Evaluation of induction by use of a combination of oxymorphone and diazepam or hydromorphone and diazepam and maintenance of anesthesia by use of isoflurane in dogs with experimentally induced hypovolemia

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Objective—To compare induction with hydromorphone and diazepam (HydroD) or oxymorphone and diazepam (OxyD) followed by maintenance with isoflurane in dogs with induced hypovolemia.

Animals—6 healthy mixed-breed dogs.

Procedure—The study used a crossover design. Measurements were obtained in normovolemic dogs during isoflurane. Hypovolemia was induced (blood loss of 30 mL/kg) and measurements repeated following recovery from anesthesia, after HydroD (hydromorphone, 0.1 mg/kg; diazepam, 0.2 mg/kg; IV) or OxyD (oxymorphone, 0.05 mg/kg; diazepam, 0.2 mg/kg; IV), after another dose of the same opioid, during administration of isoflurane (end-tidal concentration, 0.9%), and after glycopyrrolate (0.01 mg/kg, IV). Significant changes were identified.

Results—Induction effect was evident within 1 minute. All dogs were intubated after the second dose of opioid. No significant differences were found between inductions. The HydroD decreased heart rate (mean ± SEM, –41 ± 9.8 beats/min), whereas both inductions increased stroke index (0.4 ± 0.09 mL/kg/beat) and caused moderate respiratory depression. Cardiac index was decreased (–30.2 ± 6.04 mL/kg/min) and there was minor metabolic acidosis during isoflurane following HydroD, compared with values for anesthetized normovolemic dogs. Glycopyrrolate increased heart rate (50 ± 8.6 beats/min) and decreased systolic blood pressure (–23.2 ± 4.87 mm Hg) in dogs induced with HydroD and decreased stroke index (–0.3 ± 0.08 mL/kg/beat) for both inductions.

Conclusions and Clinical Relevance—Similar effects were detected after administration of HydroD or OxyD in hypovolemic dogs. Either combination should be safe for use in hypovolemic dogs. Administration of glycopyrrolate was not beneficial. (*Am J Vet Res* 2005;66:1227–1237)

Hypovolemia can increase morbidity and mortality rates associated with anesthesia in veterinary patients. A state of low **cardiac output** (**CO**) develops secondary to a reduced ventricular preload resulting from inadequate blood volume. Perfusion of vital organs may be compromised when perfusion pressure is not maintained. Thus, the restoration of effective circulating blood volume is recommended before animals are anesthetized. This preoperative stabilization may move a patient from a high-risk category to one that could be considered safer.[1] Although elective surgical procedures should be postponed until the animal receives appropriate treatment, emergency situations may require anesthesia and surgery in advance of complete fluid replacement.

Natural release of catecholamines can increase venous and arteriolar vasoconstriction in hypovolemic animals. Venoconstriction induces little increase in afterload but is capable of inducing large shifts of blood into the central circulation because veins contain approximately 80% of the total blood volume.[2] Although restoration of adequate blood volume has been functionally defined as maintenance of a typical **central venous pressure** (**CVP**), vascular shifts can mask deficient vascular volume, despite increases in CVP.[3] Unfortunately, anesthetic drugs may eliminate the ability to compensate for volume loss through their direct effects on vascular resistance or influence on catecholamine release, unmasking the underlying hypovolemic state. Thus, administration of anesthetic drugs and adjunctive medications requires careful consideration of these effects in hypovolemic patients. There are several methods for experimentally inducing hypovolemia for the purpose of assessing the physiologic impact of hypovolemia, varying in degree from mild to severe hypovolemia induced by removal of a specific volume or a volume to maintain a specific blood pressure. Dogs with experimentally induced hypovolemia have been subjected to various anesthetic drugs, including ketamine,[4] oxymorphone,[5] thiopental,[6] propofol,[7] etomidate,[8] and various inhalants.[9,10] To our

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knowledge, no information is available on the use of neuroleptanalgesics for the induction of hypovolemic dogs.

Opioids are generally considered to be the safest and most effective supplemental medicants used during anesthesia in patients with cardiovascular compromise, thereby assisting in achieving balanced anesthesia.[11] Cardiovascular depression associated with opioid use is less than would be expected for inhalants. Therefore, opioids are commonly used as part of an induction regimen in critically ill patients because of their ability to reduce the need for other induction agents and, subsequently, the **minimum alveolar concentration (MAC)** of the inhalant used for maintenance of anesthesia.

Some disadvantages are evident when high doses of more efficacious opioids (those that have more profound sedative and analgesic effects) are used in conjunction with anesthesia. Respiratory depression (centrally mediated) and bradycardia (mediated by enhanced vagal tone) often require the use of **intermittent positive-pressure ventilation (IPPV)** and administration of anticholinergics, respectively. The relationships between CO and **heart rate (HR)** emphasize the importance of maintaining an adequate HR to enable good perfusion and blood pressure. Cardiac output is equal to HR multiplied by stroke volume, and blood pressure is equal to CO multiplied by **systemic vascular resistance (SVR)**. In dogs, an HR < 60 beats/min can specifically reduce CO and induce hypotension.[12] A decrease in HR can be effectively treated by use of anticholinergic agents, and such treatment is recommended in healthy animals during inhalant anesthesia.[13] We are not aware of any studies in which investigators have assessed the incidence of opioid-induced bradycardia in isoflurane-anesthetized hypovolemic dogs. Also, there are no recommendations available for treatment of hypovolemic patients with bradycardia.

The specific opioids suggested for humans with cardiovascular compromise include oxymorphone, fentanyl, alfentanil, and sufentanil.[14] Although oxymorphone and fentanyl are readily available for use by veterinarians, fentanyl is less practical because of its short duration of effect, necessitating administration by infusion. Hydromorphone is an opioid that has been recommended for use in dogs for sedation, as a preanesthetic medication, and for analgesia,[15] but it has not been evaluated in critically ill patients or when used as a method of induction. Hydromorphone is a semisynthetic μ-agonist with a duration of effect that appears to be longer than for oxymorphone.[16]

Induction of profound neuroleptanalgesia followed by endotracheal intubation is usually possible when an opioid is combined with a benzodiazepine, most commonly diazepam.[17] Although benzodiazepines provide little noticeable preoperative sedation in clinically normal dogs (sometimes resulting in excitement of the dogs), these drugs enhance existing CNS depression, cause muscle relaxation, and reduce the doses needed for other induction drugs.[18] Although some information is available on the use of a combination of fentanyl-diazepam in dogs,[19,20] a controlled study on the characteristics of anesthetic induction by the use of neuroleptanalgesia in critically ill patients is required.

The objective of the study reported here was to assess the suitability of 2 induction protocols that involved the use of neuroleptanalgesia (ie, IV administration of hydromorphone or oxymorphone followed by IV administration of diazepam) in dogs with experimentally induced cardiovascular compromise with the potential for hypotension. The method consisted of inducing moderate hypovolemia in clinically normal dogs. We wanted to compare these opioid combinations for their induction characteristics as well as the cardiovascular and respiratory effects associated with induction and subsequent maintenance of anesthesia with isoflurane. With the expectation that bradycardia would develop secondary to opioid-mediated vagal tone, we also examined the influence of glycopyrrolate on cardiovascular function in anesthetized hypovolemic dogs.

Materials and Methods

Animals—Six mixed-breed dogs (5 males and 1 female) were used in the study. Dogs were between 1 and 3 years of age and weighed (mean ± SEM) 24.7 ± 4.7 kg. All dogs were judged to be in good health on the basis of results of a physical examination, CBC count, biochemical analysis, electrocardiography, and thoracic radiography. The Animal Care Committee of the University of Guelph approved the experimental protocol, and the dogs were cared for in accordance with university animal care policies.

Study design—The study was conducted as a crossover design. The dogs were randomly assigned to be induced with a combination of **hydromorphone and diazepam (HydroD)** or **oxymorphone and diazepam (OxyD)**; a 3-week period was allowed between successive anesthetic episodes. Except for the opioids, all other treatments were identical for each anesthetic episode.

Food was withheld for 12 hours from all dogs prior to each anesthetic episode. Anesthesia was induced in the dogs by administration via a face mask of isoflurane[a] in oxygen with nitrous oxide[b] at 66% (total flow, 3 L/min). When adequate depth of anesthesia was achieved, the dogs were intubated and positioned in left lateral recumbency on a padded table. Intermittent positive-pressure ventilation was initiated (tidal volume of 12 to 15 mL/kg and rate of 10 breaths/min). Anesthesia was maintained by administration of isoflurane in 100% oxygen (1 L/min), and we ensured complete washout of nitrous oxide by use of high flows of oxygen.

Catheters were percutaneously inserted into the right cephalic vein for administration of fluids and treatments and the left dorsal metatarsal artery for collection of samples for use in blood gas analysis and connection to a multiple-channel monitor[c] for determination of blood pressure. Normocapnia (Pa_{CO_2} between 35 and 45 mm Hg) was accomplished by adjusting the tidal volume before samples were collected or variables assessed. Blood gas analysis[d] involved use of a temperature-based correction (ie, it considered each dog's core temperature). Body temperature was measured by use of a rectal probe thermometer[e] during insertion of catheters, and core body temperature was measured via the thermodilution catheter thereafter. The temperature of each dog was adjusted by the use of ice packs or circulating warm water blankets to maintain normothermia (37.0° to 38.5°C). Subcutaneous wire sutures for the ECG connection were inserted to enable stress-free assessment (lead II). A catheter[f] was inserted via an introducer[g] into the right jugular vein. Fluoroscopy assisted in the placement of the tip of

the catheter in the region of the pulmonary artery, as confirmed by rapid IV injection of 480 mg of iohexol.[h] Location of the injection port was determined by identification of characteristic pressure waveforms. A sample collection tube[i] was inserted into the lumen of the endotracheal tube and advanced to the region of the thoracic inlet; the sample collection tube was connected to the multiple-channel monitor to enable us to determine end-tidal concentrations of carbon dioxide and isoflurane. Elimination of nitrous oxide was verified by use of the same monitor. This monitor was calibrated on the morning of each experiment by use of calibration gases (1.0% isoflurane, 60% nitrous oxide, and 5.0% carbon dioxide) supplied by the manufacturer.

Variables assessed following each intervention during the study included ECG (lead II), HR, **systolic arterial pressure (SAP)**, diastolic arterial pressure, **mean arterial pressure (MAP)**, CVP measured via the proximal right atrial port of the catheter inserted in the jugular vein, and **mean pulmonary artery pressure (MPAP)** recorded by use of the multiple-channel monitor. The manubrium was the anatomic site used as the zero reference point for all pressure measurements. The monitor and transducers were assessed for accuracy immediately before each anesthetic episode by use of a mercury manometer (approx 20 mm Hg for low-pressure channels and 100 mm Hg for the SAP channel). Cardiac output was assessed by use of the thermodilution technique[j] by rapid injection of 5 mL of ice-cold (0° to 5°C) 5% dextrose solution. Injections were coordinated with the respiratory pause during IPPV but not coordinated when the dogs were spontaneously breathing. Cardiac output was the mean of 3 measurements, all of which were within 10% of each other. End-tidal concentrations of gases, temperature, and arterial blood gas concentrations were also determined at each intervention. The SVR was calculated as follows:

$$SVR = (80 \times [MAP - CVP])/CO.$$

Cardiac index (CI) was calculated as follows:

$$CI = CO/\text{body weight}.$$

Stroke index (SI) was calculated as follows:

$$SI = CI/HR.$$

Inhalant-induced anesthesia was maintained at a stable depth for a minimum of 15 minutes by use of IPPV and an end-tidal concentration of isoflurane of 1.8% (1.5 MAC, as determined on the basis of the mean of a population for these same dogs in another study[16]) before we initiated assessments. Cardiorespiratory measurements were obtained in the anesthetized normovolemic dogs. The concentration of isoflurane was progressively reduced after completion of all measurements during induction of moderate hypovolemia. A volume of blood (30 mL/kg) was removed from the dorsal metatarsal artery of each dog during a 20-minute period. The blood was measured by placing the blood collection bag on a scale to accurately determine the weight (and hence the volume) removed. After blood removal, the dogs were disconnected from the monitors and allowed to recover from anesthesia until fully conscious (which was defined as a minimum of 15 minutes after a dog was able to walk and was responsive to vocal comments, petting, and gentle restraint). At that point, assessments in awake hypovolemic dogs were obtained (excluding end-tidal gas determinations) with each dog sitting or standing on the floor.

Dogs were randomly assigned to receive an induction treatment. Hydromorphone[k] (0.1 mg/kg) or oxymorphone[l] (0.05 mg/kg) was administered IV, which was followed by IV administration of diazepam[m] (0.2 mg/kg). Drugs were administered during a period of approximately 20 seconds; the catheter was flushed with 3 mL of saline (0.9% NaCl) solution[n] after administration of the diazepam. During induction, the dogs were given supplemental oxygen via a face mask.

Objective variables (excluding blood gas and end-tidal gas determinations) and a subjective evaluation of effect were assessed 5 minutes after induction. An assistant who was not aware of the treatment administered to each dog performed the subjective assessment during each induction. Subsequently, another IV injection of the same opioid (at the same dosage used for induction) was administered. Approximately 3 minutes after injection of the opioid, all objective measurements (excluding end-tidal gas determination) and subjective assessments were obtained. Ease of endotracheal intubation was also evaluated by an experienced anesthesiologist (6 years of experience), who attempted (up to 2 attempts) to insert the endotracheal tube. A dog was considered difficult to intubate when intubation was unsuccessful during the initial 2 attempts, which required a third attempt that was performed by a more experienced anesthesiologist (25 years of experience).

After endotracheal intubation, the dogs were placed in left lateral recumbency on a padded table, connected to the anesthetic machine that was used during insertion of catheters and thermometers, and ventilated by use of IPPV, as described previously. Anesthesia was maintained at an end-tidal isoflurane concentration of 0.9%, which represented approximately 1.5 MAC, as determined for these same dogs when administered hydromorphone or oxymorphone IV during another study.[16] After allowing 15 minutes for equilibration at a stable end-tidal concentration, all measurements were repeated. Glycopyrrolate[o] (0.01 mg/kg, IV) was administered, and 10 minutes was allowed for it to exert its effects before all measurements were again repeated.

Dogs were treated to correct hypovolemia while recovering from anesthesia. A balanced electrolyte solution[p] (approx 50 mL/kg) and half of the autologous blood were administered during a 1-hour period. Following a 3-week period of rest, the dogs were assessed for return of the PCV and total protein concentration to reference range values. The study was then repeated, and dogs were administered the other induction treatment.

Statistical analyses—Five of 14 comparisons were selected that were considered to be comparable and clinically relevant. Because multiple interventions were performed during the study (eg, maintenance with isoflurane and administration of glycopyrrolate) that could have influenced the effects observed for our primary drugs (ie, HydroD or OxyD), changes between these defined interventions were analyzed, as opposed to directly comparing values obtained after each intervention. These changes were analyzed in 2 ways. First, *t* tests were used to evaluate changes within the treatments (eg, the difference between the values for the first and fifth interventions for the HydroD treatment) to determine whether the intervention induced a significant change (ie, different from 0). Values for these analyses were considered significant at $P \leq 0.05$. Second, *t* tests were used on contrasts (eg, the difference between the values for the first and fifth interventions when administered the OxyD treatment subtracted from the difference between the values for the first and fifth interventions for the same dog when administered the HydroD treatment) to determine whether the treatments differed significantly in their effects (different from 0). To account for multiple comparisons performed in these analyses, a value of $P \leq 0.015$ was considered significant.

Results

Subjective measurements obtained following induction were summarized **(Table 1)**. Evidence of

Table 1—Number of dogs (6 dogs/induction treatment) that had evidence of subjective effects when evaluated 5 minutes after administration of a combination of hydromorphone and diazepam (HyrdoD) or oxymorphone and diazepam (OxyD) to induce anesthesia and again 3 minutes after administration of a second dose of the same opioid (hydromorphone [Hydro2] or oxymorphone [Oxy2], respectively).

Effect	HydroD	Hydro2	OxyD	Oxy2
Yawning	0	0	0	0
Vocalization*	1	0	0	2
Panting (> 30 breaths/min)	5	6	4	5
Twitching	0	0	0	0
Medial palpebral reflexes	6	6	6	6
Lateral palpebral reflexes	4	4	6	6
Movement†	1	1	0	0
Moderate to strong jaw tone‡	6	4	6	4
Intubation in 1 to 2 attempts§	NA	3	NA	4
Coughing during intubation	NA	2	NA	3
Drooling	0	0	1	0
Vomiting	0	0	0	0
Urination	0	0	0	0
Defecation	1	0	0	0
Profound sedation‖	6	6	6	5
Dysphoria	0	0	0	1

*Low moan or an audible sigh. †In response to limb manipulation. ‡Assessed by gently opening the mouth 3 times. §Intubation was attempted 5 minutes after Hydro2 and Oxy2. ‖Recumbent, relaxed with eyes closed and minimal response to stimulation.

NA = Not applicable because intubation was not attempted after the initial injections.

profound sedation was detected within 1 minute after the initial injection of HydroD or OxyD. After the initial injections, 1 dog in each induction treatment (but not the same dog) had persistent strong jaw tone and was considered to be unsuitable for intubation. Intubation was not performed in any dogs at that time, although 5 of 6 dogs in each treatment had signs consistent with allowing (or at least attempting) intubation. All dogs were successfully intubated following administration of the second dose of opioid. One dog was less sedated and relaxed after the second injection of oxymorphone, compared with the response after the first injections of OxyD. Although this lessened effect was recorded, the dog was considered suitable for intubation. Overall assessment of ease of intubation revealed that 2 of 6 dogs administered oxymorphone and 3 of 6 dogs administered hydromorphone were difficult to intubate (ie, required the assistance of the more experienced anesthesiologist).

Objective measurements were reported as mean ± SEM or the mean difference in the values between 2 interventions. Reliable values for MPAP were difficult to obtain because of technical difficulties following the creation of hypovolemia (ie, the tip of the catheter often was wedged or occluded). However, no apparent problems resulted with CO measurements (consistent triplicate readings). No statistical analysis was performed on MPAP values. Several cardiovascular variables were assessed (**Figure 1**). Other measurements were summarized (**Table 2**).

Baseline measurements for the normovolemic dogs anesthetized by use of isoflurane were compared with measurements for the hypovolemic, isoflurane-anesthetized dogs. Values were similar between induction treatments, and there was no indication of compromise of the second induction treatment as a result of the first treatment. Baseline measurements for HydroD and OxyD treatments were MAP (57 ± 1.4 mm Hg and 60 ± 3.1 mm Hg), CI (88.5 ± 9.57 mL/kg/min and 82.3 ± 9.23 mL/kg/min), HR (91 ± 5.0 beats/min and 88 ± 4.2 beats/min), SVR (2,094 ± 296 dynes/s/cm^{-5} and 2,106 ± 273 dynes/s/cm^{-5}), CVP (2.2 ± 0.65 mm Hg and 5.5 ± 1.28 mm Hg), and base excess (–4.1 ± 1.05 and –3.1 ± 0.89). Removal of 30 mL of blood/kg resulted in similar baseline values between HydroD and OxyD in awake hypovolemic dogs for MAP (65.5 ± 2.79 mm Hg and 63.8 ± 5.59 mm Hg), CI (74.1 ± 7.65 mL/kg/min and 71.9 ± 8.42 mL/kg/min), HR (108 ± 7.2 beats/min and 101 ± 7.7 beats/min), SVR (3,023 ± 334 dynes/s/cm^{-5} and 2,973 ± 291 dynes/s/cm^{-5}), CVP (–2.8 ± 1.66 mm Hg and –2.2 ± 1.08 mm Hg), and base excess (–7.3 ± 1.04 and –7.3 ± 1.20).

Administration of the initial injections of HydroD or OxyD resulted in no significant changes in measured variables, compared with values for the awake hypovolemic status. Administration of the second dose of opioid caused significant changes, compared with values for the awake hypovolemic status. Heart rate decreased significantly (P = 0.008) when dogs received hydromorphone (from 108 ± 7.2 beats/min to 66 ± 5.4 beats/min), whereas SI increased significantly (P = 0.006) when dogs received hydromorphone (0.71 ± 0.095 mL/kg/beat to 1.14 ± 0.1 mL/kg/beat). The pH decreased for both treatments (from 7.33 ± 0.02 to 7.23 ± 0.02 for dogs when receiving hydromorphone and from 7.33 ± 0.02 to 7.23 ± 0.01 for dogs when receiving oxymorphone), and Pa_{CO_2} increased for both treatments (from 33.2 ± 1.67 mm Hg to 46.3 ± 1.89 mm Hg for dogs when receiving hydromorphone and from 33.0 ± 1.54 mm Hg to 48.3 ± 2.50 mm Hg for dogs when receiving oxymorphone). The HCO_3^- concentration increased in dogs when they were administered oxymorphone (from 16.8 ± 1.05 mmol/L to 19.8 ± 0.98 mmol/L).

Maintenance of the induced hypovolemic dogs by administration of isoflurane resulted in significant dif-

ferences, compared with values for the same dogs when at a surgical plane of anesthesia during normovolemia. A significant (P = 0.004) reduction in CI was apparent for the HydroD treatment (from 88.5 ± 9.57 mL/kg/min to 58.3 ± 3.62 mL/kg/min), whereas the effect was similar, but not significantly (P = 0.026) different, for the OxyD treatment (from 82.3 ± 9.23 mL/kg/min to 61.0 ± 3.19 mL/kg/min). Adjusted base excess was significantly more negative for both treatments (change from –4.1 ± 1.05 to –7.3 ± 0.92 for the

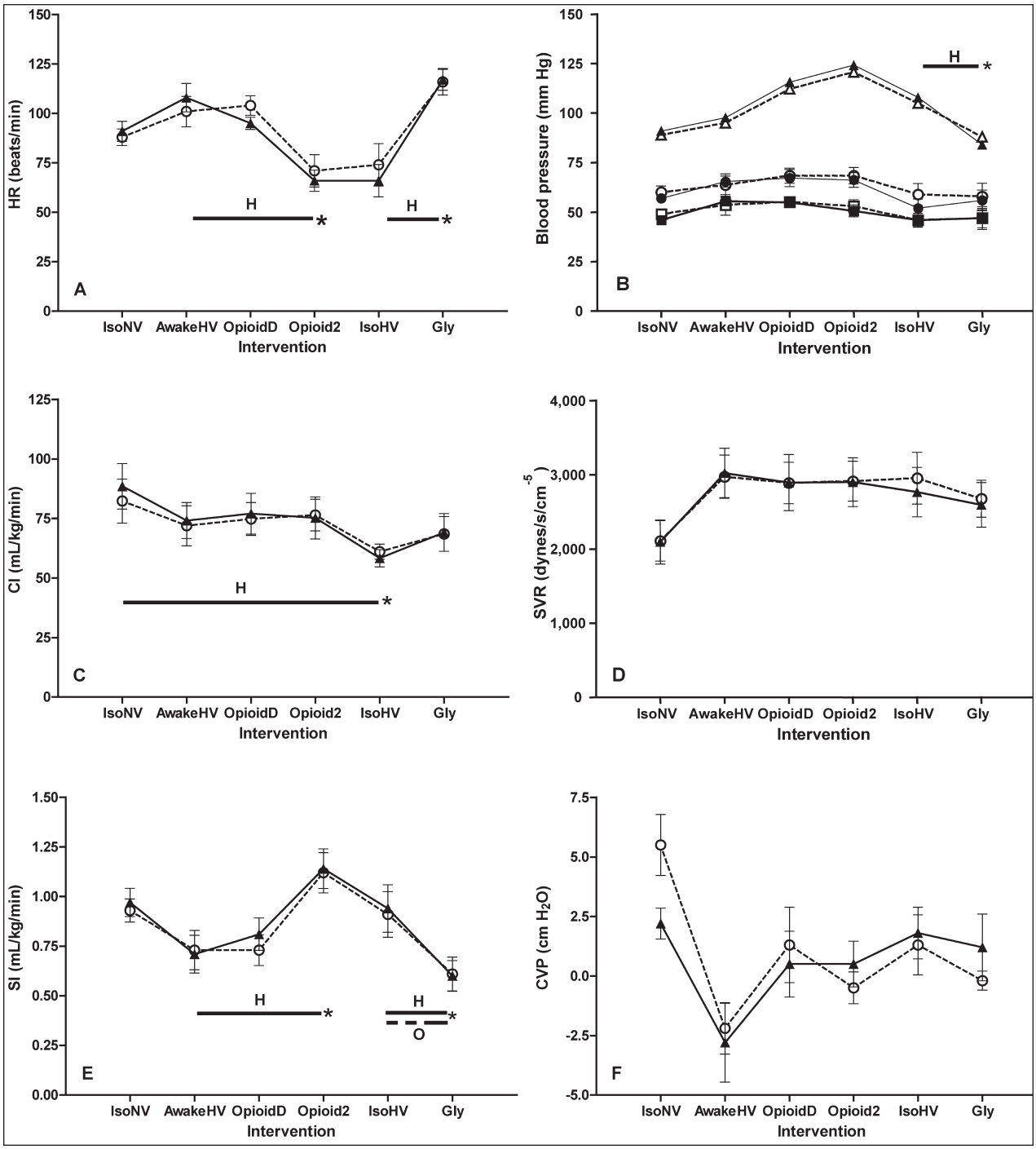

Figure 1—Mean ± SEM values for heart rate (HR; A); systolic arterial pressure (triangles), mean arterial pressure (circles), and diastolic arterial pressure (squares; B); cardiac index (CI; C); systemic vascular resistance (SVR; D); stroke index (SI; E); and central venous pressure (CVP; F) after various interventions in 6 dogs anesthetized by IV administration of hydromorphone followed by IV administration of diazepam (solid symbols) or IV administration of oxymorphone followed by IV administration of diazepam (open symbols). IsoNV = Normovolemic dogs anesthetized with isoflurane (end-tidal concentration, 1.8%). AwakeHV = Awake hypovolemic dogs. OpioidD = Induction with IV administration of an opioid (hydromorphone or oxymorphone) followed by IV administration of diazepam. Opioid2 = Administration of the second dose of the same opioid. IsoHV = Hypovolemic dogs anesthetized by use of isoflurane (end-tidal concentration, 0.9%). Gly = After glycopyrrolate administration. Bar and asterisk = Significant ($P \leq 0.015$) changes between interventions for hydromorphone-diazepam (solid; H) and oxymorphone-diazepam (dashed; O) inductions.

HydroD treatment and from –3.1 ± 0.89 mmol/L to –5.8 ± 0.86 mmol/L for the OxyD treatment). The HCO_3^- concentration decreased when dogs were administered OxyD (from 21.1 ± 0.78 mmol/L to 19.4 ± 0.61 mmol/L), and temperature also decreased for the OxyD treatment (from 37.8° ± 0.19°C to 36.8° ± 0.08°C).

Significant differences were observed between values for awake hypovolemic dogs and hypovolemic dogs anesthetized with isoflurane. There was an increase in Pa_{O_2} (from 110 ± 5.2 mm Hg to 514 ± 11.1 mm Hg and 107 ± 2.1 mm Hg to 563 ± 5.0 mm Hg for the HydroD and OxyD treatments, respectively) and a decrease in pH for the HydroD treatment (from 7.33 ± 0.02 to 7.28 ± 0.023).

The impact of glycopyrrolate administration was evaluated. Compared with values for hypovolemic dogs anesthetized with isoflurane, values after injection of glycopyrrolate were significantly (P = 0.002) increased for HR for the HydroD treatment (from 66 ± 8.2 beats/min to 117 ± 5.3 beats/min). A similar pattern in HR was detected for the OxyD treatment, but the values did not differ significantly (P = 0.021). A significant (P = 0.005) decrease in SAP was observed after glycopyrrolate injection for the HydroD treatment (from 108 ± 13.6 mm Hg to 84 ± 9.4 mm Hg), whereas the change was not significant after glycopyrrolate injection for the OxyD treatment (from 105 ± 17.0 mm Hg to 88 ± 12.4 mm Hg). The SI after glycopyrrolate injection was significantly reduced for the HydroD

Table 2—Mean ± SEM difference in measurements for various interventions, compared within and between induction treatments for 6 dogs.

Variable and comparison	Within HydroD	*P*	Within OxyD	*P*	Between HydroD and OxyD	*P*
Respiratory rate (breaths/min)						
AwakeHV – OpioidD	–25 ± 14.6	—	–19 ± 16.9	—	–31 ± 29.9	—
AwakeHV – Opioid2	–46 ± 21.3	—	–19 ± 16.9	—	–15 ± 26.1	—
IsoNV – IsoHV	–0.2 ± 0.17	—	–0.5 ± 0.22	—	0.3 ± 0.21	—
AwakeHV – IsoHV	56 ± 11.6	0.005*	48 ± 8.5	0.002*	8 ± 15.2	—
IsoHV – Gly	0	—	0	—	0	—
Temperature (°C)						
AwakeHV – OpioidD	–0.2 ± 0.13	—	0 ± 0.05	—	–0.2 ± 0.15	—
AwakeHV – Opioid2	–0.3 ± 0.10	0.048	0.02 ± 0.11	—	–0.3 ± 0.18	—
IsoNV – IsoHV	0.4 ± 0.38	—	1.0 ± 0.16	0.002*	–0.6 ± 0.47	—
AwakeHV – IsoHV	–0.08 ± 0.213	—	0.37 ± 0.256	—	–0.4 ± 0.25	—
IsoHV – Gly	–0.2 ± 0.17	—	–0.05 ± 0.133	—	–0.1 ± 0.28	—
pH						
AwakeHV – OpioidD	ND	—	ND	—	ND	—
AwakeHV – Opioid2	0.1 ± 0.007	< 0.001*	0.09 ± 0.012	< 0.001*	0.009 ± 0.012	—
IsoNV – IsoHV	0.05 ± 0.017	0.046	0.04 ± 0.018	—	0.009 ± 0.013	—
AwakeHV – IsoHV	0.04 ± 0.010	0.012*	0.02 ± 0.008	0.050	0.02 ± 0.014	—
IsoHV – Gly	–0.001 ± 0.006	—	–0.01 ± 0.010	—	0.01 ± 0.007	—
Pao2 (mm Hg)						
AwakeHV – OpioidD	ND	—	ND	—	ND	—
AwakeHV – Opioid2	–83 ± 54.8	—	–125 ± 93.3	—	41 ± 106.3	—
IsoNV – IsoHV	–33 ± 16.6	—	–24 ± 9.2	0.048	–17 ± 22.3	—
AwakeHV – IsoHV	–431 ± 14.2	< 0.001*	–455 ± 4.59	< 0.001*	23 ± 11.7	—
IsoHV – Gly	18 ± 14.0	—	25 ± 16.7	—	–8 ± 12.9	—
Paco2 (mm Hg)						
AwakeHV – OpioidD	ND	—	ND	—	ND	—
AwakeHV – Opioid2	–13.1 ± 0.85	< 0.001*	–15.3 ± 1.50	< 0.002*	2.2 ± 1.05	—
IsoNV – IsoHV	–1.6 ± 1.93	—	–0.7 ± 1.65	—	–0.8 ± 1.32	—
AwakeHV – IsoHV	–7.4 ± 1.90	0.018	–6.9 ± 2.01	0.018	0.2 ± 2.62	—
IsoHV – Gly	–1.0 ± 0.68	—	–0.08 ± 1.21	—	–1.6 ± 0.72	—
$HCO3^-$ (mmol/L)						
AwakeHV – OpioidD	ND	—	ND	—	ND	—
AwakeHV – Opioid2	–1.7 ± 0.57	0.029	–2.9 ± 0.29	< 0.001*	1.2 ± 0.55	—
IsoNV – IsoHV	1.4 ± 0.65	—	1.7 ± 0.26	0.001*	–0.1 ± 0.52	—
AwakeHV – IsoHV	–1.9 ± 0.71	—	–2.6 ± 0.69	0.014*	1.0 ± 0.72	—
IsoHV – Gly	–0.5 ± 0.07	0.002*	–0.6 ± 0.16	0.0151	-0.06 ± 0.081	—
Base excess (mmol/L)						
AwakeHV – OpioidD	ND	—	ND	—	ND	—
AwakeHV – Opioid2	1.2 ± 0.63	—	0.03 ± 0.416	—	1.2 ± 0.67	—
IsoNV – IsoHV	2.5 ± 0.59	0.014*	2.7 ± 0.52	0.004*	0.08 ± 0.538	—
AwakeHV – IsoHV	–0.5 ± 0.62	—	–1.5 ± 0.51	0.035	1.3 ± 0.35	0.019
IsoHV – Gly	–0.5 ± 0.10	0.011*	–0.7 ± 0.2	0.014*	0.3 ± 0.20	—

*Because of multiple comparisons, values were considered significant at $P \leq 0.015$.

AwakeHV = Awake hypovolemic dogs. OpioidD = Induction with IV administration of an opioid (hydromorphone or oxymorphone) followed by IV administration of diazepam. Opioid2 = Administration of the second dose of the same opioid. IsoNV = Normovolemic dogs anesthetized with isoflurane (end-tidal concentration, 1.8%). IsoHV = Hypovolemic dogs anesthetized by use of isoflurane (end-tidal concentration, 0.9%). Gly = After glycopyrrolate administration. ND = Not determined. — = Not significant ($P > 0.05$).

(from 0.94 ± 0.12 mL/kg/beat to 0.60 ± 0.077 mL/kg/beat; $P = 0.01$) and OxyD (0.91 ± 0.115 mL/kg/beat to 0.61 ± 0.085 mL/kg/beat; $P = 0.013$) treatments. The HCO_3^- concentration increased after glycopyrrolate administration for the HydroD (from 18.4 ± 0.51 mmol/L to 19.4 ± 0.70 mmol/L) and OxyD (from 19.4 ± 0.61 mmol/L to 20.0 ± 0.68 mmol/L) treatments. Adjusted base excess was significantly less negative for the HydroD (from –7.3 ± 0.92 to –6.0 ± 1.04) and OxyD (–5.8 ± 0.86 mmol/L to –5.0 ± 0.89 mmol/L) treatments.

Comparisons were performed to determine whether changes observed for each intervention were significantly different between the 2 induction treatments. However, none of the changes were significantly different for all cardiovascular ($P \leq 0.015$) or for all other measurements ($P \leq 0.05$).

Discussion

In the study reported here, we used a method for inducing hypovolemia to enable us to test anesthetic drugs in dogs in a mimicked emergency clinical setting. Techniques for inducing hypovolemia have been used in dogs in other studies. Investigators in 1 study[21] removed 30% of the blood volume to induce hypovolemia. In another study,[22] investigators induced hypovolemia in mixed-breed dogs by removing arterial blood (30 mL/kg) during a 60-minute period. Those same investigators caused hypovolemia in Beagles by rapid blood removal until MAP decreased to 40 mm Hg; that pressure was maintained for 30 minutes. The typical amount of blood removal required to achieve an MAP of 60 mm Hg reported in 1 study[5] was 38.2 ± 10.4 mL/kg. With the removal of only 30 mL of blood/kg, the compromise placed on the dogs in the study reported here was not as severe as that reported by others. However, the effects induced were similar to those reported by others, similar among the dogs of our study, and coincided with those resulting from an insult that could be equated to moderate hypovolemia that caused pale mucous membranes, slow capillary refill time, and mild lethargy.

Hemorrhage as a method to induce hypovolemia decreases CVP and atrial pressures in most studies. The decrease in atrial pressure results from a reduction in venous return. When there is a lack of compensation, CO and MAP should also decrease substantially, which results in reduced oxygen delivery to vital organs, with the potential that death may ensue. Systolic pressures < 80 mm Hg and mean pressures < 60 mm Hg are assumed to result in inadequate cerebral and coronary perfusion.[23] However, a clinically normal animal can withstand loss of 40% of the blood volume and not die, with only an approximate decrease of 10% in MAP.[24] The dogs in our study were subjected to a blood loss of approximately 37% with a decrease of at least 10% in arterial blood pressure following recovery from anesthesia, compared with the expected values in normovolemic dogs.[23]

We chose to compare normovolemic dogs anesthetized by use of isoflurane at an end-tidal concentration of 1.8% with hypovolemic dogs anesthetized by use of isoflurane at an end-tidal concentration of 0.9%, rather than having the awake normovolemic dogs as the control status. This comparison should be more valid for clinicians who are interested in the added compromise of blood loss in a patient that requires anesthesia. However, it is interesting that the awake hypovolemic dogs had little difference in blood pressures and small differences in CI, compared with values for the normovolemic dogs anesthetized with isoflurane alone. Although these values were not statistically compared because we did not consider this to be the purpose of the study, much of the compromise from hypovolemia was similar to that induced by isoflurane-induced anesthesia. This observation emphasizes the fact that anesthesia is not a benign intervention, even when an anesthetic agent (eg, isoflurane) that is considered most appropriate and to cause the least depression to the cardiovascular system is used. Balanced anesthesia with the use of MAC-sparing analgesics is clearly an advantage, considering that the cardiovascular-depressing effects of isoflurane are a dose-dependent phenomenon.[25] The concentration of the inhalant was approximately half that used for our control comparison (ie, normovolemic dogs anesthetized by use of isoflurane). It is important in critically ill patients to recognize that a substantial reduction in isoflurane concentration is required to maximize the benefit from the use of balanced anesthesia. We chose to use the population MAC for our study rather than the MAC determined for each dog. Most investigators adhere to this procedure in studies because the same dogs typically are not used in repeated experiments for cardiovascular investigations. Our results may have had less variability if we had chosen to use the dog-specific MAC for measurements in each normovolemic dog and the MAC reduction determined in the same dog following opioid administration for the measurements during isoflurane-induced anesthesia in hypovolemic dogs. However, any added effect of diazepam and hypovolemia is unknown in this population.

We selected 2 analgesics for this study to provide an MAC-sparing effect and to allow induction and intubation when they were used in combination with diazepam. Oxymorphone was considered the criterion-referenced standard,[5] whereas safe dosages and effects have not been established for the use of hydromorphone under these conditions. It has been suggested[15] that hydromorphone is effective for intraoperative and postoperative analgesia in dogs when administered within the dosage range of 0.05 to 0.2 mg/kg. In humans, a relative potency analysis indicated that hydromorphone was 10 times as potent as morphine.[26] In another study,[27] a slightly lower potency in dogs (5 to 7 times that of morphine) was suggested. Commonly used dosages of morphine for dogs range from 0.3 to 1.0 mg/kg; thus, the aforementioned dosages for hydromorphone in dogs should be similar in efficacy. Unfortunately, it is difficult for us to be sure that the doses we selected were equipotent. However, we know from results of another study[16] conducted by our laboratory group that the MAC reduction was similar, and other investigators[28] have compared administration of similar doses of each with the assumption of equipotency and similar sedative effects between drugs.

An individualized plane of anesthesia is desirable and can be achieved by titration of the induction agents, considering that the most depressant effects are a dose-dependent phenomenon. The importance of this titration technique should be greater in critically ill animals on the basis of the expected greater variation of each animal's needs and sensitivity to the drugs. To simulate this practice in our hypovolemic dogs, partial doses of each opioid were administered IV as 2 distinct boluses. The IV administration of hydromorphone (0.1 mg/kg) followed by IV administration of diazepam (0.2 mg/kg) and a repeated IV administration of hydromorphone (0.1 mg/kg) resulted in a smooth induction in all dogs in the study reported here. Similarly, IV administration of oxymorphone (0.05 mg/kg) was followed by IV administration of the same dose of diazepam and a repeated IV administration of oxymorphone. Considering that the technique to induce hypovolemia was consistent for all our dogs, we chose to test the drugs at the entire dose that may be required, rather than administer the induction drugs only as needed to achieve a desired effect. One dog in both treatments (but not the same dog) was ranked as less suitable for intubation after injection of HydroD or OxyD, as determined on the basis of clinical signs. Additional drug administration would have been required for these 2 instances in a clinical setting, whereas the other dogs may have been intubated without another dose of opioid. Our study subjected the drugs to a more stringent test because the total dose of opioid used was likely greater than necessary in some of the dogs.

Both neuroleptanalgesic combinations had suitable induction characteristics. There was some evidence for deeper sedation with HydroD, as indicated by a loss of a lateral palpebral reflex in 2 dogs, which approached an induction state more typical of other agents (eg, thiopental, propofol, and inhalants). The other measurements observed in the dogs of our study were comparable and considered acceptable for induction. Adverse responses were few. No vomiting was noticed, although dogs often vomit after opioid administration.[29] It is possible that the rapid sedative effect (approx 1 minute) induced by IV administration of these opioids in compromised dogs reduced the possibility of a response by the vomiting center.

Cardiovascular effects did not change after initial drug administration for both induction treatments, although changes were observed following the final injection of opioid, which suggested that it would be better to intubate at the lowest dose possible. It is possible that had we chosen to use a dose more specific for intubation of each dog, the results may have differed. However, it is also possible that the effects observed following the second dose of opioid were partially a result of the time required to generate the full effect from the initial dose (ie, an increased effect could have been apparent if an extended interval [10 vs 5 minutes] had been allowed after the initial injection). Our assumption was that a sufficient effect from the induction would be apparent by 5 minutes after injection. The rapid onset of sedative effects (1 minute) correlates with our assumption. Further delay before administration of more drug would be contrary to standard clinical practice because clinicians intubate animals shortly after a profound sedative effect is evident and responses allow intubation or they administer more of the induction agent when responses do not allow intubation.

In general, our findings regarding cardiovascular stability after administration of opioids are in agreement with those of another report.[17] The author of that report recommends similar doses of oxymorphone (0.05 to 0.1 mg/kg; IV, IM, or SC) as being advantageous for induction, especially in debilitated dogs. He also considers fentanyl a suitable alternative to oxymorphone and midazolam a suitable alternative to diazepam (0.2 to 0.4 mg/kg, IV or IM). These recommendations fit with the protocol we chose to assess. Moderate hypovolemia, as was induced in the study reported here, should qualify for such an induction protocol. Although we are not aware of any study in which investigators have assessed HydroD or OxyD for induction in hypovolemic dogs and then maintained those dogs on an inhalant, a study[5] evaluating the cardiopulmonary effects of oxymorphone (0.4 mg/kg, IV) used alone in hypovolemic dogs revealed a significant improvement in cardiovascular performance (increase in arterial blood pressure and CO) and tissue perfusion (increase in venous oxygen and decrease in oxygen extraction), compared with measurements obtained in the hypovolemic dogs before opioid administration. These effects were much more beneficial than any observed in the study reported here in which a lower dosage of oxymorphone was used. The addition of diazepam to induce a more profound sedative effect could explain some of the differences. Although opioids are considered to be good analgesics, an opioid cannot be used alone as a sole anesthetic drug. All patients do not respond uniformly to opioids, and there will still be some somatic and sympathetic responses to noxious stimulation.[30] Diazepam was required in our study to facilitate intubation. Diazepam alone reportedly causes minimal changes in cardiovascular variables.[18] Thus, the addition of diazepam, although necessary, was unlikely to have substantially enhanced cardiovascular depression, unless synergism results when it is combined with an opioid.

Dogs in the study had a decrease in HR with a coinciding increase in stroke volume. The decreased HR can be explained by enhanced vagal tone from the opioid component, although it is unknown whether sympathetic outflow is also depressed, as described following fentanyl administration in another study.[20] The increased SI (which was significantly increased for the HydroD treatment) may have been related to the resulting longer time for cardiac filling. However, there was no overall change in CI or blood pressure. This is in contrast to results of a study[20] in dogs administered a combination of fentanyl-diazepam in which a reduction in blood pressure was enhanced with the fentanyl-diazepam combination, compared with values for fentanyl alone, as a result of depression of the baroreflex associated with diazepam. Differences exist between studies for the initial volume state, dose, and drugs, which makes it difficult to compare results.

Of the inhalation anesthetics currently used in veterinary practices, isoflurane appears to be the most commonly used and causes minimal cardiovascular compromise.[25] Unfortunately, anesthesia is expected to impair compensatory mechanisms that may be effective in conscious animals,[31] considering that sympathetic drive is responsible for much of the compensatory response to hypovolemia. Sympathetic dampening is reported with halothane, although it is considered to be minimal following administration of isoflurane.[32] Isoflurane was chosen for the study reported here because of the limited compromise expected from this inhalant, which would thus be an advantage in hypovolemic patients. However, maintenance with the inhalant was not tailored to each dog; instead, we provided the same percentage of isoflurane to all dogs. Some dogs may have been at a deeper plane of anesthesia and thus more depressed than required with this approach. None of the dogs appeared to be in a light plane of anesthesia, as determined on the basis of our clinical judgment; thus, it may be assumed that the depth of anesthesia used in the study was adequate for surgery.

The cardiovascular results in our dogs following isoflurane-maintained anesthesia could suggest a degree of inhibition of sympathetic drive, although significant differences were not detected. Blood pressures were slightly lower during isoflurane-maintained anesthesia than in the awake hypovolemic dogs or the dogs after induction with HydroD or OxyD. Although opioids induced a minimal reduction in blood pressure prior to administration of the inhalant, subsequent addition of the inhalant caused a clinically unacceptable MAP (HydroD, 52 ± 4.8 mm Hg; OxyD, 59 ± 5.6 mm Hg), compared with an MAP of > 60 mm Hg before the addition of the inhalant. The CI values for hypovolemic dogs anesthetized with isoflurane were similar between the induction treatments (HydroD, 58.3 ± 3.62 mL/kg/min; OxyD, 61.0 ± 3.19 mL/kg/min), although the change observed from values for the awake hypovolemic dogs differed significantly from the values for HydroD. The CI for the OxyD induction was slightly lower than CI for the HydroD induction, which slightly confounded the results. However, the SVR and SI were similar between treatments. These similarities suggest that the slight decrease in HR was at least partially responsible for the decrease in CI. The fact that comparison of the changes between the drugs did not reveal significant differences confirms that there was a similar but smaller change in CI for the OxyD treatment.

Bradycardia is a common response to opioid administration and is related to the parasympathomimetic effects of this group of drugs. Both treatments in our study caused a decrease in HR after the second opioid injection, compared with values for awake hypovolemic status; these values differed significantly when the dogs were administered hydromorphone. The awake hypovolemic dogs had a slightly higher HR, which was possibly an aspect of compensation for the degree of hypovolemia or indicative of awareness of external stimuli (eg, handling). For both treatments, 3 of 6 dogs had an HR < 60 beats/min after the second opioid injection. It is possible that bradycardia did not develop in more of our dogs because they were hypovolemic. A degree of sympathetic drive related to hypovolemia could persist in maintaining a higher HR despite opioid-induced vagal tone. In other studies of opioid use in normovolemic anesthetized dogs, HR decreased to 55 beats/min during anesthesia achieved by use of fentanyl and enflurane[33] and to approximately 75 beats/min for anesthesia achieved by epidural administration of oxymorphone and use of halothane.[34] In the latter study, dogs received an electrical stimulus that may have increased the HR, compared with dogs that were anesthetized without stimuli. Authors of these studies recommend treatment with an anticholinergic drug when opioids are used in conjunction with general anesthesia in normovolemic dogs. On the basis of these studies, anticholinergic treatment improved CO significantly. In another study,[12] administration of atropine increased all measured cardiovascular variables, including measures of tissue perfusion, in nonanesthetized dogs given oxymorphone.

We hypothesized that maintenance of a higher HR could prevent significant reductions in CO and arterial blood pressure in hypovolemic dogs during isoflurane-maintained anesthesia. To test this hypothesis, glycopyrrolate was chosen as the anticholinergic and administered IV following measurement of variables. After the glycopyrrolate injection, HR increased for all dogs (ie, both induction treatments), although the change was only significantly different for the HydroD induction treatment. There was also a coinciding decrease in SAP (HydroD) and SI (both inductions). The change in SAP for the HydroD induction was not significantly different from that for the OxyD induction, and changes in CI were not significantly different for either induction treatment. The actual mean SI value after glycopyrrolate administration was similar between induction treatments but significantly reduced within each treatment group, although CI did not decrease. Because an increase in HR is usually associated with an increase in myocardial work, this added work would be contraindicated without evidence of other benefits.

When the cardiovascular changes were compared between the induction treatments, they were not different within any interventions assessed. Our conclusion is that the 2 opioids are comparable in hypovolemic dogs with respect to cardiovascular impact when administered with diazepam and following transfer to isoflurane.

The respiratory rate recorded was quite variable in our dogs during spontaneous breathing (eg, awake hypovolemic dogs and after initial injection of HydroD or OxyD) but typically was high throughout the study. In another study,[5] investigators verified that the respiratory rate and minute ventilation decreased immediately after oxymorphone administration to hypovolemic dogs but returned to or exceeded the values at 5 minutes in hypovolemic dogs, remaining comparatively higher than those values. In the study reported here, respiratory evaluations were conducted 5 minutes after opioid injections; however, we did not detect

a change from baseline values. Panting has been associated with clinically normal dogs sedated by use of neuroleptanalgesics,[35] and it is difficult to separate effects related to changes in the set-point of the thermoregulatory center (opioid-related effect), central respiratory depression with the induction state (increasing respiratory rate at the expense of tidal volume), and the effects of hypovolemia in our dogs. However, the changes in ventilation resulted in a higher Pa_{CO_2} with a resultant lower pH for both inductions, and this would be most suggestive of a respiratory depressive effect in the CNS from the combination of HydroD or OxyD and hypovolemia. In consideration of the respiratory data collected, it is important to recognize that isoflurane-anesthetized dogs were ventilated and on 100% oxygen. Blood gas measurements during isoflurane-induced anesthesia in our study were obtained following IPPV at values consistent with normocapnia determined in the same dogs.

Oxygenation may be impaired following administration of oxymorphone in hypovolemic dogs. The Pa_{O_2} significantly and persistently decreased after oxymorphone administration and remained significantly less than the value for the control group for the duration of 1 study.[5] In the study reported here, there was no decrease in Pa_{O_2} but supplemental oxygen was provided during induction, which would have impaired detection of any ventilation-perfusion mismatch. Analysis of our results indicated that there was no significant difference related to respiration or oxygenation between induction with HydroD or OxyD in hypovolemic dogs.

Base excess (as a measure of metabolic acid-base status) became more negative for both induction treatments following the transfer to isoflurane, and this may have been related to poorer perfusion of tissues with accumulation of lactic acid as a consequence of hypovolemia. Serum concentrations of electrolytes and lactate were not assessed in these dogs, but measurement of those concentrations would have enlightened us as to the reason for the change.

A significant decrease in core body temperature (from $37.8^{\circ} \pm 0.19^{\circ}$C to $36.8^{\circ} \pm 0.08^{\circ}$C) was apparent when values for normovolemic anesthetized dogs were compared with values for hypovolemic anesthetized dogs induced by use of OxyD, despite attempts to maintain normothermia. There was no obvious explanation for this difference, and it is unlikely that cardiovascular differences could be responsible, considering that the OxyD and HydroD treatments were not different in this respect (ie, similar CO and SVR).

We conclude that hydromorphone or oxymorphone in combination with diazepam provided comparable induction characteristics in dogs with experimentally induced moderate hypovolemia. Similar cardiovascular and respiratory effects were observed at induction and subsequent maintenance with isoflurane. Half of the dogs became bradycardic (≤ 60 beats/min) with this induction and maintenance, despite the hypovolemia. Glycopyrrolate for reversal of opioid-associated bradycardia during isoflurane-maintained anesthesia in hypovolemic dogs provided no cardiovascular advantage. In our opinion, it would be safe to use HydroD for induction of critically ill dogs as an alternative to induction with OxyD. We would not advise the use of glycopyrrolate for the treatment of bradycardia under these circumstances.

a. Isoflurane USP, BIMEDA-MTC Animal Health/Sante Animale, Cambridge, ON, Canada.
b. BOC gases, Division of BOC Canada Ltd, Mississauga, ON, Canada.
c. Criticare 1100 patient monitor, Criticare Systems, Waukeska, Wis.
d. Radiometer ABL 3-MK, Blood Microsystems, London, ON, Canada.
e. Tele-thermometer, Yellow Springs Instrument Co, Yellow Springs, Ohio.
f. 7-F, 110-cm, balloon-tipped, thermodilution catheter, Baxter Healthcare Corp, Edwards Critical Care Division, Irvine, Calif.
g. 8.5-F catheter introducer, Baxter Healthcare Corp, Edwards Critical Care Division, Irvine, Calif.
h. Omnipaque, iohexol 52%, 240 mg/mL, Nycomed Imaging AS, Brampton, ON, Canada.
i. 8-F feeding tube (PVC), Bard Canada Inc, Mississauga, ON, Canada.
j. COM-2 cardiac output computer, Baxter Healthcare Corp, Irvine, Calif.
k. Hydromorphone hydrochloride injection (10 mg/mL), SABEX, Boucherville, QC, Canada.
l. Numorphan (1.5 mg/mL), Dupont Pharmaceuticals, Scarborough, ON, Canada.
m. Diazepam (5 mg/mL), SABEX Inc, Boucherville, QC, Canada.
n. Physiological saline, sodium chloride injection USP 0.9%, MTC Pharmaceuticals, Cambridge, ON, Canada.
o. Glycopyrrolate injection (0.2 mg/mL), SABEX Inc, Boucherville, QC, Canada.
p. Plasmalyte 148 electrolyte solution, Baxter Corp, Toronto, ON, Canada.

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