AJVR

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Sedative and cardiopulmonary effects of intramuscular combinations of hydromorphone, acepromazine, dexmedetomidine, and glycopyrrolate followed by intravenous propofol and inhalant isoflurane anesthesia in healthy dogs

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https://doi.org/10.2460/ajvr.22.06.0098

OBJECTIVE
To evaluate the sedative and cardiopulmonary effects of various combinations of acepromazine, dexmedetomidine, hydromorphone, and glycopyrrolate, followed by anesthetic induction with propofol and maintenance with isoflurane in healthy dogs.

ANIMALS
6 healthy adult female Beagles.

PROCEDURES
Dogs were instrumented for hemodynamic measurements while anesthetized with isoflurane. Two hours after recovery, dogs received 1 of 4 IM combinations in a crossover design with 1 week between treatments: hydromorphone (0.1 mg/kg) and acepromazine (0.005 mg/kg; HA); hydromorphone and dexmedetomidine (0.0025 mg/kg; HD); hydromorphone, acepromazine, and dexmedetomidine (HAD); and hydromorphone, acepromazine, dexmedetomidine, and glycopyrrolate (0.02 mg/kg; HADG). Sedation was scored after 30 minutes. Physiologic variables and cardiac index were measured after sedation, after anesthetic induction with propofol, and every 15 minutes during maintenance of anesthesia with isoflurane for 60 minutes (target expired concentration at 760 mm Hg, 1.3%).

RESULTS
Sedation scores were not significantly different among treatments. Mean ± SD cardiac index was significantly higher for the HA (202 ± 45 mL/min/kg) and HADG (185 ± 59 mL/min/kg) treatments than for the HD (88 ± 31 mL/min/kg) and HAD (103 ± 25 mL/min/kg) treatments after sedation and through the first 15 minutes of isoflurane anesthesia. No ventricular arrhythmias were noted with any treatment.

CLINICAL RELEVANCE
In healthy dogs, IM administration of HADG before propofol and isoflurane anesthesia provided acceptable cardiopulmonary function with no adverse effects. This combination should be considered for routine anesthetic premedication in healthy dogs.

Premedication to reduce stress, provide preoperative analgesia, and facilitate subsequent treatments or interventions are a routine part of canine anesthesia.[1] Opioids such as hydromorphone are often combined with sedatives (eg, dexmedetomidine) or tranquilizers (eg, acepromazine) for this purpose and to induce neuroleptanalgesia.[2,3] Although premedication can reduce the requirement for subsequent administration of drugs with negative physiologic effects, the premedicant drugs themselves also have important effects on cardiopulmonary function.

Dexmedetomidine is a highly selective α_2-adrenoreceptor agonist that provides excellent sedation and has biphasic cardiovascular effects. The initial phase is characterized by peripheral vasoconstriction with baroreceptor-mediated reflex bradycardia leading to a decrease in cardiac output (CO).[4,5] This is followed by a decrease in vascular tone with a centrally mediated reduction in sympathetic tone and sustained CO reduction.[5] The duration of cardiovascular effects of α_2-adrenoreceptor agonists is dose dependent, with the vasoconstrictive phase

prolonged at higher doses.[6] Attempts to attenuate the bradycardia associated with α_2-adrenoreceptor agonists through the use of an anticholinergic drug (eg, atropine or glycopyrrolate) can result in tachycardia, hypertension, and ventricular arrhythmias.[7–9]

Acepromazine, conversely, is an α_1-adrenoreceptor antagonist that induces a reduction in mean arterial blood pressure via a reduction in systemic vascular resistance while maintaining CO.[4] The clinical perception that acepromazine could potentiate the sedative effect and lessen the pressor effect of dexmedetomidine in dogs has been disproven.[8] This could be dependent on the route of administration of premedicants, as giving dexmedetomidine at a dose of 0.005 mg/kg, IV is likely to mask any additional sedation acepromazine may provide. Despite this, the clinical practice to combine opioids with low doses of dexmedetomidine and acepromazine for preanesthetic sedation in dogs has gained popularity because of a perceived improvement in sedation and recovery quality and reduction in intensity of the cardiovascular effects, compared with the effects of either drug used alone.

The primary objective of the study reported here was to investigate the sedative and cardiopulmonary effects of IM administration of hydromorphone combined with low doses of dexmedetomidine, acepromazine, or both in healthy dogs in which anesthesia was subsequently induced with propofol IV and maintained with isoflurane. A secondary aim was to determine the effects of adding glycopyrrolate to the combination, because the mixture of an anticholinergic drug with acepromazine and dexmedetomidine at these doses has not been previously described. We hypothesized that the combination of dexmedetomidine, acepromazine, and hydromorphone would provide superior sedation, compared with hydromorphone with dexmedetomidine or hydromorphone with acepromazine, and that the addition of glycopyrrolate would improve cardiac output without altering sedation quality or causing deleterious arrhythmias.

Materials and Methods

Animals

Six healthy (as determined on the basis of results of a physical examination, CBC, and serum biochemical profile) sexually intact female Beagles (mean ± SD weight, 9.4 ± 0.9 kg; mean ± SD age, 4.6 ± 0.5 years) were used in the study. The study protocol was approved by the Colorado State University Institutional Animal Care and Use Committee (protocol No. 1511). A power analysis indicated a sample size of 6 dogs was required to achieve a power of 80% ($\alpha = 0.05$) with an expected difference in CO (ie, the primary response variable) between treatments of approximately 25 ± 15% (mean ± SD). Dogs were housed in temperature-controlled kennels with ad libitum access to fresh water and commercial dry dog food. They were acclimated to the research environment for 5 days prior to the start of the study. Prior to each study day, dogs were fasted for 12 hours with free access to water.

Instrumentation and study design

At the beginning of each study day, a physical examination was performed, which included measurement of heart rate (HR), respiratory rate (RR), rectal temperature, mucous membrane color, capillary refill time, and noninvasive blood pressure (NIBP). NIBP was measured with a cuff with a width approximately 40% the circumference of the limb that was secured above the tarsal region and attached to a multiparametric anesthetic monitor (Mindray DS; Mindray). Dogs were then anesthetized with isoflurane (5%) in oxygen delivered at a rate of 4 L/min via a mask connected to a small animal circle breathing system until orotracheal intubation was possible. After intubation, dogs were allowed to breathe spontaneously, and the vaporizer setting was adjusted to maintain an acceptable plane of anesthesia for subsequent venous and arterial catheterization.

Anesthetic monitoring during this phase included a lead II ECG and measurement of arterial hemoglobin oxygen saturation (Spo_2), esophageal temperature (T_E), end-tidal partial pressure of carbon dioxide (P_{ETCO_2}), and NIBP. A 22-gauge, 25-mm catheter (Insyte; Becton Dickinson Infusion Therapy Systems Inc) was placed aseptically into a cephalic vein for drug and fluid delivery. Lactated Ringer solution (Hospira Inc) was administered at a rate of 3 mL/kg/h, IV during anesthesia with a syringe pump. A 22-gauge, 25-mm catheter (Insyte; Becton Dickinson Infusion Therapy Systems Inc) was placed aseptically into a dorsal pedal or brachial artery (under ultrasound guidance) and was connected to a pressure transducer (Trans-Model 2/Macro; Argon Medical) zeroed and positioned at the midline of the sternum (ie, the approximate level of the right atrium in lateral recumbency) for continuous invasive monitoring of systolic arterial pressure (SAP), diastolic arterial pressure (DAP), and mean arterial pressure (MAP). The accuracy of all pressure transducers was assessed with a mercury manometer (range of 0 to 200 mm Hg in 20-mm Hg increments). Obtained values were corrected on the basis of calibration of the transducers in the working pressure range.

A 6F introducer (Fast-Cath Hemostasis Introducer; Abbott) was placed aseptically into a jugular vein, and a 5F, 75-cm Swan-Ganz catheter (132FS Swan-Ganz Pediatric Thermodilution Catheter; Edwards Lifesciences Corp) was inserted through the introducer until the proximal port was located in the right atrium and the distal tip was located in the pulmonary artery. Correct placement was verified by observation of characteristic pressure waveforms obtained by connecting the proximal and distal ports of the Swan-Ganz catheter to a pressure transducer and anesthetic monitor. Once all catheters were secured in place with bandages, the isoflurane vaporizer was turned off, the monitoring equipment was removed, and the dogs were allowed to recover. All dogs were monitored closely after extubation to prevent inadvertent removal of catheters.

At least 2 hours after extubation following instrumentation, a premedication combination was administered IM in the left quadriceps muscle. Each of

4 premedication combinations was administered in a randomized (Graphpad; Dotmatics) crossover design with a minimum of 1 week between treatments: hydromorphone (0.1 mg/kg [Hospira Inc]) and acepromazine (0.005 mg/kg; HA treatment); hydromorphone and dexmedetomidine (0.0025 mg/kg [Dexdomitor; Zoetis]; HD treatment); hydromorphone, acepromazine, and dexmedetomidine (HAD treatment); and hydromorphone, acepromazine, dexmedetomidine, and glycopyrrolate (0.02 mg/kg [Hikma Farmaceutica]; HADG treatment). All drugs were independently drawn up, mixed in a single syringe, and delivered via a 22-gauge needle. The syringe was covered in white tape to hide the volume of the contents so that investigators would be blinded to the treatment.

Thirty minutes after IM premedication, the level of sedation was assessed by a single investigator (BMK) unaware of the treatment. Sedation was graded on a scale from 0 (least sedate) to 21 (most sedate) previously used in dogs administered an opioid and dexmedetomidine.[10,11] Dogs were then lightly restrained in right lateral recumbency on a padded table. Standard physiologic variables, CO, mean right atrial pressure (MRAP), mean pulmonary arterial pressure (MPAP), and pulmonary arterial occlusion pressure (PAOP) were measured. CO was measured at the end of exhalation with the thermodilution method; 3 mL of iced (0 to 0.5 °C) saline (0.9% NaCl) solution (Hospira Inc) and a CO computer (Explorer Oximetry Computer; Baxter Healthcare Corp). CO was measured 4 to 5 times, and the mean of 3 values within 10% of each other was calculated as the CO at each time point. This value was then indexed to body weight to obtain cardiac index (CI). On a single occasion for each dog, CO was also measured prior to premedication.

After measurement of CO, 1 mL of arterial blood and 1 mL of mixed venous blood were simultaneously, anaerobically collected for analysis of pH, Pa_{O_2}, mixed venous partial pressure of oxygen ($P\bar{v}_{O_2}$), Pa_{CO_2}, mixed venous partial pressure of carbon dioxide ($P\bar{v}_{CO_2}$), bicarbonate (HCO_3^-) concentration, base excess (BE), hemoglobin (Hb) concentration, PCV, total protein (TP) concentration, lactate concentration, and creatinine concentration. Samples were collected using dedicated blood-gas syringes (safePICO; Radiometer America Inc) and run on a blood-gas analyzer (800ABL Flex; Radiometer America Inc) calibrated every 4 hours against known metabolite solutions. Samples were stored on ice and analyzed within 30 minutes of collection.

General anesthesia was then induced with propofol (Zoetis Inc) IV titrated in 1-mg/kg increments that were hand delivered with a 10-second pause between increments until orotracheal intubation was possible. Total dose required for intubation was recorded. The endotracheal tube was connected to a standard small animal circle breathing system delivering oxygen at a rate of 1 L/min, and the dog was allowed to spontaneously ventilate while CO, MPAP, MRAP, PAOP, HR, RR, Sp_{O_2}, SAP, MAP, and DAP were measured immediately following anesthetic induction. Once these measurements were completed, anesthetic maintenance was achieved with isoflurane in oxygen at a target expired concentration (F_{EISO}) comparable to 1.3% at sea level (760 mm Hg), as measured with a gas analyzer with a sidestream sampling line located between the endotracheal tube and the Y-piece of the anesthesia circuit. The multiparameter monitor used to measure expired isoflurane concentration was checked daily with 5 known isoflurane concentration standards (compressed gas containing 0.5%, 1.0%, 1.5%, 2.0%, or 2.5% isoflurane with the balance nitrogen; Scott Medical Products). On the basis of a regression equation, measured F_{EISO} was adjusted to the calibration curve generated daily. These values were then further corrected for local barometric pressure, which ranged from 632 to 640 mm Hg (84.3 to 85.3 kPa), as measured with a barometer within the blood-gas analyzer (local height, 1,519 m above sea level). Each dog was mechanically ventilated (Bird Mark 7 Respirator; CareFusion) to maintain Pa_{CO_2} between 35 and 45 mmHg (4.7 to 6.0 kPa). A constant F_{EISO} was achieved within 15 minutes.

HR, Sp_{O_2}, SAP, MAP, DAP, P_{ETCO_2}, and F_{EISO} were recorded every 5 minutes throughout anesthesia. External heating devices (Bair Hugger Warming Unit Model 585 [Arizant Healthcare Inc]; Model PUL-300 HD heat lamp [Fostoria Industries Inc]) were used to maintain T_E within the range of 37.5 to 38.5 °C. Lactated Ringer solution was administered IV at a rate of 3 mL/kg/h for the duration of anesthesia. CO, MPAP, MRAP, and PAOP were measured at 15, 30, 45, and 60 minutes of isoflurane anesthesia. Arterial and mixed-venous blood gas samples were collected at the same time points. CI, systemic vascular resistance index (SVRI), oxygen delivery (D_{O_2}), oxygen consumption ($\dot{V}_{O_2}$), and oxygen extraction ratio (ER_{O_2}) were then calculated on the basis of canine-specific references.[12] The rate-pressure product (RPP) was calculated as HR × SAP for all time points.

After the 60-minute measurements were completed, cefazolin (Hikma Famaceutica) was administered at a dosage of 22 mg/kg, IV to reduce the risk of catheter-site infections. The IV, arterial, and pulmonary artery catheter and jugular introducer were removed, and their insertion sites were bandaged. Administration of isoflurane was discontinued, and carprofen (4.4 mg/kg, SC [Rimadyl; Zoetis Inc]) and maropitant (1 mg/kg, SC [Cerenia; Zoetis Inc]) were administered to minimize inflammation and postanesthetic nausea. Dogs were extubated when the swallow reflex returned and were continuously monitored until ambulatory. Anesthetic recovery quality was rated on a 5-point scale as poor (1), fair (2), good (3), very good (4), or excellent (5) by the same investigator who scored sedation (BMK).

Following recovery, dogs were returned to group housing and their normal feeding schedule. They were monitored for signs of discomfort or complications resulting from the study every hour after each anesthesia for 4 hours and then twice daily for 7 days.

Statistical analysis

Statistical analyses were performed with SAS version 9.4 (SAS Institute Inc). Mixed models were fit

for each response variable separately. Residual diagnostic plots were used to evaluate for assumptions of normality and equal variance.

Propofol dose was measured at a single time point. Treatment (HA, HD, HAD, or HADG) and experimental week were included as fixed effects, and dog was included as a random effect to account for the crossover design. The Tukey method was used to test for differences between treatments. Sedation and recovery scores were summarized as median and range, and the Friedman test was used to compare scores between treatments.

All other variables (HR, RR, SAP, DAP, MAP, Spo_2, T_E, P_{ETCO_2}, Pa_{O_2}, Pa_{CO_2}, BE, $HCO3^-$ concentration, creatinine concentration, lactate concentration, Hb concentration, PCV, TP concentration, CI, SVRI, D_{O_2}, $\dot{V}_{O_2}$, ER_{O_2}, and RPP) had repeated observations over time. Treatment, experimental week, and time (before sedation, after sedation, after anesthetic induction, and at 15, 30, 45, and 60 minutes of isoflurane anesthesia) were included as fixed effects, with dog and dog-by-treatment as random effects to account for the crossover design. ANOVA *F* tests (not shown) were used to test for main effects (treatment, time, and experimental week) and their interaction (treatment by time). For those variables that showed evidence of differences (ie, an *F* test *P* value < .05) for treatment or the treatment-by-time interaction, the Tukey method was used to compare values between treatments at each time point. For those variables that showed evidence of differences (ie, an *F* test *P* value < .05) for time or the treatment-by-time interaction, the Dunnett method was used to compare values obtained at later time points with the value obtained at the earliest available time point for the variable (either before or after sedation). DAP, MAP, RR, SVRI, $\dot{V}_{O_2}$, and RPP were log transformed to better satisfy model assumptions. The Dunnett method was also used to compare CI values for each treatment with the CI measured when dogs were awake. For all analyses, a value of $P < .05$ was considered evidence of a difference.

Results

All dogs successfully completed the study. Presedation measurements were not significantly different among dogs or treatment. All dogs vomited within 5 to 10 minutes of IM drug administration with each treatment. Sedation score, propofol dose required for intubation, and recovery score were summarized **(Table 1)**. There was no evidence of statistical differences between treatments for these variables.

Mean ± SD CI measured when dogs were awake was 195 ± 42.0 mL/min/kg. CI was lowest with the HD and HAD treatments and was significantly ($P \leq .002$) decreased at all time points, compared with awake values **(Table 2)**. CI with the HA treatment was not significantly different from the awake value at any time point, and CI with the HADG treatment was significantly ($P = .047$) different from the awake value only at 60 minutes of isoflurane anesthesia. Differences in cardiopulmonary variables were found between treatments after sedation and primarily at 15 and 30 minutes of isoflurane anesthesia. HR and RPP were highest after sedation with the HADG treatment and decreased over time. Ventricular arrhythmias were not seen in any dog with any treatment.

Arterial blood gas and other selected laboratory results were summarized **(Table 3)**. Significant differences between treatments were noted only for Hb concentration and PCV.

Table 1—Sedation and recovery scores and IV dose of propofol required to induce anesthesia 30 minutes after premedication for 6 healthy adult female Beagles premedicated IM with each of the following combinations: hydromorphone (0.1 mg/kg) and acepromazine (0.005 mg/kg; HA); hydromorphone and dexmedetomidine (0.0025 mg/kg; HD); hydromorphone, acepromazine, and dexmedetomidine (HAD); and hydromorphone, acepromazine, dexmedetomidine, and glycopyrrolate (0.02 mg/kg; HADG).

	Treatment			
Variable	**HA**	**HD**	**HAD**	**HADG**
Sedation score	9.5 (5–14)	13 (10–19)	13 (7–16)	15.5 (10–18)
Recovery score	4.3 (3–5)	4.3 (1–5)	4.2 (2–5)	4.3 (2–5)
Propofol dose (mg/kg)	4.2 ± 0.7	2.9 ± 1.6	4.1 ± 1.9	2.4 ± 1.2

There was a minimum 1-week washout period between treatments. Data are given as median (range) or mean ± SD. Sedation was scored 30 minutes after premedication on a scale from 0 (least sedate) to 21 (most sedate).[10] Following induction of anesthesia with propofol, anesthesia was maintained with isoflurane (target expired concentration comparable to 1.3% at sea level [760 mm Hg]), and recovery was scored on a 5-point scale as poor (1), fair (2), good (3), very good (4), or excellent (5).

Table 2—Mean ± SD cardiopulmonary variables for the dogs in Table 1.

	Time point						
Variable/ Treatment	**Before sedation**	**After sedation**	**After induction**	**15 minutes**	**30 minutes**	**45 minutes**	**60 minutes**
HR (beats/min)							
HA	90 ± 20	100 ± 25[a]	112 ± 22[a,†]	96 ± 21[a,b]	94 ± 23[a,b]	97 ± 27	99 ± 28
HD	93 ± 15	69 ± 7[b,†]	76 ± 5[b]	90 ± 18[a]	89 ± 20[a,b]	88 ± 20	88 ± 18
HAD	95 ± 13	71 ± 13[b,†]	81 ± 12[b]	85 ± 16[a]	84 ± 16[a]	84 ± 16	84 ± 17
HADG	94 ± 12	149 ± 27[c,†]	129 ± 27[a,†]	120 ± 23[b,†]	115 ± 22[b,†]	109 ± 21	107 ± 21

Table 2—(*continued*).

Variable/ Treatment	Time point						
	Before sedation	After sedation	After induction	15 minutes	30 minutes	45 minutes	60 minutes
SAP (mm Hg)							
HA	132 ± 13	123 ± 22	102 ± 18†	75 ± 7†	78 ± 5†	80 ± 4†	80 ± 8†
HD	129 ± 10	106 ± 12†	97 ± 13†	82 ± 11†	78 ± 7†	78 ± 5†	79 ± 4†
HAD	132 ± 13	108 ± 9†	98 ± 8†	81 ± 6†	77 ± 4†	77 ± 5†	80 ± 8†
HADG	130 ± 15	140 ± 38	108 ± 22†	85 ± 5†	84 ± 6†	87 ± 20†	86 ± 20†
MAP (mm Hg)							
HA	110 ± 10	88 ± 19a,†	80 ± 18a,†	63 ± 4a,†	63 ± 5†	65 ± 6†	64 ± 5†
HD	109 ± 11	89 ± 11a,†	81 ± 13a,†	68 ± 13a,b,†	64 ± 9†	64 ± 6†	64 ± 4†
HAD	109 ± 9	90 ± 7a,†	82 ± 8a,b,†	68 ± 8a,b,†	63 ± 4†	62 ± 4†	64 ± 6†
HADG	110 ± 9	127 ± 37b	100 ± 26b	76 ± 9b,†	72 ± 7†	68 ± 8†	66 ± 7†
DAP (mm Hg)							
HA	99 ± 10	78 ± 19a,†	73 ± 17a,†	57 ± 6†	56 ± 5†	57 ± 7†	57 ± 5†
HD	97 ± 11	81 ± 12a,b	73 ± 15a,†	62 ± 14†	57 ± 10†	60 ± 7†	56 ± 5†
HAD	97 ± 12	82 ± 8a	73 ± 10a,†	63 ± 10†	57 ± 6†	55 ± 4†	57 ± 6†
HADG	99 ± 8	120 ± 36b	100 ± 39b	70 ± 10†	66 ± 9†	61 ± 8†	60 ± 7†
CI (mL/min/kg)							
HA	NM	202 ± 45a	223 ± 37a	162 ± 56a,†	152 ± 50†	157 ± 60a,†	151 ± 52†
HD	NM	88 ± 31b	115 ± 53b	114 ± 17a,b	122 ± 42	108 ± 26b	110 ± 30
HAD	NM	103 ± 25b	112 ± 30b	102 ± 15b	110 ± 21	110 ± 29b	113 ± 25
HADG	NM	185 ± 59a	153 ± 65b	158 ± 33a	148 ± 30	142 ± 26ab,†	138 ± 39†
SVRI (mm Hg/mL/min/kg)							
HA	NM	0.5 ± 0.2a	0.4 ± 0.1a	0.4 ± 0.1a	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1
HD	NM	1.1 ± 0.7b	0.8 ± 0.6b	0.6 ± 0.2a,b,†	0.5 ± 0.2†	0.5 ± 0.1†	0.5 ± 0.1†
HAD	NM	0.8 ± 0.2b	0.7 ± 0.3b	0.6 ± 0.1b,†	0.5 ± 0.1†	0.5 ± 0.1†	0.5 ± 0.1†
HADG	NM	0.7 ± 0.4a,b	0.7 ± 0.5b	0.5 ± 0.2a,b,†	0.5 ± 0.1†	0.4 ± 0.1†	0.4 ± 0.1†
RPP (mm Hg·beats/min)							
HA	11,805 ± 2,555	12,629 ± 5,842a	11,695 ± 3,991a	7,220 ± 1,929a,†	7,354 ± 2,110a,b,†	7,834 ± 2,554a,b,†	8,091 ± 3,069†
HD	12,078 ± 2,474	7,200 ± 916b,†	7,315 ± 990b,†	7,434 ± 2,433a,†	7,031 ± 2,162a,†	6,951 ± 1,907a,b,†	6,988 ± 1,476†
HAD	12,581 ± 2,292	7,691 ± 1,493b,†	8,000 ± 1,500b,†	6,942 ± 1,513a,†	6,448 ± 1,293a,†	6,454 ± 1,255a,†	6,647 ± 1,356†
HADG	12,243 ± 2,214	20,739 ± 6,442c,†	13,850 ± 3,745a	10,320 ± 2,422b	9,630 ± 2,196b	9,577 ± 3,363b	9,316 ± 1,449
Do_2 (mL/min/kg)							
HA	NM	35 ± 11a	NM	34 ± 11a	28 ± 7a,b,†	28 ± 8†	27 ± 5†
HD	NM	16 ± 6b	NM	23 ± 4b	23 ± 8a,b	20 ± 5	20 ± 6
HAD	NM	20 ± 5b	NM	21 ± 5b	21 ± 5a	20 ± 5	20 ± 4
HADG	NM	36 ± 11a	NM	34 ± 8a	31 ± 6b	28 ± 4†	27 ± 6†
$\dot{V}o_2$ (mL/min/kg)							
HA	NM	5.0 ± 2.2	NM	5.5 ± 2.6	4.4 ± 1.3	4.5 ± 1.1	4.5 ± 1.2
HD	NM	4.0 ± 1.0	NM	4.2 ± 0.5	4.5 ± 0.8	3.7 ± 0.8	4.0 ± 0.9
HAD	NM	4.3 ± 0.6	NM	3.3 ± 0.6	3.5 ± 0.5	4.0 ± 0.8	3.7 ± 0.6
HADG	NM	5.1 ± 1.0	NM	3.9 ± 0.6	4.2 ± 0.7	4.1 ± 0.7	3.9 ± 0.5
ERo_2 (%)							
HA	NM	17 ± 10	NM	16 ± 4	16 ± 5	17 ± 5	17 ± 5
HD	NM	27 ± 8	NM	19 ± 4†	20 ± 6†	20 ± 7†	21 ± 7
HAD	NM	22 ± 5	NM	16 ± 4†	17 ± 3†	20 ± 5	18 ± 4
HADG	NM	15 ± 4	NM	12 ± 2	14 ± 2	14 ± 3	15 ± 3

CI = Cardiac index. DAP = Diastolic arterial pressure. Do_2 = Oxygen delivery. ERo_2 = Oxygen extraction. HR = Heart rate. MAP = Mean arterial pressure. NM = Not measured. RPP = Rate pressure product. SAP = Systolic arterial pressure. SVRI = Systemic vascular resistance index. $\dot{V}o_2$ = Oxygen consumption.

a–cIn each row, values were different superscript letters differed significantly ($P < 0.05$).

†Value was significantly ($P < 0.05$) different from earliest measured value (ie, value measured before or after sedation).

CI measured on 1 occasion in each dog when the dog was awake was 195 ± 42 mL/min/kg.

Table 3—Mean ± SD blood gas and clinicopathologic variables for the dogs in Table 1.

Variable/Treatment	Time point				
	After sedation	15 minutes	30 minutes	45 minutes	60 minutes
pH					
HA	7.35 ± 0.03	7.30 ± 0.05	7.31 ± 0.04	7.31 ± 0.04	7.30 ± 0.05†
HD	7.33 ± 0.03	7.31 ± 0.04	7.31 ± 0.05	7.29 ± 0.03†	7.25 ± 0.03†
HAD	7.38 ± 0.08	7.31 ± 0.03†	7.33 ± 0.06†	7.31 ± 0.04†	7.31 ± 0.03†
HADG	7.33 ± 0.02	7.31 ± 0.05†	7.32 ± 0.04	7.31 ± 0.04	7.29 ± 0.03
$Paco_2$ (mm Hg)					
HA	38 ± 2	42 ± 3†	43 ± 4†	43 ± 5†	42 ± 4†
HD	39 ± 2	43 ± 6	45 ± 3†	46 ± 3†	51 ± 9†
HAD	39 ± 3	44 ± 7†	43 ± 4†	44 ± 5†	44 ± 4†
HADG	40 ± 2	43 ± 6†	42 ± 4†	44 ± 5†	43 ± 4†

Table 3—(*continued*).

Variable/Treatment	Time point				
	After sedation	15 minutes	30 minutes	45 minutes	60 minutes
Pao_2 (mm Hg)					
HA	79 ± 7	449 ± 27[†]	437 ± 23[†]	428 ± 26[†]	442 ± 34[†]
HD	76 ± 5	444 ± 38[†]	416 ± 48[†]	438 ± 24[†]	432 ± 25[†]
HAD	78 ± 5	448 ± 19[†]	441 ± 22[†]	442 ± 19[†]	423 ± 21[†]
HADG	76 ± 5	456 ± 27[†]	450 ± 26[†]	444 ± 18[†]	443 ± 26[†]
HCO_3^- (mmol/L)					
HA	20.0 ± 1.8	21.4 ± 1.7[†]	21.5 ± 1.5[†]	21.3 ± 1.3[†]	21.0 ± 1.5[a,b,†]
HD	20.4 ± 1.4	20.7 ± 1.5	21.2 ± 1.3[†]	20.9 ± 1.4	21.3 ± 1.7[a,b,†]
HAD	20.8 ± 1.5	21.3 ± 1.8	21.3 ± 1.3	21.5 ± 1.2[†]	21.7 ± 1.2[a,†]
HADG	20.7 ± 1.4	20.8 ± 1.4	20.9 ± 1.3	21.0 ± 1.2	20.2 ± 1.7[b]
BE (mmol/L)					
HA	−4.6 ± 2.0	−4.1 ± 2.0	−4.1 ± 1.5	−4.0 ± 1.0	−4.3 ± 1.1
HD	−4.5 ± 2.0	−5.0 ± 1.5	−4.8 ± 1.5	−5.1 ± 1.6	−5.3 ± 1.4[†]
HAD	−4.0 ± 1.3	−4.4 ± 1.3	−4.3 ± 1.3	−4.1 ± 1.3	−4.1 ± 1.1
HADG	−4.3 ± 1.6	−5.0 ± 2.0	−4.4 ± 1.4	−4.6 ± 1.2	−5.4 ± 1.8[†]
Hb (g/dL)					
HA	14 ± 2a	12 ± 2[a,†]	12 ± 1[a,†]	11 ± 2[a,†]	11 ± 2[a,†]
HD	15 ± 1[a,b]	14 ± 1[b,†]	14 ± 1[b,†]	13 ± 1[b,†]	13 ± 1[b,†]
HAD	15 ± 2[b]	14 ± 2[b,†]	13 ± 1[b,†]	13 ± 1[b,†]	13 ± 1[b,†]
HADG	16 ± 1[b]	15 ± 2[b,†]	14 ± 2[b,†]	14 ± 1[b,†]	14 ± 2[b,†]
PCV (%)					
HA	41 ± 3[a]	37 ± 3[a,†]	35 ± 4[a,†]	34 ± 4[a,†]	33 ± 3[a,†]
HD	44 ± 3[a,b]	43 ± 3[b]	40 ± 1[b,†]	39 ± 1[b,†]	39 ± 3[b,†]
HAD	45 ± 4[b]	43 ± 3[b,†]	40 ± 4[b,†]	39 ± 4[b,†]	37 ± 4[a,b,†]
HADG	46 ± 5[b]	45 ± 5[b]	43 ± 4[b]	42 ± 4[b,†]	41 ± 3[b,†]
TP (g/dL)					
HA	5.5 ± 0.7	5.4 ± 0.5[†]	5.2 ± 0.5[†]	5.1 ± 0.5[†]	5.1 ± 0.5[†]
HD	5.5 ± 0.3	5.2 ± 0.6[†]	5.1 ± 0.2[†]	5.0 ± 0.4[†]	4.9 ± 0.4[†]
HAD	5.6 ± 0.6	5.4 ± 0.6	5.0 ± 0.4[†]	4.9 ± 0.4[†]	4.8 ± 0.4[†]
HADG	5.5 ± 0.4	5.4 ± 0.4	5.3 ± 0.3	5.3 ± 0.3	5.3 ± 0.3
Creatinine (µmol/L)					
HA	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1
HD	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1
HAD	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1
HADG	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1
Lactate (mmol/L)					
HA	2.0 ± 1.0	1.5 ± 0.6[†]	1.4 ± 0.6[†]	1.4 ± 0.4[†]	1.5 ± 0.4[†]
HD	1.7 ± 0.6	1.4 ± 0.5	1.3 ± 0.4[†]	1.4 ± 0.4	1.5 ± 0.4
HAD	1.2 ± 0.8	0.8 ± 0.6[†]	0.9 ± 0.5[†]	0.9 ± 0.5[†]	1.1 ± 0.5
HADG	1.5 ± 1.0	1.3 ± 0.8	1.2 ± 0.7	1.3 ± 0.6	1.4 ± 0.6

BE = Base excess. Hb = Hemoglobin. HCO_3^- = Bicarbonate. $Paco_2$ = Arterial partial pressure of CO_2. Pao_2 = Arterial partial pressure of O_2. TP = Total protein.

Dogs were mechanically ventilated to maintain $Paco_2$ between 35 and 45 mm Hg (4.7 to 6.0 kPa). Oxygen supplementation was not provided at the time postsedation measurements were obtained.

See Table 2 for remainder of key.

Discussion

In the present study, preanesthetic sedation with IM administration of hydromorphone in combination with a low dose of acepromazine (HA treatment), a low dose of dexmedetomidine (HD treatment), low doses of both drugs (HAD treatment), or low doses of both drugs and glycopyrrolate (HADG treatment) provided similar sedation and recovery quality scores and required similar doses of propofol for intubation in healthy dogs. Cardiopulmonary effects typical of acepromazine (lower SVRI and higher CI and HR) were seen with the HA treatment, and those typical of dexmedetomidine (higher SVRI and lower CI and HR) were seen with the HD and HAD treatments.[4,5] However, after 15 to 30 minutes of isoflurane anesthesia, cardiopulmonary differences between treatments dissipated.

The addition of glycopyrrolate in the HADG treatment prevented the bradycardic effects associated with dexmedetomidine. Mild hypertension and a significant increase in RPP, compared with other treatments and baseline values, was seen after sedation, but sustained hypertension and ventricular arrhythmias were not. RPP can be used as an estimate for an increase in oxygen demand; however, widely accepted RPP values have not been established for clinically normal dogs.[6,9] Preemptive anticholinergic administration has been shown to prevent the reduction in HR associated with α_2-adrenoceptor agonists. Previous studies[7–9,13–15] of anticholinergic–α_2-adrenoceptor agonist combinations also reported

severe hypertension and deleterious arrhythmias that were suspected to be related to increased myocardial workload and oxygen demand, as reflected by increased RPP, leading to the recommendation that these drugs not be combined. However, findings of the present study do not directly align with that conclusion. Although RPP increased significantly with the HADG treatment, compared with the baseline and postsedation values, this increase was brief and did not appear to be associated with adverse effects. This can likely be attributed to the lower dose of dexmedetomidine used (0.0025 mg/kg vs 0.005 to 0.01 mg/kg or equivalently higher doses of other α_2-adrenoceptor agonists) and the subsequent administration of propofol and isoflurane. Although propofol did not significantly change vascular tone, compared with postsedation measurements, SVRI differences between treatments after 15 minutes of isoflurane anesthesia were not noted.

The maximal vasoconstrictive effect of a low dose of dexmedetomidine would be expected to last < 30 minutes in dogs.[6] Because postsedation measurements were taken 30 minutes after IM premedication in the present study, one would expect most vasoconstrictive effect to have waned by this time. Therefore, it is possible that transient severe hypertension or arrhythmias were simply missed. However, peak sedation following IM administration of dexmedetomidine is reported at around 30 minutes.[9] Measuring cardiopulmonary variables prior to 30 minutes could have altered overall sedation quality by arousing the dogs. Because sedation was also an important and clinically relevant study outcome, we elected to wait 30 minutes to assess cardiopulmonary function.

An additional factor that may have contributed to the lack of arrhythmias was the use of acepromazine with the HADG treatment. Consistent with results of a previous study,[8] acepromazine did not appear to alter the vascular effects of dexmedetomidine. Acepromazine has however demonstrated a protective influence against bigeminy, premature ventricular contractions, multifocal ventricular tachycardia, and ventricular fibrillation associated with the use of the α_2-adrenoceptor agonist xylazine with halogenated inhalant anesthetics.[16,17] Because a treatment group combining hydromorphone with dexmedetomidine and glycopyrrolate but without acepromazine was not included in the present study, a possible antiarrhythmic effect of acepromazine is merely hypothetical.

In previous studies, combining an anticholinergic drug with an α_2-adrenoceptor agonist and increasing HR improved CI, but not to or near baseline values.[7,9,18] In the present study, CI and Do_2 were significantly improved with the HADG treatment after sedation and through the first 15 or 30 minutes of isoflurane anesthesia. These values most closely approximated values from the treatment without dexmedetomidine (HA). For CI, values with the HADG treatment were similar to awake values. This was also likely attributable to the rapidly waning vasoconstrictive effects of the low dose of dexmedetomidine. In addition, after 15 or 30 minutes of isoflurane anesthesia, cardiopulmonary values were similar between groups and appeared to be most representative of effects of isoflurane and not the premedications.

The decrease in Hb concentration and PCV with the HA treatment was likely secondary to erythrocyte sequestration within the spleen, which is a reported side effect of acepromazine.[19] Although Hb concentration and PCV decreased with all treatments over time, clinically important changes were noted only with the HA treatment. The effect of acepromazine on PCV was not as profound when the drug was combined with dexmedetomidine and glycopyrrolate. Because all dogs were maintained at a constant IV fluid rate of 3 mL/kg/h throughout the study, the minor changes in PCV and Hb concentration with the other treatments were likely related to the addition of dexmedetomidine. Previous studies[20–22] have observed a significant increase in PCV in dogs during dexmedetomidine infusion, and Grasso et al[4] reported higher PCV values when using dexmedetomidine IM as a premedicant, in comparison with acepromazine. The effects on PCV of dexmedetomidine likely offset the effects of acepromazine.

Vomiting occurred in all dogs with each treatment in the present study, which was likely a result of hydromorphone administration.[23] Vomiting during the anesthetic period has been shown to increase the risk of aspiration pneumonia and therefore morbidity and mortality rates in dogs undergoing general anesthesia,[24] but opioid-related vomiting can be prevented with the use of an antiemetic drug (eg, maropitant) prior to premedication.[23] Acepromazine, which has been shown to have antiemetic effects,[25] did not prevent vomiting in the present study. Therefore, the addition of an antiemetic drug to the HADG protocol should be considered.

There were important limitations to the present study. The first was that the use of research dogs accustomed to handling and well acclimated to the quiet study environment did not reflect the reality of a clinical environment. On the basis of the scale used, differences in sedation quality were not evident. However, in a clinical setting, hydromorphone combined with only a low dose of acepromazine may not be expected to reliably provide similar sedation to combinations including dexmedetomidine. In addition, the use of a different sedation scale or > 1 scale might have revealed differences in sedation score. A second limitation was that cardiopulmonary variables were only assessed 30 minutes after IM premedication. Knowing the reported temporal effects of dexmedetomidine, measuring these values earlier may have revealed additional valuable information, in particular about the combination of dexmedetomidine and glycopyrrolate. Third, because the power calculation, which was based only on the primary response variable (CO), dictated a relatively small sample size of 6 dogs, there were some differences between treatments that were not found to be significant but for which significant differences may have been detected if the sample size had been

increased. Last, the study could have been stronger if awake (ie, presedation) CI had been measured on each study day, rather than on only one occasion.

In conclusion, premedication of healthy dogs with IM administration of hydromorphone (0.1 mg/kg) and acepromazine (0.005 mg/kg; HA); hydromorphone and dexmedetomidine (0.0025 mg/kg; HD); hydromorphone, acepromazine, and dexmedetomidine (HAD); or hydromorphone, acepromazine, dexmedetomidine, and glycopyrrolate (0.02 mg/kg; HADG) provided good sedation and good recovery quality after 60 minutes of isoflurane anesthesia. The addition of glycopyrrolate to the hydromorphone-acepromazine-dexmedetomidine combination prevented cardiopulmonary alterations induced by dexmedetomidine without causing sustained hypertension or ventricular arrhythmias. This combination should be considered for premedication in healthy dogs.

Acknowledgments

The authors thank Sierra Hightower and Kevin Brewer of the Colorado State University James L. Voss Veterinary Teaching Hospital for technical assistance analyzing blood gas samples.

Funding for this study was provided by Colorado State University College Research Council Shared Research Program.

The authors declare that there were no conflicts of interest.

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