Comparison of the effects of morphine administered by constant-rate intravenous infusion or intermittent intramuscular injection in dogs

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Objective—To compare physiologic and analgesic effects of morphine when given by IV constant-rate infusion or by IM injection to dogs undergoing laparotomy and to determine pharmacokinetics of morphine in dogs following IV constant-rate infusion.

Design—Prospective randomized controlled trial.

Animals—20 dogs.

Procedure—Dogs undergoing laparotomy were treated with morphine beginning at the time of anesthetic induction. Morphine was administered by IV infusion (0.12 mg/kg/h [0.05 mg/lb/h] of body weight) or by IM injection (1 mg/kg [0.45 mg/lb]) at induction and extubation and every 4 hours thereafter. Treatments continued for 24 hours after extubation.

Results—Blood gas values did not indicate clinically significant respiratory depression in either group, and degree of analgesia (determined as the University of Melbourne Pain Scale score) and incidence of adverse effects (panting, vomiting, defecation, and dysphoria) were not significantly different between groups. Dogs in both groups had significant decreases in mean heart rate, rectal temperature, and serum sodium and potassium concentrations, compared with preoperative values. Mean ± SEM total body clearance of morphine was 68 ± 6 ml/min/kg (31 ± 3 ml/min/lb). Mean steady-state serum morphine concentration in dogs receiving morphine by constant-rate infusion was 30 ± 2 ng/ml.

Conclusions and Clinical Relevance—Results indicated that administration of morphine as a constant-rate IV infusion at a dose of 0.12 mg/kg/h induced effects similar to those obtained with administration at a dose of 1 mg/kg, IM, every 4 hours in dogs undergoing laparotomy. Panting was attributed to an opioid-induced resetting of the hypothalamic temperature set point, rather than respiratory depression. (*J Am Vet Med Assoc* 2001;218:884–891)

The level of analgesia provided by morphine is the reference standard by which other opioids are evaluated.[1] Despite this, morphine is infrequently used in small animal practice because of concerns about potential adverse effects and uncertainty about the most appropriate dosage. Morphine has a reputation for causing respiratory depression[2] and can cause other undesirable adverse effects such as panting, vomiting, defecating, and dysphoria.[3] All of these effects are considered to be dose dependent.[3,4]

Use of morphine has also been restricted by the limited options for routes of administration. The bioavailability of morphine when given orally[5] or rectally[4] in dogs is approximately 20%, which makes these routes of administration impractical. Intravenous administration of morphine boluses is avoided, except for administration of very small doses, because of morphine's propensity to cause histamine release and subsequent hypotension.[6] Although morphine can be given epidurally, SC and IM injection are still the most common methods of administering morphine in small animal practice. The half-life of morphine following IM administration in dogs is approximately 1 hour,[5] and the usual practice is to administer it every 4 hours. For drugs that have a high therapeutic index, repeating the dose every 4 half-lives is quite appropriate, but morphine does not have a high therapeutic index. The incidence of adverse effects could potentially be reduced if a smaller dose were given more frequently.

Intravenous constant-rate infusion (CRI_{IV}) of morphine offers some theoretical and practical advantages over intermittent IM or SC administration. The variations in serum morphine concentration associated with intermittent IM administration can cause corresponding variations in analgesia levels, and CRI_{IV} could minimize these variations. Constant-rate infusion may also help to minimize dose-dependent adverse effects by avoiding the peaks in serum morphine concentrations that are seen when morphine is given as a bolus. Changes in dosage are easily accomplished and have a predictable onset when an infusion pump is used for CRI_{IV}. Compared with intermittent IM injections, CRI_{IV} also decreases patient handling and documentation requirements.

Just as antibiotics are evaluated in terms of their minimum inhibitory concentration, analgesics can be evaluated in terms of their **minimum effective concentration (MEC)**. The MEC is the concentration required to maintain an acceptable level of analgesia after tissue injury. The reported MEC of morphine in humans ranges from 6 to 39 ng/ml, with a mean of 16 ± 9 ng/ml in 1 study[7] and a mean of 14.7 ± 4.8 ng/ml in another.[8] To the best of our knowledge, the concept of MEC has not been explored, nor have physiologic measurements of MEC been attempted, in dogs. To do so would require simultaneous measurement of physiologic

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parameters, degree of analgesia, and serum morphine concentrations. The purposes of the study reported here were to compare physiologic and analgesic effects of morphine given by CRI_{IV} versus intermittent IM injection and to determine the pharmacokinetics of morphine during CRI_{IV} in dogs.

Materials and Methods

Determination of morphine dosage—On the basis of human data and results of pilot studies performed at the University of Melbourne Veterinary Clinic and Hospital, we chose a steady-state serum morphine concentration of 50 ng/ml as our target MEC for dogs included in the study. This was approximately twice the upper limit of the MEC of morphine in humans. Using reported values of 40 ml/kg/min (18 ml/lb/min) of body weight for total clearance and 4,000 ml for **volume of distribution (V_d)** following IV administration,[5] we calculated the necessary dosage for CRI_{IV} to be 0.002 mg/kg/min, or 0.12 mg/kg/h (0.05 mg/lb/h).

Having determined the dosage for CRI, we derived a dosage for intermittent IM administration. Using the reported value of 3,200 ml as the V_d following IM administration,[5] we calculated expected serum concentrations for 3 dosages: 0.5, 1, and 2 mg/kg (0.23, 0.45, and 0.9 mg/lb, respectively), IM, every 4 hours. Although a 0.5 mg/kg dose would be almost mathematically equal to the CRI_{IV} dose, further calculations showed that the 0.5 mg/kg dose would result in concentrations less than the target concentration for 60% of the 4-hour dosing interval, which was unacceptable for comparison of effects. A dose of 1 mg/kg would be expected to result in a maximum serum concentration of 328 ng/ml (6 times the target concentration) and a mean serum concentration of 104 ng/ml (2 times the target concentration), with serum concentrations greater than the target concentration for 60% of the 4-hour dosing interval. A 2 mg/kg dose would provide concentrations greater than the target concentration for almost 90% of the dosing interval, but would also result in serum concentrations of > 650 ng/ml (13 times the target concentration and 26 times the MEC in humans), which carried an unacceptable risk of adverse effects in clinical patients. Therefore, a 1 mg/kg IM dose was chosen for comparison with the CRI_{IV} dose.

Dogs—Twenty dogs undergoing laparotomy at the University of Melbourne Veterinary Clinic and Hospital were included in the study. Dogs of either sex and any breed were eligible for inclusion in the study; however, dogs that were < 1 year old, that were receiving analgesics prior to the study, or that had any preexisting cardiac, respiratory, hepatic, renal, or neurologic diseases were excluded. Dogs were assigned a **University of Melbourne Pain Scale (UMPS)** score prior to inclusion in the study, and any dog with a score > 6 was excluded (**Appendix**).

Experimental protocol—The University of Melbourne Animal Experimentation Ethics Sub-Committee approved the study protocol. Dogs were randomly assigned by odds-and-evens number draw to receive morphine by CRI_{IV} (n = 10) or IM by intermittent injection (10). Dogs in the CRI_{IV} group were given morphine at a constant rate of 0.12 mg/kg/h (0.05 mg/lb/h) from the time of anesthetic induction until 24 hours after extubation. The morphine infusion was prepared by adding 60 mg of morphine to 500 ml of a 5% glucose solution and was administered with an infusion pump at a rate of 1 ml/kg/h (0.45 ml/lb/h). Dogs in the IM group were given morphine (1 mg/kg [0.45 mg/lb]) IM in the lumbar musculature at the time of anesthetic induction, at the time of extubation (time 0), and 4, 8, 12, 16, and 20 hours after extubation. Any reactions to the injections were recorded.

All dogs were given a physical examination prior to anesthesia. Baseline rectal temperature, heart rate, respiratory rate, and UMPS score were recorded at this time. Central venous blood samples were collected for baseline determination of blood gas values, serum electrolyte concentrations, PCV, and total solids concentration. Anesthesia was induced with 1 of 2 regimens: acepromazine maleate (0.1 mg/kg [0.045 mg/lb], SC, to a maximum dose of 3 mg) followed by a barbiturate (thiopental (12.5 mg/kg [5.68 mg/lb], IV) or methohexital (6 mg/kg [2.73 mg/lb], IV); or diazepam (0.25 mg/kg [0.11 mg/lb], IV) and ketamine (5 mg/kg [2.27 mg/lb], IV). An orotracheal tube was placed, and anesthesia was maintained with halothane or isoflurane in oxygen. Oxygen flow rate was approximately 20 ml/kg/min (9 ml/lb/min), because all dogs weighed > 10 kg (22 lb).

Lactated Ringer's solution was administered at a rate of 10 ml/kg/h (4.5 ml/lb/h), IV, from the time of preoperative assessment until extubation. After extubation, the rate of IV fluid administration was reduced to 2.5 ml/kg/h (1.1 ml/lb/h) for the remainder of the study. An infusion pump was used to control the rate of fluid administration. If serum potassium concentration was < 3.6 mmol/L at any time during the study, potassium chloride (13.4 mmol/L) was added to the lactated Ringer's solution. If a transfusion of packed RBC was required, 0.9% sodium chloride was substituted for the lactated Ringer's solution while the transfusion was being given. Dogs were not allowed to eat or drink during the study period.

Administration of atropine, α_2-adrenoceptor agonists, and nitrous oxide was not permitted at any time, and no other analgesics were administered during the study. Administration of diazepam (0.5 mg/kg [0.27 mg/lb], IV) was permitted if a dog developed severe dysphoria.

Heart rate, respiratory rate, **end-tidal partial pressure of carbon dioxide ($P_{ET}CO_2$)**, and **arterial oxygen saturation (SpO_2)** were monitored[a,b] throughout surgery. **Intermittent positive-pressure ventilation (IPPV)** was initiated, if necessary, to maintain $P_{ET}CO_2$ < 55 mm Hg. A transfusion of packed RBC was administered if the dog's PCV was < 20% at any time during the study.

For each dog, at the time of extubation, central venous blood samples were collected for determination of blood gas values, serum electrolyte concentrations, packed cell volume, and total solids concentration. Blood gas samples were analyzed as soon as possible. If analysis could not be performed within 3 minutes after sample collection, the sample was placed in an ice-water bath. All blood gas samples were analyzed within 15 minutes after collection. Blood gas analyses ($PvCO_2$, bicarbonate concentration, and pH) were performed with 1 of 3 machines[c-e] and corrected for the dog's rectal temperature; all 3 machines were maintained and calibrated according to the manufacturers' instructions. Serum electrolyte concentrations were determined within 1 hour after sample collection, using a bench-top chemistry analyzer.[f] Packed cell volume and total solids concentration were measured by use of a microhematocrit centrifuge and a refractometer. Additional blood samples were collected and analyzed at predetermined times during the remainder of the 24-hour study period.

At the time of extubation, a UMPS score was assigned to each dog, which included measurement of temperature, heart rate, and respiratory rate. Possible UMPS scores ranged from 0 to 27, with higher scores indicating greater pain.[9] A UMPS score ≤ 6 is considered normal for a dog that has undergone general anesthesia; healthy awake dogs typically have scores of 2 or 3. University of Melbourne Pain Scale scoring was performed 10 times during the 24-hour study period. If a morphine injection was scheduled for the same time as UMPS scoring, the UMPS score was assessed first.

Six dogs in each group had central venous blood sam-

ples collected for determination of serum morphine concentrations in the first 4 hours after extubation. Samples were allowed to clot, and the serum was recovered and stored at –20 C until analyzed. For dogs in the IM group, blood samples were collected prior to administration of morphine.

Measurement of serum morphine concentration—Serum morphine concentration was measured by a commercial laboratory.[g] Briefly, 0.5 to 1 ml aliquots of serum were diluted to 2 ml with water, and 40 ng of d_3-morphine[h] was added as internal standard. Diluted serum was then subjected to solid phase extraction,[i] and the extract was derivatized with trifluoracetic anhydride. Samples were analyzed by means of gas chromatography-mass spectrometry.[j] Samples were injected onto the column[k] by use of a split-less technique at 75 C. After 1 minute, the column temperature was increased to 320 C at a rate of 30 degrees/min and held at 320 C for 4 minutes. The mass spectrometer was operated in the positive ion chemical ionization mode, using methane as the reagent gas. Calibration graphs for serum morphine concentrations ranging from 0 to 100 ng/ml were constructed by analyzing serum samples spiked with known amounts of morphine.

For dogs receiving morphine by CRI_{IV}, serum morphine concentrations 1, 2, and 4 hours after extubation were used to calculate the steady-state serum morphine concentration. Total clearance was calculated by dividing the rate of morphine infusion by the steady-state serum concentration.

Statistical methods—A single repeated-measures ANOVA[l] was used to compare results within and between groups. Within each group, we analyzed differences between the baseline value (ie, the value obtained prior to anesthetic induction) and the value obtained at each time for heart rate, rectal temperature, $PvCO_2$, bicarbonate concentration, pH, serum sodium concentration, serum potassium concentration, serum chloride concentration, serum morphine concentration, and UMPS score. Mean values for heart rate, rectal temperature, $PvCO_2$, bicarbonate concentration, pH, serum sodium concentration, serum potassium concentration, serum chloride concentration, serum morphine concentration, and UMPS score were compared between groups at each time. The Satterthwaite estimate of the denominator *df* was used, along with a compound symmetry covariance matrix.[10] The fixed effects were time, treatment, and time × treatment interaction.

A 2-sample *t*-test was used to compare the means of the most extreme postoperative measurements for maximum UMPS score, minimum rectal temperature, maximum $PvCO_2$, and minimum pH between groups. A 2-sample *t*-test was also used to compare the **area under the curve for UMPS scores from the time of extubation until 4 hours after extubation (AUC_4)** and **from the time of extubation until 12 hours after extubation (AUC_{12})** between groups. The Fisher exact test was used to compare the proportions of Greyhounds and non-Greyhounds with dysphoria. Data are given as mean ± SEM. For all analyses, a value of $P < 0.05$ was considered significant.

Results

Demographics—One Samoyed, 1 Golden Retriever, 1 German Shepherd Dog, 1 Boxer, 1 Poodle, 1 Cocker Spaniel, 1 Bull Terrier, and 13 Greyhounds were included in the study. Four dogs were male, and 16 were female. Surgical procedures included exploratory laparotomy (n = 1), intestinal biopsy (1), portal vein cannulation (1), intestinal foreign body removal (1), umbilical hernia repair (1), cystotomy (1), ovariectomy and intrauterine suture placement (2), splenectomy (2), and ovariectomy and uterine flush (10). The predominance of females and Greyhounds was a result of using dogs included in an unrelated study.

Table 1—Serum morphine concentrations (ng/ml) in dogs (n = 6/group) undergoing laparotomy that received morphine IM as an intermittent injection (1 mg/kg [0.45 mg/lb] of body weight, q 4 h) or IV (0.12 mg/kg/h [0.05 mg/lb/h]) as a constant-rate infusion (CRI)

		Time after extubation (h)			
Group	**Baseline**	**0**	**1**	**2**	**4**
IM	0	101 ± 14†*	177 ± 18†*	82 ± 14†*	35 ± 6*[b]
CRI	0	22 ± 6†[a]	36 ± 3†*	29 ± 3†*	26 ± 4*

Baseline values were obtained prior to anesthetic induction. Data are given as mean ± SEM.
*Significantly ($P < 0.05$) different from baseline value for that group.
†Significantly ($P < 0.05$) different from value for the other group.
[a]Value for only 4 dogs. [b]Value for only 5 dpgs.

Anesthesia was induced with thiopental (n = 6), methohexital (9), or diazepam and ketamine (5). Anesthesia was maintained with halothane (n = 14) or isoflurane (6). Mean time from the preoperative assessment to extubation for dogs in the CRI group (83.5 ± 7.8 minutes) was not significantly different from mean time for dogs in the IM group (96 ± 10.5 minutes).

Five dogs in the IM group and 4 in the CRI group needed IPPV to maintain $PETCO_2 < 55$ mm Hg during anesthesia. One dog in each group lost > 5 ml of blood/kg during surgery (splenectomy); the dog in the CRI group required a transfusion of packed RBC after surgery.

Serum morphine concentrations and pharmacokinetics—Mean serum morphine concentration for dogs in the IM group was 177 ± 17 ng/ml 1 hour after extubation (**Table 1**). Mean serum morphine concentration for dogs in the CRI group was 36 ± 3 ng/ml 1 hour after extubation; steady-state serum concentration was 30 ± 2 ng/ml. Mean serum morphine concentration for dogs in the CRI group was significantly lower than mean concentration for dogs in the IM group at the time of extubation and 1 and 2 hours after extubation. Four hours after extubation, however, mean serum morphine concentration was not significantly different between groups. Mean total clearance was 68 ± 6 ml/min/kg (31 ± 3 ml/min/lb).

Physiologic effects—Mean heart rate of dogs in the IM group was significantly increased at the time of extubation and significantly decreased 6, 10, 12, 16, and 24 hours after extubation, compared with baseline heart rate (**Table 2**). Mean heart rate of dogs in the CRI group was significantly increased at the time of extubation and significantly decreased 12, 16, and 24 hours after extubation, compared with baseline heart rate. Mean heart rate for dogs in the IM group was significantly lower than that for dogs in the CRI group 1 and 2 hours after extubation.

At 5 of the 10 postoperative observation times, 25% of the dogs were panting (respiratory rate ≥ 40 breaths/min), which precluded analysis of respiratory rate.

Mean rectal temperature of dogs in the IM group was significantly decreased at all postoperative measurement times, compared with baseline rectal temper-

Table 2—Physiologic measurements in dogs (n = 10/group) undergoing laparotomy that received morphine IM as an intermittent injection (1 mg/kg [0.45 mg/lb] of body weight, q 4 h) or intravenously (0.12 mg/kg/h [0.05 mg/lb/h]) as a constant rate infusion (CRI)

		Time after extubation (h)									
Variable and group	**Baseline**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**24**
Rectal temperature (C)											
IM	38.5 ± 0.08	36.71 ± 0.37*	36.84 ± 0.39*	36.9 ± 0.42*	37.7 ± 0.32*	37.85 ± 0.28*	37.48 ± 0.29*	37.49 ± 0.29*	37.55 ± 0.30*	37.35 ± 0.34*	37.46 ± 0.42*
CRI	37.95 ± 0.11	36.56 ± 0.27*	37.01 ± 0.34*	37.29 ± 0.29*	37.76 ± 0.20	38.01 ± 0.21	38.06 ± 0.16	38.19 ± 0.26	37.9 ± 0.25	37.65 ± 0.34	37.621 ± 0.3011
Heart rate (beats/min)											
IM	106.8 ± 6.53	141.9 ± 12.17*	100 ± 7.71†	90.9 ± 9.23†	96.2 ± 13.55	76.5 ± 5.76*	93.9 ± 15.27	82.8 ± 7.67*	76.0 ± 6.07*	85.2 ± 7.43*	84.5 ± 4.86*
CRI	108.3 ± 7.29	140.4 ± 11.77*	128.8 ± 10.17†	125.2 ± 10.45†	107.2 ± 8.10	94.4 ± 7.94	87.8 ± 6.72	89.8 ± 5.76	82.8 ± 8.83*	81.8 ± 7.29*	86.1 ± 5.62*
Venous pH											
IM	7.381 ± 0.013	7.33 ± 0.016*	7.319 ± 0.009*		7.346 ± 0.009*				7.343 ± 0.006*		7.318 ± 0.009*
CRI	7.349 ± 0.016	7.336 ± 0.028	7.345 ± 0.016		7.336 ± 0.013				7.343 ± 0.013		7.329 ± 0.013[a]
$Pvco_2$ (mmol/L)											
IM	41.2 ± 0.85	47.47 ± 1.69*	48.51 ± 1.17*		45.16 ± 1.41				44.85 ± 0.98†		46.13 ± 2.37†*
CRI	45.68 ± 1.89	47.58 ± 3.10	46.91 ± 1.11		48.53 ± 1.13				51.17 ± 1.061*		51.58 ± 1.88†*[a]
Bicarbonate (mmol/L)											
IM	24.14 ± 0.66	24.86 ± 0.49	24.61 ± 0.43		24.47 ± 0.61				24.12 ± 0.26†		23.7 ± 0.73†
CRI	25.03 ± 1.15	25.09 ± 0.77	25.47 ± 0.73		25.76 ± 0.96				27.46 ± 0.70*†		26.77 ± 0.80†*[a]
Sodium (mmol/L)											
IM	155.0 ± 0.61	154.1 ± 0.78	152.9 ± 0.90*		153 ± 0.92*				153.7 ± 0.84†		153.31 ± 0.80*
CRI	153.9 ± 0.74	152.8 ± 0.71	152.1 ± 0.60*		151.7 ± 0.86*				150.9 ± 0.641*		151.6 ± 0.79*
Potassium (mmol/L)											
IM	3.94 ± 0.11	3.71 ± 0.21	3.57 ± 0.13*		3.72 ± 0.15				3.84 ± 0.11		3.99 ± 0.13
CRI	4.19 ± 0.13	3.72 ± 0.13*	3.53 ± 0.09*		3.72 ± 0.08*				3.93 ± 0.13		4.01 ± 0.10
Chloride (mmol/L)											
IM	116.8 ± 0.53	116.6 ± 0.48	116.2 ± 0.65		115.6 ± 1.08				118.1 ± 0.71†		117.7 ± 0.67†
CRI	116.6 ± 0.69	116 ± 0.63	116.3 ± 1.04		114.1 ± 0.62*				114.3 ± 0.581*		114.3 ± 0.71†*
UMPS score											
IM	2.2 ± 0.25	4.4 ± 1.19	2.6 ± 0.93	3.7 ± 1.41	4.7 ± 1.05*	2.7 ± 0.58	4.7 ± 0.79*	2.9 ± 0.66	2.9 ± 0.92	4.1 ± 1.07	4 ± 0.82
CRI	2.2 ± 0.25	4.8 ± 0.88*	3.2 ± 0.90	4.4 ± 1.19*	4.4 ± 1.16*	4.9 ± 1.01*	4.5 ± 0.67*	4.1 ± 0.67	4.7 ± 0.84*	4.5 ± 0.62*	3.2 ± 0.29

Baseline values were obtained prior to anesthetic induction. Data are given as mean ±SEM.
*Significantly ($P < 0.05$) different from baseline value for that group. †Significantly ($P < 0.05$) different from value for the other group.
[a]Value for only 9 dogs.
UMPS = University of Melbourne Pain Score.

ature (Table 2). Mean rectal temperature of dogs in the CRI group was significantly decreased at the time of extubation and 1 and 2 hours after extubation, compared with baseline temperature. However, rectal temperature was not significantly different between groups at any time, and mean minimum rectal temperature for dogs in the IM group (36.3 ± 0.3 C [97.3 ± 0.5 F]) was not significantly ($P = 0.92$) different from mean minimum rectal temperature for dogs in the CRI group (36.3 ± 0.2 C [97.4 ± 0.4 F]). Warming measures (eg, heating pads and blankets) were used on 8 dogs in each group in an effort to maintain normothermia.

For all postoperative measurement times, mean venous pH for dogs in the IM group was significantly lower than baseline venous pH (Table 2). For dogs in the CRI group, however, postoperative venous pH was not significantly different from the baseline value. Venous pH was not significantly different between groups at any time. Mean minimum pH for dogs in the IM group (7.298 ± 0.010) was not significantly ($P = 0.96$) different from mean minimum pH for dogs in the CRI group (7.299 ± 0.025).

Mean $Pvco_2$ for dogs in the IM group was significantly increased at the time of extubation and 1 and 24 hours after extubation, compared with the baseline value (Table 2). Mean $Pvco_2$ for dogs in the CRI group was significantly increased 12 and 24 hours after extubation, compared with the baseline value. Mean $Pvco_2$ for dogs in the IM group was significantly lower than mean $Pvco_2$ for dogs in the CRI group 12 and 24 hours after extubation. However, mean maximum $Pvco_2$ for dogs in the IM group (52.39 ± 1.36 mmol/L) was not significantly ($P = 0.22$) different from mean maximum $Pvco_2$ for dogs in the CRI group (55.39 ± 1.95 mmol/L).

Mean bicarbonate concentration for dogs in the IM group was not significantly different from the baseline value at any time (Table 2). Mean bicarbonate concentration for dogs in the CRI group was significantly increased 12 and 24 hours after extubation, compared with the baseline value. Mean bicarbonate concentration for dogs in the IM group was significantly lower than mean bicarbonate concentration for dogs in the CRI group 12 and 24 hours after extubation.

Mean serum sodium concentration for dogs in the IM group was significantly decreased 1, 4, and 24 hours after extubation, compared with the baseline value (Table 2). Mean serum sodium concentration for dogs in the CRI group was significantly decreased 1, 2, 12, and 24 hours after extubation. Mean serum sodium concentration for dogs in the IM group was significantly higher than that for dogs in the CRI group 12 hours after extubation.

Mean serum potassium concentration for dogs in the IM group was significantly decreased 1 hour after extubation, compared with the baseline value (Table 2). Mean serum potassium concentration for dogs in the CRI group was significantly decreased at the time of extubation and 1 and 4 hours after extubation. Serum potassium concentration was < 3.6 mmol/L in 9 dogs in the IM group and 6 dogs in the CRI group; for 14 of these 15 dogs, the low concentration was detected within the first 4 hours after extubation. Mean serum potassium concentration was not significantly different between groups at any time.

Mean serum chloride concentration for dogs in the IM group was not significantly different from baseline concentration at any time (Table 2). Mean serum chloride concentration for dogs in the CRI group was significantly decreased 4, 12, and 24 hours after extubation, compared with the baseline value. Mean serum chloride concentration for dogs in the IM group was significantly higher than mean serum chloride concen-

tration for dogs in the CRI group 12 and 24 hours after extubation.

Adverse effects—Two dogs in the IM group and 3 dogs in the CRI group had signs of dysphoria; all 5 of these dogs were Greyhounds. The percentage of Greyhounds with dysphoria (5/13) was not significantly (P = 0.11) different from the percentage of non-Greyhounds with dysphoria (0/7). Dysphoria was evident 1, 4, 8, 10, and 12 hours after extubation. Two dogs in each group vomited 16 and 24 hours after extubation. Four dogs in the IM group and 5 dogs in the CRI group defecated at various times during the study period. At 1 or more injection times, all dogs in the IM group turned their heads toward the site of the injection. Two dogs in this group vocalized at the time of injection.

Two dogs in the IM group were reported to be semiconscious, one at 10 hours and one from 2 to 10 hours after extubation. None of the dogs in the CRI group was reported to be semiconscious at any time after extubation.

Pain scores—Mean UMPS score for dogs in the IM group was significantly increased 4 and 8 hours after extubation, compared with baseline score (Table 2). Mean UMPS score for dogs in the CRI group was significantly increased at the time of extubation and 2, 4, 6, 8, 12, and 16 hours after extubation; however, mean UMPS score was < 6 at all times. Mean UMPS score was not significantly different between groups at any time. Similarly, mean maximum UMPS score (IM, 7.3 ± 1.1 points; CRI, 7.9 ± 0.9 points, P = 0.66), AUC_4 (IM, 15.1 ± 3.9 point-hours; CRI, 16.6 ± 3.6 point-hours, P = 0.77) and AUC_{12} (IM, 89.7 ± 16.7 point-hours; CRI, 101.9 ± 9.1 point-hours, P = 0.53) were not significantly different between groups.

Discussion

Results of the present study indicated that the effects of morphine administered to dogs undergoing laparotomy were similar, whether morphine was given as a CRI_{IV} at a dosage of 0.12 mg/kg/h (0.05 mg/lb/h) or injected at a dosage of 1 mg/kg (0.45 mg/lb), IM, every 4 hours. At the dosages used, mean heart rates were significantly decreased from baseline values more often in the IM group, but in both groups, mean heart rate was > 80 beats/min throughout the study period. Mean rectal temperature decreased by approximately 2 C (3.8 F) in both groups and remained subnormal throughout the study period. Remarkably, despite this mild hypothermia and the clinically normal $PvCO_2$ values, panting was observed in as many as 25% of the dogs at any time. Incidences of dysphoria, vomiting, and defecation were low and similar in the 2 groups. Levels of analgesia, as measured by use of the UMPS score, were acceptable and similar in the 2 groups. Intravenous CRI was an effective method of achieving consistent serum morphine concentrations; dogs in the CRI group had mean serum morphine concentrations that varied by < 15 ng/ml during a 4-hour period. The general lack of significant differences between the 2 groups suggests that the 2 dosages were comparable to each other, even though dogs in the CRI group received half the total amount of morphine that dogs in the IM group received.

Mean total clearance of morphine for dogs in the present study was 68 ± 6 ml/min/kg (31 ± 3 ml/min/lb), which was within the 33 to 79 ml/min/kg (15 to 36 ml/min/lb) range previously reported by Milne[11] but outside of the 41 to 51 ml/min/kg (18 to 23 ml/min/lb) range previously reported by Dohoo.[5] We anticipated that dogs undergoing surgery may have compromised hepatic circulation, so we used a conservative value of 40 ml/min/kg for clearance when calculating the CRI dosage. The rapid achievement of steady-state concentrations among dogs in the CRI group suggests that clearance was < 68 ml/min/kg (31 ± 3 ml/min/lb) until 1 hour after extubation. That the actual total clearance was higher than 40 ml/kg/min suggests that clearance was not necessarily compromised following surgery.

Mean serum morphine concentration for dogs in the IM group was 177 ng/ml 1 hour after extubation, compared with 36 ng/ml for dogs in the CRI group. This large difference was undoubtedly attributable to administration of an IM dose at the time of extubation, which was only 90 minutes after the first dose. Despite this difference, UMPS scores were not significantly different between groups at any time. By 4 hours after extubation, mean serum morphine concentration was approximately 30 ng/ml in both groups. Although this concentration was less than the target concentration of 50 ng/ml, mean UMPS scores plus 1 SEM were < 6 at all times. In dogs that have undergone general anesthesia but have not undergone surgery, UMPS scores are typically < 6,[9] and in dogs that have undergone surgery, a UMPS score < 6 can be interpreted to indicate than any pain associated with surgery is well controlled. Therefore, the fact that dogs in the present study had such low pain scores after surgery suggests that the MEC of morphine in dogs undergoing laparotomy may be closer to 30 ng/ml than to the 50 ng/ml we had initially targeted. Future studies are needed to establish the MEC for other surgical procedures in dogs.

In both groups of dogs, mean heart rate increased from a preoperative value of approximately 100 beats/min to approximately 140 beats/min at the time of extubation. Tachycardia at the time of extubation was likely attributable to hypovolemia, sympathetic stimulation, pain, or a combination of these factors. One hour after extubation, the mean heart rate for dogs in the IM group was no longer significantly different from the baseline value, whereas mean heart rate was still increased for dogs in the CRI group. At this time, mean serum morphine concentration for dogs in the IM group was 177 ng/ml. Beginning 6 hours after extubation, mean heart rate for dogs in the IM group was significantly less than the baseline value. Mean heart rate for dogs in the CRI group was also significantly less than the baseline value during the final 12 hours of the study period. Without simultaneous measurement of cardiac output, there was no way of knowing whether these later changes in heart rate were simply a return to normal values for these dogs or represented a depression in heart rate associated with increasing con-

centrations of a morphine metabolite.

The degree of hypothermia was clinically important in the present study, as 80% of dogs required active measures to maintain rectal temperature between 37.5 and 39.0 C (99.5 and 102 F). Often, a dog's rectal temperature increased in response to warming measures and promptly decreased again as soon as such measures were reduced or discontinued. This hypothermia seemed incongruent with the observation that up to 25% of the dogs were panting at any given time. Panting has often been attributed to hypercarbia, but clinically significantly hypercarbia was not detected in the present study. Results of the present study are most consistent with the hypothesis that morphine acts directly on the hypothalamus to lower the thermoregulatory set point by 0.5 to 1.4 C (1 to 3 F).[1,12] Several studies[13] have defined the relationship between body temperature, panting, and morphine administration. In previous studies, administration of morphine to dogs at a dosage of 10 mg/kg (22 mg/lb), SC,[14] or 3 mg/kg/h (6.6 mg/lb/h), IV,[15] caused body temperature to decrease from 39 C to 36 C (102.2 to 96.8 F) within 4 hours, while respiratory rate increased. In another study,[16] attempts to warm a morphine-treated dog with a heat lamp simply induced panting, which continued until the dog had cooled itself to 36 C (96.8 F) again. Results of the present study support the suggestion that panting in dogs treated with morphine may be a result of opioid-induced resetting of the hypothalamic temperature set point, rather than a compensatory response to acidemia.

Dogs in both groups had statistically significant, but not clinically important, changes in blood gas parameters at various times during the study. In both groups, mean venous pH was not less than 7.3, mean $PvCO_2$ did not exceed 52 mmol/L, and mean bicarbonate concentration was between 23 and 27 mmol/L at all times. These results clearly support the premise that morphine can be infused IV at the dosage studied without causing marked clinical changes in blood gas parameters. The variability of results in this study was increased because more than 1 machine had to be used for blood gas analyses, owing to assorted technical problems. Minor differences among machines may have increased the variability in measured $PvCO_2$, bicarbonate concentration, and pH. However, variability may have been decreased because of some of the long gaps in the sampling schedule, so that peaks in $PvCO_2$ may have been missed. It seems unlikely that hemoglobin played any substantial role in buffering the observed changes in one group more than the other, because hemoglobin concentration remained stable except in the dogs that underwent splenectomy. Further studies with larger numbers of patients are needed to define the nature of respiratory and metabolic changes secondary to morphine administration.

Only 25% of the dogs became dysphoric, and all of these were Greyhounds. These dogs seemed hyperresponsive to the slightest stimuli such as opening the cage door or touching them on the ear. Some dogs vocalized; others displayed grossly agitated uncoordinated activity. These episodes did not occur at any particular time or among dogs in 1 group more frequently than the other. Four of the 5 Greyhounds responded favorably to a person sitting quietly with them and talking in a calm voice. One Greyhound was also given diazepam and responded well. Two dogs in the IM group vocalized at the time of IM injection, but this vocalization did not appear to be related to dysphoria. Further studies of the association between physiologic indicators of pain such as serum cortisol concentration,[17] opioid receptor distribution, and opioid pharmacokinetics would be useful to determine any breed differences in opioid analgesia management.

Dogs in this study were not given any anxiolytics or sedatives so that the effects of morphine could be clearly identified. However, it is common clinical practice to administer anxiolytics or sedatives in conjunction with opioids, and we recommend doing so whenever it will reduce patient stress.

Twenty percent (4/20) of the dogs vomited during the postoperative period, and all did so at least 16 hours after surgery. Because the dogs were not allowed to eat or drink during the study period, ileus was the most likely explanation for vomiting. Ileus may have been secondary to the surgical procedure, morphine, or both.

Seventy-five percent (15/20) of dogs developed hypokalemia. Both groups of dogs in the present study had significant hypokalemia 1 hour after extubation, and mean serum potassium concentration was not significantly different between groups. The most likely cause of this hypokalemia was hemodilution secondary to the administration of lactated Ringer's solution during surgery. Hypokalemia was still present in some dogs in the CRI group 4 hours after extubation, possibly because of the additional free water associated with morphine administration in this group. The study protocol called for potassium supplementation if serum potassium concentration was < 3.6 mmol/L; therefore, the potential for severe hypokalemia was limited in this study. Potassium supplementation was effective, because by 4 hours after extubation, serum potassium concentrations were not significantly different from baseline concentrations.

We did not find any significant differences between groups in regard to mean UMPS score, mean maximum UMPS score, AUC_4, or AUC_{12}, which suggests that the 2 routes of administration provided comparable levels of analgesia. Mean UMPS scores were < 6 points at all times, which was consistent with a previously published report of scores for dogs that underwent ovariohysterectomy and received analgesics postoperatively.[9] For dogs in the IM group, UMPS scores that were obtained between doses of morphine (1, 2, and 6 hours after extubation) were not significantly different from the baseline value, whereas scores obtained immediately before administration of doses 4 and 8 hours after extubation were significantly increased. This finding is consistent with what would be expected with the known pharmacokinetics of morphine; serum concentration should peak 1 to 2 hours after a dose has been given, and pain levels should be lowest at that time.

University of Melbourne Pain Scale scores may have been affected by a number of factors. A single observer was used throughout the study (ANL), which

likely increased the consistency of assessments. However, the observer was not blinded to treatment group, which may have decreased the objectivity of scoring. Pain scores may also have been affected by physiologic changes characteristic of morphine. Because of its physiologic effects, morphine could potentially have minimized differences between groups by affecting subscores related to heart rate, pupillary dilation, and rectal temperature and exaggerated differences by affecting subscores related to movement and vocalization. Differences in UMPS scores attributable to differences in pain expression among breeds should have been minimal, since approximately half of each group were Greyhounds.

Fear of respiratory depression is the most-often cited reason for avoiding postoperative use of morphine in dogs.[2] The major risk to a patient lies in the possibility that because morphine facilitates an increased P_{CO_2} tolerance and blunts the patient's urge to breathe,[18] the respiratory rate may decrease to the point that oxygenation is compromised even if 100% oxygen is available. Dogs in the present study were clearly capable of modulating their own respiratory rate, as demonstrated by their ability to pant and cool themselves. The second major risk associated with morphine is that P_{CO_2} may increase to such an extent that the tissue environment becomes acidotic, which would impair cellular functionality. These risks are most likely to become clinical issues if other respiratory-depressant drugs, especially general anesthetics, are being used concurrently, or if the patient is incapable of modulating its own respiratory rate and gas exchange, as seen with brain injury or cardiopulmonary compromise. In the present study, clinically important respiratory depression occurred only during anesthesia, when 9 of the 20 dogs had a $P_{ETCO_2} > 55$ mm Hg and received IPPV. It is possible that the use of a barbiturate for anesthetic induction in the Greyhounds contributed to this result. Regardless of how morphine is administered, veterinarians should use audible respiratory monitors or capnography to monitor patients when administering morphine and anesthetics concurrently. Although patients with serious medical conditions were excluded from this study, the fact that patients in the present study had no clinically important changes in blood gas parameters suggests that morphine administration to a selected patient population carries minimal risk of causing significant acidemia.

[a]Drager PM 8050, Dragerwerk AG, Lubeck, Germany.
[b]OxiCap 4700, Ohmeda, Louisville, Ky.
[c]Stat Pal 2, Model SP2, SenDx Medical Inc, Carlsbad, Calif.
[d]Radiometer ABL5, Radiometer Medical A/S, Copenhagen, Denmark.
[e]AVL Omni 4, AVL Scientific Corp, Roswell, Ga.
[f]Idexx VetLyte, Idexx Laboratories Inc, Westbrook, Me.
[g]Racing Analytical Services Ltd, Flemington, Victoria, Australia.
[h]Radian, Austin, Tex.
[i]Bond Elut Certify Cartridge, Varian, New South Wales, Australia.
[j]TSQ70 gas chromatograph/mass spectrometer, ThermoQuest, Rydalmere, New South Wales, Australia.
[k]HP1, 12.5 m × 0.2 mm internal diameter, 33-µm film thickness, Agilent Technologies, Melbourne, Victoria, Australia.
[l]Proc MIXED, SAS Institute, Cary, NC.

Appendix

University of Melbourne Pain Scale (UMPS) for assessing severity of pain in dogs that have undergone surgery

Category and descriptor	Score
Physiologic data	
All physiologic data within reference limits	0
Dilated pupils	2
Heart rate (increase compared with rate prior to surgery; choose only one)	
> 20%	1
> 50%	2
> 100%	3
Respiratory rate (increase compared with rate prior to surgery; choose only one)	
> 20%	1
> 50%	2
> 100%	3
High rectal temperature	1
Salivation	2
Response to palpation (choose only one)	
No change from preoperative behavior	0
Guards or reacts* when touched	2
Guards or reacts before being touched	3
Activity (choose only one)	
At rest	
Sleeping	0
Semi-conscious	0
Awake	1
Eating	0
Restless (pacing continuously; getting up and down)	2
Rolling or thrashing	3
Mental status (choose only one)†	
Submissive	0
Overtly friendly	1
Wary	2
Aggressive	3
Posture	
Guarding or protecting affected area	2
Position (choose only one)	
Lateral recumbency	0
Sternal recumbency	1
Sitting or standing	1
Standing with head hanging	2
Moving	1
Abnormal posture (eg, prayer position or hunched back)	2
Vocalization (choose only one)‡	
Not vocalizing	0
Vocalizing when touched	2
Intermittent vocalization	2
Continuous vocalization	3

Scores for the 6 categories are totaled to obtain the UMPS score. The minimum possible score is 0; the maximum possible score is 27.

*Includes turning head toward affected area, biting, licking, or scratching at wound, snapping at the handler, and tensing muscles in a protective posture. †For this category, score recorded is the score obtained after surgery minus the score obtained before surgery. ‡Does not include alert barking.

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