Sedative and cardiopulmonary effects of buccally administered detomidine gel and reversal with atipamezole in dogs

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Received January 7, 2018.
Accepted April 19, 2018.

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OBJECTIVE
To evaluate hemodynamic, respiratory, and sedative effects of buccally administered detomidine gel and reversal with atipamezole in dogs.

ANIMALS
8 adult purpose-bred dogs.

PROCEDURES
Arterial and venous catheters were placed. Baseline heart rate, respiratory rate, cardiac output (determined via lithium dilution with pulse contour analysis), oxygen delivery, systemic vascular resistance, arterial blood gas values, and sedation score were obtained. Detomidine gel (2.0 mg/m^2) was administered on the buccal mucosa. Cardiopulmonary data and sedation scores were obtained at predetermined times over 180 minutes. Atipamezole (0.1 mg/kg) was administered IM at 150 minutes. Reversal of sedation was timed and scored. Data were analyzed with an ANOVA.

RESULTS
Compared with baseline values, heart rate was lower at 45 to 150 minutes, cardiac output and oxygen delivery were lower at 30 to 150 minutes, and systemic vascular resistance was increased at 30 to 150 minutes. There were no significant changes in $Paco_2$, Pao_2, or lactate concentration at any time point, compared with baseline values, except for lactate concentration at 180 minutes. All dogs became sedated; maximum sedation was detected 75 minutes after administration of detomidine. Mean ± SD time to recovery after atipamezole administration was 7.55 ± 1.89 minutes; sedation was completely reversed in all dogs. No adverse events were detected.

CONCLUSIONS AND CLINICAL RELEVANCE
Buccally administered detomidine gel was associated with reliable and reversible sedation in dogs, with hemodynamic effects similar to those induced by other α_2-adrenoceptor agonists. Buccally administered detomidine gel could be an alternative to injectable sedatives in healthy dogs. (*Am J Vet Res* 2018;79:1253–1260)

Options for safe and effective orally administered sedatives have traditionally been limited, regardless of species. Historically, the only widely used noncontrolled orally administered sedative available for use in dogs has been acepromazine, which is a phenothiazine that induces sedation as a dopamine receptor antagonist in the CNS.[1] However, absorption of orally administered acepromazine and sedation provided by oral administration of that drug is inconsistent.[2,3] Acepromazine is associated with a reduction in stroke volume, CO, and hypotension mediated by the drug's action as an α_1-adrenoceptor antagonist and the subsequent vasodilation[1]; effects of the drug are not reversible, which leaves clinicians without recourse should an animal develop undesirable or substantial compromising cardiovascular effects. Therefore, owners and veterinarians have few options for sedating anxious pets for stressful events.

The α_2-adrenoceptor agonists are a commonly used class of sedatives that cause consistent and reliable sedation in a variety of veterinary species. Sedation associated with α_2-adrenoceptor agonists is a result of activation of α_{2A}-adrenoceptors in the cerebral cortex and pons. The α_2-adrenoceptor agonists also cause dose-dependent, biphasic cardiovascular effects. Common changes include hypertension, reflex bradycardia, reductions in CO and stroke volume, and increases in SVR, which are later followed by a decrease in blood pressure.[1,4,5] Historically, these drugs have been available in formulations only for

ABBREVIATIONS

CO	Cardiac output
DAP	Diastolic arterial blood pressure
Do_2	Oxygen delivery
LiDCO	Cardiac output measured by use of lithium dilution
MAP	Mean arterial blood pressure
Sao_2	Arterial oxygen saturation
SAP	Systolic arterial blood pressure
SVR	Systemic vascular resistance

parenteral administration. An oral transmucosal gel formulation of detomidine hydrochloride is available for use in horses; the product was developed to facilitate sedation or chemical restraint of horses for minor procedures.[6] The pharmacokinetics and pharmacodynamics of sublingual use of detomidine gel in horses have been reported.[7] Detomidine gel can provide reliable, transient sedation in dogs and ferrets,[8,9] and the pharmacokinetics of detomidine gel in dogs has been reported.[10] The sedation provided by buccally administered detomidine gel may be appropriate for common veterinary procedures in dogs.

To our knowledge, there has been no published evaluation of the hemodynamic and respiratory effects of buccally administered detomidine gel in dogs. Similarly, subsequent reversal of these effects with atipamezole in healthy dogs has not been evaluated. Therefore, the purpose of the study reported here was to characterize the hemodynamic, respiratory, and sedative effects of a buccally administered detomidine gel in dogs and the subsequent reversal of these effects with atipamezole. The hypothesis was that detomidine gel would cause predictable sedation and hemodynamic depression, similar to results for other α_2-adrenoceptor agonists. Additionally, it was hypothesized that the hemodynamic effects would return to baseline values following IM administration of atipamezole and that the sedative effects would be reversed.

Materials and Methods

Animals

Eight adult purpose-bred institution-owned dogs were used in the study. There were 6 sexually intact male dogs and 2 sexually intact female dogs. Mean ± SD body weight was 28.8 ± 7.74 kg (range, 16.9 to 38.8 kg). Complete physical examinations were performed by an investigator (JIK) prior to the initiation of the study. A CBC, biochemical analyses, and heartworm serum ELISA were performed prior to the study; all results were within acceptable limits established by the university laboratory. All dogs were current on vaccinations and dewormed in accordance with the institutional protocol. Dogs were group housed in university laboratory animal resource facilities, fed a standard commercial diet, and provided water ad libitum throughout the study period, except for the morning of the experiment (prior to anesthesia and sedation). Food was withheld from all dogs for approximately 12 hours prior to the procedures. Dogs were weighed immediately prior to the experiment. The study protocol was approved by the North Carolina State University Institutional Animal Care and Use Committee (protocol No. 13-059).

Experimental procedures

Experiments were performed in a quiet room with only 1 dog at a time. Dogs were placed on an examination table for the experimental procedures. Anesthesia was induced by use of a face mask with sevoflurane (5% to 8%) in oxygen (flow rate, 3 to 4 L/min) via an F-circuit attached to a rebreathing anesthesia machine. Anesthetized dogs were placed in right or left lateral recumbency and intubated with an appropriately sized endotracheal tube. Anesthesia was maintained with sevoflurane (2% to 4%) in oxygen (flow rate, 1 to 2 L/min) to enable instrumentation. Monitoring of anesthetized dogs included measurement of oscillometric blood pressure, ECG, capnometry, and pulse oximetry.

Sites for catheter insertion were aseptically prepared. An 18-gauge, 2.95-cm catheter[a] was placed and secured in a cephalic vein, and a 20-gauge, 4.45-cm catheter[b] was placed and secured in a dorsal pedal artery. After the catheters were placed, the dogs were maintained in lateral recumbency, sevoflurane was discontinued, and the dogs were allowed to recover from anesthesia while breathing 100% oxygen until the time of extubation.

After the dogs were extubated, they were allowed to breathe room air for 10 minutes (equilibration period). Then, baseline arterial blood gas values (pH, Pa_{O_2}, Pa_{CO_2}, serum HCO_3^- concentration, Sa_{O_2}, and lactate concentration) were obtained by use of a commercially available handheld analyzer[c] and cartridges.[d] Arterial blood samples were obtained from the previously placed arterial catheter. Approximately 3 mL of waste blood was withdrawn, then a 3-mL blood sample was collected in a 3-mL heparinized syringe. The arterial catheter was flushed with heparinized saline (0.9% NaCl) solution, and the waste blood was returned to the dog via the previously placed venous catheter. Arterial blood gases were analyzed immediately, and the PCV and total solids concentration were obtained with heparinized microtubes and centrifugation.

Cardiac output was determined by use of a lithium dilution technique with subsequent pulse contour analysis in accordance with the manufacturer's instructions.[e] The LiDCO monitor was calibrated with 0.3 or 0.15 mmol of lithium chloride,[f] IV. The dose of lithium used was determined on the basis of body weight of each dog and ranged from 0.0084 to 0.0108 mmol/kg.

After LiDCO calibration was completed and the arterial wave form reestablished, baseline values for SAP, MAP, DAP, heart rate, SVR, CO, cardiac index, stroke volume, respiratory rate, Do_2, and Sa_{O_2} were recorded. The LiDCO software calculated several variables. Body surface area was calculated as 10.1 × body weight$^{0.67}$/100. The CO was calculated as heart rate × stroke volume/1,000. Cardiac index was calculated as CO/body surface area. The SVR was calculated as 80 × (MAP – right arterial pressure)/CO. Stroke volume was calculated as CO/heart rate × 1,000. The Do_2 was calculated as arterial oxygen concentration × CO × 10. Rectal temperature was obtained with a standard digital thermometer. Sedation was scored by use of a previously published 5-part scale for which the maximum sedation score was 16.[11] The scale was

modified slightly for conditions of the present study **(Appendix)**.

Detomidine hydrochloride gel[g] (2.0 mg/m^2) was administered via the oral transmucosal route in the right or left buccal cavity (between the gingiva of the teeth and cheek mucosa; time 0 [baseline]). Hemodynamic values were recorded at 5, 10, 15, 30, 45, 60, 67, 75, 82, 90, 105, 120, 135, and 150 minutes. Sedation was scored at 30, 45, 60, 75, 105, and 150 minutes by 1 investigator (JIK). Arterial blood gas values were determined at 30, 75, 120, and 150 minutes. The PCV and total solids concentration were obtained at 75 and 150 minutes. Rectal temperature was recorded at 45, 75, 105, and 150 minutes. Electrocardiographic rhythm abnormalities (eg, second-degree atrioventricular block) and subjective adverse effects were recorded throughout the study period. Dogs were gently restrained in lateral recumbency during all measurements.

At 150 minutes, each dog received an injection of atipamezole (0.1 mg/kg, IM) administered in a triceps muscle. Hemodynamic values were recorded every 10 minutes for 30 minutes after atipamezole injection. Rectal temperature was measured, and arterial blood gas values were determined 30 minutes after atipamezole injection. Assessment of reversal was based on several observations. Arousal time was recorded as the interval from atipamezole injection to the first signs of an altered state of sedation. Walking time was recorded as the interval from atipamezole injection to the first spontaneous steps taken by a dog. Total recovery time was recorded as the interval from atipamezole injection to the stage of vigilance at which a treated dog could not be distinguished from untreated animals. The overall effect of reversal was assessed by 1 investigator (JIK) who evaluated the posture of each dog in accordance with a previously reported scale[12] (0 = clinically normal, 1 = relaxed [tired] but standing, 2 = lying but able to stand, 3 = lying but able to stand with difficulty, and 4 = lying and unable to stand).

At the conclusion of the 180-minute hemodynamic monitoring period, the LiDCO instrumentation was removed from the dogs. As part of a concurrent pharmacokinetic study, arterial blood samples were collected in the previously described manner at predetermined times for a period of 2 to 6 hours. The dogs were continuously monitored during that time. After samples were obtained for the pharmacokinetic study, the venous and arterial catheters were removed; the dogs were then returned to their group housing and fed a meal. Seven days after the experiment, venous blood samples were obtained from each dog and used to measure BUN and creatinine concentrations for assessment of kidney function.

Statistical analysis

Data were analyzed with commercially available software.[h] Data were analyzed for normality by use of the Shapiro-Wilk test. A Friedman repeated-measures ANOVA on ranks was used to analyze nonparametric data, which was followed by a Dunn post hoc test for multiple comparisons. Parametric data were analyzed by use of a repeated-measures ANOVA, which was followed by a Dunnett post hoc test to compare values at various time points with values obtained at baseline. Significance was established at $P < 0.05$.

Results

Heart rate **(Figure 1)**, CO **(Figure 2)**, cardiac index, and Do_2 were all significantly ($P < 0.001$) lower, compared with baseline values, at 30 (exept for heart rate), 45, 60, 67, 75, 82, 90, 105, 120, 135, and 150 minutes after buccal administration of detomidine. Values for these variables were not significantly different at all time points after reversal with atipamezole, compared with baseline values. There was a significant ($P < 0.001$)

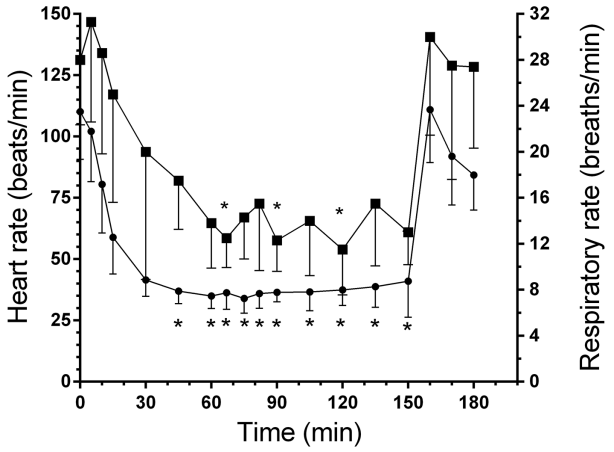

Figure 1—Mean ± SD values for heart rate (circles) and respiratory rate (squares) of 8 dogs over time after buccal administration of detomidine gel (2.0 mg/m^2) at time 0 (baseline) and injection of atipamezole (0.1 mg/kg, IM) at 150 minutes. *Value differs significantly ($P < 0.05$) from the value at time 0.

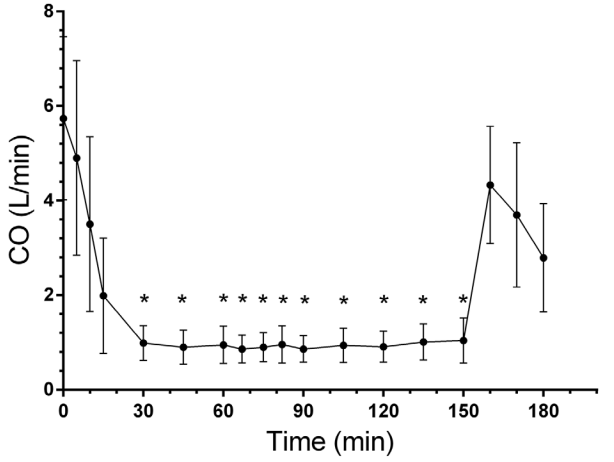

Figure 2—Mean ± SD values for CO of 8 dogs over time after buccal administration of detomidine gel and IM injection of atipamezole. **See** Figure 1 for remainder of key.

increase in SVR, compared with the baseline value, at 30, 45, 60, 67, 75, 82, 90, 105, 120, 135, and 150 minutes after detomidine administration **(Figure 3)**. There was a significant decrease in respiratory rate, compared with the baseline value, at 67, 90, and 120 minutes after detomidine administration. There was no significant change in SAP at any time point after administration of detomidine gel or reversal with atipamezole. There was a significant increase in MAP and DAP, compared with baseline values, at 160, 170, and 180 minutes after administration of detomidine gel (10, 20, and 30 minutes after reversal with atipamezole; **Figure 4**). Stroke volume was significantly lower, compared with the baseline value, at 45, 60, 67, 75, 82, 120, 135, and 150 minutes **(Figure 5)**. There was no significant change in stroke volume, compared with the baseline value, after reversal with atipamezole.

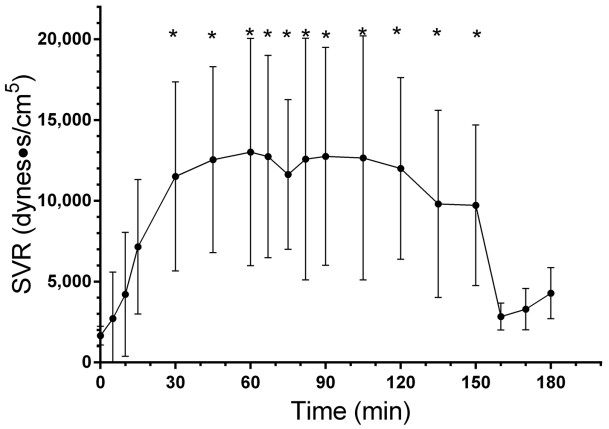

Figure 3—Mean ± SD values for SVR of 8 dogs over time after buccal administration of detomidine gel and IM injection of atipamezole. ***See*** Figure 1 for remainder of key.

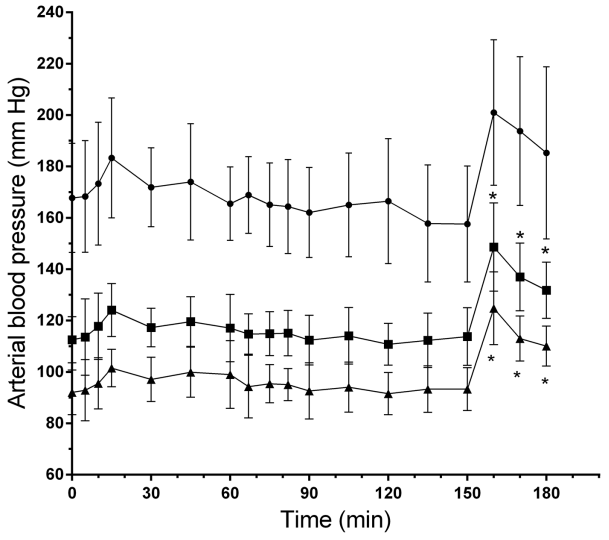

Figure 4—Mean ± SD values for SAP (circles), MAP (squares), and DAP (triangles) of 8 dogs over time after buccal administration of detomidine gel and IM injection of atipamezole. ***See*** Figure 1 for remainder of key.

All dogs developed sinus arrhythmia after buccal administration of detomidine gel, which resolved following atipamezole administration. Subjectively, the mucous membranes of all dogs had increased pallor, compared with the color at baseline, after buccal administration of detomidine gel.

Mean ± SD baseline rectal temperature was 37.7 ± 0.44°C. Compared with the baseline value, mean rectal temperature was significantly higher at 45 (38 ± 0.44°C; $P = 0.011$) and 180 (38.1 ± 0.72°C; $P = 0.017$) minutes but significantly ($P = 0.002$) lower at 150 minutes (37.3 ± 0.47°C) These changes were not considered clinically important because they were within reference limits for healthy dogs.

Values for pH, $Paco_2$, Pao_2, base excess, HCO_3^- concentration, Sao_2, and total solids concentration did not differ significantly from the baseline values at any time point after detomidine administration **(Tables 1 and 2)**. However, there was a significant ($P < 0.001$) increase in PCV at 75, 150, and 180 minutes. The only time point when there was a potentially clinically important change in PCV was 180 minutes, when mean ± SD PCV increased to 54.8 ± 3.3%. There also was a significant change in lactate concentration at 180 minutes, compared with the concentration at baseline, but the mean value was still within reference limits for healthy dogs.

Compared with the score at baseline, sedation scores were significantly ($P < 0.001$) higher at all time points, except at 150 minutes, prior to reversal with atipamezole. Peak sedation was detected at 75 minutes **(Figure 6)**.

After atipamezole was administered, mean ± SD arousal time was 3.51 ± 1.09 minutes (range, 2.0 to 5.7 minutes), mean walking time was 5.19 ± 1.23 minutes (range, 4.0 to 7.2 minutes), and mean total recovery time was 7.55 ± 1.89 minutes (range, 5.5 to 11.0 minutes).

The BUN and serum creatinine concentrations were within the respective reference ranges of the

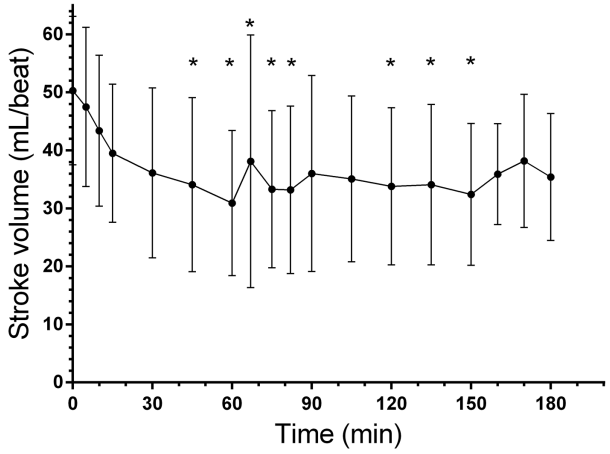

Figure 5—Mean ± SD values for stroke volume of 8 dogs over time after buccal administration of detomidine gel and IM injection of atipamezole. ***See*** Figure 1 for remainder of key.

Table 1—Mean ± SD arterial blood gas values and lactate concentration for 8 dogs buccally administered detomidine gel (2.0 mg/m^2) at time 0 and atipamezole (0.1 mg/kg, IM) at 150 minutes.

	Time (min)					
Variable	**0**	**30**	**75**	**120**	**150**	**180**
pH	7.36 ± 0.03	7.36 ± 0.02	7.35 ± 0.03	7.35 ± 0.01	7.37 ± 0.04	7.35 ± 0.03
$Paco_2$ (mm Hg)	32.0 ± 1.6	29.9 ± 3.7	30.3 ± 3.0	30.2 ± 2.1	28.5 ± 4.8	32.3 ± 3.1
Pao_2 (mm Hg)	89.5 ± 9.4	84.0 ± 5.7	87.0 ± 3.9	89.5 ± 5.1	91.4 ± 9.1	84.8 ± 5.3
Base excess (mmol/L)	–7.4 ± 3.1	–8.1 ± 3.1	–8.4 ± 4.0	–9.1 ± 3.4	–7.7 ± 3.6	–7.3 ± 3.2
HCO_3^- (mmol/L)	18.0 ± 1.2	16.8 ± 1.9	16.9 ± 2.3	16.7 ± 1.1	16.31 ± 3.1	17.8 ± 2.0
Sao_2 (%)	96.4 ± 1.3	96.0 ± 0.8	96.1 ± 0.6	96.6 ± 0.7	96.8 ± 0.9	95.9 ± 0.6
Lactate (mmol/L)	0.9 ± 0.5	0.8 ± 0.2	0.8 ± 0.4	0.8 ± 0.3	0.7 ± 0.2	1.3 ± 0.5*

*Value differs significantly ($P < 0.05$) from the value at time 0.

Table 2—Mean ± SD values for PCV and total solids concentration for 8 dogs buccally administered detomidine gel (time 0) and atipamezole (150 minutes).

	Time (min)			
Variable	**0**	**75**	**150**	**180**
PCV (%)	41.4 ± 2.7	45.9 ± 3.7*	46.9 ± 4.0*	54.8 ± 3.3*
Total solids (g/dL)	5.3 ± 0.3	5.2 ± 0.6	5.0 ± 0.5	5.7 ± 0.8

See Table1 for key.

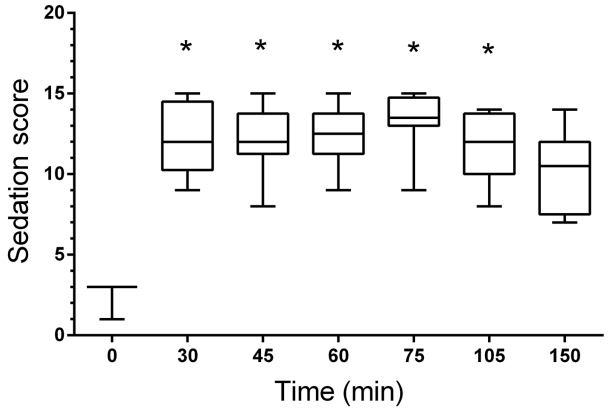

Figure 6—Box-and-whisker plots of sedation score for 8 dogs over time after buccal administration of detomidine gel and IM injection of atipamezole. Sedation was scored by the same observer at each time point by use of a scale of 0 (no sedation) to 16 (maximum sedation). Peak sedation was detected at 75 minutes. Each box represents the 25th to 75th percentiles, the horizontal line in each box represents the median, and the whiskers represent the minimum to maximum values. ***See*** Figure 1 for remainder of key.

university laboratory at 7 days after administration of detomidine gel.

Discussion

The α_2-adrenoceptor agonists can cause dose-dependent sedation and cardiovascular depression in dogs.[1] Cardiovascular effects of buccally administered detomidine gel in dogs of the study reported here were similar to those reported with the use of other α_2-adrenoceptor agonists in dogs.[13,14] There was a significant decrease in respiratory rate, CO, and Do_2 and a significant increase in SVR 30 minutes after buccal administration of detomidine gel. These changes persisted until the time of reversal with atipamezole at 150 minutes. The difference in time of onset of action of buccally administered detomidine gel versus parentally administered α_2-adrenoceptor agonists can explain the delay from time of administration to time to onset of cardiorespiratory effects of the drug. The decrease in respiratory rate can be attributed to the centrally mediated sedation that occurs with α_2-adrenoceptor agonists.[4] The increase in SVR was the result of vasoconstriction primarily caused by the drug's action at α_{2B}-adrenoceptors, but potentially there could have been some activity of detomidine as an α_1-adrenoceptor agonist.[15] The decrease in CO and, by extension, Do_2 was secondary to bradycardia and an increase in SVR, which is consistent with results of studies[16,17] that involved the use of other α_2-adrenoceptor agonists in dogs and horses.

Heart rate was significantly lower at 45 minutes and all subsequent time points prior to reversal with atipamezole. Heart rate began to slow, although not significantly, within 5 minutes after buccal administration of detomidine. The gradual decrease in heart rate was consistent with the slower onset of action of the buccally administered gel product, compared with the onset of action for parenterally administered α_2-adrenoceptor agonists. Bradycardia may have been centrally mediated by detomidine's action at α_{2A}-adrenoceptors and as a reflex following the increase in SVR[15] (SVR was significantly increased at 30 minutes). Although less consistent when compared with results for other hemodynamic variables, stroke volume was significantly lower than the baseline value at 45, 60, 67, 75, 82, 120, 135, and 150 minutes. This decrease in stroke volume may have been attributable

to depression of ventricular contractility and an increase in afterload.[18] Stroke volume was not significantly lower at 90 and 105 minutes, which was most likely a result of the high degree of variability among dogs.

The SAP, DAP, and MAP did not change significantly, compared with baseline values, at any time point after buccal administration of detomidine gel and before administration of atipamezole. On the basis of the action of other α_2-adrenoceptor agonists and the increase in SVR, significant increases in SAP, MAP, and DAP were anticipated. Although SVR increased and there was clinically apparent vasoconstriction with a decrease in heart rate, the combination of factors did not result in a significant increase in blood pressure. Hemodynamic changes are dose-related events for α_2-adrenoceptor agonists. If a higher dose of buccally administered detomidine had been investigated, perhaps changes in blood pressure would have been detected.

Significant increases in MAP and DAP, compared with baseline values, were detected at the 3 time points after atipamezole administration. These increases have also been detected at 5 and 10 minutes after injection of atipamezole in dogs that had previously received medetomidine.[19] The most likely explanation for this effect was the return (increase) of heart rate back to baseline values owing to activity as an α_{2A}-adrenoceptor antagonist,[1] which is responsible for the centrally mediated bradycardia evident with the administration of α_2-adrenoceptor agonists.

Additionally, there was a significant, clinically important increase in PCV at 180 minutes. The most likely explanation for that increase was splenic contraction secondary to direct sympathetic stimulation or lessening of the sympathetic inhibition that was caused by reversal of the detomidine gel, the latter of which has been reported in horses.[20] This significant increase in hemoglobin concentration after atipamezole administration has also been reported for dogs.[21] It is possible that if data had been collected for a longer period after atipamezole administration, the PCV may have returned to baseline values, which has been reported for horses.[20]

Except for the aforementioned changes in MAP and DAP after atipamezole administration, there were no significant changes in the hemodynamic data, compared with baseline values, at all 3 time points after administration of atipamezole. The lack of significant differences may indicate that atipamezole successfully reversed the cardiovascular effects of buccally administered detomidine in healthy dogs.

Although there was a significant decrease in respiratory rate after buccal administration of detomidine, there was no significant change in pH, $Paco_2$, Pao_2, and HCO_3^- concentration. These results are consistent with effects of other α_2-adrenoceptor agonists in dogs.[5,13] No significant increase in lactate concentration, compared with the baseline value, was observed, except at 180 minutes; however, that lactate concentration was still within the reference limit for dogs.[22] Given the significant decrease in CO and Do_2 and that dexmedetomidine has been associated with increases in lactate concentration,[23] increased lactate concentrations were anticipated. It is possible that lactate concentrations increased significantly to values greater than the upper reference limit at time points beyond the study period. When combined with the fact that BUN and creatinine concentrations were within reference limits 7 days after the experiment, the results suggested that decreases in CO and Do_2 caused by buccally administered detomidine gel were well tolerated by these healthy dogs.

The dose of detomidine gel (2 mg/m^2) was chosen on the basis of the authors' experiences with the sedative effects of lower doses of the drug.[8,10] Although sedation was achieved in those studies,[8,10] the authors believed that sedation would be more profound at a higher dose. A dose based on body surface area was chosen because it provided a metabolically more appropriate dose.[24]

The dose of atipamezole used in the present study (0.1 mg/kg) is the dose routinely used to reverse the effects of dexmedetomidine in dogs at the authors' institution.[25] Although antagonists of xylazine and dexmedetomidine are listed on the label (yohimbine and atipamezole, respectively), there is no labeled α_2-adrenoceptor antagonist for detomidine. In the present study, mean ± SD arousal time was 3.51 ± 1.09 minutes, and mean total recovery time was 7.55 ± 1.89 minutes. Because of the short interval from administration to total recovery, the authors concluded that atipamezole would be an appropriate antagonist for buccally administered detomidine in dogs. Because the use of xylazine, and by extension yohimbine, is becoming less common in small animal practice as a result of the widespread availability of dexmedetomidine, it is more likely that practitioners will have greater access to atipamezole.

A limitation of the study reported here was that it was potentially statistically underpowered as a result of the small sample size. A post hoc power analysis suggested that 12 dogs would have been optimal to determine a significant difference, compared with baseline values, with 95% confidence and 80% power. As anticipated on the basis of results of previous studies on other α_2-adrenoceptor agonists in healthy dogs, significant changes in heart rate, respiratory rate, CO, SVR, and stroke volume were detected in the present study. It was possible that the lack of significant increases in SAP, MAP, and DAP that were anticipated because of the vasoconstrictive effects of detomidine was attributable to the fact the study was underpowered. For a variety of reasons, it was not possible to perform this study on a larger homogenous group of dogs that were of similar age, breed, sex, and body weight. Consequently, results of the present study should be used with caution in clinical practice because of the limited number of dogs enrolled.

A limitation for the calculation of SVR was identified in the present study. The LiDCO software used the following equation: SVR = 80 × (MAP – right arterial pressure)/CO; however, right arterial pressure was not measured. Instead, a default value of 7 mm Hg was used for all calculations of SVR. The administration of detomidine can change right arterial pressure in horses.[18] In that study,[18] 3 doses of detomidine were administered IV to horses, and cardiovascular variables were measured. The largest increase in mean right arterial pressure was 13.4 mm Hg for a dose of 40 µg/kg. However, changes in right arterial pressure induced by detomidine administration are not known for dogs. Therefore, the authors decided to use a value of 15 mm Hg to determine the effects on SVR, compared with results for the default setting of 7 mm Hg, at the time points of significant changes in SVR (30, 60, 90, 120, and 150 minutes). The change in SVR, compared with the value for the default setting, was approximately 9%. Therefore, the exact SVR values obtained and reported for the present study may not have been accurate, but the overall increase in SVR after buccal administration of detomidine gel should have been valid.

Another potential limitation of the study results was the accuracy of arterial pulse power analysis for CO determination in the face of large changes in SVR. This limitation has been indicated in several studies, including a study[26] on evaluation of the agreement of CO determined by LiDCO and by pulse measurements in ponies receiving inotropes and a study[27] of dogs with systemic inflammatory response syndrome. In addition, it was concluded that changes in the pulse contour waveform necessitated recalibration to maintain accuracy for pigs after induced hemorrhage and administration of vasopressors.[28] However, pulse power analysis, which converts pressure data into a power number and also evaluates arterial tree compliance and the reflective waveform from the periphery, allows for changes in the SVR index.[29] Investigators of another study[30] also determined the accuracy of the LiDCO and pulse CO methods for hemodynamically stable patients with a wide variation in arterial pressure waveforms; however, the authors of that study[30] acknowledged that changes in the SVR index could lead to inaccuracies with pulse power analysis. It may be argued that the arterial pulse waveform changed dramatically and therefore the system should have been recalibrated frequently during the present study. However, recalibration was not performed after the administration of the α_2-adrenoceptor agonist detomidine because it would have interfered with the sensor used in the calibration of LiDCO and led to overestimation of CO.[31] Additionally, α_2-adrenoceptor agonists, especially xylazine, can affect the voltage of the LiDCO sensor,[32,33] which can lead to overestimation of measurements when such drugs are administered to horses prior to the determination of CO.[31] As previously discussed, the determination of CO in the present study was completed before administration of the detomidine gel. Therefore, on the basis of results of another study,[5] the robust cardiovascular changes detected in the present study should have been valid, although the exact values we obtained may not have been accurate.

The 10-minute equilibration period between extubation after anesthesia with sevoflurane for purposes of instrumentation and baseline measurement of arterial blood gases was a potential limitation of the study reported here. All baseline values were at the low end or just outside of published reference limits of arterial blood gas values for dogs breathing room air.[34]

In the study reported here, buccally administered detomidine gel was associated with reliable sedation in healthy dogs and was readily reversible with atipamezole administered IM. There were no clinically important adverse effects detected in the healthy dogs of this study. Oral transmucosal administration of detomidine gel at a dose of 2 mg/m^2 caused hemodynamic changes similar to those detected after the administration of other α_2-adrenoceptor agonists that were also reversed with atipamezole administration.

Acknowledgments

Supported by the Molecular Biomedical Sciences Department, College of Veterinary Medicine, North Carolina State University, Raleigh, NC. Dr. Messenger has received grants or honoraria from Zoetis, Jurox, Mallinckrodt, and Piedmont Animal Health.

The authors declare that there were no conflicts of interest.

Presented in abstract form at the American College of Veterinary Anesthesia annual symposium, Indianapolis, September 2014.

Footnotes

a. BD Insyte, Becton Dickinson Infusion Therapy Systems, Sandy, Utah.
b. Radial artery catheterization set, Arrow International Inc, Asheboro, NC.
c. Abbott-iStat, Abbott Laboratories, Abbott Park, Ill.
d. CG4+ cartridges, Abbott Laboratories, Abbott Park, Ill.
e. LiDCO Plus hemodynamic monitor, LiDCO Ltd, London, England.
f. Lithium chloride, LiDCO Ltd, London, England.
g. Dormosedan Gel, Orion Corp, Turku, Finland.
h. SigmaPlot, version 12.0, Systat Software Inc, Chicago, Ill.

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Appendix

System used to score sedation in dogs buccally administered detomidine gel and subsequently injected with atipamezole.

	Score				
Behavior	**0**	**1**	**2**	**3**	**4**
Spontaneous posture	Standing	Tired but standing	Lying but can stand	Lying but difficulty standing	Unable to stand
Placement on side	Strong resistance	Modest resistance	Slight resistance	No resistance	—
Response to noise	Jumps	Hears and moves	Hears and twitches ears	Barely perceives	No response
Jaw relaxation	No relaxation	Slight relaxation	Good relaxation	—	—
General attitude	Excitable	Awake and normal	Tranquil	Stuporous	—

Minimum score possible is 0, and maximum score possible is 16.

— = Not applicable.

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