Cardiovascular effects of a high dose of romifidine in propofol-anesthetized cats

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Objective—To determine the hemodynamic effects of IM administration of romifidine hydrochloride in propofol-anesthetized cats.

Animals—15 adult domestic shorthair cats.

Procedure—Cats were randomly assigned to receive romifidine (0, 400, or 2,000 µg/kg, IM). Cats were anesthetized with propofol and mechanically ventilated with oxygen. The right jugular vein, left carotid artery, and right femoral artery and vein were surgically isolated and catheterized. Heart rate; duration of the PR, QRS, and QT intervals; mean pulmonary artery pressure; mean right atrial pressure; systolic, diastolic, and mean arterial pressures; left ventricular systolic pressure; left ventricular end-diastolic pressure; and cardiac output were monitored. Systemic vascular resistance, rate of change of left ventricular pressure, and rate pressure product were calculated. Arterial and venous blood samples were collected anaerobically for determination of pH and blood gas tensions (P2O and PCO2).

Results—Administration of romifidine at 400 and 2,000 µg/kg, IM, decreased heart rate, cardiac output, rate of change of left ventricular pressure, rate pressure product, and pH. Arterial and pulmonary artery pressures, left ventricular pressure, left ventricular end-diastolic pressure, and right atrial pressure increased and then gradually returned to baseline values. Arterial blood gas values did not change, whereas venous PCO2 increased and venous PO2 decreased. Significant differences between low and high dosages were rare, suggesting that the dosages investigated produced maximal hemodynamic effects.

Conclusions and Clinical Relevance—Romifidine produces cardiovascular effects that are similar to those of other α2-agonists. High dosages of romifidine should be used with caution in cats with cardiovascular compromise. (Am J Vet Res 2002;63:1241–1246)

The α2-agonists are commonly used to produce sedation, analgesia, and muscle relaxation in dogs, cats, and horses and are adjuncts administered during general anesthesia to reduce the amount of injectable and inhalant anesthetic required. Although recognized for their relatively predictable sedative and analgesic properties, α2-agonists, including xylazine hydrochloride, detomidine hydrochloride, and medetomidine hydrochloride, are also known for their cardiovascular effects including bradycardia, decreases in cardiac output, and increases in systemic vascular resistance.7-17 Arterial blood pressure remains unchanged, or increases initially, followed by a longer period of reduced pressure below baseline values. Interestingly, indices of cardiac contractility and myocardial oxygen consumption (ie, pressure rate product) remain relatively unchanged or decrease only minimally with time.7-15 These hemodynamic effects may not be dose-dependent throughout the clinical range, and a plateau or ceiling effect has been reported for cardiovascular effects when medetomidine is administered at high dosages to cats and dogs (> 150 µg/kg in cats8 and > 120 µg/kg in dogs9).

Sedative and analgesic effects of α2-agonists are attributed to the activation of presynaptic α2-agonist receptors in the CNS, whereas cardiovascular effects are attributed to a decrease in CNS sympathetic outflow and activation of peripheral vascular α2-agonist receptors.4,13 Activation of peripheral vascular α2-agonist receptors causes vasoconstriction, increasing arterial blood pressure and decreasing vascular (particularly venous) capacitance, which thereby increases baroreflex activity to produce bradycardia.14,15 Similar to other members of this class of drugs, romifidine, which is estimated to be one-fifth as potent as medetomidine, can cause sedation in dogs, cats, and horses.12,15 In dogs, heart rate, cardiac index, and stroke work index decrease following romifidine administration, whereas central venous pressure, pulmonary capillary wedge pressure, and systemic vascular resistance increase.19 Furthermore, arterial blood pressure initially increases, followed by a prolonged decrease, and rate pressure product (RPP) decreases.19 Analysis of results of those studies3,10 suggests that relatively low dosages of romifidine produce effects that are not dose-dependent and produce less severe hemodynamic effects than medetomidine, although the authors admitted that the degree of sedation was also diminished.

Propofol is an ultra-short acting, nonbarbiturate, hypnotic, injectable anesthetic used to produce and maintain general anesthesia in dogs and cats.19-21 In contrast to thiopental, propofol does not accumulate because of its rapid clearance and large volume of distribution.22 Propofol often is used to induce general anesthesia in dogs and cats prior to the administration of inhalant anesthetics (isoflurane, sevoflurane) and has been used in combination with α2-agonists in dogs as part of a total intravenous anesthetic protocol.18,23 The objective of the study reported here was to determine the cardiovascular effects for 2 dosages of romifidine when administered to propofol-anesthetized cats. We selected a dosage of romifidine that...
was at the upper limit of the clinically recommended dosage range (400 µg/kg) for cats and another dosage that was 5 times that value to determine whether administration of these doses would produce dose-dependent effects.

Materials and Methods

Animals—Fifteen purpose-bred domestic shorthair cats that were > 1 year old and weighed between 3.9 and 5.5 kg were used in the study. Cats were judged to be healthy on the basis of results of physical examination and analysis of an ECG and hemogram. This study was approved by the Laboratory Animal Care and Use Committee of The Ohio State University and was conducted in compliance with good laboratory practices.

Surgical procedures—Propofol was administered for the induction (6 mg/kg, IV) and maintenance (10 mg/kg/h, IV) of anesthesia. Cats were endotracheally intubated with a cuffed endotracheal tube, which was then attached to a ventilator that was set to deliver 100% oxygen at a rate of 6 to 10 breaths/min and volume of 12 to 15 ml/kg. The Paco2 was maintained between 35 and 40 mm Hg. A small amount (0.1 ml) of 2% lidocaine hydrochloride was diluted to a volume of 1 ml by the addition of saline (0.9% NaCl) solution and injected into the right and left jugular furrow and right inguinal area prior to surgical isolation of the right jugular vein, left carotid artery, and right femoral vein and artery, respectively.

A 4-F flow-directed thermodilution catheter was introduced into the right jugular vein and advanced until the distal tip was positioned in the pulmonary artery. This catheter was used to determine core (pulmonary artery) temperature, pulmonary artery pressure, and cardiac output. Cardiac output was measured by injecting 1 ml of ice-cold saline solution into the proximal port of the catheter. Mean value for 3 injections was used to calculate cardiac output for each recording period. A 4-F catheter that contained 2 pressure-sensing micromanometers located at the tip was advanced into the left carotid artery and positioned so that the distal pressure sensor was located in the left ventricle and the proximal pressure sensor was located in the ascending aorta. The right femoral artery and vein were catheterized by use of polyethylene 90 tubing and polyethylene 160 tubing, respectively. Taps of those catheters were advanced to the level of the diaphragm. A lead-II ECG was continuously recorded. A circulating hot-water blanket and heat lamp were used to maintain body temperature between 37 and 39 C. All cats were administered warmed, lactated Ringer’s solution (5 ml/kg/h) throughout the procedure.

Procedure—The procedures facilitated measurement of heart rate, duration of the PR, QRS, and QT intervals, mean pulmonary artery pressure (mPAP), mean right atrial pressure (RAP), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), left ventricular systolic pressure (LVSP), left ventricular end-diastolic pressure (LVEDP), and cardiac output. These hemodynamic variables were used to calculate systemic vascular resistance (SVR), left ventricular rate of change of pressure (+dP/dt), and RPP. The RPP was calculated as the product of heart rate times MAP. All data were continuously monitored and periodically recorded by use of a computer-based data acquisition system for physiologic measurements. Blood samples collected anaerobically from the right femoral vein and artery were used to determine venous and arterial pH and blood gas tensions (P02 and Pco2), respectively. All cats were euthanatized at the end of the study by IV administration of an overdose of sodium pentobarbital (120 mg/kg).

Experimental design—Cats were allowed to stabilize for 15 minutes after insertion of all catheters and recording instruments. Baseline data for heart rate, duration of the PR, QRS, and QT intervals, mPAP, RAP, SAP, DAP, MAP, LVSP, LVEDP, cardiac output, SVR, left ventricular +dP/dt, and RPP were obtained 15 and 5 minutes before drug administration (time 0), and data were also obtained 5, 15, 30, 60, 90, 120, and 240 minutes after drug administration. The cats were randomly assigned into 3 groups and administered romifidine IM as follows: group 1 (3 cats), 0.0 µg/kg; group 2 (6), 400 µg/kg; and group 3 (6), 2,000 µg/kg.

Statistical analysis—Data within and among groups were compared by use of an ANOVA for repeated measures. Pairwise comparisons within and among groups were performed by use of the Dunnet and Tukey post hoc tests. A value of P < 0.05 was considered significant.

Figure 1—Mean ± SD hemodynamic effects after IM administration of romifidine (0 µg/kg [circle], 400 µg/kg [square], and 2,000 µg/kg [triangle]) to 3 groups of propofol-anesthetized cats. Time 0 = Time of romifidine administration. †Within a treatment group, value differs significantly (P < 0.05) from value for 0 µg/kg. ‡Within a treatment group, value differs significantly (P < 0.05) from value for 5 minutes.

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### Results

All measured and calculated hemodynamic variables remained unchanged from baseline values in cats of group 1. Heart rate decreased from baseline values in cats of groups 2 and 3 after IM administration of romifidine. Heart rate remained decreased for approximately 120 minutes and then began to return toward baseline values. The decrease in heart rate was similar after administration of romifidine at 400 and 2,000 μg/kg (Fig 1). The QRS interval did not change from baseline values after administration of romifidine at 400 or 2,000 μg/kg, whereas the PR and QT intervals increased from baseline values 5 minutes after IM administration of romifidine; however, those values were within reference ranges for cats (data not shown).

The increases in PR and QT intervals paralleled changes in heart rate. Cardiac arrhythmias were not observed, and changes in intervals for the ECG variables were similar after administration of romifidine at 400 and 2,000 μg/kg.

The SAP, DAP, and MAP increased from baseline values in both groups of cats that received romifidine. The MAP remained increased for approximately 60 minutes and then gradually returned to baseline values by 90 minutes after drug administration (Fig 1). Changes in MAP were similar after administration of romifidine at 400 and 2,000 μg/kg. The LVSP increased from baseline values in cats administering romifidine.

### Table 1

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<thead>
<tr>
<th>Romifidine (μg/kg)</th>
<th>Time (min)</th>
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<tr>
<td></td>
<td>-15</td>
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<td>Systolic arterial pressure (mm Hg)</td>
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<td>133 ± 48</td>
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<tr>
<td>400</td>
<td>127 ± 29</td>
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<td>Diastolic arterial pressure (mm Hg)</td>
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<td>97 ± 27</td>
</tr>
<tr>
<td>400</td>
<td>97 ± 27</td>
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<tr>
<td>2,000</td>
<td>93 ± 27</td>
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<td>Left ventricular systolic pressure (mm Hg)</td>
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<tr>
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<tr>
<td>Left ventricular diastolic pressure (mm Hg)</td>
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<tr>
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**Table 1**—Mean ± SD hemodynamic and metabolic effects after IM administration of various doses of romifidine to 3 groups of propofol-anesthetized cats.
Cardiac output decreased from baseline values in cats administered romifidine, it reached a nadir value 5 minutes after romifidine administration (Fig 1). The decrease in cardiac output paralleled the decrease in heart rate. Cardiac output remained decreased for the duration of the study period but began to return toward baseline values at 90 minutes in cats administered 400 µg/kg. Left ventricular +dP/dt did not change in any cat immediately following IM administration of romifidine, but it began to decrease at approximately 60 minutes after administration of 400 and 2,000 µg/kg (Table 1). Changes in left ventricular +dP/dt were similar after administration of 400 and 2,000 µg/kg. The SVR increased from baseline values in all cats administered romifidine. The SVR remained increased for approximately 90 minutes after IM administration of romifidine and then gradually decreased but did not return to baseline values by the end of the 240-minute recording period. The RPP decreased but at later times after the administration of 400 or 2,000 µg/kg.

Arterial pH, PaCO2, and PaCO2 did not change in any cat in any of the 3 groups at any time point following administration of romifidine (Table 1). Venous PCO2 gradually increased from baseline values after the administration of 400 and 2,000 µg/kg, reaching peak values at 240 minutes. Changes in venous PCO2 were similar after administration of 400 and 2,000 µg/kg. Venous PO2 decreased from baseline values 5 minutes after administration of 400 and 2,000 µg/kg and remained decreased for the duration of the experiments. The changes in venous PO2 were similar after administration of 400 and 2,000 µg/kg. Blood temperature was unchanged from baseline values after IM administration of romifidine.

Discussion

To our knowledge, the results reported here are the first to document that romifidine produces hemodynamic effects in cats that are qualitatively similar to those reported after administration of xylazine, medetomidine, and detomidine in cats, dogs, and horses. Bradycardia may account for most but not all of the decrease in cardiac output, because cardiac output continues to decrease after change in heart rate reaches a plateau. Dramatic decreases in cardiac output following the administration of α2-agonists in general and romifidine in particular in the study reported here are responsible for the associated decrease in venous PO2 and increase in venous PCO2, because blood would be expected to spend more time in the capillary exchange vessels. The decrease in cardiac output is probably not related to a direct effect on cardiac
interfere with pressor effects of romifidine, but it may contribute to the long-term decreases in arterial blood pressure. Additional studies are required in spontaneously breathing cats to determine whether a combination of propofol-romifidine negatively impacts cardiovascular stability.

Additional studies are indicated in cats to investigate the dose-response characteristics of lower dosages of romifidine than those used in the study reported here, as well as those of other commonly used α2-agonists, to determine the dose at which maximal cardiovascular effects are produced. It also is necessary to determine whether such doses would produce clinically relevant sedative, analgesic, and anesthetic-sparing effects.

References


