Profound postanesthetic hypoglycemia attributable to glucocorticoid deficiency in 2 dogs

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Abstract — Glucocorticoid deficiency was diagnosed as the cause of severe postanesthetic hypoglycemia in 2 dogs. Prior signs of systemic illness were not described in either dog; however, preoperative hematologic findings were consistent with glucocorticoid deficiency. Fasting hypoglycemia is a possible complication of chronic adrenal insufficiency primarily because of impaired gluconeogenesis.

Résumé — Forte hypoglycémie postanesthésique attribuable à une déficience en glucocorticoïdes chez 2 chiens. Une déficience en glucocorticoïdes a été diagnostiquée comme cause d'une forte hypoglycémie postanesthésique chez 2 chiens. Les signes avant-coureurs d'une maladie systémique n'avaient pas été décrits chez aucun des chiens; cependant, les résultats de l'hématologie préopératoire étaient compatibles avec une déficience en glucocorticoïdes. L'hypoglycémie à jeun est une complication possible de l'insuffisance surrénalienne chronique principalement à cause d'une néoglucogénèse insuffisante.

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The signs of hypoadrenocorticism usually occur because of both glucocorticoid and mineralocorticoid deficiency and hyponatremia and hyperkalemia (1). However, dogs with normal electrolyte concentrations and apparent glucocorticoid deficiency alone are also encountered (2–6). Most dogs with glucocorticoid deficiency exhibit lethargy, weakness, anorexia, sporadic vomiting, and weight loss, similar to chronic typical hypoadrenocorticism (2–3,6). We describe 2 dogs without overt clinical signs of adrenal disease in which glucocorticoid deficiency was identified after the dogs developed profound hypoglycemia following general anesthesia.

Dog 1

A 5.5-kg, 8-year-old, neutered male miniature schnauzer was referred to the Colorado State University Veterinary Teaching Hospital because of a transverse fracture of the distal part of the radius and ulna, sustained when the dog jumped off a dry-docked boat. Other than having the fractured limb, the dog appeared normal. There was a relative neutropenia (5.8×10^9/L cells) and lymphocytosis (3.4×10^9/L cells) on the preoperative complete blood cell count (CBC), although absolute numbers of neutrophils and lymphocytes fell within reference ranges (Table 1; Day 1). There was also a mild anemia (hematocrit 0.30 L/L). Serum glucose, sodium, and potassium concentrations were normal (Table 2). General anesthesia and surgical fracture repair were completed the following day (Day 2). Acepromazine (0.04 mg/kg body weight (BW), SC) and fentanyl (0.01 mg/kg BW, SC) were given as premedicants. Anesthesia was induced with thiopental (13 mg/kg BW, IV) and maintained with halothane. After 1 h of anesthesia, indirect systolic blood pressure recordings dropped to 60 mmHg, and a dopamine infusion (5–7 μg/kg BW/min) was initiated. Systolic blood pressure remained between 60 and 90 mmHg for the remainder of the procedure. The total time of anesthesia was approximately 3 h. Twelve hours postanesthesia the dog was recumbent, hypothermic (35.9°C), and poorly responsive. Whole blood glucose measured on a glucose strip (Chemstrip BG, Boehringer Mannheim, Indianapolis, Indiana, USA) was 0.0 mmol/L. Samples were obtained for a CBC and glucose and electrolyte determinations (Table 2). Hypoglycemia was confirmed by a serum glucose concentration of 0.60 mmol/L. Sodium concentration was normal (146 mmol/L) and potassium concentration was mildly reduced (3.5 mmol/L). Immediate treatment included IV fluid replacement, glucose administration (dextrose 0.5 g/kg BW, IV, followed by fluids supplemented with 2.5% dextrose) and rewarming.

Potential causes of hypoglycemia are prolonged starvation, toy breed hypoglycemia, sepsis, hepatic insufficiency, hypoadrenocorticism, insulinoma, nonislet cell neoplasia, hunting dog hypoglycemia, or glycogen storage disease. Sepsis and hypoadrenocorticism

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Table 1. Selected hematologic findings in 2 dogs with glucocorticoid deficiency

	HEM (L/L)	WBC ($\times 10^9$/L)	NEU ($\times 10^9$/L) (% of WBC)	LYM ($\times 10^9$/L) (% of WBC)	EOS ($\times 10^9$/L) (% of WBC)
Dog 1					
Preoperative (Day 1)	0.30	9.8	5.8 (59)	3.4 (35)	0.3 (3)
27 mo postdiagnosis	0.40	10.6	6.5 (61)	2.2 (21)	1.5 (13)
Dog 2					
Preoperative (Day 1)	0.38	6.0	2.4 (40)	2.6 (43)	0.6 (10)
10 mo postdiagnosis	0.43	7.6	5.7 (46)	2.5 (44)	0.4 (7)
24 mo postdiagnosis	0.41	8.8	5.6 (64)	2.4 (28)	0.4 (5)
Reference range	0.37–0.55	6.0–17.1	3.6–11.5 (60–77)	1.0–4.8 (12–30)	0.1–1.2 (2–10)

HEM — Hematocrit; WBC — Total white blood cells; NEU — Neutrophils; LYM — Lymphocytes; EOS — Eosinophils

Table 2. Serum glucose, electrolyte, and cortisol concentrations in 2 dogs with glucocorticoid deficiency

	GLU (mmol/L)	Na (mmol/L)	K (mmol/L)	Na/K ratio	Pre-ACTH cortisol (nmol/L)	Post-ACTH cortisol (nmol/L)
Dog 1						
Preoperative (Day 1)	5.72	145	4.8	30.2		
12 h postanesthesia	0.60	146	3.5	41.7		
24 h postanesthesia					< 6.3	< 6.3
15 mo postdiagnosis	nd	150	4.9	30.6		
27 mo postdiagnosis	5.94	148	6.1	24.3		
4 y postdiagnosis	6.38	142	4.8	29.6		
5 y postdiagnosis	5.23	147	4.4	33.4	8.8	14
Dog 2						
Preoperative (Day 1)	4.13	146	4.8	30.4		
6 h postanesthesia	0.59	144	3.8	37.9		
24 h postanesthesia					< 7.0	< 7.0
10 mo postdiagnosis	5.83	150	4.7	31.9	< 1.1	< 1.1
24 mo postdiagnosis	5.23	150	4.8	31.3		
Reference range	3.03–6.71	145–158	4.1–5.5	> 27:1	14–180	231–571

GLU — Glucose; Na — Sodium; K — Potassium; ACTH — Adrenocorticotropic hormone; Pre-ACTH cortisol — serum cortisol measured prior to the administration of exogenous ACTH; Post-ACTH cortisol — serum cortisol measured following administration of exogenous ACTH

were considered most likely in this dog, because of the normal preoperative glucose concentration and a lack of other clinical features supporting hepatic disease or episodic hypoglycemic disorders. Serum cortisol was measured prior to and 1 h following administration of exogenous adrenocorticotropic hormone (ACTH, Parke-Davis, Morris Plains, New Jersey, USA), 0.25 U/kg BW, IV. While we waited for the results of the ACTH stimulation test, we added prednisone (0.4 mg/kg BW, PO, q24h) and cefazolin (20 mg/kg BW, IV, q8h) to the treatment regimen. The dog improved markedly within 12 h and was alert and eating the following morning. Glucocorticoid deficiency was confirmed by pre- and post-ACTH serum cortisol concentrations of < 6.3 nmol/L (reference ranges 14 to 180 nmol/L and 231 to 571 nmol/L, respectively). The dog was discharged on Day 7 receiving prednisone (0.4 mg/kg BW, PO, daily).

The dog responded well and the dosage of prednisone was gradually reduced to 0.2 mg/kg BW, given every other day and as needed in stressful situations. Twenty-seven months following the diagnosis of glucocorticoid deficiency, the dog had mild electrolyte abnormalities consistent with mineralocorticoid deficiency (serum potassium 6.1 mmol/L, sodium to potassium ratio 24.3, Table 2). Electrolyte concentrations on subsequent rechecks were normal, and mineralocorticoid supplementation was not prescribed. Five years after the initial diagnosis, the dog was presented for acute vomiting, lethargy, and diarrhea. Prior to this visit, the owner had independently reduced the prednisone supplementation to 0.2 mg/kg BW, PO, twice weekly. An ACTH stimulation test confirmed continued glucocorticoid deficiency (pre-ACTH cortisol 8.8 nmol/L, post-ACTH cortisol 14 nmol/L). The clinical signs resolved with supportive therapy, and the owners were advised to give prednisone once daily indefinitely.

Dog 2

A 20-kg, 7-year-old, spayed female border collie mix was evaluated at the Atlantic Veterinary College Veterinary Teaching Hospital for refractory unilateral otitis externa. The dog had been treated with topical antibiotic, and antifungal and anti-inflammatory otic preparations (Otomax and Gentocin Otic, Schering Plough, Point Claire, Quebec). Otic examinations confirmed a significant otitis externa and a ruptured tympanic membrane in the right ear. Inflammation was associated with large numbers of *Malassezia* sp. organisms and occasional cocci. Otic preparations containing steroids were discontinued; oral chloramphenicol (25 mg/kg BW, PO,

q8h) and topical vinegar and water ear flushes were prescribed. Following a poor response, the dog was admitted 3 wk later for anesthesia, tympanic bullae radiographs, and deep ear cleaning. On preoperative evaluation, there was a neutropenia (2.4×10^9 cells/L) and low-normal hematocrit (0.378 L/L) (Table 1). Serum biochemical results were normal (Table 2). The dog was premedicated with meperidine (4 mg/kg BW, IM) and atropine (0.04 mg/kg BW, SC). General anesthesia was induced with thiopental (7 mg/kg BW, IV) and maintained with isoflurane inhalation. Radiographs of both tympanic bullae were normal. The middle and external ear canals were flushed thoroughly. Total time of anesthesia was approximately 3 h.

Six hours after cessation of inhalant anesthesia and extubation, the dog was still recumbent, hypothermic (36.3°C), and minimally responsive to stimuli. Naloxone was administered (200 mg, IV, 200 mg, SC) to reverse any residual effects of the narcotic premedicant, without effect. A generalized seizure was observed 2 h later. Samples were obtained for packed cell volume, plasma protein, blood glucose, and electrolyte determinations (Table 2). The blood glucose measured by glucometer (Accucheck II, Boehringer Mannheim) was 0.59 mmol/L. Sodium concentration was normal, while the potassium concentration was mildly decreased (3.8 mmol/L). Supportive therapy was initiated with IV dextrose administration (0.5 g/kg BW, IV), IV fluids (5% dextrose), and rewarming. Seizure activity resolved immediately following the dextrose administration, and within an hour the dog was alert, responsive, and would accept food and fluids orally. An ACTH stimulation test (ACTH-40 gel, Sanofi Sante Animale, 2.2 U/kg BW, IM) completed the following day confirmed glucocorticoid deficiency (< 7 nmol/L, reference ranges 14 to 180 nmol/L pre-ACTH and 231 to 571 nmol/L post-ACTH).

Following results of diagnostic tests, treatment was initiated with oral prednisone (0.2 mg/kg, PO, q24h), a topical antifungal preparation, and systemic ketoconazole (10 mg/kg BW, PO, q12h). Seven and 14 d later, the otitis was resolving, and the owner reported a marked improvement in the dog's general attitude, strength, and activity level. Otic medications were discontinued after 21 d and otitis did not recur. Ten months later, resting serum cortisol measurement and serum cortisol measured post-ACTH administration remained subnormal, both < 1.1 nmol/L. Plasma aldosterone concentration following ACTH administration was also subnormal (pre-ACTH aldosterone 36 pmol/L, reference range 14 to 957 pmol/L; post-ACTH aldosterone 27 pmol/L, reference range 197 to 2103 pmol/L). Electrolyte concentrations were normal 24 mo following diagnosis (Table 2). The dog has remained normal by receiving prednisone at a dosage of 0.1 to 0.25 mg/kg BW, PO, every 24 to 48 h.

Delayed anesthetic recovery and severe hypoglycemia in these 2 dogs was attributed to glucocorticoid deficiency. In the healthy animal, cortisol stimulates endogenous glucose production and lipolysis, facilitates glycogen storage, and limits peripheral glucose utilization. Specifically, cortisol favors release of alanine and lactate from muscle and glycerol from fat, induces enzymes required for gluconeogenesis, and modulates the sensitivity of peripheral glucose receptors (7). The overall effect of cortisol on glucose metabolism tends to raise the plasma glucose concentration. With glucocorticoid deficiency, hepatic gluconeogenesis is impaired, because of depressed hepatic enzyme activity and reduced mobilization of gluconeogenic precursors. Peripheral tissues exhibit enhanced sensitivity to insulin and decreased sensitivity to the counterregulatory hormones glucagon and epinephrine, such that glucose utilization is favored (7). Secretion of epinephrine may also be compromised in secondary hypoadrenocorticism, in which ACTH secretion is impaired (7).

Mild to moderate hypoglycemia has been reported in 3% to 37% (1–3,8) of dogs with primary hypoadrenocorticism; it has also been reported in dogs with glucocorticoid deficiency and normal electrolyte concentrations (2,5–6). Hypoglycemic seizures occurred in one dog with typical hypoadrenocorticism (9), and another dog had exercise intolerance attributed to hypoglycemia (5). In a review of 18 dogs with glucocorticoid deficiency, 6 of the 18 had serum glucose concentrations < 3.58 mmol/L, and 2 of these 6 presented for hypoglycemic collapse (6). In most dogs with hypoadrenocorticism, severe hypoglycemia is averted by a relative reduction in insulin secretion and regular feeding (1,7); signs of hypoglycemia are rarely observed (1,5,6,8,9). During a 24- to 48-hour fast, however, hepatic glycogen is depleted and gluconeogenesis becomes the exclusive source of glucose production (7). Since cortisol enhances substrate mobilization and enzyme induction for gluconeogenesis, a glucocorticoid deficient animal lacks the mechanisms required to maintain euglycemia during prolonged fasting, particularly when glycogen stores are poor due to chronic adrenal dysfunction (7). Although other hormones, including glucagon and epinephrine, also facilitate gluconeogenesis, their effects are short-lived, especially in a hypoglycemic crisis (7). Thus, fasting associated with anesthetic preparation, surgical or other procedures, and recovery could be sufficient to cause hypoglycemia in hypocortisolemic dogs. Hypotension during or following anesthesia may have contributed to the delayed recovery and development of hypoglycemia in Dog 1. Glucocorticoids help to maintain blood pressure by preserving vascular smooth muscle reactivity to catecholamines; rapid development of hypotension under general anesthesia has been described in one dog with atypical hypoadrenocorticism (10). Hypotension and hypoperfusion also promote anaerobic metabolism in tissues, thereby increasing peripheral glucose consumption.

Cortisol deficiency was determined by ACTH stimulation testing in both dogs. Iatrogenic suppression of glucocorticoid production was considered in Dog 2, because this dog had been treated intermittently with steroidal topical otic preparations. Otic preparations containing dexamethasone or triamcinolone acetate can blunt ACTH responses within 7 d and for at least 14 d after application is discontinued (11). In Dog 2, however, otic steroids had been withdrawn 21 d prior to initial adrenocortical testing, and serum cortisol and aldosterone responses remained subnormal on repeat ACTH stimulation tests completed months later. It is also unlikely that anesthetic agents affected the ACTH stimulation test results, although narcotics can transiently affect adrenocortical responses (12–14). Fentanyl administered at

induction dosages of 15 to 50 µg/kg BW, IV, blunted increases in ACTH, plasma cortisol, and glucose concentrations typically observed during pelvic surgery in humans; however, plasma cortisol measurements remained within normal baseline ranges (12). A suppressive effect of etomidate on cortisol responses to surgical stimulation in dogs (13) and humans (14) dissipates approximately 6 h following administration, with rebound hypercortisolemia observed 20 to 24 h later. In these dogs, suppression of adrenocortical function 24 h following one dose of IM fentanyl or meperidine seems unlikely.

Primary hypoadrenocorticism has been attributed to idiopathic adrenal atrophy, immune-mediated destruction of the adrenal cortex, administration of adrenolytic drugs, and destruction of adrenal tissue by infarction, granulomatous disease, or neoplastic disease. Glucocorticoid deficiency may result from selective or incomplete adrenocortical destruction (primary glucocorticoid deficiency), or from secondary hypoadrenocorticism, in which production or secretion of ACTH is impaired (2). We did not measure endogenous ACTH concentrations, so secondary disease cannot be completely ruled out. Dogs with primary hypoadrenocorticism and normal electrolyte concentrations at the time of diagnosis may later develop electrolyte abnormalities suggestive of mineralocorticoid deficiency (2,6). Persistent electrolyte abnormalities have not been observed in either of these dogs during long-term follow-up, although aldosterone secretion in response to ACTH appears to be impaired in Dog 2. Plasma aldosterone concentrations measured in this dog were similar to those observed in dogs with primary hypoadrenocorticism and electrolyte abnormalities, in which basal aldosterone concentrations fell within normal ranges but aldosterone secretion and release did not rise following ACTH administration (15). Low aldosterone measurements have also been observed in 2 dogs with secondary hypoadrenocorticism (1). Aldosterone responses may be suppressed by exogenous glucocorticoid administration (15), but this effect would be expected to be minimal with physiologic replacement dosages. Although both dogs periodically received prednisone at 48-hour intervals, daily glucocorticoid replacement is recommended to prevent hypoadrenal crises (1).

Hypoadrenocorticism was an unexpected finding, because both dogs had a history of good health, exhibited no systemic signs of illness prior to anesthesia, and were being evaluated for unrelated, routine clinical problems. In retrospect, hemogram abnormalities (mild anemias, relative neutropenias, lymphocytoses, and normal eosinophil counts) observed prior to anesthesia were consistent with glucocorticoid deficiency (1,3,4,6,8). The observation of normal eosinophil or lymphocyte numbers in stressed or ill animals is now well recognized as a possible indication of adrenal insufficiency. Adrenal dysfunction also should be considered when significant hypoglycemia develops in an anesthetized patient, particularly if no other etiology is readily identifiable.

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