>98.1 ± 11.1</td>
<td>96.2 ± 8.4</td>
</tr>
<tr>
<td>SpO2 (%)</td>
<td>SR</td>
<td>96.4 ± 1.1</td>
<td>95.4 ± 0.5</td>
<td>97.5 ± 0.7</td>
<td>95.0 ± 4.2</td>
<td>95.6 ± 1.5</td>
<td>97.0 ± 2.0</td>
<td>97.0 ± 1.1</td>
<td>96.7 ± 0.8</td>
</tr>
<tr>
<td>RT (C)</td>
<td>SR</td>
<td>38.7 ± 0.4</td>
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<td>38.2 ± 0.4</td>
<td>38.8 ± 0.5</td>
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<td>38.2 ± 0.8</td>
<td>38.5 ± 0.8</td>
<td>37.9 ± 0.4</td>
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</table>

*Significantly (P < 0.05) different from baseline (~10 minute) value.

HR = Heart rate, SR = Saline solution and romifidine, SRB = Saline solution and romifidine-butorphanol, ARB = Atropine and romifidine-butorphanol, RR = Respiratory rate, SABP = Systolic arterial blood pressure, DABP = Diastolic arterial blood pressure, MABP = Mean arterial blood pressure, SpO2 = Arterial hemoglobin oxygen saturation, RT = Rectal temperature.

**Within columns, values with different superscripts are significantly (P < 0.05) different.
tion, although the difference was not significant. Overall, SABP, DABP, and MABP were higher in cats treated with romifidine alone than in cats treated with romifidine-butorphanol, but differences were not significant.

Discussion
Results of this study suggest that IM administration of a combination of romifidine (40 µg/kg) and butorphanol (0.2 mg/kg) in cats that have received atropine has minimal effects on cardiorespiratory function and that administration of romifidine alone (100 µg/kg, IM) causes a significant decrease in HR.

Time to onset of lateral recumbency was longer in this study than that obtained in dogs; however, in our study IM administration may have been responsible for the slower onset of recumbency. One cat that received romifidine alone and another that received romifidine-butorphanol after saline administration were excluded from the study because the degree of sedation was insufficient to allow monitoring of the evaluated parameters. A similar response was observed in a dog following administration of medetomidine. Possibly, the drug combination was deposited between muscle sheaths during injection, or the response could be attributed to previous adrenergic stimulation in these cats, which partially blocked the sedative effects of romifidine or romifidine-butorphanol.

Cats given romifidine alone had similar scores for sedation, muscle relaxation, and analgesia as when they were given romifidine-butorphanol. Lack of differences could be attributed to the lower dose of romifidine used in combination with butorphanol, which may have resulted in lack of synergistic sedative effects.

α2-Adrenoceptor agonists induce bradycardia through an increase in arterial pressure and partially by central sympatho-mimetic mechanisms. Romifidine is a specific α2-adrenoceptor agonist and has actions and adverse effects typical of this group of drugs. In dogs, romifidine alone or combined with butorphanol induces significantly decreased heart and respiratory rates following IV administration. Heart rate and RR decrease significantly in cats given atropine followed by romifidine (100 µg/kg [45.4 µg/lb], IM) and ketamine (20 mg/kg [9 mg/lb]) and in cats given medetomidine (80 µg/kg [36.3 µg/lb]) followed by ketamine (5 mg/kg [2.3 mg/lb]). Heart rate and RR are affected in a dose-dependent manner following romifidine administration. In our study, HR decreased significantly following administration of romifidine alone or after administration of romifidine-butorphanol in cats that received saline solution and after 50 minutes in cats given atropine. Results of a recent study indicate that concurrent administration of medetomidine (30 µg/kg [13.6 µg/lb]), butorphanol (0.2 mg/kg, IM), and glycopyrrolate (0.01 mg/kg [0.0045 mg/lb]) in dogs causes a significant decrease in HR and RR (both after 5 minutes) and that HR returns to baseline values 10 minutes after drug administration; RR remained less than baseline values up to 50 minutes after drug administration. It has been reported that IM administration of anticholinergics concurrent with administration of medetomidine does not prevent medetomidine-induced bradycardia. Short concluded that administration of atropine or glycopyrrolate prior to administration of medetomidine (30 or 60 µg/kg [13.6 or 27.2 µg/lb]) is effective in preventing medetomidine-induced bradycardia. Results of recent studies have also confirmed this finding. Concurrent administration of butorphanol with lower dosages of romifidine may have facilitated the increase in parasympathetic tone associated with romifidine, thereby increasing the incidence of bradycardia, defined as HR < 140 beats/min, as observed in cats that received the romifidine-butorphanol combination; however, HR decreased only after 50 minutes of sedation in cats given atropine 10 minutes prior to administration of romifidine-butorphanol, probably because of the short duration of action of atropine.

Respiratory rate was not affected by administration of romifidine alone or romifidine-butorphanol administration in cats. Results of a recent study indicate that IM administration of romifidine (100 µg/kg) and ketamine (20 mg/kg) after atropine significantly decreases RR. Similarly, use of medetomidine (80 µg/kg [36.3 µg/lb]) and ketamine (5 mg/kg [2.3 mg/lb]) in cats also causes a significant reduction in RR. In dogs, medetomidine-butorphanol causes a significant decrease in RR, compared with medetomidine alone or medetomidine-ketamine. The reason RR was not significantly affected in our study might be that we used lower doses, compared with previous studies in which α2-adrenoceptor agonists were combined with butorphanol.

In dogs, IV administration of doses ranging from 25 to 100 µg/kg (11.3 to 45.4 µg/lb) of romifidine causes an increase in SABP 3 minutes later, but blood pressure decreases thereafter. When lower doses (5 and 10 µg/kg) are used, this finding is not observed. Medetomidine-ketamine significantly increased SABP in cats and dogs. In dogs given atropine, followed 10 minutes later by medetomidine (range, 10 to 40 µg/kg), a significant increase in SABP, MABP, and DABP is observed, but not in dogs that receive saline solution prior to medetomidine administration. In our study, neither treatment caused a significant effect on SABP, MABP, or DABP, possibly because a lower dose of romifidine was used or because of the technique used to monitor blood pressure. However, results of a recent study indicate that oscillometric pressure monitoring in anesthetized cats correlates well with direct arterial pressure monitoring. Mean arterial blood pressure was increased at 20 and 60 minutes after administration of romifidine alone, which could be explained by an increase in SABP at these times; however, these differences were not significant. The higher values obtained for arterial pressure when cats where given romifidine alone could be related to the dose-dependent increase in systemic vascular resistance, as observed in a recent study with dogs.

Clonidine, an α2-adrenoceptor agonist, is used in
humans to correct hypertension.\textsuperscript{9} Clonidine causes hypotension when plasma concentrations are 2 ng/ml; concentrations of 2 to 10 ng/ml cause less hypotension, and concentrations > 10 ng/ml cause mild hypertension.\textsuperscript{10} Findings of our study contrast those of studies in cats in which anesthesia was induced by a combination of xylazine and ketamine\textsuperscript{16} or medetomidine and ketamine.\textsuperscript{10} In the former study, the drugs induced hypotension, whereas in the latter study, the drugs caused hypertension. It is possible that although the drugs have similarities, they may induce different effects. It may be speculated that IM administration of 100 µg/kg of romifidine in cats does not cause significant changes in arterial pressure, as observed in this study.

A significant decrease in SpO\textsubscript{2} 5 minutes after administration of romifidine-butorphanol in cats given atropine could have resulted from atropine- and romifidine-induced hypotension; however, this did not correlate with the values obtained by use of the oscillometric technique to monitor blood pressure. However, detectable changes in arterial blood pressure could have been observed if the monitoring been done before the fifth minute after administration of romifidine or romifidine-butorphanol.

Emesis is a common effect of α\textsubscript{2}-adrenoceptor agonists in cats.\textsuperscript{17,18} Vomiting was observed in 30% of cats given romifidine-ketamine and in 1 cat given xylazine-ketamine following atropine.\textsuperscript{1} In our study, 4 of 6 cats given saline solution vomited after romifidine-butorphanol administration, whereas only 1 cat given atropine vomited after romifidine-butorphanol administration. Cats given romifidine alone did not vomit but did have excessive salivation. This corroborates the fact that atropine prevents vomiting induced by α\textsubscript{2}-adrenoceptor agonists.\textsuperscript{19}

We conclude that romifidine alone (100 µg/kg) or a combination of romifidine (40 µg/kg) and butorphanol (0.2 mg/kg) induces the same degree of sedation, but prior administration of atropine is indicated to prevent bradycardia in cats when a romifidine-butorphanol combination is used.

\begin{itemize}
\item Sedivet, Boehringer, São Paulo, SP, Brazil.
\item Torbugesic, Fort Dodge, Iowa.
\item Dixtal DX 2010, Dixtal do Brasil, AM, Brazil.
\item Digital clinical thermometer, Omrom, China.
\end{itemize}

\section*{Appendix}

Criteria for scoring sedation, analgesia, and muscle relaxation in cats

<table>
<thead>
<tr>
<th>Score</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No sedation</td>
</tr>
<tr>
<td>1</td>
<td>Mild sedation (recumbent, head down, strong palpebral reflex, normal eye position)</td>
</tr>
<tr>
<td>2</td>
<td>Moderate sedation (recumbent, head down, moderate palpebral reflex, partial ventromedial eye rotation)</td>
</tr>
<tr>
<td>3</td>
<td>Profound sedation (recumbent, head down, palpebral reflex absence, complete ventromedial eye rotation)</td>
</tr>
</tbody>
</table>

\section*{References}


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