Intravenous administration of levothyroxine for treatment of suspected myxedema coma complicated by severe hypothermia in a dog

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Continuous electrocardiographic monitoring revealed an irregular supraventricular rhythm without visible P waves. Packed cell volume was 33%, serum total protein concentration was 8.4 g/dl, serum glucose concentration was 384 mg/dl, and BUN concentration was estimated to be between 5 and 15 mg/dl. Serum biochemical analyses and CBC obtained by the referring veterinarian 10 days earlier revealed hypercholesterolemia, normoglycemia (Table 1), and anemia (PCV, 33%; reference range, 37 to 55%). A catheter was placed in a cephalic vein, and warmed lactated Ringer's solution (20 ml/kg [0.9 ml/lb] of body weight) was administered. Atropine (0.01 mg/kg [0.0043 mg/lb]) was administered IV in an attempt to increase heart rate, and dexamethasone (1.0 mg/kg [0.45 mg/lb] IV) was added for the management of possible cerebral edema. Oxygen was delivered by face mask, recirculating water heating pads were placed over and under the dog, and a forced-air warming unit was placed around the dog's body. Increase in heart rate was not detected after atropine administration.

Urine production was detected within 1 hour of initiating fluid therapy. Blood was drawn for serum biochemical analyses (Table 1), CBC, and coagulation tests after 1,000 ml of lactated Ringer's solution had been administered. Serum for thyroid hormone analysis was sent to a reference laboratory. The CBC revealed nonregenerative anemia (PCV, 31%; reference range, 37 to 55%), mature neutrophilia (13,950 cells/µl; reference range, 3,000 to 11,500 cells/µl), and lymphopenia (600 cells/µl; reference range, 1,000 to 4,800 cells/µl). Platelet count was >137,000/µl (reference range, 145,000 to 440,000/µl), and platelets were clumped. Coagulation tests revealed activated partial thromboplastin time (APTT) of 22.5 seconds (reference range, 28.3 to 40.0 seconds), one-stage prothrombin time (OSPT) of 10.9 seconds (reference range, 5.9 to 8.5 seconds), and fibrinogen and fibrin degradation products (FDP) concentrations within the reference ranges.

After a 3-hour period, body temperature reached 28.3 C (83 F), and 0.9% NaCl solution was substituted for the lactated Ringer's solution. Sinus P waves became apparent with each QRS complex on the electrocardiogram, and heart rate was 48 beats/min. After 4 hours of warming, the dog was responsive, and cranial nerve abnormalities resolved. Shivering was not observed throughout the warming process. Core body temperature reached 35.4 C (95.7 F) by 7 hours, heart rate was 68 beats/min with a sinus arrhythmia, and the dog ate food when offered.

A tentative diagnosis of profound hypothyroidism was made on the basis of dermatologic abnormalities, hypercholesterolemia, nonregenerative anemia, and...
susceptibility to hypothermia. **Levothyroxine sodium** (T4; 4.0 µg/kg [1.8 µg/lb] q 12 h) was administered orally. The dosage of T4 was a quarter of calculated maintenance requirements, because concern of preexisting cardiac disease warranted a gradual increase in metabolic rate to avoid precipitating cardiac failure or other adverse effects such as arrhythmias.1,2 The dog was placed in a heated cage overnight, and IV administration of 0.9% NaCl solution was continued.

On the second morning of hospitalization, the dog could maintain a body temperature of 37.7 °C (99.8 °F) with assistance from an external heat source; therefore, a decision was made to increase serum thyroid hormone concentrations more quickly by use of IV administration of T4, in addition to oral administration. Bioavailability of orally administered T4 in dogs is estimated to range from 10 to 50%. Decreased gastrointestinal motility and blood flow attributable to hypometabolism and continued hypothyroidism in the dog may also have decreased bioavailability of orally administered T4. Because parenterally administered T4 is 100% bioavailable, the dosage chosen for IV administration (1.0 µg/kg [0.45 µg/lb], q 12 h) was a quarter of the oral dosage. The parenteral dosage of T4 necessary to normalize serum total and free T4 concentrations in surgically thyroparathyroidectomized dogs is 10 µg/kg/d (4.5 µg/lb/d), or 500 µg/d for this patient. Oral administration of T4 (4.0 µg/kg [1.8 µg/lb] q 12 h) was also continued to provide sustained delivery of T4.

Thoracic radiographs, an ECG, and an echocardiogram were performed on the second day of hospitalization. Radiography revealed right-sided dependent pulmonary atelectasis consistent with the dog lying on its right side at the time of referral, but cardiac abnormalities were not detected. Low-voltage R wave height (< 1 mV in lead II) and prolonged P-wave duration (0.06 seconds) were the only electrocardiographic abnormalities identified. Echocardiography revealed heart chambers of normal size, with mildly reduced to low-normal left ventricular fractional shortening (20 to 26%; reference range, 25 to 35%). Paroxysmal tachycardia, which was suspected by the referring veterinarian, was not detected during telemetric monitoring of the cardiac rhythm. Coagulation tests were repeated and revealed a decrease in the OSPT to within the reference range and continued, although less severe, prolongation in APTT (16.7 seconds).

By the third day of hospitalization, the dog had a rectal temperature of 38.3 °C (101 °F) and was removed from the heated cage. Plasma was obtained for measurement of APTT and was within the reference range. Intravenous administration of T4 was discontinued, and the dog was discharged, with oral administration of T4 (4.0 µg/kg [1.8 µg/lb] q 12 h) to be continued. At reexamination 7 days later, body weight had decreased to 47 kg (103.4 lb), and heart rate was 112 beats/min with a respiratory sinus arrhythmia. The wounds over the coccygeal vertebrae were partially healed, and other physical examination findings, except for areas of alopecia, were unremarkable. The owner reported that the dog was less ataxic and was starting to run for the first time in months. On the basis of calculated maintenance levothyroxine requirements, the dosage of orally administered T4 was increased by 4.2 µg/kg (1.9 µg/lb) q 12 h weekly until a maximum dosage of 17 µg/kg (7.7 µg/lb) was administered twice daily.

Results of the thyroid hormone analysis of the serum sample obtained at the time of referral revealed **thyroid stimulating hormone (TSH)** concentration of 38 mU/L (reference range, 0 to 30 mU/L), total T4 concentration of 0 nmol/L (reference range, 15 to 50 nmol/L), total **triiodothyronine (T3)** of 0.1 nmol/L (reference range, 1.0 to 2.5 nmol/L), free T4 of 0 pmol/L (reference range, 12 to 33 pmol/L), and free T3 of 2.4 pmol/L (reference range, 2.8 to 6.5 pmol/L). Canine TSH was measured by use of a commercially available immunoradiometric kit, and free T4 was measured by use of direct radioimmunoassay.17

At reexamination 3 months later, after 6 weeks of oral administration of a full replacement dosage of T4 (19 µg/kg [8.7 µg/lb] PO, q 12 h), body weight was 42 kg (92.4 lb), and all physical examination findings were unremarkable. Serum chemical values (Table 1) were near or within reference ranges, and PCV was within the reference range. Electrocardiography revealed heart rate of 100 beats/min with a sinus rhythm and an increase in the height of the R wave (1.7 mV), compared with the previous value (0.9 mV). Echocardiography revealed a decrease in the left ventricular and left atrial diameters, compared with previous measurements, but hypocontractility (fractional shortening, 20%) was still evident. The excellent clinical response to T4 administration without additional medications supported the diagnosis of primary hypothyroidism, and the dosage of orally administered T4 was decreased from 19 µg/kg (8.7 µg/lb) every 12 hours to once-daily administration, on the basis of serum T4 concentration (55 nmol/L) determined 6 hours after oral T4 administration.

The thyroid profile in this dog must be interpreted in light of the effects of severe illness (ie, severe hypothyromia) and dexamethasone administration.
Systemic illness in dogs may cause decreased T₄ concentration; therefore, measurement of free T₄ by the equilibrium dialysis method is advised because free T₄ concentration is less affected by nonthyroidal illness.³ Although increased TSH is expected in dogs with primary hypothyroidism, TSH may be increased in 7⁴ to 12%⁵ of dogs with nonthyroidal illness. Rarely, T₄ or free T₄ may be undetectable in dogs with severe non-thyroidal illness, although TSH concentration within reference range is expected.⁶ In the dog reported here, the dermatoic manifestations and hypercholesterolemia may have been compatible with hyperadrenocorticism, but the 1.5-year history of weakness and nonregenerative anemia and susceptibility to hypothermia were more suggestive of hypothyroidism. In addition, hyperadrenocorticism is more commonly associated with erythrocytosis and increased serum activity of alkaline phosphatase,⁷ which were not detected. Corticosteroid administration may decrease free T₄, T₃, and TSH concentrations;⁸ therefore, TSH concentration in this dog may have been higher if dexamethasone had not been given 2 hours prior to obtaining blood for thyroid hormone analysis. In humans with hypothyroidism, plasma cortisol concentration may be inappropriately low, and TSH concentration does not increase in response to low body temperature.⁹ Although the dog of this report was severely ill, the finding of decreased free T₄ or T₃ concentration in combination with increased TSH concentration strongly suggested primary hypothyroidism.¹⁰

Clinical signs were compatible with myxedema coma and severe hypothyraemia. Myxedema coma is a term that describes a hypothermic, stuporous state attributable to severe hypothyroidism. Hypothyraemia, usually without shivering,²¹,²² develops as a result of severe hypothyroidism, which may reduce the metabolic rate by as much as 40%.²³ Shivering requires a functional hypothalamic thermoregulatory center, and abnormalities such as edema in the thermoregulatory center may alter the thermal set point and thereby cause loss of the ability to shiver.²⁴ Because immediate thermoregulation is controlled by the sympathetic nervous system,¹⁰ and T₄ amplifies or has a permissive effect on catecholamine function,¹⁶ normal muscular activity and shivering may not be possible with T₄ deficiency.

Additional clinical findings with myxedema coma following prolonged hypothyroidism include hypoventilation caused by respiratory muscle weakness or impairment of the function of the respiratory center,⁷ hypotension, bradycardia, and typical dermatologic manifestations of hypothyroidism.¹⁵ Laboratory abnormalities may include hypoxemia, hypercarbia, hypona-træmia, hypocortisolemia, and hypoglycaemia, in addition to the typical findings of hypercholesterolemia, anæmia, and hypertriglyceridaemia.¹⁷

Myxedema coma associated with severe hypothyroidism is infrequently seen in dogs, and as a result, may not be immediately recognized and appropriately treated. Most reported cases have been in Doberman Pinschers,¹¹,¹²,¹³,¹⁰,²⁰ therefore, its occurrence in a breed other than Doberman Pinscher may also lead to a delay in the diagnosis and treatment with T₄. Because of poor organ and tissue perfusion and severe hypometabolism, absorption of therapeutic agents from the gastrointestinal tract, subcutaneous tissues, or muscle is usually slow and unpredictable; hence, thyroid medications should be administered IV.²¹ Invasive administration of a low dose of T₄ (ie, 1.0 µg/kg [0.45 µg/l]) in dogs seems prudent, because dilatative cardiomyopathy may develop in the same breeds of dogs that are prone to hypothyroidism (eg, Doberman Pinschers). Two Doberman Pinschers that were administered 500 µg of T₄ IV died 24 hours later; 1 of the dogs had congestive heart failure, cardiomegaly, and tachyarrhythmias, but the second had normal cardiac findings at necropsy.¹¹,¹²

Fluid therapy is critically important in patients with hypothyroidism and hypothermia.²² Prolonged cold exposure may result in severe volume depletion and hypotension attributable to cold diuresis, additional volume losses attributable to impaired sodium and water reabsorption by the kidneys as a result of impaired function of epithelial transport mechanisms and a decrease in the sensitivity of the kidney to antidiuretic hormone, and intravascular fluid shifts leading to intracellular accumulation of fluid and peripheral edema.¹²,²³ Cold diuresis results when peripheral vasoconstriction causes shunting of blood to the central circulation with an increase in central blood volume and compensatory diuresis.²⁴ Despite the volume deficit caused by severe hypothyroidism and hypothermia, IV administration of fluids must be performed at a rate appropriate for the slow heart rate and peripheral vasoconstriction. Determination of central venous pressures may be helpful in guiding the rate of IV administration of fluids in dogs with peripheral vasoconstriction.

Warmed lactated Ringer's solution was initially administered to the dog of this report, which may have contributed to the decreased sodium, chloride, and potassium concentrations after 2 hours of fluid administration (Table 1). Lactated Ringer's solution is an alkalining fluid and is commonly used as a resuscitation fluid in veterinary medicine, because metabolic acidosis is common in sick dogs.²⁵ With hypothyraemia, however, the liver cannot metabolize lactate;²⁶ consequently, increased serum bicarbonate concentration, as estimated by serum total CO₂ concentration, existed in this dog prior to fluid administration. Although arterial blood gas analysis was not performed, chronic respiratory acidosis attributable to hypoventilation was assumed. The most effective treatment for respiratory acidosis is rapid diagnosis and elimination of the underlying cause of alveolar hypoventilation²⁷ and was accomplished by rewarmin and treatment with T₄. Provision of a parenterally administered solution with adequate amounts of chloride (eg, 0.9% NaCl) allows the kidneys to reabsorb sodium in conjugation with chloride and excrete the bicarbonate retained during compensation for chronic hypercapnia.²⁸

The initial hypokalemia in this patient may have been a result of transcellular shifts, decreased intake, or excessive losses (eg, urinary). Potassium was not added to the intravenously administered fluids, because serum total CO₂ concentration was high, and potassium moves from the intracellular to the extracel-
lular space with correction of metabolic alkalosis. In addition, potassium moves into the extracellular space during warming of the body.\textsuperscript{11}

Although hypoglycemia is often detected with myxedema coma, this finding is variable. The dog of this report may have been hyperglycemic as a result of depressed ability of the liver to utilize glucose and decreased exocrine and endocrine pancreatic function caused by hypothyroidism.\textsuperscript{24} Below 30 C (86 F), insulin secretion decreases, whereas peripheral insulin resistance increases.\textsuperscript{27} In addition, hypothermia may cause acute catecholamine-induced glycogenolysis\textsuperscript{26}; therefore, administration of exogenous insulin to a hypothermic patient is inappropriate and may lead to hypoglycemia during rewarming. Provision of glucose substrate, however, is advised for nutritionally depleted animals with decreased hepatic glucose stores.

Volume depletion in hypothermic patients may lead to hemoconcentration, increased blood viscosity, and predisposition to thrombosis. Conversely, bleeding caused by inefficient clotting at low temperatures, thrombocytopenia, and disseminated intravascular coagulation (DIC) can cause substantial blood loss from minor trauma in a hypothermic patient.\textsuperscript{13} Hypothermia reduces platelet function,\textsuperscript{25} causes platelet sequestration in the liver,\textsuperscript{29} and decreases the enzymatic activities within the coagulation cascade,\textsuperscript{30} although plasma concentrations of coagulation factors are within reference ranges.\textsuperscript{31} A coagulation profile was performed in the dog of this report to monitor for DIC as a complication of hypothermia. The APTT and OSPT were initially prolonged during hypothermia in this dog, but platelet count and fibrinogen and FDP concentrations did not support a diagnosis of DIC. Evaluation of proteins induced by vitamin K antagonism may have been helpful in determining whether coagulation precursors, induced by dysfunction of the hypothermic liver and inability to carboxylate coagulation factors, were in the circulation. Supporting this theory is the fact that OSPT returned to reference range prior to APTT; factor VII has the shortest half-life of coagulation factors in dogs and, therefore, regenerates most rapidly.

The dog reported here had multiple neuromuscular abnormalities, including a history of stiffness, weakness, and ataxia; coma, nystagmus, and unresponsive pupils were evident at the time of referral. Severe hypothyroidism can cause myopathy and profound muscle weakness, and affected dogs may have increased serum creatine kinase concentration.\textsuperscript{2} The high creatine kinase in the dog may have resulted from hypothyroid-induced myopathy; decreased clearance of creatine kinase attributable to hypothyroidism;\textsuperscript{3} and prolonged recumbency. Although the neuromuscular abnormalities reported in the history of this dog were most likely attributable to hypothyroidism, profound hypothermia resulted in the clinical signs observed at the time of referral. Core temperatures < 27 C (80.6 F) may be associated with a comatose state and absent deep tendon and brainstem reflexes.\textsuperscript{3}

The cardiovascular signs in this dog were likewise attributable to hypothyroidism and severe hypothermia. Hypothyroidism in dogs has been associated with multiple electrocardiographic abnormalities, including bradycardia and diminished P, Q, and R wave heights.\textsuperscript{32} Bradycardia may result from lack of thyroid hormone action on sinoatrial pacemaker cells, reduced systemic oxygen consumption, and increased peripheral vascular resistance.\textsuperscript{33} Cardiac hypocontractility may result from decreased numbers of cardiac \( \beta \)-adrenergic receptors and a reduced affinity for their ligand,\textsuperscript{26} reduced activity of myocardial adenylate cyclase,\textsuperscript{37} altered myosin composition,\textsuperscript{38} and a decreased rate of calcium uptake and calcium-dependent ATP hydrolysis by myocardial sarcoplasmic reticulum.\textsuperscript{39} Because hypothyroidism causes reversible impairment of left ventricular function, it is possible that, for the dog reported here, 2 months of \( T_4 \) replacement was not adequate to restore normal cardiac contractility, as measured by fractional shortening. A study\textsuperscript{40} of electrocardiographic and echocardiographic abnormalities in hypothyroid dogs revealed that up to 1 year of supplementation may be necessary to restore normal cardiovascular function.

Cardiovascular abnormalities are also a recognized complication of hypothermia. In mild hypothermia, the initial cardiac response is increased sinus rate, cardiac output, peripheral vascular resistance, and blood pressure, resulting from sympathetic stimulation.\textsuperscript{39} As hypothermia worsens, oxygen consumption and metabolic activity decrease progressively, because enzymatic reactions are temperature dependent.\textsuperscript{1} Heart rate decreases as a result of temperature-dependent suppression of pacemaker activity, and is refractory to atropine administration,\textsuperscript{26} as was observed in the dog reported here; atrial tissues are affected before ventricular tissues. The left ventricle ejects blood more slowly during hypothermia, resulting in a flat pulse wave that is difficult to palpate peripherally.\textsuperscript{1} Blood pressure may be maintained within reference range initially because of increased circulating catecholamines, a direct constrictive effect of low temperature on blood vessels, and increased blood viscosity,\textsuperscript{2} but hypotension develops below 28.9 C (84 F).\textsuperscript{41}

Cardiac arrhythmias are common with moderate to severe hypothermia, and ECG abnormalities have been reported in 88.9% of human hypothermia patients.\textsuperscript{31} Atrial arrhythmias, of which atrial fibrillation is the most common, are generally benign and resolve without specific treatment during rewarming.\textsuperscript{1,23} The dog of this report had a severely bradycardic, irregular, supraventricular rhythm without visible P waves; possible causes include slow atrial fibrillation and sinus bradycardia with P waves of extremely low amplitude caused by hypothyroidism. A major concern in severe hypothermia is ventricular fibrillation, which becomes more likely with decreasing core temperature, because the hypothermic myocardium becomes sensitized to the effects of catecholamines.\textsuperscript{33} The severely decreased metabolic rate associated with hypothyroidism in the dog of this report may have protected the myocardium from severe arrhythmias during warming; the mechanism for this protection may involve desensitization to the effects of catecholamines.\textsuperscript{42} In addition, conservative doses of replacement \( T_4 \) lessen demands on the heart caused by increasing metabolic rate.
References


