Effects of exercise-induced stress and dexamethasone on plasma hormone and glucose concentrations and sedation in dogs treated with dexmedetomidine

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Objective—To compare the effects of pretreatment with dexamethasone, physical stress (exercise), or both on sedation and plasma hormone and glucose concentrations in dogs treated with dexmedetomidine (DEX).

Animals—6 healthy purpose-bred Beagles.

Procedure—Dogs received 4 treatments each in a randomized order prior to IV administration of DEX (5 µg/kg). Pretreatments were as follows: (1) IV administration of saline (0.9% NaCl) solution and no exercise (control group); (2) IV administration of dexamethasone (0.05 mg/kg) and no exercise (DM group); (3) IV administration of saline solution and exercise (EX group; 15 minutes of trotting on a treadmill at a speed of 2 m/s); and 4) IV administration of dexamethasone and exercise (DM+EX group).

Results—Following DEX administration, all dogs had similar times to recumbency and sedation index values, irrespective of pretreatment with dexamethasone or exercise. Plasma catecholamine concentrations decreased after DEX administration. Compared with control group dogs, plasma cortisol concentrations were higher in EX-group dogs prior to DEX administration and lower in DM- and DM+EX-group dogs following DEX administration. Administration of DEX decreased plasma cortisol concentration in EX-group dogs only. Plasma glucose concentration was not influenced by exercise or dexamethasone administration but was lower than baseline concentrations at 30 minutes after DEX administration and returned to baseline values by 90 minutes. Heart and respiratory rates and rectal temperature increased during exercise. After DEX administration, these values decreased below baseline values. The decrease in heart rate was of shorter duration in dogs that underwent pretreatment with dexamethasone, exercise, or both than in control group dogs

Conclusions and Clinical Relevance—Pretreatment with dexamethasone, moderate physical stress (exercise), or both did not influence sedation or cause adverse effects in healthy dogs treated with DEX. (*Am J Vet Res* 2005;66:260–265)

It has been suggested that the sedative effect of an α_2-adrenergic receptor agonist is less in excited than in calm animals.[1] Conversely, stress may increase the analgesic effects of α_2-adrenergic receptor agonists.[2] Because **dexmedetomidine (DEX)** exerts its sedative and many other effects by α_2-adrenoceptor activation and inhibition of norepinephrine release from sympathetic nerve terminals, the effects may decrease if the concentrations of circulating catecholamines are high. Stress may also have some effect on the distribution or metabolism of medetomidine.[3] In addition, glucocorticoids regulate α_2-adrenoceptors in the brain.[4] Therefore, both stress-induced cortisol release and dexamethasone administration might decrease the sedative effect obtained from administration of an α_2-adrenergic receptor agonist.

Dexamethasone decreases cortisol concentrations in blood and blocks the cortisol response to stress, whereas the response to norepinephrine is not suppressed.[5,6] The influence of dexamethasone on epinephrine release seems to be dependent on the type of stressor.[5] α_2-Adrenergic receptor agonists are reported to decrease the concentrations of circulating catecholamines, but they have only marginal, if any, effects on plasma cortisol concentrations.[1,7] They also decrease perioperative plasma epinephrine, norepinephrine,[8,9] and cortisol concentrations.[8–10] Both α_2-adrenergic receptor agonists[7] and glucocorticoids increase blood glucose concentrations in dogs.

The combined effects of stress and dexamethasone on the sedative effects of DEX or on plasma hormone concentrations after administration of DEX are not known. The purpose of the study reported here was to investigate the effect of dexamethasone administration with and without physical stress on the sedative effects of DEX and on plasma concentrations of circulating cortisol, **antidiuretic hormone (ADH)**, epinephrine, norepinephrine, and glucose. We hypothesized that pretreatment with dexamethasone, exercise, or both may decrease the sedative effect of DEX and may influence the plasma concentrations of stress-related hormones and glucose.

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Materials and Methods

Animals—Six healthy neutered purpose-bred Beagles (3 of each sex) were used in this study. Dogs were 6 years of age, routinely housed and maintained in a group, and fed commercial dog food. Water was provided ad libitum. On the day of study, dogs were taken approximately 4 hours after feeding from the group to another facility for the experimental period. The Animal Care and Use Committee of the University of Helsinki approved this study.

Study design—A randomized placebo-controlled crossover study design was used. The researcher (EKK) who evaluated the degree of sedation was not aware of pretreatments with dexamethasone or exercise.

Treatment groups—Each dog received 4 treatments in a randomized order prior to administration of DEX. Pretreatments were as follows: (1) IV administration of saline (0.9% NaCl) solution and no exercise (control group); (2) IV administration of dexamethasone and no exercise (DM group); (3) IV administration of saline solution and exercise (EX group); and 4) IV administration of dexamethasone and exercise (DM+EX group). A 2-week washout period was applied between each treatment for each dog.

Study procedure—Heart and respiratory rates and rectal temperature were measured within 10 minutes prior to IV injection of dexamethasone or saline solution. A cannula was then placed in the cephalic vein, and blood was withdrawn for analysis of glucose concentration. Dexamethasone[a] (0.05 mg/kg, IV) or the same volume of saline solution was injected 60 minutes prior to DEX administration. Following dexamethasone or saline solution administration, a person in the examination room accompanied each dog for 30 minutes. If the dog had been assigned to pretreatment with exercise (15 minutes trotting on a treadmill at a speed of 2 m/s), this was then initiated in another room 30 minutes prior to the DEX administration. If the dog was not exercised, it stayed for another 30 minutes in the examination room.

Dexmedetomidine[b] was administered at a dose of 5 µg/kg, IV. Time from DEX administration until recumbency was recorded. The follow-up period consisted of time points before and 5, 10, 15, 20, 30, 40, 50, 60, and 90 minutes after DEX administration. Heart and respiratory rates were measured and followed by categoric assessment of sedation (**Appendix**). Rectal temperature was measured before and 30, 60, and 90 minutes after DEX administration.

Blood was withdrawn from the jugular vein with a chilled syringe and needle before and 30 and 90 minutes after DEX administration. A part of the sample was injected into a heparinized tube for glucose analysis. The rest was injected into chilled tubes containing EDTA. Plasma was separated by refrigerated centrifugation (1,670 × *g* for 15 minutes); then divided and frozen within 30 minutes of collection; and finally stored at –70°C until analyzed for cortisol, ADH, epinephrine, and norepinephrine concentrations. Plasma used for catecholamine assays was treated with an antioxidant ($Na_2S_2O_5$). Plasma glucose concentration was measured within 15 minutes by use of an autoanalyzer.[c] Cortisol was analyzed[d] by use of a competitive immunoassay.[e] Inter- and intra-assay coefficients of variation were 8.7% and 8.2%, respectively. Antidiuretic hormone was analyzed[d] by use of double antibody radioimmunoassay of arginine vasopressin.[f] Inter- and intra-assay coefficients of variation were 5.8% and 4.7%, respectively. Catecholamines were extracted from 2 mL of plasma into Al_2O_3.[g] 3,4-dihydroxybenzylamide hydrobromide[h] was used as an internal standard to correct for absolute recovery variations in catecholamines. Norepinephrine and epinephrine were eluted from Al_2O_3 into 0.2M $HClO_4^-$ solution and measured by use of high-pressure liquid chromatography with a multichannel electrochemical detector.[i] For the analysis of catecholamines, a C18 column[j] was used and the mobile phase consisted of citric acid monochloroacetic acid acetonitrile buffer (pH, 3.4). For calibration purposes, known catecholamine standards in plasma calibrator solution[k] were treated in the same way as samples.

Statistical analyses—An ANOVA model appropriate for randomized block design was used. The model included treatment, time, and treatment × time as fixed effects and dog, dog × treatment, and dog × time as random effects. A compound symmetry structure was used for covariance whenever possible. For analysis of the sedation index, a simpler variance components structure was used. Pairwise comparisons were accomplished by use of contrasts in the model. Samples collected before sedation in control group dogs were used as baseline values for hormone concentrations. For all other parameters, values detected before exercise were used as baselines. Values of $P < 0.05$ were considered significant.

Results

All dogs achieved recumbency within 3 minutes after DEX administration, and their sedation index varied between 6 and 12 (out of 15) when it was scored at 5 minutes (**Figure 1**). No significant differences were found among groups for the sedation index or for the time elapsed from DEX administration until recumbency.

Plasma catecholamine concentrations generally decreased after DEX administration. Compared with control group dogs, the plasma cortisol concentration was higher in EX-group dogs before DEX administration. Among dog groups, only EX-group dogs had significantly ($P = 0.001$) higher plasma cortisol concentrations before DEX administration, compared with after DEX administration. In DM- and DM+EX-group dogs, plasma cortisol concentration was lower after DEX administration, compared with control group dogs. Plasma ADH concentrations did not significantly

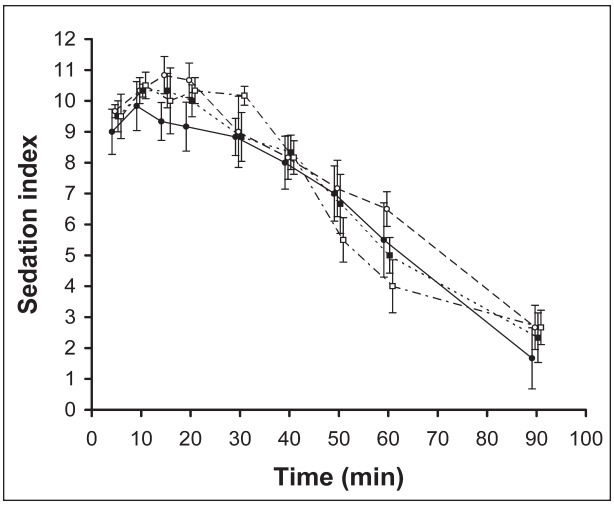

Figure 1—Mean (± SEM) sedation index versus time in 6 dogs that underwent dexamethasone treatment and exposure to physical stress (open circles), exposure to physical stress alone (open squares), dexamethasone treatment alone (closed circles), or saline (0.9% NaCl) solution treatment (control; closed squares) prior to administration of dexmedetomidine (5 µg/kg, IV). Sedation was scored at predetermined times after dexmedetomidine (DEX) administration to determine the sedation index.

Table 1—Mean ± SD plasma catecholamine, cortisol, and antidiuretic hormone concentrations in 6 dogs that underwent dexamethasone (0.05 mg/kg, IV) treatment, exposure to physical stress, and saline (0.9% NaCl) solution (IV; control) treatment prior to administration of dexmedetomidine (5 µg/kg, IV).

	Time (min) relative to DEX administration		
Variables	**0 (immediately before)**	**30 (after)**	**90 (after)**
Epinephrine (nmol/L)			
DM + EX	0.64 ± 0.29*	0.20 ± 0.13†	0.35 ± 0.18†
EX	1.38 ± 0.56	0.47 ± 0.31†	1.28 ± 0.64*
DM	1.03 ± 0.28	0.32 ± 0.24†	0.69 ± 0.26†
Control	1.21 ± 0.81	0.19 ± 0.15†	0.65 ± 0.40†
Norepinephrine (nmol/L)			
DM + EX	2.20 ± 1.41	0.88 ± 0.63†	1.01 ± 0.91†
EX	2.48 ± 0.37	1.52 ± 0.39	1.46 ± 0.83
DM	2.50 ± 0.68	1.21 ± 0.48†	1.47 ± 0.62†
Control	2.32 ± 0.70	0.82 ± 0.41†	0.97 ± 0.53†
Cortisol (nmol/L)			
DM + EX	38.6 ± 9.5	24.8 ± 3.7†*	20.5 ± 3.9†*
EX	96.8 ± 65.5*	47.2 ±18.5	52.2 ± 14.2
DM	35.7 ± 7.1	28.5 ± 6.0†*	23.8 ± 9.0†*
Control	55.3 ± 20.9	45.7 ± 9.9	61.4 ± 27.1
ADH (nmol/L)			
DM + EX	25.5 ± 11.4	19.8 ± 8.8	18.5 ± 8.3
EX	24.9 ± 5.7	20.4 ± 5.1	18.0 ± 4.5
DM	22.3 ± 7.4	18.0 ± 7.4	16.4 ± 4.9
Control	23.1 ± 9.4	19.7 ± 7.6	21.7 ± 6.7

*Significantly ($P < 0.05$) different from control values within a time point. †Significantly ($P < 0.05$) different from control values at 0 min.

DEX = Dexmedetomidine. DM = Dexamethasone. EX = Exposure to physical stress (15 minutes trotting on a treadmill at 2 m/s). ADH = Antidiuretic hormone.

Table 2—Mean ± SD plasma glucose concentration and rectal temperatures in 6 dogs that underwent dexamethasone (0.05 mg/kg, IV) treatment, exposure to physical stress, and saline solution (IV; control) treatment prior to administration of dexmedetomidine (5 µg/kg, IV).

	Baseline	Time (min) relative to DEX administration			
Variables	**Before any treatments**	**0 (immediately before)**	**30 (after)**	**60 (after)**	**90 (after)**
Glucose (mmol/L)					
DM + EX	6.0 ± 0.4	5.6 ± 0.7	4.2 ± 0.6†	NA	6.2 ± 1.0
EX	5.8 ± 0.8	5.9 ± 0.8	4.5 ± 0.8†	NA	5.6 ± 0.4
DM	6.2 ± 0.5	5.2 ± 0.5	3.5 ± 0.4†	NA	7.1 ± 1.7†*
Control	5.8 ± 0.5	5.6 ± 0.8	3.8 ± 0.7†	NA	5.6 ± 0.7
Rectal temperature (°C)					
DM + EX	38.5 ± 0.7	39.1 ± 0.2†*	38.2 ± 0.5	38.2 ± 0.4*	38.1 ± 0.4*
EX	38.4 ± 0.2	39.0 ± 0.3†*	38.4 ± 0.4	38.0 ± 0.4*	37.5 ± 0.5†
DM	38.7 ± 0.5	38.4 ± 0.1	38.1 ± 0.6†	37.9 ± 0.4†	37.7 ± 0.4†*
Control	38.7 ± 0.2	38.3 ± 0.4	38.1 ± 0.7†	37.4 ± 0.8†	37.1 ± 1.2†

*Significantly (P , 0.05) different from control values within a time point. †Significantly (P , 0.05) different from baseline.

NA = Not available.

See Table 1 for remainder of key.

change (**Table 1**). Plasma glucose concentration was not influenced by exercise or dexamethasone administration. Plasma glucose concentrations were lower than baseline values at 30 minutes after DEX administration in all dog groups (**Table 2**). The overall changes in glucose concentration over time were evaluated by combining data from dogs of all groups. The mean difference between baseline values and values at 30 minutes after DEX administration was 1.94 mmol/L (confidence interval, 1.45 to 2.43 mmol/L). Glucose returned to baseline values within 90 minutes after DEX administration.

Heart rate was higher after exercise in EX- and DM+EX-group dogs, compared with control group dogs (**Figure 2**), and respiratory rate increased after exercise, compared with baseline values (data not

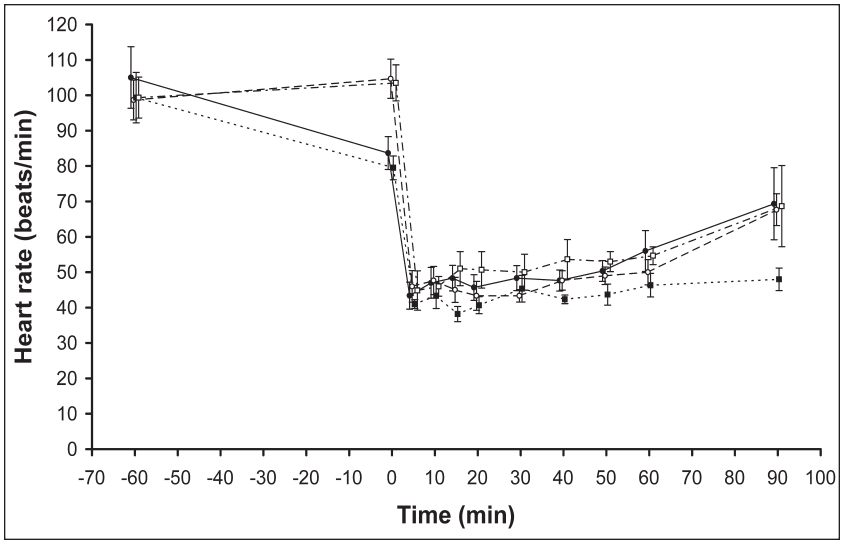

Figure 2—Mean (± SEM) heart rate versus time in 6 dogs that underwent dexamethasone treatment and exposure to physical stress (open circles), exposure to physical stress alone (open squares), dexamethasone treatment alone (closed circles), or saline solution treatment (control; closed squares) prior to administration of DEX (5 mg/kg, IV). Heart rate was recorded before any treatments (–60 minutes), immediately before dexmedetomidine administration (0 minutes), and at predetermined times after DEX administration.

shown). Heart rate decreased in all treatment groups after DEX administration, and it was lower than baseline values until the end of the follow-up period. Compared with control group dogs, heart rate was significantly ($P < 0.001$) higher for dogs of all other groups at 90 minutes (but not at any other time point) after DEX administration. For respiratory rate, no significant time or treatment effects were detected after DEX administration (data not shown). The rectal temperature increased after exercise, and in dogs of all groups, except DM+EX-group dogs, it gradually decreased after DEX administration (Table 2).

Discussion

In our study, heart and respiratory rates, rectal temperatures, and plasma cortisol concentrations increased in dogs that underwent exercise and saline solution administration, indicating that the physical stress caused by trotting on the treadmill was strong enough to induce physiologic responses. In addition to the decreased plasma cortisol concentrations, no other dexamethasone-induced hormonal changes were detected. These findings are in agreement with those of earlier reports[5,6] in which dexamethasone administration decreased the cortisol concentrations in blood, whereas norepinephrine concentrations were not suppressed. Exercise did not influence plasma cortisol concentrations in the dexamethasone-treated dogs of our study, which was expected because pretreatment with dexamethasone has been reported[5] to block the ACTH and cortisol responses to stress.

Administration of DEX induced sedation in all dogs. Neither pretreatment with dexamethasone nor exercise affected the degree of sedation induced by DEX administration. On the contrary, when administered immediately after exercise in horses, the standard doses of α_2-adrenergic receptor agonists (xylazine and detomidine) were often unable to produce sedation,[1] whereas twice the standard doses produced safe and effective sedation.[11,1] Whether the more potent sedative effect of DEX in exercised dogs, compared with that of xylazine and detomidine in exercised horses, was caused by differences between species or among drugs remains unknown.

Dexamethasone administration or exercise did not have any systemic effects on the concentrations of circulating catecholamines. Both plasma epinephrine and norepinephrine concentrations decreased after DEX administration, as has been described for dogs.[7]

Administration of DEX decreased plasma cortisol concentration in dogs that underwent exercise but not in control group dogs. This suggests that varying reports[1,7] about the influences of α_2-adrenergic receptor agonists on cortisol concentrations in conscious animals could be a result of various degrees of stress before drug administration. The influence of dexamethasone administration on cortisol concentrations was evident after sedation.

The activation of α_2-adrenoceptors is reported[12] to inhibit ADH release. Exercise increases plasma ADH concentrations in horses[13] and humans.[14,15] In an earlier report,[16] it is suggested that α_2-adrenoceptors may affect the ADH response to stress in dogs. However, in our study, plasma ADH concentrations were not influenced by exercise or administration of dexamethasone or DEX.

In our study, plasma glucose concentrations were substantially decreased by 30 minutes after IV administration of DEX. Such a finding has not been described for dogs. No decrease in blood glucose concentrations is detected in Beagles after an equipotent dose of medetomidine (10 g/kg) is administered either IM[7] or IV.[17] However, asymptomatic hypoglycemia has been reported[18] after clonidine treatment in children, suggesting that α_2-adrenergic receptor agonists may have this unexpected influence on blood glucose concentrations. The hyperglycemic effect of α_2-adrenergic receptor agonists is reported,[7] and it is primarily attributed to inhibition of insulin secretion.[7,17] No significant changes were detected in plasma glucagon concentrations in Beagles that received various doses of medetomidine or xylazine.[7] In our study, plasma glucose concentrations returned to baseline values by 90 minutes after DEX administration. The follow-up period in our study may have been too short to detect peak glucose concentrations because in an earlier study,[7] the maximum concentration was reached at 3 hours after IM administration of medetomidine.

Administration of DEX decreased heart rate and rectal temperature in our study, as reported earlier.[19] In our study, heart rate was lower in control group

dogs than in dogs of other groups at the last follow-up point, indicating that both physical stress and corticosteroids may decrease the duration of sympatholysis induced by DEX administration. However, in terms of sedation, no significant difference was found in dogs of other groups at that time point, which indicates that the scoring of sedation used in our study may not have been sensitive enough to detect minor differences between slightly sedated dogs. Dexamethasone administration or exercise did not influence the respiratory rate detected after sedation. Although no attempts were made to maintain body temperature, the moderate decrease in rectal temperature was not expected to substantially affect the metabolism of DEX or therefore the duration of sedation.

a. Dexakel, Kela Laboratoria, Hoogstraten, Belgium.
b. Dexdomitor (0.5 mg/mL solution for injection, diluted in saline 1:10), Orion Pharma, Turku, Finland.
c. Spotchem SP-4420, Arkray Factory Inc, Shiga, Japan.
d. Vetlab Ltd, Tampere, Finland.
e. IMMULITE Cortisol, Diagnostic Products Corp, Los Angeles, Calif.
f. Antidiuretic hormone, ADH, vasopressin direct RIA, Bühlmann Laboratories AG, Allschwill 1, Switzerland.
g. Bioanalytical Systems Inc, West Lafayette, Ind.
h. Sigma Chemical Co, St Louis, Mo.
i. ESA CoulArray, model 5600, ESA Inc, Chelmsford, Mass.
j. Inertsil ODS-3, 4.0×150 mm, 3 mcm, GL Sciences Inc, Tokyo, Japan.
k. Clinical Division, Bio-Rad Laboratories, Hercules, Calif.
l. Hubbell JAE, Hinchcliff KW, Schmall LM, et al. Sedative administration to horses immediately after maximal exercise: determination of drug and dose (abstr), in *Proceedings*. 43rd Annu Conv Am Assoc Equine Pract 1997;43:279.

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Appendix is printed on the next page

Appendix

Scoring of sedation before and after administration of dexmedetomidine in dogs.

Variables	Score
Spontaneous posture	
Standing	0
Able to stand with ataxia	1
Sternal, head up	2
Sternal or lateral, head down	3
Eye (palpebral reflex and eye positioning)	
Normal	0
Reflex decreased and eye middle	1
Reflex decreased and eye partly down	2
Reflex decreased and eye down	3
Reflex weak and eye down	4
Relaxation of jaw and tongue	
Normal	0
Bites jaws together strongly	1
Slight relaxation of the jaws, resists pulling of the tongue strongly	2
Moderate relaxation, slight resistance when pulling the tongue	3
No resistance when pulling the tongue	4
General appearance	
Normal	0
Slight sedation	1
Mild sedation	2
Moderate sedation	3
Deep sedation	4
Sedation index	0–15