# Comparative cardiovascular, analgesic, and sedative effects of medetomidine, medetomidine-hydromorphone, and medetomidine-butorphanol in dogs

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**Objective**—To compare sedative, analgesic, and cardiopulmonary effects after IV administration of medetomidine (20 µg/kg), medetomidine-hydromorphone (20 µg of medetomidine/kg and 0.1 mg of hydromorphone/kg), and medetomidine-butorphanol (20 µg of medetomidine/kg and 0.2 mg of butorphanol tartrate/kg) in dogs.

**Animals**—6 dogs healthy mixed-breed dogs.

**Procedure**—Instruments were surgically inserted, and heart rate (HR), respiratory rate (RR), systolic arterial pressure (SAP), mean arterial pressure (MAP), diastolic arterial pressure (DAP), mean pulmonary arterial pressure (MPAP), pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), core body temperature, and cardiac output (CO) were measured 0, 5, 10, 15, 30, 45, and 60 minutes after injection. Cardiac index (CI), stroke volume (SV), stroke index (SI), systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR) were calculated. Arterial samples for blood gas analysis were collected 0, 15, and 45 minutes after injection. Intensity of analgesia, degree of sedation, and degree of muscle relaxation were evaluated at aforementioned time points and 75, 90, 120, 150, 180, and 210 minutes after injection.

**Results**—Administration of medetomidine, medetomidine-hydromorphone, and medetomidine-butorphanol was associated with increases in SAP, MAP, DAP, MPAP, PCWP, CVP, SVR, PVR, core body temperature, and $Paco_2$ and decreases in HR, CO, CI, SV, SI, RR, pH, and $Pao_2$. Clinically important differences were not detected among treatments. Medetomidine-hydromorphone and medetomidine-butorphanol provided a longer duration of sedation and better quality of analgesia, compared with medetomidine alone.

**Conclusions and Clinical Relevance**—Medetomidine-hydromorphone or medetomidine-butorphanol is associated with improved analgesia and sedation but has cardiopulmonary effects comparable to those for medetomidine alone. (*Am J Vet Res* 2004;65:931–937)

One of the major challenges for veterinarians in the quest for balanced anesthetic techniques is the manipulation of positive and negative adverse effects of sedative, analgesic, and anesthetic drugs. The goal is to minimize the cardiopulmonary-depressant effects of these drugs and maximize the quality of sedation, analgesia, and anesthesia. Lower doses of 2 or more sedatives or anesthetics administered in combination are associated with enhanced sedation and analgesia and less cardiovascular depression, compared with effects after administration of a high dose of a single agent.[1]

The $\alpha_2$-adrenergic agonists are widely used in injectable sedative-analgesic combinations because of their potent sedative, muscle relaxant, analgesic, and anxiolytic effects. Medetomidine, a highly specific and potent $\alpha_2$-adrenergic agonist, has been approved by the FDA for use in dogs in the United States. It induces dose-dependent sedation and analgesia in dogs. The clinically useful dosage range is 10 to 80 µg/kg. Administration at a rate of 40 µg/kg provides analgesia and sedation that is sufficient to permit completion of minor diagnostic and therapeutic procedures.[2-5] Medetomidine has a potency-sparing effect on halothane,[6,7] isoflurane,[8] propofol,[9] ketamine,[10] and thiopental.[11]

Adverse effects of medetomidine include hypertension, bradycardia, hypotension, and vomiting.[2,4,5,8] The direct action of medetomidine on postsynaptic $\alpha_2$-receptors of vascular smooth muscle leads to vasoconstriction and an initial transient hypertension followed by pronounced bradycardia, and hypotension may be observed later. Vagally mediated reflex bradycardia is possibly the most important of these effects.[12] Attempts to correct bradycardia associated with administration of $\alpha_2$-adrenergic agonists have been ineffective,[13] resulted in worsening of the bradycardia, caused development of tachycardia, or have been associated with an increase in the incidence of ventricular ectopy.[14]

To reduce adverse effects on the cardiovascular system associated with higher doses of $\alpha_2$-adrenergic agonists, lower doses of medetomidine have been investigated in dogs.[15] Medetomidine (15 µg/kg, IV) reportedly[16] has a sympatholytic effect and is antiarrhythmogenic. Therefore, a decreased dosage of medetomidine (20 µg/kg, IV) was chosen for the study reported here.

Because a lower dose of medetomidine is associated with a reduction in the amount of sedation and analgesia,[15] 2 opioids commonly used in veterinary practice (ie, hydromorphone or butorphanol) were administered in combination with medetomidine to improve sedation and analgesia while maintaining cardiovascular stability. Hydromorphone is a semisynthetic µ-agonist with an analgesic potency approximately 8

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times that of morphine.[17] Cardiopulmonary effects of hydromorphone are comparable to those of other μ–agonists.[18] Butorphanol is a synthetic opioid with κ agonist and μ-antagonist properties, with an analgesic potency 3 to 5 times that of morphine.[19] In the study reported here, hydromorphone and butorphanol were chosen to be administered in combination with medetomidine to enhance the sedative and analgesic effects of the medetomidine.

The first objective of the study was to evaluate the sedative and analgesic effects of medetomidine, medetomidine-hydromorphone, and medetomidine-butorphanol. The second objective of the study was to evaluate and compare the cardiovascular and pulmonary effects of these combinations in dogs.

## Materials and Methods

**Animals**—Six healthy mixed-breed dogs (3 females and 3 males) that weighed (mean ± SD) 22.6 ± 1.9 kg and were between 1 and 2.5 years of age were used in the study. The dogs were current on their vaccination and deworming programs. Dogs were housed in an approved facility located at the College of Veterinary Medicine of Washington State University. An institutional animal care and use committee approved the study protocol.

**Experimental design**—A random-order, crossover design was used for the study, with each dog receiving 3 drug treatments; successive treatments were separated by a 1-week interval. Medetomidine treatment consisted of administration of only medetomidine[a] (20 μg/kg, IV). Treatment with medetomidine-hydromorphone consisted of IV administration of a combination of medetomidine (20 μg/kg) and hydromorphone[b] (0.1 mg/kg). Treatment with medetomidine-butorphanol consisted of IV administration of a combination of medetomidine (20 μg/kg) and butorphanol tartrate[c] (0.2 mg/kg). For medetomidine and medetomidine-butorphanol treatments, a small amount of sterile water was added to provide a volume equivalent to that of the medetomidine-hydromorphone combination. The appropriate amount of each product was measured separately and combined in a single syringe immediately before injection. Food was withheld from dogs overnight prior to any drug treatments. One researcher (RDK) was not aware of the treatment administered to each dog, which allowed objective evaluation of analgesic and sedative effects.

Anesthesia was induced by administration of 5% sevoflurane[d] in oxygen via a face mask by use of a small animal anesthesia machine[e]; oxygen flow rate was 5 L/min. The trachea was then intubated and the dog placed in right lateral recumbency. Anesthesia was maintained by administration of sevoflurane (end-tidal concentration, 2.8%) for 30 minutes to permit placement of an indwelling catheter[f] into the dorsal pedal artery and placement of a Swan-Ganz thermodilution catheter[g] into the pulmonary artery. Proper positioning of the tip of the Swan-Ganz catheter in the pulmonary artery was confirmed by observation of characteristic wave forms on a pressure monitor. Blood pressure was measured by use of a mercury-calibrated pressure transducer[h] connected to a pressure module and monitor.[i] The thermodilution catheter was connected to a cardiac output module and monitor.[i] Cardiac output was determined as the mean of 3 measurements at each time point, determined by injection of 5 mL of 5% dextrose solution[j] maintained at 0°C. The dorsal pedal and Swan-Ganz catheters were then securely affixed to the neck of each dog. After insertion of instruments was completed, administration of sevoflurane was discontinued. Dogs were allowed to recover for 30 minutes following extubation. Variables recorded included evaluation of sedative and analgesic effects, cardiovascular effects, respiratory effects, and calculated cardiovascular effects.

**Evaluation of sedative and analgesic effects**—To evaluate sedative effects, the interval from injection until lateral recumbency, duration of lateral recumbency, and interval from injection until each dog was able to walk normally were recorded for each treatment of each dog. In addition, intensity of analgesia as assessed by the toe-pinch response, degree of sedation as assessed by noise response (hand clap near the head) and eyeball position (unfocused and ventromedial rotation), and degree of muscle relaxation as assessed by jaw tone were evaluated 5, 10, 15, 30, 45, 60, 75, and 90 minutes after injection and at 30-minute intervals thereafter until the dogs returned to sternal recumbency. When performed at the same time points as for cardiovascular measurements, evaluation of sedative and analgesic effects was measured after cardiovascular measurements were obtained. A visual analogue scoring chart (scale of 0 to 100) was applied for recording these effects.

**Evaluation of cardiovascular effects**—Instruments were inserted to enable measurement of **heart rate (HR)**, **systolic arterial pressure (SAP)**, **mean arterial pressure (MAP)**, **diastolic arterial pressure (DAP)**, **mean pulmonary arterial pressure (MPAP)**, **pulmonary capillary wedge pressure (PCWP)**, **central venous pressure (CVP)**, core body temperature (ie, pulmonary arterial temperature), and **cardiac output (CO)**. These variables were measured prior to drug injection (time 0) and 5, 10, 15, 30, 45, and 60 minutes after injection. A physiologic monitor was used to record the aforementioned variables. Electrocardiography was used to monitor HR and rhythm. One pressure transducer was connected to the arterial catheter for monitoring SAP, MAP, and DAP. A second transducer was used for recording CVP, MPAP, and PCWP.

**Calculation of cardiovascular effects**—Calculation of several cardiovascular variables required the use of **body surface area (BSA)**, which was determined by use of the following equation[20]: BSA = (body weight$^{0.667}$ × 10.1)/10$^4$. **Cardiac index (CI)** was calculated as CI = CO/BSA. **Stroke volume (SV)** was calculated as SV = CO/HR. **Stroke index (SI)** was calculated as SI = SV/BSA. **Systemic vascular resistance (SVR)** was calculated as SVR = ([MAP – CVP]/CO) × 80. **Systemic vascular resistance index (SVRI)** was calculated as SVRI = SVR/BSA. **Pulmonary vascular resistance (PVR)** was calculated as PVR = ([MPAP – PCWP]/CO) × 80. **Pulmonary vascular resistance index (PVRI)** was calculated as PVRI = PVR/BSA. **Rate pressure product (RPP)** was calculated as RPP = HR × SAP. Values for the aforementioned cardiovascular variables were calculated for the time points 0, 5, 10, 15, 30, 45, and 60 minutes after injection.

**Evaluation of respiratory effects**—To measure pH, $Pa_{O_2}$, and $Pa_{CO_2}$, arterial blood samples were obtained from the dorsal pedal artery before drug injection (time 0) and 15 and 45 minutes after injection. Samples were stored on ice and analyzed after the dogs recovered from sedation. Analysis was performed by use of a blood gas analyzer.[k] **Respiratory rate (RR)**, mucous membrane color, and capillary refill time were evaluated before drug injection (time 0) and 5, 10, 15, 30, 45, and 60 minutes after injection.

**Statistical analysis**—All statistical analyses were performed by use of commercially available software.[l] All data were reported as mean ± SD. Data were analyzed by use of an ANOVA for repeated measures. When significant ($P < 0.05$) differences were detected, pairwise Bonferroni multiple-comparison tests were performed to detect significant differences between means.

## Results

**Sedative and analgesic effects**—We did not detect differences for the onset of lateral recumbency follow-

ing drug administration for any treatment. The transition to lateral recumbency was smooth, and all dogs became laterally recumbent within 2 minutes after injection (**Table 1**). Administration of medetomidine-hydromorphone and medetomidine-butorphanol was associated with a significantly ($P < 0.001$) longer duration of lateral recumbency (163.7 ± 37.5 minutes and 141.6 ± 21.5 minutes, respectively), compared with the duration when dogs were treated with medetomidine (103.4 ± 25.3 minutes). The medetomidine-hydromorphone treatment had the longest interval from injection until return to normal walking (236.8 ± 39.2 minutes), whereas the medetomidine treatment had the shortest interval (153.7 ± 21.7 minutes).

Quality of sedation was significantly ($P = 0.002$) better for the medetomidine-hydromorphone and medetomidine-butorphanol treatments, compared with sedation quality for the medetomidine treatment (**Figure 1**). The medetomidine-hydromorphone and medetomidine-butorphanol treatments were associated with significantly ($P = 0.04$) greater muscle relaxation, compared with values for the medetomidine treatment (data not shown), similar to the results for quality of sedation. In addition, the medetomidine-hydromorphone and medetomidine-butorphanol combinations were associated with a significant ($P = 0.004$) improvement in analgesia as measured by the response to toe-pinch stimulation, compared with results for the medetomidine treatment. Although we did not detect significant differences between the medetomidine-hydromorphone and medetomidine-butorphanol treatments, all dogs in the medetomidine-hydromorphone treatment had higher scores at each time point, indicating an improvement in sedation, muscle relaxation, and analgesia, compared with results for the medetomidine-butorphanol treatment.

Excitement was observed in 3 dogs following administration of medetomidine-hydromorphone; it was characterized by sudden movement after the IV injection. Excessive salivation was observed in 1 dog during the recovery period after the medetomidine-hydromorphone treatment. None of the dogs vomited during the study.

**Cardiovascular effects**—Cardiovascular data were summarized (**Table 2**). For all treatments, HR decreased significantly ($P < 0.001$) at 5 minutes after drug administration and remained lower than the baseline value throughout the remainder of the study. Sinus arrhythmia was observed in all treatment groups throughout the study. Second-degree atrioventricular block, a wandering pacemaker, and escape beats were also observed in some dogs.

For all treatments, MAP, MPAP, PCWP, and CVP increased significantly at 5 minutes after drug administration and then gradually decreased but maintained a value higher than the baseline value throughout the study. There was not a significant difference among treatments for these variables, except for MAP. The MAP for the medetomidine-hydromorphone treatment (128 ± 27 mm Hg) was significantly lower, compared with the MAP for the medetomidine (160 ± 17 mm Hg) and medetomidine-butorphanol (158 ± 20 mm Hg) treatments, only at the 10-minute time point. Values for SAP and DAP had responses similar to that of MAP.

Core body temperature was significantly increased for 15 minutes after drug administration, then gradu-

Table 1—Mean ± SD duration of sedation in 6 dogs after IV administration of medetomidine (20 µg/kg; M), a combination of medetomidine (20 µg/kg) and hydromorphone (0.1 mg/kg; M-H), and a combination of medetomidine (20 µg/kg) and butorphanol (0.2 mg/kg; M-B).

| Variable | M | M-H | M-B |
|---|---|---|---|
| Interval from injection until lateral recumbency (min) | 1.8 ± 1.0 | 1.2 ± 0.3 | 1.4 ± 0.4 |
| Duration of lateral recumbency (min) | 103.4 ± 25.3 | 163.7 ± 37.5* | 141.6 ± 21.5* |
| Interval from injection until normal walking (min) | 153.7 ± 21.7 | 236.8 ± 39.2* | 187.1 ± 20.7*,† |

*Within a row, value differs significantly ($P < 0.05$) from the value for M. †Within a row, value differs significantly ($P < 0.05$) from the value for M-H.

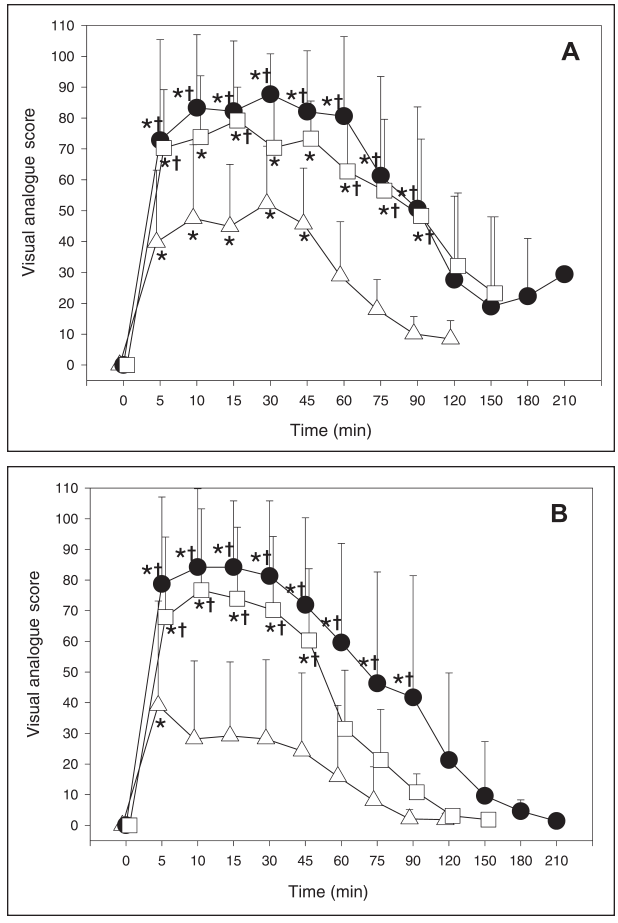


Figure 1—Effect of IV administration of medetomidine (20 µg/kg; open triangle), a combination of medetomidine (20 µg/kg) and hydromorphone (0.1 mg/kg; solid circle), and a combination of medetomidine (20 µg/kg) and butorphanol (0.2 mg/kg; open square) on sedation (A) and analgesia (B) in 6 dogs. Values reported are mean ± SD for a visual analogue scoring chart (scale of 0 to 100). Time 0 = Time of IV administration of drugs. *Within a treatment, value differs significantly ($P < 0.05$) from value at time 0. †Within a time point, value differs significantly ($P < 0.05$) from the value for the medetomidine treatment.

ally decreased and returned to baseline values at 60 minutes after injection for all treatments. We did not detect significant differences among the 3 treatments.

Values for CO and CI decreased significantly ($P < 0.001$) at 5 minutes after drug injection and were maintained lower than baseline values throughout the study for all treatments. Values for CO and CI did not differ significantly among the 3 treatments. Similar to CO, SV and SI were decreased at 5 minutes after drug administration and then gradually increased, but they were maintained at lower values than the baseline values throughout the study for all treatments. The overall SV and SI of the medetomidine-butorphanol treatment were lower than values for the medetomidine treatment; however, there was not a significant difference between these 2 treatments at any time point.

Both SVR and SVRI were significantly increased at 5 minutes after drug administration and then gradually decreased, but they were maintained at higher values than the baseline values throughout the study for all treatments. The PVR and PVRI were increased after drug administration through the 10-minute time point only (data not shown). There were no significant differences among the 3 treatments for these 4 variables. The RPP was significantly decreased at 5 minutes after drug injection for all treatments. Dogs receiving the medetomidine-butorphanol treatment had significantly higher values for RPP, compared with values when dogs received the medetomidine-hydromorphone treatment, at only the 5-minute time point.

**Respiratory effects**—Arterial blood gas data were summarized (**Table 3**). The $Paco_2$ increased significantly after administration of the medetomidine-hydromorphone and medetomidine-butorphanol treatments and was maintained through 45 minutes at values higher than the baseline value. The $Paco_2$ for the medetomidine-hydromorphone treatment was signifi-

Table 2—Effects of administration of M, M-H, and M-B on cardiovascular variables in 6 dogs.

| | | Time (min) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Variable** | **Treatment** | **0** | **5** | **10** | **15** | **30** | **45** | **60** |
| HR (beats/min) | M | 132 ± 25 | 46 ± 6* | 47 ± 9* | 49 ± 9* | 46 ± 10* | 47 ± 11* | 51 ± 14* |
| | M-H | 131 ± 16 | 50 ± 2* | 48 ± 10* | 44 ± 4* | 47 ± 10* | 53 ± 7* | 52 ± 5* |
| | M-B | 118 ± 18 | 59 ± 16* | 59 ± 13* | 58 ± 12* | 53 ± 13* | 54 ± 12* | 54 ± 12* |
| MAP (mm Hg) | M | 98 ± 29 | 157 ± 49* | 160 ± 17* | 152 ± 17* | 139 ± 13* | 135 ± 7* | 125 ± 8 |
| | M-H | 104 ± 5 | 150 ± 23* | 128 ± 27† | 132 ± 21 | 118 ± 16 | 109 ± 12 | 105 ± 8 |
| | M-B | 96 ± 11 | 182 ± 19*,‡ | 158 ± 20* | 144 ± 17* | 128 ± 10* | 120 ± 9 | 111 ± 6 |
| CI (L/min/$m^2$) | M | 7.0 ± 2.0 | 1.5 ± 0.4* | 1.5 ± 0.3* | 1.9 ± 0.6* | 1.6 ± 0.5* | 1.7 ± 0.4* | 1.9 ± 0.6* |
| | M-H | 6.2 ± 1.8 | 1.3 ± 0.3* | 1.5 ± 0.3* | 1.6 ± 0.2* | 1.5 ± 0.2* | 1.8 ± 0.4* | 1.7 ± 0.4* |
| | M-B | 6.0 ± 1.8 | 1.4 ± 0.4* | 1.4 ± 0.3* | 1.5 ± 0.2* | 1.5 ± 0.4* | 1.7 ± 0.3* | 1.6 ± 0.2* |
| SI (mL/beat/$m^2$) | M | 52.7 ± 7.0 | 34.1 ± 10.7* | 33.6 ± 9.0* | 39.5 ± 10.8 | 34.0 ± 6.1* | 36.6 ± 7.1* | 38.3 ± 14.6 |
| | M-H | 46.9 ± 8.3 | 25.9 ± 5.1* | 33.2 ± 10.7 | 36.1 ± 7.1 | 33.8 ± 10.8 | 34.9 ± 8.8 | 32.8 ± 8.9 |
| | M-B | 51.5 ± 15.5 | 26.3 ± 10.6* | 24.4 ± 8.4* | 26.4 ± 5.6* | 30.7 ± 12.9* | 32.7 ± 10.4* | 31.6 ± 10.7* |
| MPAP (mm Hg) | M | 15.7 ± 4.2 | 28.8 ± 5.1* | 27.0 ± 5.5* | 25.2 ± 4.6* | 23.2 ± 4.2* | 21.3 ± 3.6 | 21.0 ± 3.7 |
| | M-H | 14.3 ± 5.9 | 29.8 ± 3.8* | 25.3 ± 1.6* | 24.8 ± 3.1* | 23.7 ± 2.3* | 22.0 ± 3.0* | 21.8 ± 3.0* |
| | M-B | 13.7 ± 5.3 | 30.2 ± 5.7* | 26.7 ± 4.8* | 24.2 ± 2.4* | 22.8 ± 1.3* | 21.5 ± 3.3* | 20.7 ± 1.9* |
| CVP (mm Hg) | M | 0.7 ± 4.3 | 16.5 ± 4.1* | 14.7 ± 3.3* | 13.8 ± 2.8* | 13.2 ± 4.1* | 11.8 ± 2.7* | 11.2 ± 2.9* |
| | M-H | 2.8 ± 3.9 | 14.5 ± 1.4* | 13.7 ± 1.6* | 14.2 ± 1.5* | 12.8 ± 1.3* | 12.0 ± 1.4* | 11.7 ± 1.2* |
| | M-B | 0.8 ± 2.9 | 15.5 ± 2.8* | 14.5 ± 1.9* | 13.5 ± 1.9* | 12.0 ± 1.7* | 10.8 ± 2.0* | 10.7 ± 1.8* |
| PCWP (mm Hg) | M | 4.0 ± 2.3 | 23.7 ± 4.1* | 21.8 ± 3.5* | 21.2 ± 3.4* | 19.5 ± 3.8* | 17.8 ± 3.4* | 16.8 ± 3.7* |
| | M-H | 5.3 ± 7.8 | 24.7 ± 2.5* | 20.3 ± 2.5* | 20.2 ± 3.8* | 17.8 ± 2.1* | 16.2 ± 1.5* | 15.7 ± 2.1* |
| | M-B | 6.8 ± 6.4 | 25.8 ± 6.1* | 20.0 ± 2.0* | 19.7 ± 3.9* | 18.0 ± 2.9* | 16.5 ± 3.3* | 15.7 ± 3.1* |
| SVRI ([dynes•s]/[$cm^5$•$m^2$]) | M | 1,831 ± 690 | 12,684 ± 6,386* | 11,911 ± 2,014* | 9,483 ± 2,570* | 10,623 ± 2,912* | 9,279 ± 2,141* | 8,152 ± 2,451* |
| | M-H | 2,150 ± 630 | 13,849 ± 4,332* | 9,585 ± 2,671* | 9,543 ± 2,516* | 8,910 ± 2,140* | 6,980 ± 1,923* | 7,083 ± 1,402* |
| | M-B | 2,102 ± 696 | 15,191 ± 4,611* | 13,619 ± 4,340*,‡ | 11,194 ± 3,052* | 9,976 ± 3,120* | 8,408 ± 2,431* | 7,922 ± 1,956* |
| RPP (mm Hg• [beats/min]) | M | 17,448 ± 5,312 | 9,516 ± 2,773* | 9,242 ± 1,468* | 9,351 ± 1,715* | 8,148 ± 1,816* | 7,903 ± 1,731* | 8,177 ± 2,328* |
| | M-H | 17,179 ± 3,678 | 8,757 ± 1,060* | 7,414 ± 1,000* | 7,195 ± 1,404* | 7,365 ± 2,036* | 7,397 ± 1,120* | 7,224 ± 1,402* |
| | M-B | 15,855 ± 2,977 | 12,907 ± 4,209‡ | 11,065 ± 2,800* | 10,023 ± 2,275* | 8,613 ± 2,230* | 8,551 ± 1,957* | 8,036 ± 2,280* |
| RR (breaths/min) | M | 41 ± 38 | 14 ± 4* | 13 ± 5* | 14 ± 3* | 10 ± 4* | 11 ± 3* | 14 ± 11 |
| | M-H | 47 ± 35 | 14 ± 8* | 15 ± 9* | 14 ± 11* | 12 ± 9* | 10 ± 5* | 10 ± 4* |
| | M-B | 50 ± 42 | 11 ± 5* | 12 ± 6* | 12 ± 8* | 11 ± 6* | 10 ± 5* | 10 ± 3* |
| Core body temperature (°C) | M | 38.6 ± 0.3 | 39.0 ± 0.3* | 38.9 ± 0.3* | 38.9 ± 0.4* | 38.9 ± 0.4* | 38.8 ± 0.5 | 38.7 ± 0.5 |
| | M-H | 38.6 ± 0.2 | 38.9 ± 0.2* | 38.9 ± 0.3* | 38.8 ± 0.3* | 38.7 ± 0.3 | 38.7 ± 0.4 | 38.6 ± 0.4 |
| | M-B | 38.3 ± 0.4 | 38.7 ± 0.4* | 38.7 ± 0.4* | 38.6 ± 0.4* | 38.5 ± 0.4 | 38.4 ± 0.4 | 38.3 ± 0.5 |

Values reported are mean ± SD. *Within a row, value differs significantly ($P < 0.05$) from value for time 0. †Within a column within a variable, value differs significantly ($P < 0.05$) from the value for M. ‡Within a column within a variable, value differs significantly ($P < 0.05$) from the value for M-H.

HR = Heart rate. MAP = Mean arterial pressure. CI = Cardiac index. SI = Stroke index. MPAP = Mean pulmonary artery pressure. CVP = Central venous pressure. PCWP = Pulmonary capillary wedge pressure. SVRI = Systemic vascular resistance index. RPP = Rate pressure product. RR = Respiratory rate.

Table 3—Effects of administration of M, M-H, and M-B on results of arterial blood gas analysis, PCV, and total protein (TP) concentration in 6 dogs.

| Time after injection | Group | pH | $Paco_2$ (mm Hg) | $Pao_2$ (mm Hg) | PCV (%) | TP (g/dL) |
|---|---|---|---|---|---|---|
| 0 | M | 7.350 ± 0.036 | 36.2 ± 2.8 | 99.8 ± 10.1 | 46.3 ± 4.7 | 6.4 ± 0.3 |
| | M-H | 7.386 ± 0.022 | 34.4 ± 2.8 | 105.1 ± 15.1 | 46.8 ± 4.6 | 6.4 ± 0.5 |
| | M-B | 7.365 ± 0.043 | 36.8 ± 4.1 | 103.9 ± 10.2 | 44.8 ± 3.1 | 5.9 ± 0.6 |
| 15 | M | 7.313 ± 0.038 | 37.2 ± 4.3 | 95.1 ± 21.3 | 47.5 ± 3.4 | 6.0 ± 0.4* |
| | M-H | 7.296 ± 0.028* | 42.4 ± 3.9* | 72.4 ± 11.0*,† | 48.8 ± 3.7 | 5.8 ± 0.5* |
| | M-B | 7.298 ± 0.023* | 42.1 ± 3.8* | 77.0 ± 7.2*,† | 48.5 ± 4.0 | 5.6 ± 0.6* |
| 45 | M | 7.320 ± 0.048 | 39.5 ± 2.8 | 93.4 ± 14.5 | 45.8 ± 3.5 | 5.9 ± 0.4* |
| | M-H | 7.281 ± 0.015* | 46.2 ± 1.4*,† | 73.5 ± 8.7*,† | 46.7 ± 3.1 | 5.7 ± 0.5* |
| | M-B | 7.308 ± 0.029* | 42.6 ± 3.4* | 85.0 ± 8.3* | 46.5 ± 3.4 | 5.5 ± 0.6* |

Values reported are mean ± SD. *See* Table 2 for key.

cantly ($P$ = 0.02) higher than that for the medetomidine treatment 45 minutes after injection. The pH predictably had the opposite response to that of the $Paco_2$. The $Pao_2$ decreased after administration of medetomidine-hydromorphone and medetomidine-butorphanol and was maintained through 45 minutes at values lower than the baseline value. The $Pao_2$ for the medetomidine-hydromorphone treatment was significantly lower than that for the medetomidine treatment 15 and 45 minutes after injections. There was not a significant difference for bicarbonate concentration, total $CO_2$ content, and base excess throughout the study for any treatment (data not shown). Total protein concentration was significantly decreased for all treatments 15 and 45 minutes after drug administration. However, we did not detect significant differences in PCV within or among treatments.

## Discussion

Feline and canine practitioners and researchers clearly need an effective sedative technique that provides sedation that lasts 30 to 60 minutes. This technique must be convenient, simple, and safe and provide good muscle relaxation and analgesia. Therefore, a lower dosage of medetomidine (20 µg/kg) in combination with hydromorphone (0.1 mg/kg) or butorphanol (0.2 mg/kg) was evaluated in an attempt to find appropriate combinations for daily clinical needs.

In the study reported here, all 3 treatments were associated with a rapid and smooth sedative effect; however, the medetomidine-hydromorphone and medetomidine-butorphanol combinations had a better quality of sedation and analgesia, especially for the medetomidine-hydromorphone treatment. Analysis of these results suggests that hydromorphone and butorphanol potentiate the sedative and analgesic properties of medetomidine.

In another study,[13] MAP was significantly increased after medetomidine (40, 80, and 160 µg/kg) was administered IV or IM, but it then returned to the baseline value or below during the subsequent 30 minutes. This initial response was confirmed in the study reported here. Intravenous administration of medetomidine is associated with a biphasic effect on arterial pressure. Initial hypertension is believed to be attributable to an increase in peripheral vascular resistance as a result of postsynaptic activation of $\alpha_2$-receptors within the peripheral vasculature, whereas the hypotension that develops later is attributable to a centrally mediated reduction in sympathetic outflow.[21] Because MAP was maintained at greater-than-baseline values throughout the 60-minute study period, the hypotension associated with a lower dose of medetomidine may not have been as profound as for higher doses. In 2 other studies,[15,22] investigators reported that there was no difference in MPAP associated with administration of medetomidine. However, the MPAP was increased in the study reported here as well as 2 other studies.[23,24]

The PCWP is an approximation of left ventricular preload. This variable was significantly increased in the study reported here. Other investigators[15] have reported a transient increase in PCWP in dogs after IV administration of medetomidine that appeared to be a dose-dependent response. Values for CVP were increased after administration of medetomidine in our study. Changes in CVP may be related to direct peripheral vascular effects similar to those that affect arterial pressure.[6] In addition, changes in CVP may also be related to a decrease in venous capacitance and CO, both of which can be evident after administration of medetomidine.[25]

In another study,[15] SVRI increased in response to medetomidine administration, which was attributable to direct vasoconstrictive effects. That result was confirmed in our study. Increased MPAP with concurrent decreased CI suggests an increase in PVR.[24] In the study reported here, it appears that the increase in PCWP offset the increase in MPAP so that the slightly increased PVR had returned to baseline values within 10 minutes after drug injection.

Because of the significant decrease in HR and SI, CI decreased significantly. The reduction in CI after administration of dexmedetomidine has been attributed to the precipitous decrease in HR as well as to the increase in afterload induced by the increase in peripheral vascular resistance.[26] Indeed, increases in PCWP and SVR detected in our study are consistent with the hypothesis that the decrease in CI is likely attributable to an increase in afterload rather than to a decrease in preload. Medetomidine reportedly[6] increases SVR by stimulation of $\alpha_2$-adrenoceptors located in vascular smooth muscle. The reduction of SVR could be attributable to diminished central sympathetic outflow, or it may be a result of increased afterload.

The RPP is calculated as the product of SAP and HR and has been used as an estimate of myocardial oxygen consumption.[22,25] In the study reported here, RPP decreased significantly after drug administration, probably because of the vagally mediated reflex reduction in HR and resultant decrease in myocardial oxygen demand and myocardial work.

Hypoventilation was induced with medetomidine-hydromorphone and medetomidine-butorphanol treatments; it was characterized by significant increases in $Pa_{CO_2}$ and decreases in $Pa_{O_2}$ and pH, which probably were attributable to respiratory depression as a result of opioid administration. This was confirmed by the fact that we did not detect changes for these variables with the medetomidine treatment. These changes in blood gas values are similar to those reported in another study.[25] However, all of these values for the 3 treatments were within the clinically acceptable ranges for dogs not administered supplemental oxygen. In a clinical setting, supplemental oxygen can be provided to improve the $Pa_{O_2}$.

Total protein concentration gradually decreased during the course of the study for each treatment. This was probably attributable to the fact that a minimum of 120 mL of 5% dextrose solution (including 15 mL during the instrumentation period) was given to each dog for each treatment during measurement of CO. Despite administration of the dextrose solution and the decrease in total protein concentration, the PCV did not change during the study, indicating possible splenic contraction.[15,25]

Core body temperature increased after drug administration for all treatments and remained significantly higher than baseline values through 15 minutes. These finding are similar to those in another study[3] in which it was reported that the influence of medetomidine on body temperature was greater when medetomidine was administered IV, compared with results after IM administration. The increase in core body temperature in the study reported here is consistent with results of another study[24] conducted by our laboratory group in which core body temperature increased by a mean of 0.2°C within 15 minutes after IV administration of medetomidine. Other studies[25,27] have documented a decrease in body temperature following administration of medetomidine. A decrease in body temperature following administration of medetomidine has been attributed to decreased heat production as a result of decreased muscular activity and a direct hypothalamic effect.[28] The transient increase in core body temperature may be attributable to $\alpha_2$-mediated peripheral vasoconstriction resulting in centralization of circulating blood volume and decreased heat loss via the peripheral vessels. It is possible that there is a biphasic effect on core body temperature following administration of medetomidine, with the initial effect being a modest and transient increase in core temperature as a result of peripheral vasoconstriction followed by a sustained decrease in core temperature attributable to decreased muscular activity.

Although vomiting associated with medetomidine administration has been reported in other studies,[2,4,5] it was not observed in the study reported here. This may have been attributable to the various routes of administration for medetomidine.

In the study reported here, the addition of hydromorphone or butorphanol did not adversely affect cardiovascular performance, compared with results after administration of medetomidine alone. Because hydromorphone and butorphanol significantly enhanced the sedative and analgesic effects of medetomidine and did not add to cardiovascular depression, the medetomidine-hydromorphone and medetomidine-butorphanol combinations appear to offer substantial advantages without causing detrimental effects. The additional analgesic effect gained from the addition of butorphanol or hydromorphone to medetomidine may provide sufficient analgesia and sedation to permit minor surgical or diagnostic procedures. However, all medetomidine combinations used in this study were associated with significant cardiovascular changes and therefore should be used with caution in dogs with cardiac disease.

[a]Domitor, Pfizer Animal Health, Pfizer Inc, New York, NY.
[b]Hydromorphone, Elkins-Sinn Inc, Cherry Hill, NY.
[c]Torbugesic, Fort Dodge Laboratories Inc, Fort Dodge, Iowa.
[d]SevoFlo, Abbott Laboratories, North Chicago, Ill.
[e]Narkomed AVE, North American Drager Co, Telford, Pa.
[f]20 SWG, 5 cm, Abbott Laboratories, North Chicago, Ill.
[g]7-F, 110-cm catheter, Edwards Lifesciences LLC, Irvine, Calif.
[h]Transpac II, Abbott Critical Care Systems, North Chicago, Ill.
[i]HP Omni Care CMS model 24, Hewlett-Packard Co, Andover, Mass.
[j]5% dextrose injection USP, Baxter Healthcare Corp, Deerfield, Ill.
[k]AVL 995, Diamond Diagnostics Inc, Holliston, Mass.
[l]NCSS 2000 for Windows, NCSS Inc, Kaysville, Utah.

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