

# Behavioral, Physiologic, and Stress-Related Hormonal and Metabolic Responses to Intravenous and Epidural Morphine in Goats

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## ABSTRACT

**Objective:** To establish the effects of epidural and intravenous (IV) morphine on stress-related hormones, metabolites, and behavior in goats. **Animals:** Six 6-year-old neutered goats (3 males, 3 females) weighing  $62.5 \pm 16.5$  kg (mean  $\pm$  SD). **Material and Methods:** Study was a prospective cross-over design in which morphine (0.1 mg/kg, epidural and IV) was administered in 2 trials 1 week apart. Epidural catheters were placed 24 hours before study. Blood samples were collected, physiologic variables were measured, and behavior was scored (0 to 3; 0 = normal, 3 = fractious) at 0, 15, and 30 minutes and 1, 2, 4, 6, and 8 hours (IV trial) and at 0, 1, 2, 4, 6, 8, 12, and 24 hours (epidural trial). Analysis included repeated measures analysis of variance and Tukey-Kramer multiple comparisons test. A  $P$  value  $<0.05$  was considered significant. **Results:** For IV morphine, differences were found for respiratory rate ( $17 \pm 10$  to  $27 \pm 11$  breaths/

min) and temperature. Temperature ( $38.6 \pm 0.1^\circ$  C) increased at 8 hours ( $39.0 \pm 0.2^\circ$  C). After epidural morphine, heart rate ( $96 \pm 24$  beats/min) decreased at 8 ( $73 \pm 15$  beats/min), 12 ( $74 \pm 13$  beats/min), and 24 ( $74 \pm 19$  beats/min) hours; systolic blood pressure (indirect) ( $106 \pm 31$  mmHg) increased at 6 ( $157 \pm 18$  mmHg), 8 ( $151 \pm 18$  mmHg), and 24 ( $142 \pm 10$  mmHg) hours; diastolic blood pressure (indirect) ( $71 \pm 23$  mmHg) increased at 6 ( $120 \pm 23$  mmHg) and 8 ( $111 \pm 28$  mmHg) hours; and mean blood pressure (indirect) ( $84 \pm 25$  mmHg) increased at 6 ( $134 \pm 20$  mmHg) and 8 ( $125 \pm 24$  mmHg) hours. Glucose concentrations increased from 0 minutes ( $55.6 \pm 4.6$  mg/dL) to 60 minutes ( $73.1 \pm 15.2$  mg/dL) and 120 minutes ( $70.7 \pm 13.4$  mg/dL) before returning to baseline at 720 minutes ( $55.9 \pm 6.0$  mg/dL). Temperature ranged from  $38.8 \pm 0.1^\circ$  C to  $39.3 \pm 0.2^\circ$  C; and cortisol increased from baseline ( $1.15 \pm 0.91$   $\mu$ g/dL) to 60 minutes ( $2.23 \pm 0.78$   $\mu$ g/dL), which was higher than subsequent cortisol concentrations. Free fatty acids were maximal at 60 minutes ( $317 \pm 183$  mmol/L) and decreased after 480 minutes ( $145 \pm 28$  mmol/L). During the epidural

trial, all goats vocalized and changed posture upon injection of the morphine. Conclusions and Clinical Relevance: Behavioral, physiologic, and stress-related hormonal and metabolic responses are minor after IV morphine in goats. Physiologic changes after epidural morphine may interfere with the postoperative evaluation of pain in goats that received epidural morphine. However, it is possible that epidural injection of any substance may initiate the stress-related changes seen in this study.

## INTRODUCTION

Goats used for biomedical research are covered by the Animal Welfare Act, and are not exempt from appropriate standards of care during perioperative periods. This has led to renewed interest in evaluating stress reduction and analgesia in ruminants. Behavioral indices have not been validated, while hormonal and physiologic indices of stress are inconsistent. The relative importance of behavioral changes (vacant stare, loss of mobility or repetitive motor activity, increased recumbency, tachypnea, guarding, changing avoidance patterns, vocalization, loss of socialization, inappetence, and decreased grooming) in predicting the degree of pain is unknown.<sup>1</sup> Physiologic responses (eg., heart rate and respiration) may<sup>2</sup> or may not<sup>3</sup> be useful in assessing pain. Evaluation of the pituitary-adrenocortical axis for assessment of animal welfare has been criticized due to variability among studies.<sup>4</sup> Evaluation of analgesia in clinical patients and unconditioned animals is confounded by anxiety and stress. Inconsistencies may relate to the comparison of indices of stress immediately before, during, and after a specific surgery or treatment, without accounting for environmental and management changes immediately prior to study. Such studies may not separate the influence of environment, treatment, and pain. Assessment of behavior, physiologic variables, and stress-related hormones and metabolites in non-painful conditioned goats, in which variables due to environment, fear, and distress can be removed, should allow establishment of a

baseline to which the influence of pharmacologic interventions, such as morphine, may be compared.

Behavioral changes or physiologic responses, as well as stress-related hormones and metabolites, have not been assessed after morphine administration, IV or epidurally, in conditioned goats. Once the effects of IV and epidural morphine are known for conditioned goats, the behavioral, physiologic, and stress-related hormonal and metabolic responses associated with surgery in goats may be used to help evaluate analgesic efficacy and side effects of morphine.

## MATERIALS AND METHODS

With permission of the Institutional Animal Care and Use Committee at Texas A&M University, 6 (3 female and 3 male) Spanish crossbred surgically neutered meat goats, determined to be in good health by physical examination and complete blood counts, were studied. Goats were 6 years old and weighed a mean  $\pm$  SD (range) of  $62.5 \pm 16.5$  kg (44.5-89.5 kg). Goats were members of a stable herd conditioned to handling and restraint over several years, but intensively trained for 8 weeks before the study. Consistent pairs of goats were confined in adjoining fenced pens (18 inches wide, 4 feet long, and 36 inches tall) in an air-conditioned (22° C) fluorescent-lit room with 21.7 air changes per hour. The pens allowed the goats to stand, assume sternal recumbency, and turn around. During the last 2 weeks, the goats were confined for up to 1 hour at least twice weekly, during which time physiologic variables were measured. In addition, the goats were accustomed to placement of ECG leads in a base-apex configuration and placement of an indirect blood pressure measurement cuff.

After a 12-hour fast and 24 hours before the epidural trial, goats were sedated (xylazine 0.11 mg/kg, IM) and epidural catheters (19-gauge 94.1 cm; Arrow International, Reading, PA, USA) were placed at the lumbosacral junction using a Tuohy needle with a lidocaine block (20 mg). Correct epidural catheter placement was determined by

aspiration and loss of resistance technique. Catheters were advanced 4 cm and sutured in place with 2-0 nylon (Ethilon<sup>®</sup>; Johnson and Johnson Company, Somerville, NJ, USA) and dressed with a bandage. Sedation was antagonized with tolazoline (IV to effect up to 2 mg/kg).

On the morning of each trial, a lidocaine (20 mg) skin block was used to facilitate placement of an 18-gauge catheter (I-cath<sup>®</sup> Charter Medical, Ltd., Lakewood, NJ, USA) into the right external jugular vein of each goat; the catheter facilitated administration of drugs and collection of blood samples. A pair of goats was led into the procedures room for baseline measurements and blood collection 2 hours after catheter placement. Physiologic measurements included heart rate (beats/min), respiratory rate (breaths/min), surface electrocardiogram (ECG; base-apex configuration; Protocol Propaq<sup>®</sup> 106 EL; Protocol Systems, Inc., Beaverton, OR, USA), rectal temperature (°C), and indirect blood pressure using oscillometric measurement with a cuff on the metacarpus (mm of Hg; Dinamap<sup>®</sup>; Criticon, Tampa, FL, USA). The behavior scoring system was developed during a previous study<sup>5</sup> in which non-painful goats became aroused rather than sedated after butorphanol administration. The behavioral scores were 3 = fractious (jumping, crying); 2 = pulling against leash, shifting weight from limb to limb (fidgety), biting; 1 = standing still or laying down, but eyes wide open; 0 = relaxed normal posture. Immediately after collection of baseline data, goats were administered morphine (0.1 mg/kg) epidurally (Duramorph 0.5 mg/mL; Elkins-Sinn, Inc., Cherry Hill, NJ, USA<sup>2,3</sup>) or IV (Duramorph; Elkins-Sinn, Inc., Cherry Hill, NJ, USA<sup>1</sup>). Physiologic variables and behavior were measured and blood samples were collected at baseline (Time = 0), 15, and 30 minutes and 1, 2, 4, 6, and 8 hours after IV morphine administration, and at 0, 1, 2, 4, 6, 8, 12, and 24 hours after epidural morphine administration.

Blood samples (6 mL) were drawn into chilled syringes, injected into cold EDTA

glass vacutainers, and maintained on ice until they were centrifuged for 15 minutes at 760 × g in a refrigerated centrifuge. The plasma was separated and frozen in five 0.7-mL aliquots at -80° C. Plasma samples were analyzed in the Neuroendocrine/Neurochemical Core Facility (Texas A&M University). Epinephrine and norepinephrine concentrations were determined by high performance liquid chromatography with electrochemical detection. Specifically, the catecholamines were extracted with alumina from 1 mL of plasma, eluted from a C-18 reversed phase, 5- $\mu$ m, 25-cm column with a phosphate-buffered mobile phase, and detected at 0.68 V.<sup>6</sup> The peak heights of the samples were compared with the peak heights of standards processed identically and adjusted appropriately with the use of an internal standard, dihydroxybenzylamine.

Plasma cortisol concentrations were determined using a radioimmunoassay kit (Coat A Count; Diagnostic Products, Los Angeles, CA, USA) that utilizes antibody-bound tubes and has been characterized for use in goat plasma. The least detectable concentration for this assay is 0.2  $\mu$ g/dL with an intra-assay variability of less than 4%. Glucose levels were analyzed by an enzymatic colorimetric assay (#510 A; Sigma Chemical Co., St. Louis, MO, USA) that involves the conversion of glucose to gluconic acid and hydrogen peroxide. The quantity of hydrogen peroxide produced is determined by a color reaction with o-dianisidine and is directly proportional to the original amount of glucose present in the sample. This assay can measure glucose levels below 25 mg/dL with an intra-assay variability below 4%.

Non-esterified free fatty acids (FFAs) were also determined by a modified enzymatic colorimetric assay (#990 75401; Wako Chemicals USA, Inc., Richmond, VA, USA).<sup>7</sup> This assay also involves the production and measurement of hydrogen peroxide as an indicator of the quantity of FFAs present in the samples. This assay can determine FFA levels below 50  $\mu$ Eq/L with an intra-assay variability below 5%.

Data are reported as mean  $\pm$  standard deviation. Continuous data were analyzed using repeated measures analysis of variance (ANOVA); if significant differences were detected over time, means were compared using Tukey-Kramer multiple comparisons test (SigmaStat 1.0, Jandel Scientific Software, San Rafael, CA, USA). A *P* value  $<0.05$  was considered significant.

## RESULTS

For IV morphine, differences over time were found for respiratory rate and temperature (Table 1). Respiratory rate ranged from  $17 \pm 10$  (30 minutes) to  $28 \pm 9$  (480 minutes) breaths/min. Temperature increased from Time 0 ( $38.6 \pm 0.1^\circ\text{C}$ ) to 8 hours ( $39.0 \pm 0.2^\circ\text{C}$ ). There were no significant changes in stress-related or hormonal variables (Table 2).

After epidural morphine, heart rate (Time 0 =  $96 \pm 24$  beats/min) decreased at 8 ( $73 \pm 15$  beats/min), 12 ( $74 \pm 13$  beats/min), and 24 ( $74 \pm 19$  beats/min) hours (Table 3); temperature ranged from  $38.8 \pm 0.1^\circ\text{C}$  to  $39.3 \pm 0.2^\circ\text{C}$ . Systolic arterial pressure (Time 0 =  $106 \pm 31$  mmHg) increased at 6 ( $157 \pm 18$  mmHg), 8 ( $151 \pm 18$  mmHg), and 24 ( $142 \pm 10$  mmHg) hours; diastolic arterial pressure (Time 0 =  $71 \pm 23$  mmHg) increased at 6 ( $120 \pm 23$  mmHg) and 8 ( $111 \pm 28$  mmHg) hours; mean arterial pressure

(Time 0 =  $84 \pm 25$  mmHg) increased at 6 ( $134 \pm 20$  mmHg) and 8 ( $125 \pm 24$  mmHg) hours (Table 3). Cortisol increased from baseline ( $1.15 \pm 0.91$   $\mu\text{g/dL}$ ) at 60 minutes ( $2.23 \pm 0.78$   $\mu\text{g/dL}$ ), which was higher than subsequent cortisol concentrations (Table 4). Glucose concentrations increased from Time 0 ( $55.6 \pm 4.6$  mg/dL) to 60 minutes ( $73.1 \pm 15.2$  mg/dL) and 120 minutes ( $70.7 \pm 13.4$  mg/dL) before returning to baseline at 720 minutes ( $55.9 \pm 6.0$  mg/dL). Free fatty acids were maximal at 60 minutes ( $317 \pm 183$  mmol/L) and decreased after 480 minutes ( $145 \pm 28$  mmol/L).

Goats behaved normally, without sedation, during both trials. During the epidural trial, all goats vocalized and briefly kneeled on their front legs or became sternal, during injection of the morphine.

## DISCUSSION

The stress response has been used to evaluate environmental stressors,<sup>8,9</sup> anesthesia,<sup>10,11</sup> drugs,<sup>12</sup> and surgery<sup>13</sup> in goats. The difficulty with interpreting data from these studies is that the stressors are not specific. There is not an invariant stress response, but various central nervous responses to stress under dynamic conditions that are modified intrinsically and extrinsically.<sup>14</sup> Biochemical markers alone are poorly correlated with post-operative pain scores due to lack

**Table 1.** Physiologic Variables After Intravenous Administration of Morphine (0.1 mg/kg) in 6 Goats.

Mean $\pm$ SD	Time (min)							
	0	15	30	60	120	240	360	480
Heart rate (beats/min)	87 $\pm$ 22	83 $\pm$ 17	72 $\pm$ 15	71 $\pm$ 11	67 $\pm$ 8	72 $\pm$ 7	72 $\pm$ 12	73 $\pm$ 11
Respiratory rate (breaths/min)*	18 $\pm$ 7	18.5 $\pm$ 0	17 $\pm$ 10	18 $\pm$ 6	27 $\pm$ 11	23 $\pm$ 5	26 $\pm$ 6	28 $\pm$ 9
Temperature ( $^\circ\text{C}$ )*	38.6 $\pm$ 0.1 <sup>a</sup>	38.8 $\pm$ 0.2	38.9 $\pm$ 0.2	38.8 $\pm$ 0.2	38.7 $\pm$ 0.2	38.5 $\pm$ 0.2	38.6 $\pm$ 0.1	39.0 $\pm$ 0.2 <sup>b</sup>
Arterial blood pressure (mmHg)								
Systolic	131 $\pm$ 24	132 $\pm$ 11	132 $\pm$ 26	134 $\pm$ 3	144 $\pm$ 16	124 $\pm$ 23	136 $\pm$ 3	134 $\pm$ 15
Mean	113 $\pm$ 20	118 $\pm$ 10	99 $\pm$ 20	93 $\pm$ 16	115 $\pm$ 7	99 $\pm$ 22	105 $\pm$ 6	108 $\pm$ 12
Diastolic	98 $\pm$ 15	103 $\pm$ 11	74 $\pm$ 25	78 $\pm$ 25	95 $\pm$ 5	85 $\pm$ 20	89 $\pm$ 9	93 $\pm$ 14

\*Changes over time for that variable are significant. Numbers in the same row with different superscripts are different ( $P < 0.05$ ) from each other.

**Table 2.** Stress-Related Hormones and Metabolites After Intravenous Administration of Morphine (0.1 mg/kg) in 6 Goats.

Mean ± SD	Time (min)							
	0	15	30	60	120	240	360	480
Cortisol (µg/dL)	0.68 ± 0.65	0.90 ± 0.68	0.56 ± 0.35	0.37 ± 0.36	0.43 ± 0.34	0.56 ± 0.15	0.58 ± 0.43	0.64 ± 0.17
Glucose (mg/dL)	57.1 ± 10.2	61.5 ± 11.1	56.1 ± 2.4	56.0 ± 6.2	55.6 ± 3.9	58.3 ± 2.8	52.5 ± 7.8	58.4 ± 4.6
Free fatty acids (mmol/L)	387.36 ± 170.19	500.92 ± 281.75	390.68 ± 243.59	296.36 ± 155.51	324.19 ± 156.00	386.86 ± 121.50	383.79 ± 80.29	395.45 ± 102.65
Norepinephrine (ng/mL)	2.963 ± 1.412	3.669 ± 0.630	3.736 ± 0.941	3.412 ± 0.696	3.181 ± 0.897	3.781 ± 0.843	3.783 ± 0.849	3.521 ± 1.328
Epinephrine (ng/mL)	2.062 ± 0.472	1.819 ± 0.396	1.522 ± 0.772	1.821 ± 0.393	1.697 ± 0.501	1.934 ± 0.563	1.732 ± 0.359	1.537 ± 0.331

Within the same row, no significant differences were detected.

**Table 3.** Physiologic Variables After Epidural Administration of Morphine (0.1 mg/kg) in 6 Goats.

Mean ± SD	Time (min)							
	0	60	120	240	360	480	720	1440
Heart rate (beats/min)*	96 ± 24 <sup>a</sup>	85 ± 12	86 ± 24	77 ± 12	80 ± 12	73 ± 15 <sup>b</sup>	71 ± 13 <sup>b</sup>	74 ± 19 <sup>b</sup>
Respiratory rate (breaths/min)	19 ± 5	18 ± 0	21 ± 5	23 ± 7	20 ± 5	22 ± 5	20 ± 4	19 ± 4
Temperature (°C)*	39.1 ± 0.3	39.1 ± 0.1	39.0 ± 0.2	39.0 ± 0.3	39.2 ± 0.1 <sup>a</sup>	39.3 ± 0.3 <sup>a</sup>	39.2 ± 0.2	38.8 ± 0.1 <sup>b</sup>
Arterial blood pressure (mmHg)								
Systolic*	106 ± 31 <sup>a</sup>	121 ± 20	128 ± 16	136 ± 30	157 ± 18 <sup>b</sup>	151 ± 18 <sup>b</sup>	131 ± 14	142 ± 10 <sup>b</sup>
Mean*	84 ± 25 <sup>a</sup>	90 ± 24	105 ± 11	116 ± 24	134 ± 20 <sup>b</sup>	125 ± 24 <sup>b</sup>	111 ± 9	113 ± 17
Diastolic*	71 ± 23 <sup>a</sup>	77 ± 26	88 ± 13	104 ± 20	120 ± 23 <sup>b</sup>	111 ± 28 <sup>b</sup>	93 ± 10	97 ± 21

\*Changes over time for that variable are significant. Numbers in the same row with different superscripts are different ( $P < 0.05$ ) from each other.

of appropriate controls and the influence of surgical stress.<sup>15</sup> For example, a change in stress-related hormones and metabolites could be due to a direct drug effect or an environmental or internal stressor (eg, stress-related changes related to hypoxemia or hypothermia). Similarly, changes in physiologic variables may be responses to stress or a direct drug effect. Interpretation of physiologic changes or biochemical markers cannot be done alone. The use of subjective pain scores in addition to biochemical

markers advance the validity of pain scoring.<sup>15</sup> Subjective pain scores are primarily based on behavior, so it is also important to evaluate the behavioral response to any drug administered in the absence of painful stimuli.

In a conditioned herd of goats, controls are possible that might not be available in clinical patients or naïve goats. For example, immobilization is aversive in many species, inducing hypertension, hypersecretion of adrenocorticotrophic hormone (ACTH) and

**Table 4.** Stress-Related Hormones and Metabolites After Epidural Administration of Morphine (0.1 mg/kg) in 6 Goats.

Mean ± SD	Time (min)							
	0	60	120	240	360	480	720	1440
Cortisol (µg/dL)*	1.15 ± 0.91 <sup>a</sup>	2.01 ± 0.78 <sup>b</sup>	0.87 ± 0.26 <sup>a</sup>	0.65 ± 0.33 <sup>a</sup>	1.04 ± 0.63 <sup>a</sup>	0.82 ± 0.34 <sup>a</sup>	0.60 ± 0.30 <sup>a</sup>	0.45 ± 0.30 <sup>a</sup>
Glucose (mg/dL)*	55.6 ± 4.6 <sup>a</sup>	73.1 ± 15.2 <sup>b</sup>	70.7 ± 13.4 <sup>b</sup>	61.9 ± 6.3	65.9 ± 11.4	62.3 ± 8.5	55.9 ± 6.0 <sup>a</sup>	52.9 ± 3.7 <sup>a</sup>
Free fatty acids (mmol/L)*	262.41 ± 78.68	316.99 ± 183.32 <sup>a</sup>	196.86 ± 69.13	168.32 ± 71.35	172.52 ± 101.14	145.30 ± 27.79 <sup>b</sup>	164.66 ± 70.78	157.25 ± 47.17 <sup>b</sup>
Norepinephrine (ng/mL)	2.742 ± 1.427	4.254 ± 1.022	4.710 ± 1.754	4.269 ± 1.072	6.463 ± 3.774	4.850 ± 1.437	4.878 ± 1.256	5.048 ± 2.936
Epinephrine (ng/mL)	2.852 ± 0.961	2.719 ± 0.988	2.435 ± 0.526	3.334 ± 1.684	2.554 ± 0.575	2.645 ± 0.921	3.371 ± 1.170	2.525 ± 0.712

\*Changes over time for that variable are significant. Numbers in the same row with different superscripts are different ( $P < 0.05$ ) from each other.

cortisol, and enhanced adrenal enzyme synthesis.<sup>16</sup> In sheep, the greatest cause of an increase in blood cortisol concentration during management practices includes isolation and exposure to an unfamiliar environment.<sup>17</sup> Our goats were conditioned to handling and restraint in pens in the experimental room prior to the trial to avoid environmental stress; goats were paired consistently during training and testing to avoid isolation stress. Even so, the large variation in baseline values within and between goats represents individual variation, which is consistent with that seen in sheep<sup>17</sup> and in this particular herd of trained goats.<sup>12</sup>

The stress response occurs in all surgical patients, even patients in whom a high level of postoperative pain control has been provided, but can be reduced by the use of opioids.<sup>15</sup> Because parenteral opioid administration in ruminants inhibits rumenoreticular contractions for up to 20 minutes<sup>18</sup> and may cause excitement,<sup>1</sup> alternate routes of administration have become attractive. Historically, parenteral morphine was believed to be a poor analgesic in ruminants due to a paucity of  $\mu$ -receptors in the central nervous system or poor drug distribution after parenteral injection.<sup>1</sup> Epidural morphine is being used to treat post-operative pain in goats,<sup>1-3</sup> but dosing recommendations are empirical and efficacy is difficult to evaluate. In

several species, the duration of activity of epidural morphine appears to be prolonged<sup>15</sup> and morphine central nervous system concentrations are  $>10$  or  $>100$  ng/mL 24 hours after epidural administration of 0.09 or 0.18 mg/kg of morphine, respectively.<sup>19</sup> The behavioral, physiologic, and stress-related hormonal response to morphine in non-painful conditioned goats provides additional information for evaluating analgesic efficacy of morphine in painful goats.

### Behavior

The lack of behavioral response to IV morphine was unexpected. Administration of fentanyl (2.5 µg/kg, IV), also a  $\mu$ -agonist, results in increased activity and vocalization for 1 hour compared to behavior prior to fentanyl administration.<sup>20</sup> Administration of butorphanol (0.1 mg/kg, IV and IM), a mixed  $\kappa$ -agonist and  $\mu$ -antagonist, results in behavior ranging from fractiousness, jumping, vocalizing, pulling on leashes, shifting weight, and biting.<sup>5</sup> In the case of butorphanol, plasma concentrations were predictive of behavior.<sup>5</sup> These behaviors did not appear to be stressful to the goats, and in a previous study,<sup>12</sup> were not associated with increases in stress-related hormones or metabolites.

The pain scores that have been described in goats might be confused with behavioral responses to opiates alone. For example,

analgesia has been determined by using a "Pain Score" from 1 to 3 with "1" being quiet or sedate and "3" reflecting continuous vocalization with violent muscular activity.<sup>2,3</sup> Although opposite in direction, this scoring system is not dissimilar to the one used to evaluate behavior in non-painful goats administered opioids,<sup>5</sup> in which 3 equaled "fractious (jumping, crying)" and 0 equaled "relaxed with normal posture." Therefore, it is significant that morphine (0.1 mg/kg, IV) does not precipitate behavioral changes, allowing behavioral variations to be used reliably in evaluating analgesia in painful goats.

Most goats receiving epidural morphine while anesthetized, but after surgery, were sedate after recovery.<sup>3</sup> However, 1 goat became transiently excited after recovering from anesthesia, surgery, and epidural morphine administration.<sup>3</sup> The author<sup>3</sup> suggested several potential reasons, including variation in dose response, inadvertent intrathecal injection, and an idiosyncratic reaction. During epidural administration of morphine, our goats vocalized, knelt, or became sternal. The behaviors associated with epidural administration of morphine did appear to reflect transient distress. No abnormal behaviors were noted after the acute reaction. An acute change in intracranial pressure, movement of the catheter tip, or irritation from the injection may have contributed to the acute reaction. There is evidence that repeated (8 days) epidural injections of preservative-free morphine, but not saline, through an epidural catheter causes severe tissue damage (diffuse cellular inflammation, fat cell necrosis, focal exudative inflammation) in goats,<sup>21</sup> but the tissue response after 1 injection is unknown. Epidural injection of morphine or saline through a catheter over 4 minutes did not cause any behavioral changes in goats.<sup>21</sup> Rapid epidural injection of morphine in goats has been recommended,<sup>1</sup> but based on the behavioral response of our goats, a slow injection is warranted through an epidural catheter in awake goats.

## Physiologic Responses

Although histamine release might be expected after IV morphine administration in goats,<sup>22</sup> minimal changes in physiologic variables occurred. Although tachycardia has been reported after large doses of parenteral opioids,<sup>1</sup> there were no changes in heart rate in our goats after IV morphine administration. The absence of significant variations in heart rate after IV morphine are consistent with the variations reported after intravenous fentanyl in goats.<sup>20</sup> At 75 minutes after butorphanol administration (0.1 mg/kg, IV), there was a statistically significant but not a clinically important increase in heart rate ( $113 \pm 19$  to  $133 \pm 23$  beats/min) in goats.<sup>12</sup> Bradycardia did not occur.

The respiratory rate varied over time after IV morphine administration, generally increasing. The lowest respiratory rate ( $17 \pm 10$  breaths/min) was at 30 minutes and the highest was at 480 minutes ( $28 \pm 9$  breaths/min). No change in respiratory rate occurred over time after IV fentanyl administration in goats.<sup>20</sup> After butorphanol administration, respiratory rate was also variable, being significantly higher at 60 minutes.<sup>12</sup> It is difficult to assign any clinical significance to such small and variable changes in respiratory rate after IV opioid administration.

Rectal temperature usually increases after IV opioid administration in goats. The changes are generally small, and of questionable clinical significance. After IV morphine, temperature increased from  $38.6 \pm 0.1^\circ\text{C}$  at baseline to  $39.0 \pm 0.2^\circ\text{C}$  at 480 minutes. After IV fentanyl administration, rectal temperature increased from  $39.9 \pm 0.8^\circ\text{C}$  at baseline to  $40.4 \pm 0.5^\circ\text{C}$  at 15 minutes, remaining elevated through 60 minutes, returning to baseline afterwards and staying there through the recordings at 360 minutes.<sup>20</sup> Similarly, after IV butorphanol administration, rectal temperature increased from  $39.5 \pm 0.4^\circ\text{C}$  at baseline to  $39.7 \pm 0.4^\circ\text{C}$  at 30 minutes and returning to baseline at 60 minutes and throughout the recording time of 120 minutes.<sup>12</sup> Although clinically unimportant, it does support the

notion that opioids tend to increase body temperature in species that may become excited after its administration, such as goats.<sup>22</sup>

Alterations in systemic arterial blood pressure may occur as a result of several derangements (eg, hypoxemia). However, arterial blood pressure is an important indicator of pain in some species.<sup>23</sup> Systemic arterial blood pressure measured indirectly did not change over time after IV morphine administration in our goats. Since arterial blood pressure in goats may be affected by some analgesics such as medetomidine, an  $\alpha_2$ -agonist,<sup>24</sup> it was important to determine if there is a direct drug effect after IV morphine administration. Although physiologic variables alone are generally unreliable for evaluation of analgesia, the absence of a direct effect of morphine in our goats' effects indicates that physiologic variables like blood pressure may be used more reliably to assess pain in goats that receive IV morphine.

The changes in heart rate, respiratory rate, and body temperature were either minor or not significant after epidural morphine administration. The heart rate decreased from  $96 \pm 24$  beats/min at baseline to  $73 \pm 15$  beats/min at 480 minutes. Respiratory rate did not vary over time. Rectal temperature was highest at 360 and 480 minutes ( $39.2 \pm 0.1^\circ\text{C}$  and  $39.3 \pm 0.3^\circ\text{C}$ , respectively) and lowest ( $38.8 \pm 0.1^\circ\text{C}$ ) at 1440 minutes. The clinical significance of these changes is likely unimportant. However, there were significant and potentially important changes in systemic arterial blood pressure as measured indirectly. Systolic, mean, and diastolic arterial blood pressures were increased at 360, 480, and 1440 minutes. Increases in systolic arterial pressure of 51 mm Hg, mean arterial pressure of 50 mm Hg, and diastolic arterial pressure of 49 mm Hg at 360 minutes appear to be clinically important and should be considered when using blood pressure to evaluate analgesia in painful goats. Blood pressure was not monitored in goats receiving epidural morphine after abdominal surgery.<sup>2</sup> In goats receiving epidural morphine after hindlimb orthopedic

surgery, blood pressure was stable over 360 minutes.<sup>3</sup> The baseline blood pressure was higher than in our goats and was taken during anesthesia but before the epidural; direct comparisons are not possible. Further study of changes in blood pressure in postoperative goats treated preemptively with epidural morphine, are indicated.

### **Stress-Related Hormonal and Metabolic Responses**

Evaluation of plasma catecholamines as indicators of stress is complicated by their short half-lives. Epinephrine and norepinephrine are secreted within the first second of sympathetic nerve stimulation, reaching maximum concentrations within a minute of stimulation; these catecholamines are rapidly destroyed by local tissue enzymes, and their concentrations are reduced by cellular uptake.<sup>25</sup> The duration of action of these catecholamines is usually less than 3 minutes after sympathetic stimulation.<sup>25</sup> Although extensively used as an indicator for overall sympathetic stimulation, norepinephrine is not very sensitive. The source of plasma norepinephrine is primarily sympathetic nerves, with only a small amount from the adrenal medulla.<sup>26</sup> Due to local inactivation, only a small amount of norepinephrine spills into venous drainage. In our goats, significant changes were not detected in catecholamine concentrations after morphine administration (IV or epidural). Similarly, after butorphanol administration, there were no changes in epinephrine or norepinephrine concentrations.<sup>12</sup> Reasons for undetectable or unreliable changes in catecholamine concentration include sampling effects (eg, sampling times, handling, or storage), species differences, drug differences, and the large individual variability. We observed large variations in plasma catecholamine concentrations in our goats. Small numbers of research animals and large variation in plasma catecholamines have been cited previously<sup>27-29</sup> as factors that might prevent measurement of significant treatment effects.

Differences were found in cortisol and glucose concentrations after epidural, but



not after IV, administration of morphine. Behaviorally, immediately after epidural morphine administration, the goats vocalized and changed their position. The behavioral response to epidural morphine certainly appeared to be acutely stressful. Plasma cortisol has been the standard for evaluating stress in goats.<sup>8-13</sup> There was no change in cortisol after IV morphine administration in our goats. Similarly, there were no changes after IV butorphanol administration in goats.<sup>12</sup> Increases in ACTH and cortisol occur after physiologic stress such as hypoxemia. Although physiologic stress cannot be ruled out, there were no significant changes in the physiologic variables that we measured. In goats, the maximal cortisol response to transport occurs within 15 minutes and remains elevated throughout the stressful situation and for 1 to 2 hours afterwards.<sup>8</sup> After epidural morphine administration, cortisol was elevated at 60 minutes compared to baseline, but the elevation was not sustained. Since the increase was transient, it seems reasonable that the increase was related to the acute stress of rapid epidural administration of morphine and not to the pharmacologic effect of the drug itself.

The increase in glucose concentration is also consistent with acute stress. The highest glucose concentrations were recorded at 60 and 120 minutes. Increase in glucose concentration after prolonged transport in goats lagged behind increases in cortisol and remained elevated for 1 to 2 hours after the decrease in cortisol.<sup>8</sup>

High concentrations of FFAs are toxic to the heart and can cause rhythm disturbances and decreased contractility.<sup>30</sup> In a previous study with this herd of goats,<sup>12</sup> the stress of IV catheterization was believed to be reflected in elevated baseline FFA concentrations that declined over 2 hours. The time between IV catheterization and baseline sampling was increased from 1 to 2 hours to overcome any novel stress associated with catheterization in the current study. Although there were no changes in FFA after IV administration of morphine, there was

a change over time in FFA concentration after epidural administration. The highest concentration of FFA was at 60 minutes, which is consistent with the increase in glucose and cortisol concentrations seen at that time. Even though the concentration of FFA was not significantly higher than baseline, it was higher than that seen at 8 hours and 24 hours. Since the significant differences in FFA occurred between 60, 480, and 1440 minutes, any direct effect of morphine on FFA cannot be distinguished from the acute reaction of its administration. The merit of morphine administration in painful goats has been evaluated. Epidural morphine improves analgesia in goats undergoing hindlimb<sup>3</sup> and abdominal<sup>2</sup> surgery. It appears that the administration of morphine (0.1 mg/kg) epidurally and intravenously to healthy young nonpainful goats is associated with few dangerous side effects. The effect of preemptive epidural morphine on arterial blood pressure should be investigated in goats undergoing a painful surgical procedure. In conscious goats, epidural morphine should be administered slowly to minimize the unfavorable hormonal and stress-related side effects of its rapid administration.

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