Effects of acetylpromazine or morphine on urine production in halothane-anesthetized dogs

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Objective—To assess the influence of preanesthetic administration of acetylpromazine or morphine and fluids on urine production, arginine vasopressin (AVP; previously known as antidiuretic hormone) concentrations, mean arterial blood pressure (MAP), plasma osmolality (Osm), PCV, and concentration of total solids (TS) during anesthesia and surgery in dogs.

Animals—19 adult dogs.

Procedure—Concentration of AVP, indirect MAP, Osm, PCV, and concentration of TS were measured at 5 time points (before administration of acetylpromazine or morphine, after administration of those drugs, after induction of anesthesia, 1 hour after the start of surgery, and 2 hours after the start of surgery). Urine output and end-tidal halothane concentrations were measured 1 and 2 hours after the start of surgery. All dogs were administered lactated Ringer's solution (20 ml/kg of body weight/h, IV) during surgery.

Results—Compared with values for acetylpromazine, preoperative administration of morphine resulted in significantly lower urine output during the surgical period. Groups did not differ significantly for AVP concentration, Osm, MAP, and end-tidal halothane concentration; however, PCV and concentration of TS decreased over time in both groups and were lower in dogs given acetylpromazine.

Conclusions and Clinical Relevance—Preanesthetic administration of morphine resulted in significantly lower urine output, compared with values after administration of acetylpromazine, which cannot be explained by differences in AVP concentration or MAP. When urine output is used as a guide for determining rate for IV administration of fluids in the perioperative period, the type of preanesthetic agent used must be considered.(*Am J Vet Res* 2001;62:1922–1927)

Measurement of urine output in the perioperative period is an important but often overlooked monitoring technique. In animals that do not have renal disease, urine production closely reflects a patient's cardiovascular performance and hydration status.[1] Normal urine production is 1 to 2 ml/kg of body weight/h, with a rate of < 0.5 ml/kg/h considered inadequate.[2,3] A primary determinant of urine production is glomerular filtration rate, which in turn is dependent on renal perfusion and arterial blood pressure. In the perioperative period, hypovolemia can develop when IV administration of fluids does not adequately replace surgical and respiratory losses. Hypotension can develop secondary to fluid depletion, changes in cardiac output, or the use of many anesthetic drugs.

Arginine vasopressin (**AVP**; previously known as antidiuretic hormone or vasopressin) is an important determinant of renal excretion of water, **plasma osmolality (Osm)**, and circulating blood volume. Arginine vasopressin is released from the posterior part of the pituitary gland and acts at the cortical and medullary renal collecting tubules to alter permeability to water.[4] Stimulators of AVP secretion include increased Osm, hypovolemia, hypotension, pain, stress, and hyperthermia.[4,5] Water retention has been reported in humans and dogs during the postoperative period[6,7] and may partly be explained by sustained concentrations of AVP.[4,6]

Morphine's role as a stimulus for AVP release is controversial. Some texts cite it as stimulating AVP secretion,[4,8] whereas others question its ability to stimulate AVP release.[5] Some references suggest that morphine inhibits urinary flow rate via stimulation of AVP secretion in dogs and rats.[9-11] Bachman[12] agreed that morphine had an antidiuretic effect in dogs but argued that it was not related to AVP release. In rats, the antidiuretic effect of morphine may also be independent of AVP release.[13] In humans, anesthesia alone, with or without morphine administration, does not increase plasma AVP concentrations.[14,15] Surgical stimulus is associated with increases in AVP secretion and is considered to be a component of the stress, metabolic, and hormonal response reported in patients undergoing surgery.[15-18] Once surgery has begun, morphine, through its analgesic actions, may play a role in attenuating the AVP response.[15]

Increases in plasma concentrations of AVP have been associated with anesthesia in sheep[19,20] and ponies.[21,22] Until recent publication of a study,[23] little data had been published on measurement of AVP and urine output in dogs during anesthesia and surgery or information on the influence of specific preanesthetic agents. The study reported here was designed to examine the influence of morphine and acetylpromazine on preoperative and intraoperative concentrations of AVP, Osm, PCV, concentration of **total solids (TS)**, **mean arterial blood pressure (MAP)**, and urine production in halothane-anesthetized dogs receiving lactated Ringer's solution during surgery.

Materials and Methods

Dogs—Nineteen dogs were used in the study. There were 17 Beagles and 2 mixed-breed dogs. Eighteen were sex-

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ually intact females, and 1 was a sexually intact male. Mean ± SEM weight was 11.7 ± 1.1 kg. The dogs were provided by the University Laboratory Animal Resources and used for teaching purposes in our surgery laboratory for third-year veterinary students. A university animal care and use committee approved the research protocol.

Protocol—During each laboratory session, 2 dogs were included in the study. An author was assigned to each dog to ensure accurate collection of data. Dogs were assigned to 1 of 2 groups (group 1, 11 dogs; group 2, 8 dogs). Dogs in group 1 were given acetylpromazine (0.19 ± 0.01 mg/kg of body weight, IM), whereas dogs in group 2 were given morphine (1.0 mg/kg, IM). Twenty minutes later, a catheter was inserted in the cephalic vein for administration of thiopental (12 ± 1.4 mg/kg). After intubation, anesthesia was maintained by use of halothane in oxygen. Dogs breathed spontaneously during the study, with assisted breaths provided at intervals of 1 to 2 minutes.

An indwelling urinary catheter was placed and attached to a collection bag for measurement of urine volume. The bladder was emptied at the start of surgery. Administration of lactated Ringer's solution was started approximately 30 minutes before the onset of surgical procedures. Fluids were administered at a rate of 20 ml/kg/h, IV. Various surgical procedures were performed (group 1: ovariohysterectomy [n = 6], repair of femoral fracture [3], intestinal anastomosis [2]; group 2: femoral head ostectomy [7], intestinal anastomosis [1]). At the end of surgery, dogs were euthanatized by administration of an overdose of barbiturate.

Measurement of variables—Concentrations of AVP and TS, PCV, and Osm were measured at the following 5 time points: before administration of acetylpromazine or morphine (control period), 30 minutes after preanesthetic administration of the drugs, between 5 and 10 minutes after induction of anesthesia, 1 hour after onset of surgery, and 2 hours after onset of surgery. At each of those time points, 3 ml of blood was obtained by direct jugular venipuncture. The PCV was determined by the microhematocrit method, and concentration of TS was measured by refractometry. The remaining blood sample was placed in an EDTA-containing tube and stored on ice. Within 60 minutes after collection, blood was processed in a refrigerated centrifuge, and plasma was harvested. Duplicate samples were stored at –13 or –70 C. A radioimmunoassay technique was used to assay AVP concentrations.[a] Intra-assay coefficient of variation in our laboratory was 2.6%, and interassay coefficient of variation was 13.2%. Plasma osmolality was estimated, using the freezing-point depression method.[b] One indirect measurement of MAP[c] was obtained at all 5 time points by placing a cuff on a forelimb immediately proximal to the carpus. Rectal temperature was recorded in 17 dogs before administration of acetylpromazine or morphine (control period) and at 2 hours after onset of surgery.

Urine output and volume of lactated Ringer's solution administered were recorded 1 and 2 hours after the onset of surgery. End-tidal halothane concentration was measured by infrared spectrometry[d] 1 and 2 hours after the onset of surgery.

Analysis of data—Data for AVP and TS concentrations, PCV, Osm, and MAP were analyzed by use of a split-plot ANOVA in accordance with the following model:

$$Y = \mu + G + error_1 + T_{(1-5)} + GT + error_2$$

where Y is the response variable, μ is the overall mean value, G is group (acetylpromazine or morphine), T is the time point (1 to 5), GT is the interaction of group and time, $error_1$ is the error term for group comparisons, and $error_2$ is the error term for time and group-by-time comparisons. Post-hoc tests between groups were performed, using a *t*-test. Bonferroni *t*-tests were used for post-hoc analysis within groups over time.

End-tidal anesthetic concentration and urine production were analyzed by use of unpaired or paired *t*-tests, as appropriate. Data were reported as mean ± SEM. Significance was set at values of $P < 0.05$.

Results

Body weight and fluid administration—Body weight did not differ significantly between the acetylpromazine (9.9 ± 0.9 kg) and morphine (14.3 ± 2.1 kg) groups. There was not a significant difference in rate of fluid actually administered between the groups (acetylpromazine, 21.5 ± 2.0 ml/kg/h; morphine, 23.2 ± 2.2 ml/kg/h).

Urine output—Rate of urine production was not significantly different between the acetylpromazine (1.8 ± 1.0 ml/kg/h) and morphine (1.1 ± 0.5 ml/kg/h) groups at 1 hour after onset of surgery **(Fig 1)**. However, 2 hours after onset of surgery, urine production was significantly ($P = 0.02$) less in the morphine group (2.42 ± 0.8 ml/kg/h), compared with urine production in the acetylpromazine group (9.34 ± 2.4 ml/kg/h).

Mean arterial blood pressure—In dogs that received morphine, there was not a change in MAP at any time point, compared with values for the control period **(Fig 2)**. In dogs administered acetylpromazine, MAP decreased significantly from control values (91 ± 7 mm Hg) at 1 and 2 hours after onset of surgery (54 ± 5 and 56 ± 5 mm Hg, respectively). At 1 hour after onset of surgery, MAP was significantly lower in acetylpromazine-treated dogs, compared with morphine-treated dogs.

End-tidal halothane concentration—End-tidal halothane concentration did not differ significantly between the 2 groups at 1 (acetylpromazine, 1.1 ± 0.1%; morphine, 1.3 ± 0.1%) or 2 (acetylpromazine, 1.0 ± 0.03%; morphine, 1.0 ± 0.03%) hours after onset

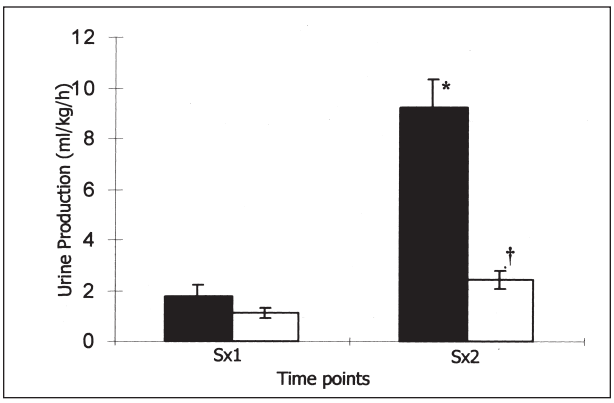

Figure 1—Mean ± SEM urine output 1 and 2 hours after onset of surgery (Sx1 and Sx2, respectively) for 2 groups of dogs that received acetylpromazine (black bars) or morphine (white bars) as a preanesthetic medication prior to halothane-induced anesthesia. *Within a group, value differs significantly ($P < 0.05$) from value during Sx1. †Within a time point, value differs significantly ($P < 0.05$) between groups of dogs.

of surgery. These values were not significantly different among times points within each group.

Concentrations of AVP—Values did not differ significantly ($P = 0.12$) between dogs in groups 1 and 2 for any time point (**Fig 3**). In the acetylpromazine group, AVP concentrations were significantly increased, compared with control values (4.8 ± 0.9 p*M*/L), in samples obtained after preanesthetic medication (49.0 ± 17.5 p*M*/L) and 1 and 2 hours after onset of surgery (76.7 ± 11.4 and 71.0 ± 12.3 p*M*/L, respectively) but not immediately after induction of anesthesia (16.1 ± 6.9 p*M*/L). In the morphine group, AVP values were significantly increased, compared with control values (4.9 ± 2.1 p*M*/L), only in samples obtained 1 hour after the onset of surgery (52.2 ± 13.4 p*M*/L).

Values for Osm—Plasma osmolality did not differ significantly ($P = 0.18$) between the groups at any time point (**Fig 4**). There was not a significant effect of time for either group.

PCV—The PCV was significantly lower in the acetylpromazine group, compared with the PCV for the morphine group, after preanesthetic medication (acetylpromazine, 38.4 ± 0.8%; morphine, 46.1 ± 1.4%) and after induction of anesthesia (acetylpromazine, 36.6 ± 0.7%; morphine, 44.8 ± 1.2%; **Fig 5**). In morphine-treated dogs, the PCV was significantly lower, compared with control values (49.9 ± 1.2%), at all subsequent time points (after preanesthetic medication, 46.1 ± 1.4%; after induction, 44.9 ± 1.2%, 1 hour after onset of surgery, 37.0 ± 2.3%; and 2 hours after onset of surgery, 36.7 ± 1.4%). In acetylpromazine-treated dogs, the PCV was significantly decreased from control values (48.2 ± 0.7%) at all subsequent time points (after preanesthetic medication, 38.4 ± 0.8%; after induction, 36.6 ± 0.7%; 1 hour after onset of surgery, 38.8 ± 0.8%; and 2 hours after onset of surgery, 36.7 ± 0.4%).

Concentration of TS—Compared with control values (6.3 ± 0.1 g/dl), concentration of TS was lower in the acetylpromazine group at all time points (after preanesthetic medication, 5.9 ± 0.2 g/dl; after induction, 5.7 ± 0.2 g/dl; 1 hour after onset of surgery, 4.7 ± 0.1 g/dl; and 2 hours after onset of surgery, 4.6 ± 0.2 g/dl; **Fig 6**). In the morphine group, concentration of TS did not decrease significantly below control values (6.5 ± 0.1 g/dl) until after onset of surgery (5.2 ± 0.2 and 4.9 ± 0.2 g/dl, respectively, for 1 and 2 hours after onset of surgery). Concentration of TS was significantly lower in the acetylpromazine group, compared with the morphine group, after preanesthetic medication,

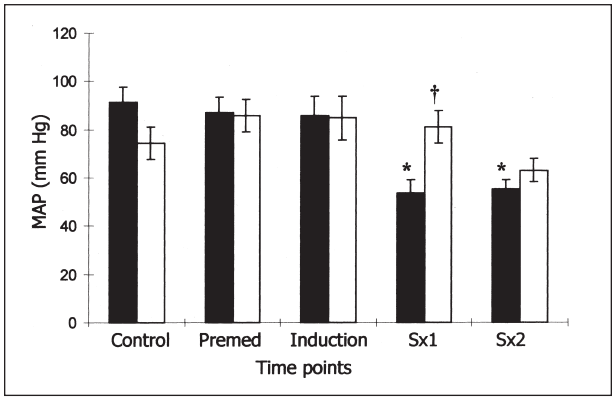

Figure 2—Mean (± SEM) arterial blood pressure (MAP) at 5 time points for 2 groups of dogs that received acetylpromazine (black bars) or morphine (white bars) as a preanesthetic medication. Control = Prior to administration of drugs. Premed = Measured 30 minutes after administration of drugs. Induction = Between 5 and 10 minutes after induction of anesthesia. *Within a group, value differs significantly ($P < 0.05$) from control value. *See* Figure 1 for remainder of key.

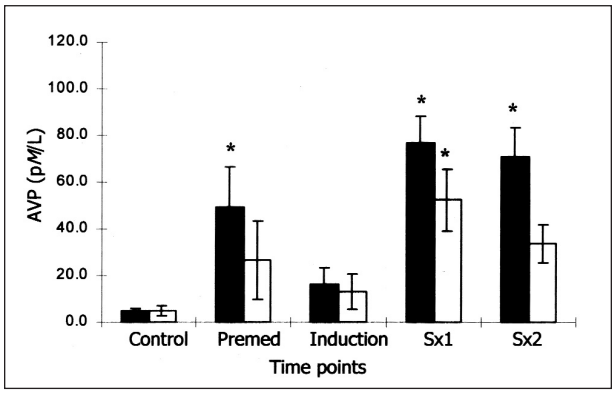

Figure 3—Mean ± SEM concentration of arginine vasopressin (AVP) at 5 time points for 2 groups of dogs that received acetylpromazine (black bars) or morphine (white bars) as a preanesthetic medication. *See* Figure 2 for key.

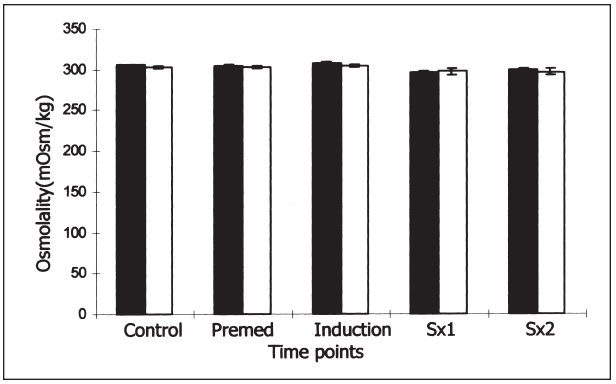

Figure 4—Mean ± SEM plasma osmolality at 5 time points for 2 groups of dogs that received acetylpromazine (black bars) or morphine (white bars) as a preanesthetic medication. *See* Figure 2 for key.

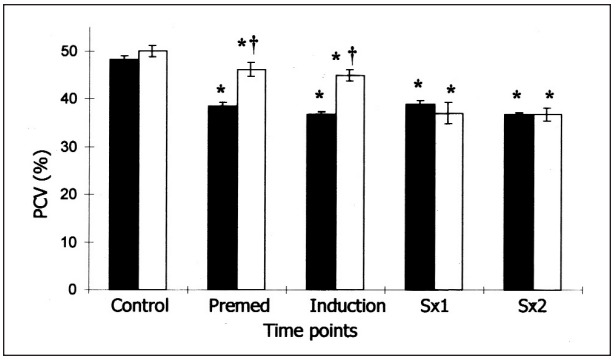

Figure 5—Mean ± SEM PCV at 5 time points for 2 groups of dogs that received acetylpromazine (black bars) or morphine (white bars) as a preanesthetic medication. *See* Figure 2 for key.

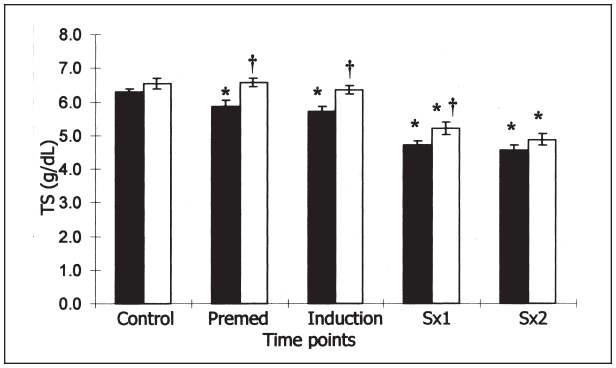

Figure 6—Mean ± SEM concentration of total solids (TS) at 5 time points for 2 groups of dogs that received acetylpromazine (black bars) or morphine (white bars) as a preanesthetic medication. *See* Figure 2 for key.

after induction, and 1 hour after onset of surgery but not for the control period or 2 hours after onset of surgery.

Rectal temperature—Temperature data were collected from 17 dogs (data were not obtained from 1 dog in each group). There was not a significant difference in mean preoperative rectal temperature (39.2 C) between the acetylpromazine and morphine groups. All dogs were hypothermic 2 hours after onset of surgery; rectal temperature was < 32.2 C in 5 of 10 dogs in the acetylpromazine group and 1 of 7 dogs in the morphine group. Mean temperature was 34.3 ± 1.24 C for the remaining 5 dogs in the acetylpromazine group and 33.7 ± 0.42 C for the remaining 6 dogs in the morphine group.

Discussion

Urine output was markedly greater (4-fold increase) 2 hours after onset of surgery in acetylpromazine-treated dogs, compared with urine output in dogs given morphine preoperatively. Although the rate of production in the morphine group was greater than the acceptable rate of 0.5 ml/kg/h quoted elsewhere,[2,3] it must be emphasized that the dogs reported here were receiving fluids at a rate of 20 ml/kg/h, IV, which is greater than the recommended rate of 5 to 10 ml/kg/h, IV, for mild to moderately severe surgical procedures.[24] In another study[23] involving halothane-anesthetized dogs that received acetylpromazine, rate of fluid administration (0 or 20 ml/kg/h) had little effect on MAP but markedly influenced urine production. In that study, urine was not produced during a 2-hour period in dogs that did not receive fluids, but urine production was acceptable during the second hour after onset of surgery in dogs given fluids at the rate of 20 ml/kg/h.

Arginine vasopressin is an important determinant of renal excretion of water through its action on permeability of the renal collecting tubules to water. Plasma AVP concentrations that will result in maximal urine concentration in humans are reportedly in the vicinity of 11 p*M*/L.[25,26] In the study reported here, mean AVP concentration for the control sample was 4.9 p*M*/L, but during surgery, mean values were well in excess of 11 p*M*/L (33.5 to 76.7 p*M*/L; Fig 3). The effects of anesthesia and surgery on AVP secretion have been studied in humans,[16,25,27] sheep,[19,20] and ponies.[21,22] In contrast, little is known about perioperative changes in AVP concentrations in dogs. In the study reported here, differences in urine output between the 2 groups of dogs cannot be explained by changes in AVP secretion. All dogs had a similar pattern of plasma AVP secretion after preanesthetic medication and 1 and 2 hours after onset of surgery. The magnitude of AVP release is dependent on the specific stressors, which include increases in Osm, hypotension, stress, and surgery, and is species-specific.[28] In humans, AVP secretion appears to be most sensitive to changes in Osm,[4] with minor increases (1% change in Osm) evoking AVP secretion and subsequent increased absorption of free water and restoration of Osm. In the study reported here, altered Osm did not play a role in AVP secretion, because there was not a change in Osm in the morphine- or acetylpromazine-treated dogs.

When systemic blood pressure decreases, AVP is secreted as a reflex response in an attempt to maintain cardiovascular stability. Compared with control values, there was a significant decrease in MAP 1 and 2 hours after onset of surgery in dogs that received acetylpromazine, which may have contributed to the increased AVP concentrations in the dogs at that time. Changes in blood pressure do not adequately explain the increase in AVP concentrations in the morphine group 1 hour after onset of surgery, because there was not a significant decrease in MAP in these dogs during the study. In this study, it is difficult to separate cause and effect; in the morphine group, AVP concentrations may have been sufficient to maintain systemic blood pressure, but they may have been inadequate in the acetylpromazine group in the face of α-blockade.

Volume depletion of approximately 10% stimulates AVP secretion.[4] Volume depletion is detected by decreased atrial filling pressures. We do not believe that volume depletion played an important role in our study, because the fluid administration rate was greater than that normally recommended for dogs during surgery. Actual vascular volume was not measured in this study, but the decrease in plasma TS concentration would suggest that vascular volume was augmented.

In halothane-anesthetized sheep that did not undergo surgery,[19] hypotension was proposed as the primary stimulus for AVP secretion. However, it also was stated by those investigators that another unidentified mechanism attributable to use of volatile anesthetic agents could not be ruled out. It is possible that halothane is a stimulus for AVP secretion in dogs; AVP responses were similar in each group, and the dose of halothane as measured by end-tidal concentration was equal in both groups. This would not explain the increase in AVP concentrations detected 30 minutes after administration of preanesthetic medication when the dogs were still conscious. The increased AVP concentration at that time may have been related to stress. Prior to that time point, dogs were moved into a busy surgery preparation area and had a catheter inserted in a cephalic vein. The decrease in AVP concentrations between 5 and 10 minutes after induction of anesthesia correlates well with its circulating half-life of 15 to 20

minutes[4] and lack of conscious stress. Other markers of stress and anxiety, such as nonesterified fatty acids, change in a similar manner in humans[29] and horses.[30]

Surgery produces an increase in neuroendocrine activity resulting in increased amounts of ACTH, cortisol, growth hormone, and AVP as well as substrate mobilization.[31] In humans, magnitude of the response is related to severity of the surgery, with anesthesia alone having little influence.[15,31,32] In horses, anesthesia alone can evoke a profound response.[21,22,33-35] The increase in AVP concentration after the onset of surgery in our study suggests that dogs, similar to humans, mount a stress response to surgery. Mean AVP values were lower in the morphine-treated dogs, but because of wide variation among dogs, these values were not significantly different. The lower values in the morphine group may correlate with the type of surgery performed. In humans, major abdominal surgery results in a greater hormonal and endocrine response than surgery in a peripheral location.[31] Melville et al[36] reported that neurogenic stimuli arising from the peritoneum and intraperitoneal structures are a potent factor for increasing AVP concentrations in humans. In the study reported here, most dogs in the morphine group underwent orthopedic surgery, whereas the dogs in the acetylpromazine group underwent extensive intra-abdominal surgery. Alternatively, it may have been an effect of morphine itself. In humans, fentanyl[37-39] and morphine[15] blunt the metabolic and endocrine response to surgery.

In our study, urine production was lower 2 hours after onset of surgery when morphine was used as a preanesthetic agent in dogs, but it was not related to AVP secretion. We did not detect a significant difference in MAP between the acetylpromazine- and morphine-treated dogs 2 hours after onset of surgery. However, we cannot rule out the possibility that there were differences in cardiac output and systemic vascular resistance. It is possible that α-blockade produced by acetylpromazine resulted in vasodilation and improvements in renal perfusion and glomerular filtration rate. We did not investigate any markers of tissue perfusion, such as plasma lactate concentrations.

The effect of morphine on urine production is controversial. Some texts cite it as stimulating AVP secretion,[4,8] whereas others question its ability to stimulate AVP secretion.[5] Some references suggest that morphine inhibits urinary flow rate via stimulation of AVP secretion in dogs and rats.[9-11] Bachman[12] reported that morphine had an antidiuretic effect in dogs but argued that it was not related to AVP release. In rats, an antidiuretic effect of morphine has been reported that is independent of AVP release.[13,40,41] Kapusta[41] has hypothesized that specific intrarenal μ-opioid receptors are involved in water reabsorption. Reversal of morphine-induced antidiuresis by administration of naloxone has been reported.[40]

Changes in PCV reported here were expected. The greatest decrease in PCV was evident following acetylpromazine injection and was similar to that reported elsewhere.[42] This is believed to be a result of α-adrenergic blockade, which causes relaxation of the splenic capsule and sequestration of erythrocytes. The decrease in Hct was significant but not as pronounced after administration of morphine. Morphine causes histamine release in dogs[43] and may have resulted in fluid shifts. Changes in concentration of TS likely reflected fluid shifts and hemodilution caused by IV administration of fluids.

Results of the study reported here must be carefully interpreted, because the rate for fluid administration was higher than that usually suggested for the type of surgical procedures performed in this study. We do not know whether urine production would have been acceptable in the morphine group at lower rates of fluid administration. When the rate of urine production is used as an indicator of a patient's cardiovascular function, hydration status, and renal function during anesthesia, the impact of the preanesthetic medication must be considered.

[a]Radioisotopic assay for vasopressin, Nichols Institute Diagnostics, San Juan Capistrano, Calif.
[b]Osmette II, Precision Systems, Natick, Mass.
[c]Dinamap veterinary blood pressure monitor, Model 8300, Critikon Inc, Tampa, Fla.
[d]PB254 anesthesia gas monitor, Puritan-Bennet Corp, Wilmington, Mass.

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