

Influence of medetomidine on stress-related neurohormonal and metabolic effects caused by butorphanol, fentanyl, and ketamine administration in dogs

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Objective—To examine stress-related neurohormonal and metabolic effects of butorphanol, fentanyl, and ketamine administration alone and in combination with medetomidine in dogs.

Animals—10 Beagles.

Procedure—5 dogs received either butorphanol (0.1 mg/kg), fentanyl (0.01 mg/kg), or ketamine (10 mg/kg) IM in a crossover design. Another 5 dogs received either medetomidine (0.02 mg/kg) and butorphanol (0.1 mg/kg), medetomidine and fentanyl (0.01 mg/kg), medetomidine and ketamine (10 mg/kg), or medetomidine and saline (0.9% NaCl) solution (0.1 mL/kg) in a similar design. Blood samples were obtained for 6 hours following the treatments. Norepinephrine, epinephrine, cortisol, glucose, insulin, and nonesterified fatty acid concentrations were determined in plasma.

Results—Administration of butorphanol, fentanyl, and ketamine caused neurohormonal and metabolic changes similar to stress, including increased plasma epinephrine, cortisol, and glucose concentrations. The hyperglycemic effect of butorphanol was not significant. Ketamine caused increased norepinephrine concentration. Epinephrine concentration was correlated with glucose concentration in the butorphanol and fentanyl groups but not in the ketamine groups, suggesting an important difference between the mechanisms of the hyperglycemic effects of these drugs. Medetomidine prevented most of these effects except for hyperglycemia. Plasma glucose concentrations were lower in the combined sedation groups than in the medetomidine-saline solution group.

Conclusions and Clinical Relevance—Opioids or ketamine used alone may cause changes in stress-related biochemical variables in plasma. Medetomidine prevented or blunted these changes. Combined sedation provided better hormonal and metabolic stability than either component alone. We recommend using medetomidine-butorphanol or medetomidine-ketamine combinations for sedation or anesthesia of systemically healthy dogs. (*Am J Vet Res* 2005;66:406–412)

threat to homeostasis.¹ Pain, anxiety, and other factors may induce stress in a surgical patient.² This reaction includes, but is not limited to, neuroendocrine and metabolic events such as catecholamine and cortisol release into the bloodstream, hyperglycemia, hypoinsulinemia, and lipolysis. Stress is important for survival, but it has a biological cost. It is generally believed that reducing perioperative stress is important for the safety and well-being of animals. This can be achieved by proper pain management with special emphasis on preemptive analgesia—the use of analgesics before pain begins.^{3–5}

Conversely, analgesic drugs may have neurohormonal and metabolic effects similar to stress when administered to pain-free humans or other animals. For example, opioid receptor agonists may increase catecholamine⁶ and corticosterone⁷ plasma concentrations, which leads to hyperglycemia.^{8,9} Also, ketamine, a dissociative anesthetic agent that has been recently used as an analgesic in the perioperative period,¹⁰ increases plasma catecholamine and cortisol concentrations in humans.^{11,12} We believe that the neurohormonal and metabolic effects of these drugs have not been paid due attention in veterinary anesthesia, although they may have effects on the patient. Opioids such as butorphanol and fentanyl and the dissociative anesthetic ketamine are often used as a part of premedication or induction in veterinary anesthesia,^{13,14} but the neurohormonal and metabolic effects of these drugs in pain-free dogs have apparently not been reported.

Medetomidine, a specific α_2 -adrenoceptor agonist, is an excellent drug to reduce stress by suppressing catecholamine and cortisol secretion and lipolysis.^{5,15–17} Therefore, the purpose of the study reported here was to examine the ability of medetomidine to suppress the stress-related neurohormonal and metabolic effects of butorphanol, fentanyl, and ketamine administration alone and in combination with medetomidine in dogs. We hypothesized that medetomidine would counteract the neurohormonal and metabolic effects of opioids and ketamine.

Stress consists of the biological responses of an animal in an attempt to cope with a disruption or

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Materials and Methods

Dogs—Ten Beagles were used, including 5 males and 5 females, weighing from 8 to 14 kg and ranging in age from 2 to 6 years. The dogs were fed standard dry dog food, and all were in good body condition. On the basis of results of physical, hematologic, and serum biochemical examinations, the dogs were found to be healthy. The dogs were dewormed^a 1 month before the experiment. The study protocol was approved by the Animal Research Committee of Tottori University.

Experimental protocols—The study consisted of 2 experiments. Five of the 10 dogs were randomly selected for the first experiment, and the other 5 were selected for the second experiment. Each dog participated in only one of the experiments. Within an experiment, each dog was assigned to each of the treatments in a randomized order at 1-week intervals.

In the first experiment, the effects of butorphanol tartrate^b (0.1 mg/kg), fentanyl citrate^c (0.01 mg/kg), and ketamine HCl^d (10 mg/kg) were compared. These drugs were administered IM as single treatments.

In the second experiment, the effects of medetomidine HCl^e (0.02 mg/kg) in combination with either physiologic saline (0.9% NaCl) solution (0.1 mL/kg; MED-SAL), butorphanol tartrate (0.1 mg/kg; MED-BUT), fentanyl citrate (0.01 mg/kg; MED-FEN), or ketamine HCl (10 mg/kg; MED-KET) were examined. Each combination was mixed in a syringe and administered IM.

Medetomidine dilution—In the second experiment, a MED-SAL mixed injection was used as the control. The rationale for this protocol was that medetomidine was also diluted by butorphanol, fentanyl, and ketamine in the combined sedation groups. Therefore, the original injection (medetomidine concentration, 1 mg/mL) was diluted by a factor of 6 in the MED-SAL and MED-BUT groups (medetomidine concentration, 0.17 mg/mL) and by a factor of 11 in the MED-FEN and MED-KET groups (medetomidine concentration, 0.09 mg/mL). In this respect, the MED-SAL group was not a perfectly fitted control for MED-FEN and MED-KET treatments but still provided a better approach than using the original medetomidine injection.

Instrumentation and sample collection—One day before the experiment, a 16-gauge central venous catheter was introduced into the jugular vein via local anesthesia.^f After fixing the catheter, the dogs were placed in individual cages to rest overnight. Food was withheld for 12 hours and water for 2 hours before the experiment. Each dog received one of the treatments the next morning. Blood samples were taken from the central venous catheter at hour 0 (initial value) just before the injection and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours after the injection. Additionally, heart rate was assessed via auscultation over the thoracic wall, and rectal temperature was measured by use of a digital thermometer after every blood sampling.

Sample processing—Tubes that contained EDTA were used to collect blood samples (2.5 mL each). The samples were immediately placed on ice and centrifuged within 15 minutes. After CBC^g was determined, the blood was centrifuged and the plasma was separated and preserved at -80°C as a single aliquot. Approximately 1 mL of plasma could be collected with this method. Catecholamine (norepinephrine and epinephrine), cortisol, insulin, glucose, and nonesterified fatty acid (NEFA) concentrations were determined in each sample. Catecholamines were measured in 0.3 mL of plasma, and 0.2 mL was used for the other measurements. Catecholamines were extracted on activated alumina and measured via high-performance liquid chromatography^h

by use of an instrument equipped with an electrochemical detector.¹⁸ⁱ Cortisol concentration was determined by use of a single antibody radioimmunoassay technique^j and insulin by use of a double antibody radioimmunoassay technique.^k Glucose and NEFAs were measured by use of a spectrophotometer.^l The intra- and interassay variations were $< 10\%$ for all of the measurements. The limit of detection was 20 pg/mL for catecholamines, 1 $\mu\text{g/dL}$ for cortisol, and 2.5 $\mu\text{U/mL}$ for insulin.

Statistical analyses—The data collected in each experiment were analyzed separately. The data of all biochemical variables were logarithmically transformed because of the inequality of their variances. These logarithmic data were analyzed via 1-way ANOVA for repeated measures^m to examine the time effect within each group. Another 1-way ANOVA was used to examine the treatment effect at each time point. When results of the ANOVA were significant, the Tukey test was used to compare the means.

Area under the concentration versus time curves (AUCs) from 0 to 6 hours were calculated by use of the original data. The sum of the trapezoids formed by the data and the baseline (a straight line fitted on the initial value and parallel to the x-axis) served as the AUC. This calculation method provided AUC values that were less affected by variations of the baseline values. These AUC data were used to examine the relationship between different variables within each group by use of simple linear regression analysis. The AUC data were also analyzed via 1-way ANOVA and the Tukey test to provide an additional comparison among the groups over time.

Sedation times across groups were also analyzed by use of 1-way ANOVA and the Tukey test. Sedation time was defined as the duration from the injection until the dog regained the presedation level of consciousness and no drowsiness could be appreciated by the examiner. The test-wise significance level was set at $P < 0.05$ in every statistical test used in the study. The data are expressed as mean \pm SEM.

Results

Sedation—In the first experiment, all dogs became mildly sedated after butorphanol or fentanyl treatments. The dogs calmly sat or lay in their cages, and excitement or muscle tremor was not noticed. Two of the 5 dogs defecated within 30 minutes after either treatment, but vomiting was not observed. However, we could not objectively assess whether the dogs had dysphoria. The sedative effect of fentanyl was shorter in duration (75 ± 9 minutes) than that of butorphanol (173 ± 32 minutes), although it was not possible to distinguish by physical examination whether the dogs had received butorphanol or fentanyl. Conversely, the dogs had severe muscle spasm, muscle tremor, and salivation after ketamine treatment. The dogs lay down at 6 ± 2 minutes after ketamine administration, and 3 of the 5 dogs defecated within 30 minutes. Complete loss of consciousness did not occur in every dog, but the mental state was severely altered. Recovery from sedation was complete at 113 ± 27 minutes after ketamine injection.

Catecholamine concentrations—In the first experiment, norepinephrine plasma concentrations significantly increased from the initial (hour 0) value at 0.5 and 1 hours after ketamine administration (Figure 1) but did not change significantly in the other groups. There were no significant differences in norep-

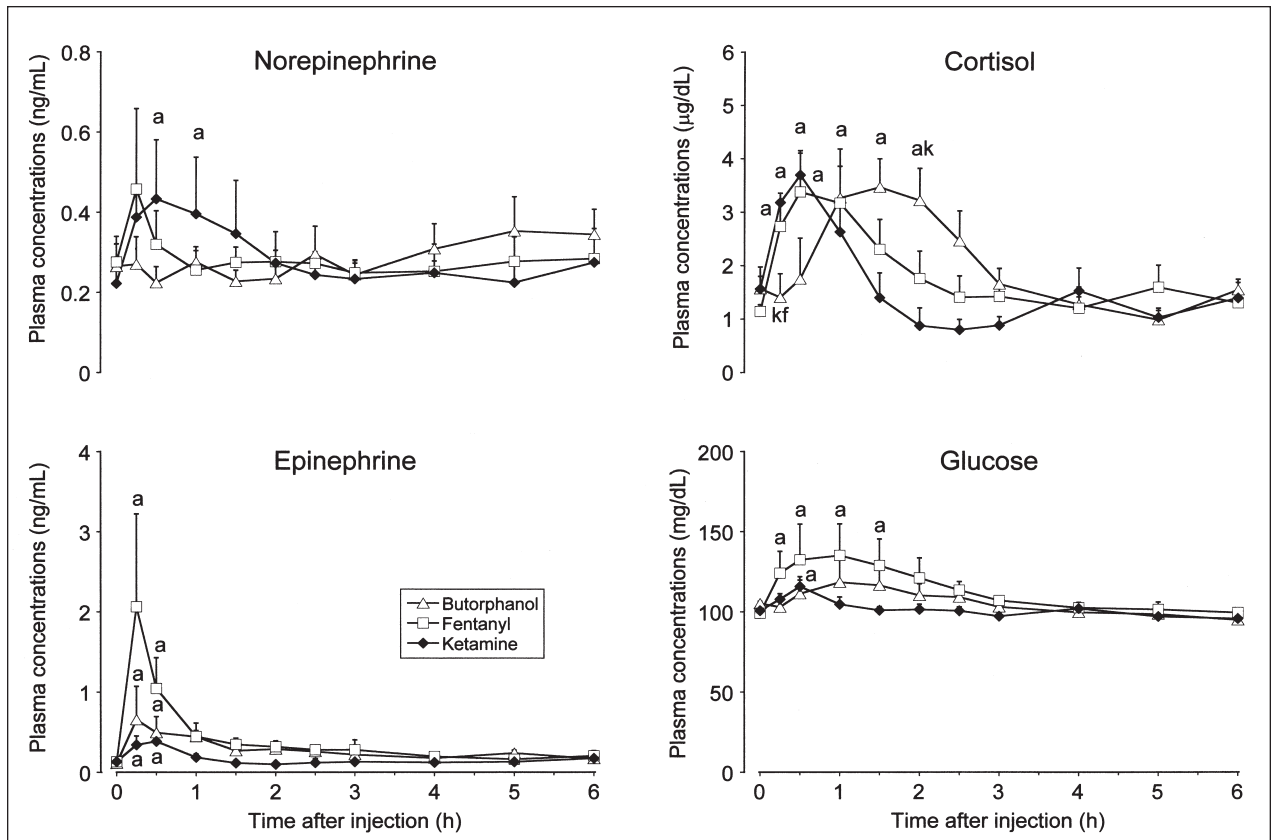


Figure 1—Plasma concentrations (mean \pm SEM) of norepinephrine, epinephrine, cortisol, and glucose in 5 dogs that were administered butorphanol (0.1 mg/kg, IM), fentanyl (0.01 mg/kg, IM), or ketamine (10 mg/kg, IM). a, f, k = Significantly ($P < 0.05$) different from value at time 0, fentanyl group, or ketamine group, respectively.

inephrine AUC values among the groups. Epinephrine plasma concentrations significantly increased in every group at 0.25 and 0.5 hours. Mean epinephrine concentration was the highest after fentanyl treatment, although the individual variability was also high; therefore, the epinephrine AUC values were not significantly different among groups. The epinephrine AUC values were significantly correlated with the norepinephrine AUC in the butorphanol group but were not correlated in the fentanyl or ketamine groups (Figure 2).

Cortisol concentrations—In the first experiment, plasma cortisol concentrations significantly increased in every treatment group (Figure 1), but this response was delayed after butorphanol administration (at 1, 1.5, and 2 hours), compared with fentanyl and ketamine (at 0.25, 0.5, and 1 hours). Cortisol concentrations in the butorphanol group were significantly lower than concentrations in the other groups at 0.25 hours and higher in the ketamine group at 2 hours, although the AUC values were not significantly different among groups. Cortisol AUC values were not correlated with the norepinephrine or epinephrine AUC values in any of the treatment groups.

Glucose concentrations—In the first experiment, plasma concentrations of glucose significantly increased after fentanyl (at 0.25, 0.5, 1, and 2 hours) and ketamine (at 0.5 hours) administrations (Figure 1). Glucose concentrations increased in the butorphanol

group but not significantly. Glucose AUC values did not differ significantly among groups. Interestingly, the epinephrine AUC values were highly and significantly correlated with the glucose AUC in the butorphanol and fentanyl groups but not in the ketamine groups (Figure 2). Similarly, a significant correlation was observed between norepinephrine and glucose AUC in the butorphanol group ($r = 0.91$), but no correlation was found in the fentanyl or ketamine group.

Insulin and NEFA concentrations—Plasma concentrations of insulin and NEFA did not change significantly in the first experiment. The NEFA AUC was significantly correlated with epinephrine ($r = 0.95$) in the butorphanol group but not in the fentanyl or ketamine group (Figure 2).

Heart rate and rectal temperature—In the first experiment, ketamine treatment significantly increased heart rate, compared with baseline values (96 ± 7.7 beats/min), at 0.25, 0.5, and 1 hours (144.4 ± 10.9 beats/min, 140 ± 10.7 beats/min, and 121.2 ± 10.9 beats/min, respectively), but butorphanol and fentanyl treatments did not change the heart rate. Even for those dogs with high epinephrine plasma concentrations after fentanyl and butorphanol treatments, heart rates were only slightly increased from the pretreatment values. Rectal temperature significantly decreased after butorphanol and fentanyl treatments from 0.25 to 3 hours. The hypothermic effect of fen-

tanyl was significantly greater than that of butorphanol. Rectal temperature did not change significantly in the ketamine group.

Sedation—In the second experiment, the dogs became recumbent at 24 ± 7 minutes after the MED-SAL injection, and the first signs of arousal were observed at 161 ± 11 minutes in that group. Time to recumbency was 8 ± 1 minutes in the MED-BUT group, 17 ± 4 minutes in the MED-FEN group, and 6 ± 1 minutes in the MED-KET group. Dogs in the MED-KET group became recumbent significantly faster than dogs in the MED-SAL group. The first signs of arousal were detected at 132 ± 9 minutes in the MED-BUT group, 110 ± 12 minutes in the MED-FEN group, and 75 ± 9 minutes in the MED-KET group. Arousal time was significantly shorter in the MED-FEN and MED-KET groups than that in the MED-SAL group. The dogs became deeply sedated or anesthetized in the MED-BUT and MED-KET groups, but the sedative effect of the MED-FEN combination was more superficial and unpredictable.

Catecholamine concentrations—In the second experiment, plasma concentrations of norepinephrine significantly decreased in every group at 0.25 and 0.5 hours after administration, compared with initial values (Figure 3). There were no significant differences among the groups at these time points. Norepinephrine concentrations remained significantly lower than the initial values until 2.5 hours in the MED-BUT and MED-FEN

groups and until 3 hours in the MED-SAL group. Conversely, norepinephrine concentrations in the MED-KET group returned to baseline at 1 hour and became significantly higher than concentrations in the MED-SAL group at 1, 1.5, 2, 2.5, and 5 hours. The norepinephrine AUC values were also significantly higher in the MED-KET group, compared with the MED-SAL group. The epinephrine plasma concentrations significantly decreased below the initial values at 0.25, 0.5, and 1 hours in every group. The epinephrine concentrations remained significantly lower than the initial values until 1.5 hours in the MED-BUT group and until 2.5 hours in the MED-FEN and MED-SAL groups. Although the epinephrine concentrations were significantly higher in the MED-KET group than in the MED-SAL group at 2 and 2.5 hours, there were no significant differences among the epinephrine AUC values. There were no significant differences among the cortisol concentrations in this experiment.

Glucose concentrations—Plasma glucose concentrations were significantly increased from the initial value at 2.5 and 3 hours in the MED-SAL group (Figure 3). Glucose concentrations in the MED-KET group were significantly increased at 1.5 hours. Glucose concentrations were significantly lower in the MED-BUT (at 3 hours), MED-FEN (at 3 hours), and MED-KET groups (at 2.5, 3, and 4 hours), compared with the MED-SAL group at these time points. Additionally, the glucose AUC was significantly lower in each combined sedation group than in the MED-SAL group.

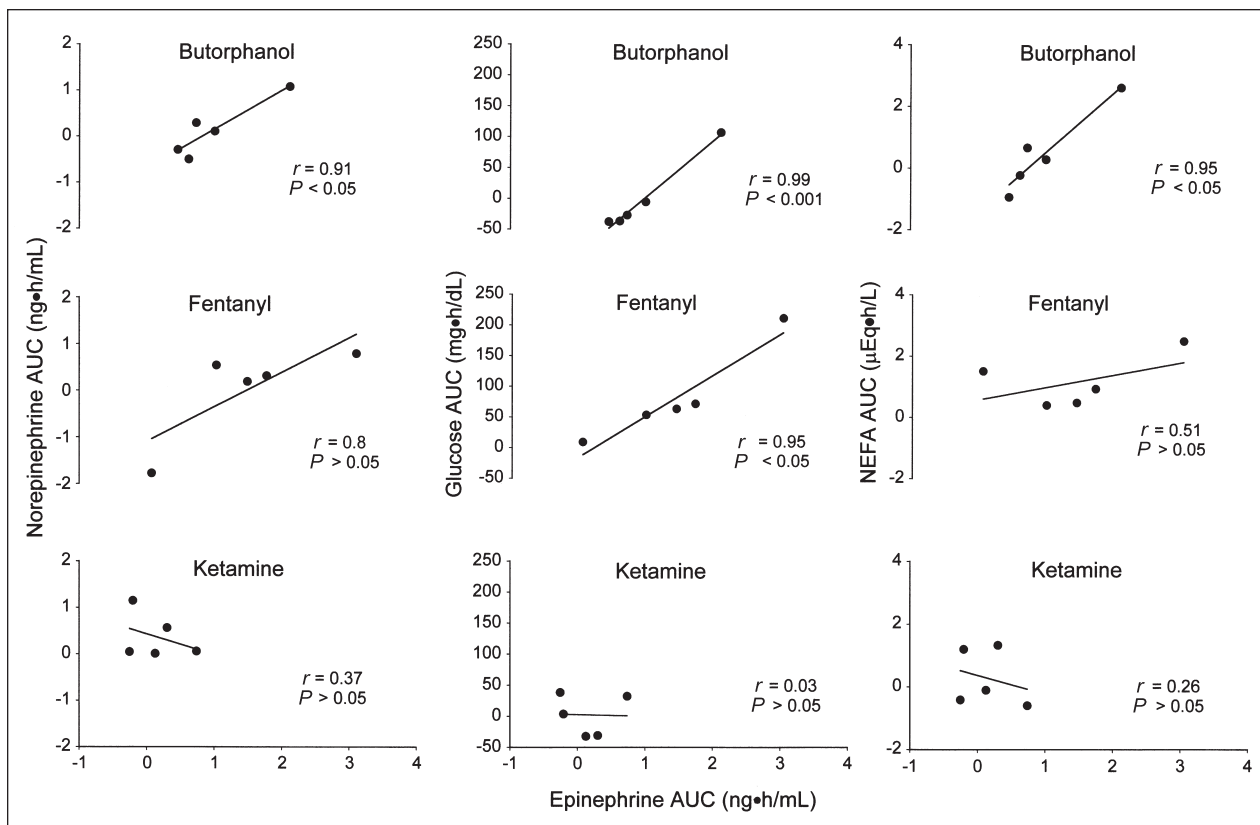


Figure 2—Scatterplots of the correlation between area under curve (AUC, 0 to 6 hours) for plasma concentrations of epinephrine versus norepinephrine, glucose, or nonesterified fatty acid (NEFA) concentrations in 5 dogs administered butorphanol (0.1 mg/kg, IM), fentanyl (0.01 mg/kg, IM), or ketamine (10 mg/kg, IM).

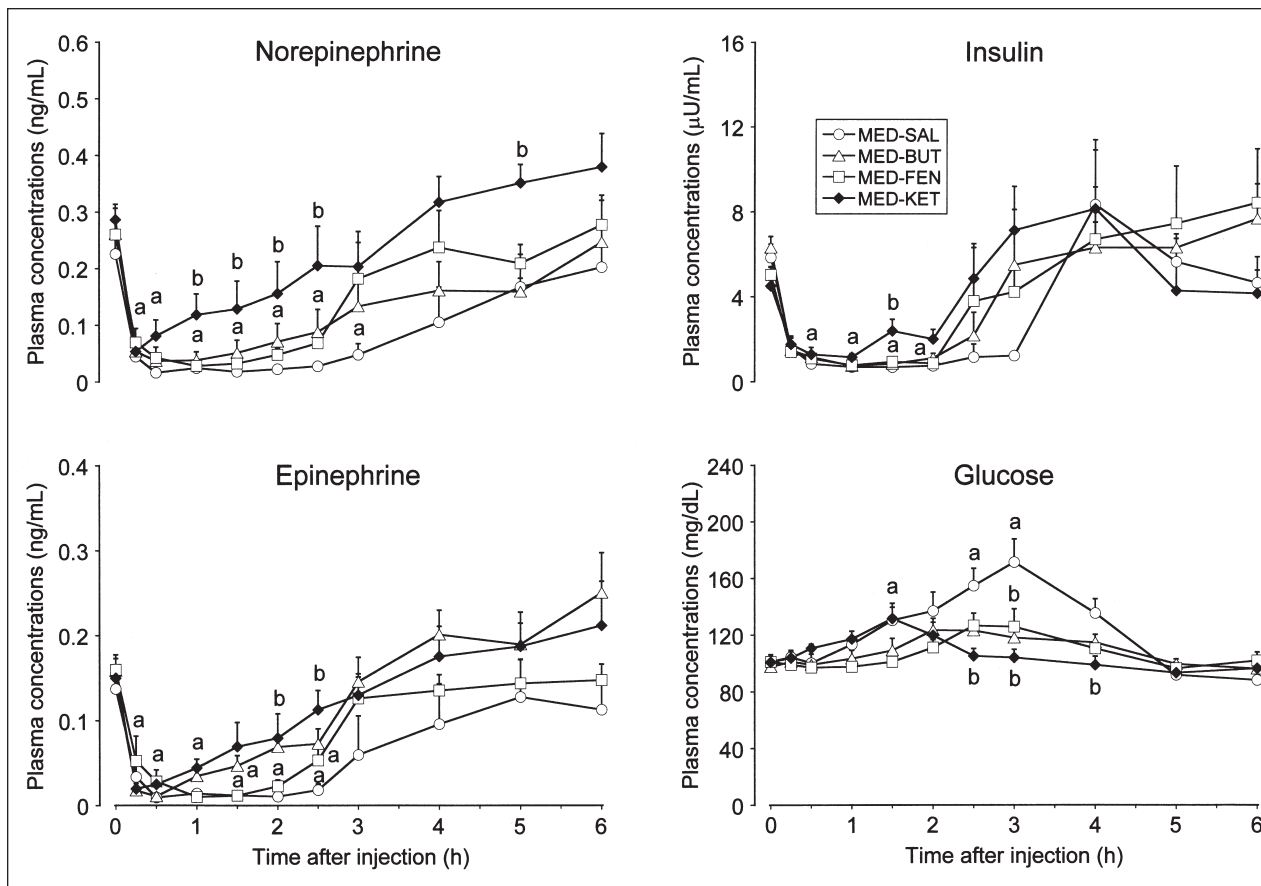


Figure 3—Plasma concentrations (mean ± SEM) of norepinephrine, epinephrine, insulin, and glucose in 5 dogs administered medetomidine (0.02 mg/kg, IM) in combination with either saline (0.9% NaCl) solution (0.1 mL/kg [MED-SAL]), butorphanol (0.1 mg/kg [MED-BUT]), fentanyl (0.01 mg/kg [MED-FEN]), or ketamine (10 mg/kg [MED-KET]). a, b = Significantly ($P < 0.05$) different from value at time 0 and the MED-SAL group, respectively.

Insulin and NEFA concentrations—Plasma concentrations of insulin (Figure 3) significantly decreased below the initial values in the MED-BUT, MED-FEN, and MED-SAL groups at 0.5, 1, 1.5, and 2 hours and then returned to baseline. Conversely, insulin concentrations in the MED-KET group were decreased significantly only at 0.5 and 1 hours, compared with the initial value, and were significantly increased at 1.5 hours, compared with the MED-SAL group. The insulin AUC values were not different among the groups. Plasma concentrations of NEFAs were significantly decreased below the initial values in every group (at 0.5, 1, 1.5, and 2 hours) except the MED-FEN group (decreased at 1, 1.5, and 2 hours). The NEFA concentrations were significantly increased above the initial value at 5 and 6 hours in the MED-KET group. The NEFA AUC values were not different among groups. No significant correlations among variables could be identified in this experiment.

Discussion

Endogenous opioid peptides are important neurotransmitters in the CNS and also modulate various neurohormonal and metabolic changes associated with stress.¹⁹⁻²¹ Opioid drugs injected systemically may mimic the effects of endogenous opioids and trigger norepinephrine, epinephrine, and cortisol release into

the bloodstream.^{6,7,22-25} The effect of opioids on plasma catecholamine concentrations is variable and may depend on the dose, study conditions, and whether the animal is in pain; interaction with other anesthetics is also possible.²⁶ This may explain why norepinephrine concentrations did not change significantly after butorphanol and fentanyl treatments in our study and why the epinephrine concentrations were highly variable among our dogs after opioid administration. Conversely, interindividual variation among cortisol plasma concentrations after butorphanol and fentanyl administrations in our study was surprisingly low, which suggested that opioids may increase epinephrine and cortisol plasma concentrations through independent mechanisms. We cannot explain why the cortisol concentrations increased later after butorphanol administration than after fentanyl administration.

The hyperglycemic effect of morphine may result from increased epinephrine blood concentrations caused by μ -receptor stimulation.^{7,22,23,25} The epinephrine and glucose AUC concentrations were strongly correlated in this study, supporting the theory that epinephrine should be the key mediator of the hyperglycemic response after butorphanol and fentanyl administration in pain-free dogs.

The correlation of the AUC data between epinephrine and NEFAs also suggests that epinephrine may

have an important role in modifying lipolysis after opioid treatments. Conversely, more factors may influence the insulin plasma concentrations. We suggest that when epinephrine concentrations are high, insulin secretion may be suppressed. Later, when epinephrine concentrations decrease, the increased plasma glucose concentrations may trigger the secretion of insulin.

Fentanyl is reported to cause norepinephrine release and associated hemodynamic changes during induction of anesthesia in humans.²⁴ However, heart rates did not change significantly after opioid administration in our study. Blood pressure might have been increased because of the α -adrenoceptor-mediated vasoconstriction caused by catecholamines. Orally administered tilidine, a μ -opioid receptor agonist, causes dysphoria in humans,²⁷ which is related to the increased epinephrine concentrations in the blood. Dysphoria is a commonly reported adverse effect of opioids used for premedication in veterinary anesthesia; therefore, we suppose that, similar to humans, there may be a relationship between dysphoria and the increase in sympathetic outflow after opioid administration in dogs.

Ketamine administration caused increased epinephrine, cortisol, and glucose plasma concentrations similar to opioids but also increased plasma norepinephrine concentrations. Ketamine blocks the reuptake of norepinephrine at the presynaptic membrane of adrenergic neurons and causes a flux of norepinephrine into the circulation.^{28,29} The increases in mean catecholamine and glucose plasma concentrations in the ketamine group were moderate, and the variances were relatively low, compared with the opioid groups. The lack of correlation between epinephrine and glucose or NEFA AUC values also suggests that in contrast to opioids, epinephrine is probably not the main mediator of hyperglycemia and lipid homeostasis after ketamine administration. Ketamine interacts with various receptors,³⁰ and the mechanisms of its endocrine and metabolic actions are poorly understood.²⁸

Medetomidine had a dominant effect on the stress-related neurohormonal and metabolic changes in the combined sedation groups because the suppression of norepinephrine, epinephrine, insulin, and NEFA that is typical for medetomidine was observed. Norepinephrine concentrations also decreased in the MED-KET group but were higher than concentrations in the other combined sedation groups, probably because ketamine can increase sympathetic outflow from the CNS.

Medetomidine and MED-KET administration caused mild but significant hyperglycemia. Results of the present study support that circulating epinephrine is responsible for the hyperglycemic effect of opioids. Because medetomidine suppressed epinephrine release in the MED-BUT and MED-FEN groups, we did not expect that opioids would contribute to hyperglycemia and further enhance the hyperglycemic effect of medetomidine, but the fact that opioids decreased medetomidine-induced hyperglycemia was unexpected. The addition of ketamine also decreased the potency of medetomidine to cause hyperglycemia. Medetomidine is often regarded as a drug that can

reduce the stress response because it is able to attenuate increases in catecholamine and cortisol plasma concentrations.⁵ Conversely, medetomidine suppresses insulin release and causes hyperglycemia, which are similar to the effects of epinephrine during stress. In this respect, medetomidine cannot be regarded as an ultimate anti-stress drug because it partially accelerates the stress. Therefore, hypoinsulinemia and hyperglycemia may be considered the adverse effects of medetomidine. In this regard, combining butorphanol, fentanyl, or ketamine with medetomidine provides the advantage of reducing the hyperglycemic adverse effect of medetomidine.

Additionally, results of our study indicated that diluting medetomidine with saline solution prolonged the onset and duration of sedation and reduced the depth of sedation, compared with that expected from IM injection of the same medetomidine dose undiluted.^{15,16} According to the Fick law of diffusion, the speed of absorption from an IM site is positively correlated with the concentration of the injected drug. The addition of butorphanol or ketamine to medetomidine resulted in deep sedation or anesthesia with a short onset of action, although medetomidine was diluted similarly, compared with the MED-SAL group. Conversely, the addition of fentanyl to medetomidine resulted in even more unreliable sedation than the MED-SAL mixture. Consequently, we do not recommend using the MED-FEN mixture administered IM as premedication for dogs. The effect of dilution on absorption of drugs injected IM may have clinical implications when mixing different premedication drugs in the same syringe.

Opioid drugs or ketamine used alone for premedication or analgesia may cause a temporary increase in plasma catecholamine concentrations, which may have hormonal and metabolic consequences and contribute to dysphoria. Medetomidine prevented or blunted these changes; therefore, we accepted our stated hypothesis. Conversely, plasma glucose concentrations were lower in the combined sedation groups than after sole medetomidine administration, which constituted reduction of 1 potential adverse effect of medetomidine. Therefore, we recommend the use of MED-BUT or MED-KET combinations for sedation or anesthesia of systemically healthy dogs.

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- a. Drontal plus, Bayer Corp, Tokyo, Japan.
 - b. Stadol, 1 mg/mL, Bristol Myers Squibb, Tokyo, Japan.
 - c. Fentanest, 0.05 mg/mL, Sankyo, Tokyo, Japan.
 - d. Ketalar, 50 mg/mL, Sankyo, Tokyo, Japan.
 - e. Domitor, 1 mg/mL, Meiji Seika Kaisha, Tokyo, Japan.
 - f. Xylocaine 2%, Fujisawa Pharmaceutical, Osaka, Japan.
 - g. K-4500, Sysmex, Hiroshima, Japan.
 - h. LaChrom, Hitachi, Tokyo, Japan.
 - i. Coulochem II, ESA, Chelmsford, Mass.
 - j. I-AE16, Eiken Chemical, Tokyo, Japan.
 - k. I-AJ16, Eiken Chemical, Tokyo, Japan.
 - l. Auto Sipper Photometer U-1080, Hitachi, Tokyo, Japan.
 - m. StatView, version 5.0, Abacus Concepts, Berkeley, Calif.
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